Expression of CXCR4 and CXCR7 in papillary thyroid carcinoma and adjacent tissues and their relationship with pathologic indicators of tumor aggressiveness

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Abstract. The receptors of chemokines play a significance role in the aggressiveness of tumor. CXCR4/CXCR7 promote metastasis of papillary thyroid carcinoma (PTC). This study examined the expression of chemokine receptors CXCR4/CXCR7 in human tissue specimens of PTC and peritumoral nonmalignant tissues. The correlation between CXCR4/CXCR7 and the clinicopathological factors in PTC was also determined. CXCR4/CXCR7 were examined in 115 PTC tissues from 115 patients using immunohistochemistry. Staining intensity was compared with patients and tumor characteristics including gender, age, tumor size, capsule invasion, multifocality, lymph node metastasis, and nature of paracancerous tissue. [Statistics: rank sum test, Spearman rank order correlation test; \( p < 0.05 \)]. Higher expression rates of CXCR4/CXCR7 exhibited in PTC compared with peritumoral nonmalignant tissues. The expression of them was correlated in cancer and paracancerous specimens. A trend toward higher CXCR4/CXCR7 expression was found among tumors showing positive lymph nodes and capsule invasion, while no association with sex, age, tumor size, and nature of paracancerous tissue. Number of lymph nodes was associated with higher intensity IHC staining for CXCR4/CXCR7. Intense staining for CXCR4 was also associated with multifocality. Expression of CXCR4/CXCR7 by PTCs was correlated with lymph node metastasis and capsule invasion. Although multiple bias, they were thought to play a significance role in the aggressiveness of PTC, which provides potential targets for therapeutic interventions.

Key words: Papillary thyroid carcinoma, Chemokine receptors, CXCR4, CXCR7, Metastasis

THYROID CARCINOMA, which is the most common endocrine neoplasm (accounting for 90% of all endocrine tumors), has been ranked the fourth most common type of cancer in women. Thyroid cancer (TC) includes follicular thyroid carcinoma (FTC), medullary thyroid carcinoma (MTC), and anaplastic thyroid carcinoma (ATC), among which papillary thyroid carcinoma (PTC) is the predominant pathological type, and PTC account for 80% of all TC. Some PTC cases exhibit aggressive characteristics, involving tumor size, extrathyroidal extension (ETE), angiolymphatic invasion (ALI), local metastasis and distant metastasis. Metastasis plays an important role in the prognosis and quality of life of TC patients [1]. The incidence of neck metastasis is 20–50%. 5–20% of patients with total thyroidectomy have local recurrence.

Distant metastasis is the main cause of death in TC. Therefore, according to the studies on PTC metastasis, a correct understanding of the postoperative metastasis mode is very important for making a reasonable postoperative follow-up plan, taking targeted interventions and improving the survival rate. Although PTC generally has a good prognosis, we need explore the expression of CXCR4 and CXCR7 and the relationship between their expressions and clinicopathological characteristics in PTC.

Stromal cell-derived factor-1 (SDF-1, CXCL12) was one of the six novel clinically relevant central genes in PTC identified from public databases [2]. CXCL12 was exclusively expressed in PTC but absent in other TC and lesions. In addition, CXCL12 is associated with CXCR4 and CXCR7 closely. Prior studies have shown that the expression level of CXCR4 was significantly correlated with the stage of PTC. It interacts specifically with CXC chemokine receptor 4 (CXCR4) to promote the migration of PTC cells. CXCR4 is a G protein-coupled receptor, which selectively binds CXCL12. It can drive EMT along with an up-regulation of cytokines and chemokine receptors [3]. Cancer cell migration induced by
CXCL12–CXCR4 involved multiple kinases such as phosphatidylinositol-3-kinase (PI3K), mitogen-activated protein kinase (MAPK), FAK (focal adhesion kinase) and so on. Some cancer research showed that CXCR4 was highly expressed in cancer tissue while absent or low expressed in normal cancer tissue. In breast cancer, CXCL12/CXCR4 was related to the expression level of phosphorylated mTOR [4]. Inhibition of dipeptidyl peptidase-4 accelerates epithelial-mesenchymal transition and breast cancer metastasis via the CXCL12/CXCR4/mTOR axis [5]. In FTC, the expression of CXCR4 was significantly higher in distant metastases than in primary tumour cores [6].

Little research has been done about CXCR7 on PTC. CXCR7 was later found to be the ligand of CXCL12, which was recognized as an orphan receptor. Currently it was considered to be a novel molecular linkage in the chain of connections between inflammation and cancer. By binding with CXCL12, CXCR7 mediates a series of cellular activities such as survival, proliferation, and adhesion. In the lung cancer microenvironment, the interaction of chemokines and cytokines is critical to the acquisition of the metastatic potential of cancer cells. Y-C Wu et al. revealed that CXCR7 and CXCL12 were the highest induced chemokine and its receptor in response to TGFβ1 [7]. One gene microarray analysis showed that CXCR7 modulated the progression of PTC via the regulation of PI3K/AKT pathway, its downstreamed NF-κB signaling and the Notch signaling [8].

CXCR4 and CXCR7 were widely expressed in some types of cancer such as breast cancer, small lung cancer [3, 7, 9]. The combination of a CXCR4 inhibitor with chemotherapy significantly reduces metastasis formation. CXCR4/CXCR7 has been found that these two receptors play a significant role in development of cancer cell. The role of CXCR4/CXCR7 in papillary thyroid carcinoma (PTC) has been increasingly recognized. CXCR4/CXCR7 is expressed at a higher level in metastasis thyroid carcinoma. Prior studies have shown that CXCR4 was expressed in 62.5% of PTC and in 30–40% of other malignancies, and weakly expressed in benign lesions [10]. CXCR4 and CXCR7 may be an effective marker for PTC. In order to supplement the contribution of chemokine system to PTC metastasis, we conducted a clinical retrospective study. The purpose of this study is to find the differences between CXCR4 and CXCR7 in cancer and paracancerous tissues, and to explore the correlation between them and the clinical data of PTC patients, especially the relevance to PTC aggressiveness.

Materials and Methods

Patient selection

We obtained 115 matched paired of pathologically-confirmed post-operative PTC tumor archival paraffin blocks samples from 115 patients who underwent total thyroidectomy and cervical lymph node dissection by 4 different senior surgeons in Department of Thyroid and Breast Surgery at the 960th Hospital of the PLA Joint Logistics Support Force between January, 2019 and January 2020. Considering the portability of the specimen, we studied the largest tumor of each patient when there were multiple cancer foci. The present study was approved by the Ethics Committee of the 960th Hospital of the PLA Joint Logistics Support Force.

Because this is a retrospective study, patient informed consent was waived. The malignancy of 115 samples had been examined by histopathological examination. All the patients had undergone total or subtotal thyroidectomy with regional lymphadenectomy. Peritumoral nonmalignant tissues are more than 2 cm away from the tumor and without cancer cell infiltration. Each patient’s clinical and pathology parameters includes gender, the age at the time of diagnosis, number of tumors, and tumor size, the number of lymph node, the number of positive lymph nodes, extrathyroidal extension, focality, presence of thyroiditis, or nodular hyperplasia. All the information were obtained from the patient database in hospital. All the PTCs were classified according to the World Health Organization criteria. The TNM stage of PTC was characterized according to American Joint Committee on Cancer (AJCC) Cancer Staging Manual (2018th edition). All methods were carried out in accordance with the relevant guidelines of the Ethics (ID: 2019083).

Clinical parameters were obtained from hospital records. The patients’ ages ranged from 16 to 73 (46.33 ± 12.29, 48) (mean ± Std. Deviation, median). The biggest tumor size ranged from 0.60 to 4.20 cm (1.21 ± 0.66 cm, 1.00 cm) , the number of tumors ranged from 1 to 4+ (Some lesions cannot be counted), the number of lymph node ranged from 3 to 59 (27.75 ± 12.14, 26), the number of positive lymph nodes ranged from 0 to 24 (3.80 ± 5.11, 2.00). No distant metastases at presentation was noted.

Immunohistochemistry (IHC)

5-μm-thick consecutive sections were cut from archival paraffin blocks of 115 cases. They were transferred to adhesive slides and then waited for drying after maintaining in a drying oven at 56–60°C for 2 hours. The chip should be placed in 60°C bake for 20 minutes in the constant temperature box. Paraffin slices were immersed in fresh dimethylbenzene for 10 min × 3
times. After removing excess liquid, soaked for 3 min × 3 times in anhydrous ethanol, then soaked for 3 min × 2 times in 95% ethanol and 75% ethanol; rinsed them with distilled water for 1 min and place them in PBS buffer. Added antigen retrieval buffers (1:49) in the boiling water, putted the slide into water. Heated them for 2.5 minutes after the start of air jet rotation of pressure limiting valve. Then cooled them for 5 minutes naturally, washed with tap water, took out the slice and washed them with PBS buffer for 3 min × 3 times, and entered into the operation steps of immunohistochemistry. The slide were incubated with 3% H₂O₂ for 10 min at room temperature. Afterwards they were incubated with monoclonal mouse anti-human CXCR4 (1:50; Abcam, Cambridge, UK) or monoclonal mouse anti-human CXCR7 (1:100; Abcam, Cambridge, UK) at 37°C for 60 min. 100 μL were added to each section according to the size of the tissue. The slide were added 100 μL reaction enhancer at 37°C for 20 min and incubated with secondary antibody (1:100; Abcam, Cambridge, UK) at 37°C for 30 min. Then they were stained with DAB (OriGene, WA, USA) at 37°C for 10 min and counter-stained with haematoxylin for 20 s. Subsequently, rinsed with water for several hours, transparented for 30 min in xylene I and 20 min in xylene II. The tissue sections were washed in PBS for 3 minutes × 3 times after each reaction. Appropriate negative controls lacking primary antibody were performed. We found the most appropriate concentration of antibodies by pre-experiment.

**Sections**

To improve the accuracy of the examination, the stained samples was observed under a microscope by 2 separate pathologists. All the patients underwent central neck dissection, lateral neck dissection, superior mediastinal dissection or combination of the above. The stained sections were observed by two experienced pathologists under the light microscope at 40× or 20× magnification in 10 random fields. The staining intensity were scored according to the following criteria: 0 represents absent staining, 1+ represents weak intensity, 2+ represents intermediate intensity, and 3+ represents strong intensity. The amount of positively stained cells were scored like 0 for 0~4%, 1 for 5~25%, 2 for 26~50%, 3 for 51~75%, and 4 for 76%~100%. Sum of the two scores represented the expression level of CXCR4 and CXCR7. The specimen was considered negative when the staining intensity score was 0 and positive when the score was 1+, 2+, 3+. 1~3 points defined low expression, 4~7 points defined high expression. The antibodies against CXCR in this study were from different manufacturers. All the reagent was used according to the manufacturer’s instructions.

**Statistical analysis**

Data analysis was performed using the software SPSS 19.0 (SPSS Inc., Chicago, IL, USA). Continuous variables all didn’t follow a normal distribution except for age. Nonparametric methods were used to test the two associated population whose variances weren’t equal. As the differences between each pair didn’t follow a normal distribution, so we adopted Wilcoxon signed-rank test for matched pair design to test two groups of measuring data. Each group was divided into seven grades according to the scores, and each pair were compared Wilcoxon rank test for independent samples to test for the difference of the ordinal scale between two groups. We also chosen Wilcoxon rank test for independent samples to test two groups according to high and low expression of scores. The association between each two groups was assessed using Spearman rank order correlation test. P-values for every test was all 2-sided and less than 0.05 was considered statistically significant.

**Results**

**Expression levels of CXCR4 and CXCR7 protein in PTC and peritumoral non-malignant tissues**

The expression level of CXCR4 and CXCR7 in the PTC and peritumoral specimens was examined by immunohistochemical techniques. The CXCR4 and CXCR7 immunohistochemical staining signals were mainly located in the cytoplasm of cancer cells and they were diffuse. Representative images of CXCR4 and CXCR7 expression in the PTC and paracancerous tissues are shown in Fig. 1.

Immunohistochemical staining results for the chemokine receptor CXCR4 and CXCR7 are summarized in Table 1. The expression of CXCR4 and CXCR7 varied in cancer and paracancerous tissue specimens. The results showed that the high expression rates of CXCR4 and CXCR7 in cancer tissues were significantly higher than peritumoral non-malignant tissues (Table 2). In PTC, the high expression rates of CXCR4 and CXCR7 were 53.91% (62/115) and 41.74% (48/115), respectively. CXCR4 was highly expressed in 7.83% (9/115) of paracancerous tissue specimens. CXCR7 was 23.48% (27/115) of paracancerous tissue specimens. About half of PTC specimens showed low CXCR4/7 expression (53/115 vs. 67/115). The majority of noncancerous tissue specimens showed low CXCR4/7 expression (106/115 vs. 88/115). As the assumptions for t test could not be met, we used three nonparametric methods to test the target groups. The results showed p < 0.05, which meant that there were significant differences between carcinoma and peritumoral nonmalignant tissue; that was, the expression of CXCR4/7 in cancer was higher than that of paracancerous tissue.
The results of the two methods of expression difference between CXCR4 and CXCR7 in cancer and paracancerous tissue specimens (Table 3). Spearman coefficient test showed that the expression of CXCR4 and CXCR7 was correlated in cancer and paracancerous tissue specimens (Table 4). Combined co-expressions of these two receptors were shown to be difference (Table 5) ($p < 0.001$). CXCR4 (high) CXCR7 (low) accounted for the highest proportion, followed by CXCR4 (high) CXCR7 (high). Lymph node metastasis rate of CXCR4 (high) CXCR7 (high), CXCR4 (high) CXCR7 (low), CXCR4 (low) CXCR7 (high), CXCR4 (low) CXCR7 (low) were 27/30, 25/32, 11/18, 15/35. Lymph node metastasis rate of CXCR4 (high) CXCR7 (high) is higher than other group.

Correlation between CXCR4/CXCR7 expressions and clinicopathological characteristics in PTC

The patients' clinicopathological characteristics and the CXCR4/CXCR7 expression were summed up in Table 6. We analysis the relationship between CXCR4/ CXCR7 and patients and tumor characteristics. Although

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### Table 1 Expression of CXCR4 and CXCR7 in PTC and peritumoral non-malignant tissues

| Scores | Carcinoma tissues | Adjacent tissues | Carcinoma tissues | Adjacent tissues |
|--------|------------------|-----------------|------------------|-----------------|
| Low expression | 1 | 13 | 53 | 46 | 106 | 1 | 67 | 51 | 88 |
| 2 | 8 | 30 | 38 | 20 |
| 3 | 32 | 30 | 28 | 17 |
| High expression | 4 | 24 | 62 | 6 | 9 | 19 | 48 | 21 | 27 |
| 5 | 17 | 3 | 17 | 4 |
| 6 | 8 | 0 | 9 | 2 |
| 7 | 13 | 0 | 3 | 0 |

### Table 2 Expression difference between carcinoma and peritumoral nonmalignant tissue

| | CXCR4 | | CXCR7 | |
|----------------|-------|-------|-------|-------|
| Cancer | Paracancerous tissues | | Cancer | Paracancerous tissues | | |
| Low expression | 53 | 106 | $p = 0.000$ | 67 | 88 | $p = 0.003$ |
| High expression | 62 | 9 | | 48 | 27 |

Wilcoxon rank test for independent samples to test
a trend towards higher CXCR4 and CXCR7 expression was observed among tumors from the elderly versus the young, there is no significant association of CXCR4/7 staining intensity with the patients characteristics evaluated such as age and sex.

With regard to tumor characteristics, a strong association between intense staining for CXCR4/CXCR7 and capsule invasion, the presence of regional nodal metastasis (p < 0.05) was detected, which included some of tumor aggressiveness. CXCR4/7 was also associated with the quantity of positive lymph nodes or the percentage of positive lymph nodes (Table 7). About 75/115 percent of patients with PTC have tumors with lymph node metastasis. The proportion of specimens with high expression of CXCR4 in PTC without lymph node metastasis (13/40) is lower than that (49/75) in PTC with lymph node metastasis. The proportion of specimens with high expression of CXCR7 in PTC without lymph node metastasis (10/40) is lower than that (38/75) in PTC with lymph node metastasis. While the correlation between CXCR4/CXCR7 expression and tumor size, TNM stage, thyroiditis, nodular hyperplasia was not detected, which were probably due to the selection bias. Intense staining for CXCR4 was associated with multifocality.

**Discussion**

PTC standard treatments include surgery, suppression of thyroid-stimulating hormone (TSH), and selective treatment with radioactive iodine. Selective use of radioactive iodine (RAI) and thyroid hormone therapy seem to be the most effective therapeutic option for PTCs. Approximately 5% of them lose thyroid-differentiating features and become radioactive iodine-refractory (RAI-R), which reduces the survival rate for these tumors. For patients who are not cured of their disease with surgery and radioactive iodine, few treatment options exist. Therefore, an unmet need remains to develop additional molecularly targeted agents for treatment of these patients [11]. A novel preclinical study of mebendazolene demonstrated that it had promising therapeutic implications for patients with treatment refractory papillary thyroid cancer [12]. Treatment with the combination of the BRAF inhibitor Vemurafenib and Bortezomib accelerate mitochondrial dysregulation and apoptosis of TC cells

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### Table 3  Expression difference between CXCR4 and CXCR7

| Cancer tissues | Adjacent non-malignant tissues |
|----------------|-------------------------------|
| CXCR4 | CXCR7 | CXCR4 | CXCR7 |
| Low expression | 53 | 67 | p = 0.065, z = -1.844 | 106 | 88 | p = 0.001, z = -3.259 |
| High expression | 62 | 48 | 9 | 27 |

Wilcoxon rank test for independent samples to test; rank 1–2

### Table 4  Correlation between CXCR4 and CXCR7

| PTC | Adjacent non-malignant tissues |
|-----|-------------------------------|
| p = 0.000, Rs = 0.489 | p = 0.000, Rs = 0.455 |

Spearman rank order correlation test; rank 1–2

### Table 5  Relationship between the expressions of CXCR4 and CXCR7 in PTC

| Rank | PTC | Adjacent non-malignant tissues | p (Wilcoxon rank test for independent samples to test) |
|------|-----|-------------------------------|-----------------------------------------------|
| CXCR4 (high) CXCR7 (high) | 1 | 30 | 1 | p = 0.000, z = -7.3 |
| CXCR4 (high) CXCR7 (low) | 2 | 32 | 8 |
| CXCR4 (low) CXCR7 (high) | 3 | 18 | 26 |
| CXCR4 (low) CXCR7 (low) | 4 | 35 | 80 |

p (Spearman rank order correlation test) p = 0.000, Rs = 0.488 | p = 0.006, Rs = -0.180
But these drugs are not widely applied to in clinical practice. Therefore, many experiments try to find predictive factor and therapeutic target for RAI-RTC and they will be helpful for the effective identification [14]. Various molecular detection technologies allow us to have a deeper understanding of PTC pathogenesis at the molecular level. It is critical to understand the pathogenesis of PTC to develop effective diagnosis methods. What’s

Table 6  Correlation between immunohistochemical staining for CXCR4/CXCR7 and tumor characteristics in PTC

|                      | CXCR4          |     | CXCR4          |     |
|----------------------|----------------|-----|----------------|-----|
|                      | High expression| p value | Low expression | p value |
| Mean tumor size (cm) | 1.33 ± 0.76 (1.00) | p = 0.02 | 1.07 ± 0.49 (1.00) | p = 0.02 |
| Age (y)              |                |     |                |     |
| ≥55                  | 62             | 53  | 48             | 67  |
| <55                  | 83             | 49  | 36             | 47  |
| Sex (F/M)            |                |     |                |     |
| Male                 | 22             | 11  | 8              | 14  |
| Female               | 93             | 51  | 40             | 53  |
| Tumor size (cm)      |                |     |                |     |
| >2                   | 11             | 8   | 5              | 6   |
| ≤2                   | 104            | 54  | 43             | 61  |
| Capsule invasion     |                |     |                |     |
| Yes                  | 35             | 27  | 22             | 13  |
| No                   | 80             | 39  | 26             | 44  |
| Regional lymph       |                |     |                |     |
| Yes                  | 75             | 49  | 38             | 37  |
| No                   | 40             | 13  | 10             | 30  |
| TNM stage            |                |     |                |     |
| T1                   | 99             | 54  | 38             | 61  |
| T2                   | 13             | 6   | 8              | 5   |
| T3                   | 2              | 1   | 1              | 1   |
| T4                   | 1              | 1   | 1              | 0   |
| Focality             |                |     |                |     |
| Unifocal             | 64             | 29  | 27             | 37  |
| Multifocal           | 51             | 33  | 30             | 21  |
| Thyroiditis          |                |     |                |     |
| Y                    | 26             | 15  | 12             | 14  |
| N                    | 89             | 47  | 36             | 53  |
| Nodular hyperplasia  |                |     |                |     |
| Y                    | 11             | 7   | 4              | 7   |
| N                    | 104            | 55  | 44             | 60  |

Table 7  Correlation between CXCR4/CXCR7 and some of the patient/tumor characteristics

|                      | Cancer          |     | Paracancerous tissue |     |
|----------------------|-----------------|-----|----------------------|-----|
|                      | CXCR4           |     | CXCR7                |     |
| Number of lymph nodes| Rs = 0.873, p = 0.000 |     | Rs = 0.457, p = 0.000 |     |
| Age                  | Rs = –0.568, p = 0.000 |     | Rs = –0.173, p = 0.000 |     |
| Tumor size           | Rs = 0.686, p = 0.000 |     | Rs = 0.563, p = 0.000 |     |
| Number of foci       | Rs = 0.597, p = 0.000 |     | Rs = 0.383, p = 0.000 |     |
|                      | Rs = –0.337, p = 0.000 |     | Rs = –0.081, p = 0.000 |     |

Spearman rank order correlation test

[13].
more, it’s significance to find marker proteins that can predict the invasion and metastasis of PTC.

Recent studies showed that chemokines and their receptors play key role in many types of tumors, and their action was bidirectional. Blocking specific chemokine/chemokine-receptor axes does reduce the development of metastasis in several cancers. Current research shows that several chemokine receptors play a role in TC. These include CXCR1, CXCR2, CXCR3, CXCR4, CXCR7, CCR3, CCR6, CCR7 and DARC [15]. Although normal thyroid cells express specific chemokine receptors, but the above receptors exert several biological effects and influence the course of the disease. CXCR4 and CXCR7, bind CXCL12, activate multiple pathways such as ERK1/2, p38, SAPK/JNK, AKT, mTOR and the Bruton Tyrosine kinase (BTK), and so on. Many CXCR4 antagonists are under clinical investigation to offer proof of concept and create new line for treatment [16]. Studies are necessary to define the mechanisms underlying this association and to determine its clinical application value. More and more evidences show that CXCR4/CXCR7/CXCL12 plays an important role in tumor cell proliferation, angiogenesis, invasion and metastasis [17, 18].

There are studies where one can see that CXCR4/CXCR7/CXCL12 axis plays an important role in MTC. In Medullary thyroid carcinoma (MTC), high CXCR4 expression was associated with large tumour size and metastatic. CXCR4 antagonists significantly reduced tumour cell invasiveness [19]. The association between PTC aggressiveness and CXCR expression needs further investigation. CXCL12 might serve as an effective novel supplementary diagnostic marker for PTC, because CXCL12 expression was exclusively found in PTC compared to other thyroid lesions (90.8% vs. 3.2%) [20]. A clinical study indicate that CXCL12 might be an effective supplementary diagnostic marker for PTC [21]. Sijia Zhang et al. compared mRNAs and lncRNAs in PTC tissues and normal tissues and obtained 14 genes which involved in methylation and could act as potential biomarkers. Among them CXCL12 play an important role and may be an potential therapeutic target for PTC [22]. The receptor CXCR7 and CXCR4 binding to CXCL12 regulated the invasion, metastasis and migration of PTC.

Studies had shown that the expression level of CXCR4 was correlated with the clinical stage of PTC [23]. What’s more, the expression of CXCR4 and CXCR7 by PTCs was associated with indicators of tumor aggressiveness, including tumor size, angiolymphatic invasion (ALI), extrathyroidal extension (ETE), and lymph node metastasis [24]. A Meta-analysis on CXCR4 indicated that CXCR4 expression was frequent and cancer-specific event in 8 eligible studies about 661 patients. CXCR4 expression was significantly higher in PTC than in normal tissue and benign thyroid nodule [25]. Zhen Liu et al. considered that SDF-1 and CXCR were negative in non-malignant tissues. Positive expression rates of CXCR7 was 65.8% in PTC, 30.3% in thyroid benign tissues [26]. The next experiments confirmed that CXCR7 could regulate proliferation, apoptosis, invasion, and cell cycle. Knockdown of CXCR7 in PTC cells suppressed cell proliferation and invasion, induced S phase arrest, and promoted apoptosis [27]. Senescent, especially senescence-associated secretory phenotype (SASP), can promote tumorigenesis. Senescent cells were involved in the collective invasion and metastasis of PTC. This action was proved to related to CXCL12/CXCR4 signalling [4].

The expression of them in PTC is controversial and further molecular biological experiments are needed to confirm the relationship between CXCR4/CXCR7 and clinical characteristics or pathological aggressiveness of PTC patients. To evaluate the difference of CXCR4 and CXCR7 expression between PTC and paracancerous tissue, and evaluate the statistical associations between clinicopathological characteristics and the expression of them, we used immunohistochemical staining to test both of them. In this study, we have demonstrated that CXCR4 and CXCR7 were over-expressed in PTC tissue compared with adjacent non-malignant tissues. There were significant differences in the level of high expression of them in PTC versus that in nonmalignant tissue (62/115 vs. 9/115, 48/115 vs. 27/115, respectively; p < 0.05). Significant correlation was detected between CXCR4 and CXCR7 expression in PTC and adjacent tissue (p = 0.000), indicating a possible tendency toward co-expression of these two receptors in PTC. These two receptors were positively correlated with lymph node metastasis and capsule invasion, no association with sex, age, tumor size. Taken together, these analysis results indicated that CXCR4/CXCR7 play an important role in invasion and metastasis of tumor, which provided preclinical proof that CXCR4/CXCR7 may be two potential targets for the therapeutic intervention. Additionally, more studies are needed to examine the the concrete mechanism of this two receptors.

Since the data is from one hospital in a year, it may deviate from all big data of thyroid cancer epidemiology, such as the age, stage, etc. Because it is not operated by a single fixed surgeon, data bias may occur due to different operators. What’s more, due to the difference of pathologist’s technique, there is a certain bias in pathological section. Minor difference in immunohistochemical staining procedures could cause slight variation of staining.
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Disclosure

There are no conflicts of interest in this work.

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Human and Animal Rights and Informed Consent

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