The Expression of Functional Chemokine Receptor CXCR4 Is Associated with the Metastatic Potential of Human Nasopharyngeal Carcinoma

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Abstract

Purpose: Chemokine receptors are implicated in metastasis of several malignant tumors. This study was done to evaluate the contribution of chemokine receptors CXCR4 and CCR7 to metastasis of human nasopharyngeal carcinoma.

Experimental Design: Reverse transcription-PCR, immunohistochemistry, and flow cytometry were used to evaluate mRNA and protein expression of CXCR4 and CCR7 in nasopharyngeal carcinoma tumor tissues and cell lines. Chemotaxis assays were used to evaluate the function of CXCR4 in nasopharyngeal carcinoma cells. Antisense CXCR4 was used to inhibit receptor expression and to block metastasis of human nasopharyngeal carcinoma cells in vivo in athymic mice.

Results: CXCR4 protein was detected in tumor cells in 31 of 40 primary human nasopharyngeal carcinoma and in 13 of 15 lymph node metastases. CXCR4 transcripts were detected in eight CXCR4 protein–positive primary nasopharyngeal carcinoma tissues and seven nasopharyngeal carcinoma cell lines tested. On the other hand, the transcripts for CCR7 were detected only in four primary nasopharyngeal carcinoma tissues and in none of the nasopharyngeal carcinoma cell lines. In functional experiments, metastatic nasopharyngeal carcinoma cell lines that expressed high levels of CXCR4 were found to migrate in response to the CXCR4 ligand SDF-1α. Transfection of antisense CXCR4 in metastatic nasopharyngeal carcinoma cells inhibited the expression of CXCR4 and SDF-1α-induced cell migration in vitro and reduced the capacity of the tumor cells to form metastasis in the lungs and lymph nodes when injected in athymic mice.

Conclusion: The expression of functional CXCR4 but not CCR7 is correlated with the metastatic potential of human nasopharyngeal carcinoma cells. Therefore, CXCR4 may be considered as a potential target for the prevention of nasopharyngeal carcinoma metastasis.

The incidence of nasopharyngeal carcinoma is most prevalent in Southeast Asia (1). Nasopharyngeal carcinoma is notorious for its potential to metastasize at the early stages of the disease via both lymph and blood vessels (2). Whereas cervical lymph nodes are the primary sites of nasopharyngeal carcinoma metastasis (3), a considerable proportion of patients will develop distant metastasis to the bone, lung, liver, and central nervous system (4). The mechanisms that control nasopharyngeal carcinoma metastasis remain poorly understood.

Recently, chemokines, originally identified as mediators of leukocyte trafficking and homing (5), have been reported to also participate in tumor growth and metastasis by promoting angiogenesis or by inducing directional migration of tumor cells (ref. 6) and reviewed in (ref. 7). In fact, many tumor cells of the nonhematopoietic origin express one or multiple functional G-protein–coupled chemokine receptors. For instance, CCR7, which was cloned from an EBV-positive Burkitt lymphoma (8), is involved in lymph node metastasis of esophageal squamous cell carcinoma (9), non–small cell lung cancer (10), gastric carcinoma (11), and malignant melanoma (12). On the other hand, CXCR4, which is also an HIV coreceptor (13), has been reported to mediate melanoma metastasis to the lung (14), prostate cancer metastasis to the bone (15), and neuroblastoma metastasis to the bone marrow (16). Both CXCR4 and CCR7 are highly expressed in human breast cancer cell lines, and injection of anti CXCR4 antibody significantly reduced the metastasis of breast cancer cells to regional lymph nodes and lungs in animal models (17). Based on the accumulating evidence for the involvement of chemokine receptors in the metastasis of human malignant tumor, we...
tested whether such receptors might also mediate the metastasis of human nasopharyngeal carcinoma. We report that CXCR4 is highly expressed by human primary nasopharyngeal carcinoma tissues and established nasopharyngeal carcinoma cell lines and contributes to the metastasis of tumor cells in vivo.

Materials and Methods

**Animals and cell lines.** Female BALB/c nude mice (6-8 weeks old) from Shanghai Experimental Animal Center (Chinese Academy of Sciences, Shanghai, China) were used in all experiments. Nasopharyngeal carcinoma cell lines 5-8F and 6-10B were kindly provided by Dr. H.M. Wang of the Cancer Center, Sun Yat-sen University, P.R. China (18). HNE1, HNE2, HNE3, CNE1, and CNE2 are established nasopharyngeal carcinoma cell lines (19). Human CXCR4 cDNA was cloned as described (20), was reversely subcloned into the vector pcDNA3.1(+) (Invitrogen, Carlsbad, CA), and transfected into 5-8F cell line as an antisense CXCR4. All cells were maintained at 37°C in DMEM containing 10% FCS.

**Reverse transcription-PCR.** Total RNA was extracted from 5 × 10^6 cells using Trizol (Life Technologies, Gaithersburg, MD) as described by the manufacturer. mRNA was reverse transcribed with RevertAid (MBI Fermentas, Burlington Ontario, Canada) at 42°C for 60 minutes, and the resulted cDNA was subjected to PCR (94°C for 2 minutes followed by 25-35 cycles of 94°C for 30 seconds, 65°C for 30 seconds, 72°C for 1 minute, and an extension for 10 minutes at 72°C). For human CCR7, the forward primer 5’-ACTCCATCATTTGTTCGTGG-3’ and the reverse primer 5’-TAGTATCCAGATGCTGG-3’ yield a 362-bp product. For human CXCR4, the forward primer 5’-ATGCAAGGCGACTCATGTCAT-3’ and the reverse primer 5’-ATGATGTCACCTGCGGCACAC-3’ yield a 692-bp product. For human glyceraldehyde-3-phosphate dehydrogenase (GAPDH), the forward primer 5’-ATCCCATCATCATTCC-3’ and the reverse primer 5’-CCCTGTTCACACCTTCTTG-3’ were used. For measuring human tumor cell metastasis in nude mice, human GAPDH primers that do not detect mouse counterpart, were designed as follows: forward, 5’-AGACACAGGGAAGGTGAA-3’ and reverse, 5’-ATGCCATTGTCGTGCACAC-3’. The primers 5’-TGGAATGGGTCGG-3’ and reverse, 5’-TCTTGAGGCTG-3’ (with a 454-bp product). Primers 5’-TGGGAATGGGTCGG-3’ (forward) and 5’-TTTATGTCAGCACGTTCCT-3’ (reverse) yield a 514-bp product of mouse β-actin. PCR products were separated on 1.5% agarose gels and visualized by ethidium bromide. Detection of a human housekeeping gene with primers that do not amplify mouse counterpart in mouse organs has been used as a sensitive and reliable approach to assessing metastasis of transplanted human tumors (17).

**Immunohistochemical analysis.** Tissues of primary and metastatic nasopharyngeal carcinoma from routine diagnostic biopsy specimens were obtained from the Department of Pathology, Xiang-Ya Hospital, Xiang-Ya School of Medicine, Central-South University and Tumor Hospital of Hunan Province, Changsha, as well as Institute of Cancer Res.

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**Table 1.** The expression of CXCR4 in primary nasopharyngeal carcinoma and cervical lymph node metastases

<table>
<thead>
<tr>
<th>NPC grade</th>
<th>Primary NPC</th>
<th>NPC metastases</th>
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<tbody>
<tr>
<td></td>
<td>CXCR4 (+)</td>
<td>CXCR4 (-)</td>
</tr>
<tr>
<td>2</td>
<td>14 (96.3%)</td>
<td>5 (35.7%)</td>
</tr>
<tr>
<td>3</td>
<td>26 (84.6%)</td>
<td>4 (15.4%)</td>
</tr>
<tr>
<td>Total</td>
<td>40 (77.5%)</td>
<td>9 (22.5%)</td>
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NOTE: Biopsies of human primary nasopharyngeal carcinoma (all were squamous cell carcinoma) and cervical lymph node metastases were obtained during routine diagnostic procedures. The specimens were sectioned, stained with anti-CXCR4 antibody, and counter stained with hematoxylin. Abbreviation: NPC, nasopharyngeal carcinoma.

*Significantly increased rate of CXCR4-positive specimens in grade 3 than in grade 2 nasopharyngeal carcinomas as evaluated with χ² test (P < 0.05).

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**Fig. 1.** The expression of CXCR4 in nasopharyngeal carcinoma tissues. A, the CXCR4 protein was detected by immunohistochemistry in primary nasopharyngeal carcinoma tissues (original magnification, ×400). Red arrows indicate positive membrane staining of CXCR4 in cancer cells. B, in a more-differentiated grade 2 nasopharyngeal carcinoma tissue, CXCR4 protein was not detected in cancer cells (red arrow) or in normal cells (black arrow) adjacent to cancer nest (original magnification, ×400). C, CXCR4 staining (red arrow) was also positive in cells of a poorly differentiated grade 3 squamous cell carcinoma metastatized to cervical lymph node, with CXCR4-negative stromal cells (black arrow; original magnification, ×400). D, the expression of CXCR4 and CCR7 transcripts in primary human nasopharyngeal carcinoma tissues was examined by reverse transcription-PCR. GAPDH transcripts were measured as control. Nasopharyngeal carcinoma tissues (E) and a metastatic lymph node section (F) were also stained for CCR7 with negative results.
Pathology, Southwest Hospital, Chongqing, P.R. China, according to institutional regulations. Tissues were fixed with 4% formaldehyde, embedded in paraffin, and sectioned. Endogenous peroxidase activity was blocked by hydrogen peroxide (0.3%). The slides were stained with chemokine receptor antibodies (R&D Systems, Minneapolis, MN), followed by incubation with a biotinylated anti-mouse secondary antibody, and a horseradish peroxidase–conjugated streptavidin (SWBC, Beijing, China). Color was developed with diaminobenzidine and sections were counterstained with hematoxylin.

**Flow cytometry.** Nasopharyngeal carcinoma cells were grown to subconfluency, detached with cold Dulbecco’s PBS (5 mmol/L EDTA), and washed with fluorescence-activated cell sorting buffer (5 mmol/L EDTA, 0.1% NaN₃, and 1% FCS, in Dulbecco’s PBS). After incubation with a monoclonal antibody against human CXCR4 (R&D Systems) for 30 minutes on ice, the cells were stained with a FITC-labeled secondary antibody and examined for CXCR4 expression by flow cytometry (BD Bioscience, San Jose, CA).

**Chemotaxis.** Chemotaxis assays were done using 48-well chemotaxis chambers (Neuro Probe, Cabin John, MD) as described previously (21). Aliquots of 27- to 29-μL assay medium (RPMI 1640 containing 1% bovine serum albumin, 30 mmol/L HEPES) with different concentration of SDF-1α were placed in the lower wells of the chamber. Cell suspension (50 μL, 1 × 10⁶ cells/mL) was placed in the upper wells. The upper and lower wells were separated by a polycarbonate filter (Osmonics, Livermore, CA; 10-μm pore size) which was precoated with 50 μg/mL collagen type I (Collaborative Biomedical Products, Bedford, MA). After incubation at 37°C for 5 hours, the filter was removed, stained, and the cells migrated across the filter were counted under light microscope after coding the samples. The results were expressed as chemotaxis index, which represents the fold increase in the number of migrated cells in response to chemoattractants over the spontaneous cell migration in response to control medium.

**Implantation of nasopharyngeal carcinoma cells in nude mice.** For i.v. injection, nasopharyngeal carcinoma cells in exponential growth phase were injected into the tail veins of the BALB/c nude mice (1 × 10⁶ cells/0.2 mL HBSS). After 5 weeks, the animals were euthanized and the lungs were collected and separated into two parts used to extract total RNA for detecting human GAPDH expression as a measurement for human cell metastasis or to be fixed and embedded in paraffin for histology analyses. For s.c. injection, 1 × 10⁷ nasopharyngeal carcinoma cells in 0.2 mL HBSS were injected into the right flank of the BALB/c nude mice. After 5 to 8 weeks, the animals were euthanized and the draining lymph nodes were
collected. Total RNA was extracted from the lymph nodes to detect human GAPDH to determine the presence of human tumor cell metastasis.

**Statistical analysis.** All experiments were done for at least thrice and representative results are shown. The significance of the difference between various groups was analyzed with the Student's t test or $\chi^2$ test.

**Results**

*Nasopharyngeal carcinoma tissues express chemokine receptor CXCR4.* We first examined CXCR4 protein expression in biopsy specimens of primary human nasopharyngeal carcinoma and metastatic lymph nodes. Sections from 31 of 40 nasopharyngeal carcinoma tissues were stained positively for CXCR4 protein with immunohistochemistry. Among those, 22 of 26 (84.6%) poorly differentiated nasopharyngeal carcinoma (grade 3) were CXCR4 positive, whereas 9 of 14 (64.3%) more differentiated tumor sections (grade 2) were CXCR4 positive (Table 1 and Fig. 1 for representative sections). In biopsies of lymph nodes, 13 of 15 (86.7%) samples expressed CXCR4 protein. CXCR4-positive tumor cells were surrounded by CXCR4 negative stroma and in a more differentiated (grade 2) primary nasopharyngeal carcinoma specimen, there was no detectable CXCR4 staining (Fig. 1B). These results suggest that CXCR4 is expressed in a majority of poorly differentiated primary nasopharyngeal carcinoma and lymph node metastases. Additional experiments showed that eight primary nasopharyngeal carcinoma tissues expressing CXCR4 protein contained high levels of CXCR4 mRNA (Fig. 1D) as determined by reverse transcription-PCR. The expression of CCR7 mRNA was examined in parallel but only four of eight primary nasopharyngeal carcinoma tissues were positive (Fig. 1D). No positive staining was obtained with an anti-CCR7 monoclonal antibody in primary (Fig. 1E) or metastatic (Fig. 1F) nasopharyngeal

**Fig. 3.** Chemotactic activity of SDF-1α for nasopharyngeal carcinoma cells. The migration of 5-8F and 6-10B nasopharyngeal carcinoma cells in response to SDF-1α was measured by using chemotaxis chambers. Tumor cells migrating across polycarbonate filters were photographed. A and B, 5-8F cell migration in response to medium alone and to 50 nmol/L SDF-1α, respectively. C and D, 6-10B cell migration in response to medium or 50 nmol/L SDF-1α. E, dose-response curves of nasopharyngeal carcinoma cells migrating toward SDF-1α. Black arrow, one of the micropores in the filter; white arrow, a migrated cell. *, $P < 0.01$, statistically significant increase in chemotaxis compared with medium control.

**Fig. 4.** HNE3 cell migration to SDF-1α and metastasis in lymph nodes. A, HNE3 cells migrating in response to different concentrations of SDF-1α. B, lymph node metastases of HNE3. BALB/c nude mice were injected s.c. in the flank regions with $10^7$ HNE3 nasopharyngeal carcinoma cells. Eight weeks after injection, the inguinal draining lymph nodes were collected for measurement of human GAPDH by reverse transcription-PCR as an indicator for the presence of disseminated human tumor cells. Mouse β-actin mRNA was used as control. *, $P < 0.05$, significantly increased cell migration in response to SDF-1α compared with medium.
carcinoma tumor cells, suggesting that CXCR4 is more widely expressed in nasopharyngeal carcinoma tissues than CCR7. Thus, CXCR4 but not CCR7 may contribute to the progression of nasopharyngeal carcinoma.

CXCR4 is expressed by nasopharyngeal carcinoma cell lines and is functional in metastatic nasopharyngeal carcinoma cells. To more precisely examine the role of CXCR4 in metastasis of nasopharyngeal carcinoma, we used several established nasopharyngeal carcinoma cell lines that are capable of forming tumors in immune compromised mice. All seven nasopharyngeal carcinoma cell lines tested expressed CXCR4 mRNA (Fig. 2A). In contrast, none of these nasopharyngeal carcinoma cell lines expressed mRNA for CCR7 (Fig. 2A), despite its reported involvement in mediating metastasis of certain tumors (11, 12). 5-8F and 6-10B cells were subcloned from a nasopharyngeal carcinoma cell line SUPE-1, and when injected s.c. in nude mice, both cell lines form solid tumors. However, only 5-8F metastasized to regional draining lymph nodes and lungs, whereas 6-10B did not show any metastasis (18). These two nasopharyngeal carcinoma cell subsets were further studied for the role of CXCR4 in controlling metastasis in mice. Both 5-8F and 6-10B cells expressed CXCR4 transcripts and protein as detected by reverse transcription-PCR (Fig. 2A) and flow cytometry analyses (Fig. 2B-C). However, in in vitro chemotaxis assays, only the metastatic 5-8F nasopharyngeal carcinoma cells migrated in response to the CXCR4 ligand SDF-1α in a concentration-dependent manner (Fig. 3A, B, and E). In contrast, the nonmetastatic 6-10B nasopharyngeal carcinoma cells did not show any migratory response to SDF-1α, despite expression of CXCR4 by these cells (Fig. 3C-E). In addition to 5-8F and 6-10B, other five nasopharyngeal carcinoma cell lines studied also expressed CXCR4 protein on the cell surface (Fig. 2D-H). However, only HNE3 migrated in response to SDF-1α in vitro (Fig. 4A), and was capable of forming metastatic foci in draining lymph nodes when implanted in nude mice (Fig. 4B). Thus, CXCR4 seems functional in metastatic but not nonmetastatic nasopharyngeal carcinoma cells.

Inhibition of CXCR4 expression in nasopharyngeal carcinoma cells and blockade of tumor metastasis by antisense CXCR4. We then determined the contribution of CXCR4 to the metastatic

Fig. 5. The effect of antisense CXCR4 on CXCR4 mRNA and protein expression. A, 5-8F cells were transfected with human antisense CXCR4 cDNA and were examined for CXCR4 mRNA expression by reverse-transcription-PCR (RT-PCR). Mock-transfected cells were used as control. B, quantitation of CXCR4 mRNA expression in 5-8F cells with and without antisense CXCR4. C and D, CXCR4 protein staining (red) in mock and antisense CXCR4-transfected 5-8F cells as detected by flow cytometry. Control immunoglobulin staining (blue). Percentage CXCR4 positive cells. *, P < 0.05, significantly reduced expression of CXCR4 mRNA in 5-8F cells with antisense CXCR4.
behavior of nasopharyngeal carcinoma cells in vivo. We generated antisense CXCR4 cDNA and transfected the construct into 5-8F nasopharyngeal carcinoma cells. Figure 5 shows that transfection with antisense CXCR4 down-regulated the expression of CXCR4 mRNA (Fig. 5A-B) and protein (Fig. 5C-D) in 5-8F cells which no longer migrated in vitro in response to SDF-1α (data not shown). When injected i.v. in nude mice, mock-transfected 5-8F cells formed lung metastasis as detected by the expression of human GAPDH in the lungs of all mice 5 weeks after tumor cell injection (Fig. 6A). In contrast, only two of five mice injected with 5-8F cells transfected with antisense CXCR4 exhibited lung metastatic foci (Fig. 6A). This pattern of metastasis inhibition by antisense CXCR4 was highly reproducible in multiple experiments. We further injected 5-8F cells s.c. into flanks of nude mice to examine the capacity of the tumor cells to metastasize via lymphatics. Five weeks after tumor cell injection, the draining lymph nodes were collected to extract total RNA and measure human GAPDH as an indicator of tumor cell metastasis. Results of a representative experiment shown in Fig. 6B shows that human GAPDH was detected in three of five mice injected with mock-transfected 5-8F cells compared with mice injected with antisense CXCR4-transfected 5-8F cells in which none of the lymph nodes was positive for human GAPDH (Fig. 6B). Histologic analyses showed large cancer cell nests in the lungs isolated from mice injected with mock-transfected 5-8F cells (Fig. 7A-B), whereas no apparent tumor nests were detectable in the lungs of mice injected with antisense CXCR4-transfected 5-8F cells (Fig. 7C-D). These results indicate the active participation of CXCR4 in the metastasis of nasopharyngeal carcinoma cells via blood or lymph vessels.

**Discussion**

Tumor metastasis and leukocyte trafficking share similar mechanisms (6, 17). Leukocytes traffic to specific sites through high endothelial venules or to lymph nodes through afferent lymphatic vessels. In leukocyte extravasation through high endothelial venules, CCR7 and its ligand, the EBV-induced molecule-1 (ELC/CCL19), and secondary lymphoid tissue chemokine (SLC/CCL21), play a crucial role (22), whereas the contribution of CXCR4 seems redundant (23). CCR7 and its ligands also play important roles in the process of leukocyte trafficking through afferent lymphatic vessels. Despite the assumption that CXCR4 does not play a major role in mediating leukocyte trafficking and homing, its ligand SDF-1α is expressed in a number of organs including lung, liver, bone marrow, and lymph nodes (17). CXCR4 was implicated in tumor metastasis to distant organs via blood vessels in several tumor models, including breast carcinoma (17), neuroblastoma (16), prostate cancer (15), rhabdomyosarcoma (24), melanoma (14), and lung cancer (25). CCR7 was also an important receptor that directs metastasis of tumor cells to draining lymph nodes via lymphatic vessels (9–12). Recently, CXCR4 was further reported to participate in tumor metastasis to regional lymph nodes (26). In head and neck squamous cell carcinomas, CXCR4 has been suggested to act as a regulator of metastatic processes by increasing tumor cell adhesion and secretion of matrix metalloproteinase-9, which may enhance the detachment of highly motile tumor cells from the primary lesions (27). In human oral squamous cell carcinoma, CXCR4 has not been shown responsible for lung metastasis but was associated with the establishment of secondary tumor foci in regional lymph nodes (28, 29). CXCR4 was also expressed in squamous cell carcinoma of the tongue, and in tumor cells metastasized to lymph nodes, its expression seemed more potent than in cells of the primary tumors (30). In addition, CXCR4 expression has been reported in several human nasopharyngeal carcinoma cell lines and has been suggested to correlate with the state of tumor cell differentiation grade and proliferation (31). However, no animal models were used to test the relevance of CXCR4 to nasopharyngeal carcinoma cell metastasis and no clinical specimens have been evaluated for CXCR4 expression. Thus, to the best of our knowledge, our present study for the first time provides strong evidence to correlate the expression of functional CXCR4 to the metastatic potential of human nasopharyngeal carcinoma cells.
In our study, CXCR4 protein was detected in tumor cells of a majority of poorly differentiated primary nasopharyngeal carcinoma and lymph node metastases. CXCR4 mRNA was also detected in nasopharyngeal carcinoma tissues that expressed CXCR4 protein. This is in contrast to CCR7 of which the mRNA was positive in four of eight of tissue extracts but none of the tumor sections were stained positively for CCR7 protein suggesting this chemokine receptor may not be exploited by nasopharyngeal carcinoma for metastasis. The relevance of CXCR4 in promoting nasopharyngeal carcinoma metastasis was further supported by in vivo studies with nude mice in which the antisense CXCR4 potently inhibited the incidence of lung and lymph node metastasis of the nasopharyngeal carcinoma cell line 5-8F. It is interesting to note that the metastatic cell lines 5-8F and HNE3 migrated in response to SDF-1α in vitro, but the nonmetastatic cell lines despite their expression of CXCR4 mRNA and protein, did not migrate toward SDF-1α gradient. Whether the cells do not possess the machinery that controls chemotaxis to SDF-1α is currently under further investigation. It should be mentioned that in CXCR4-positive nasopharyngeal carcinoma sections and cell lines, not every tumor cell was stained with anti-CXCR4 antibody. In addition, in our study, 2 of 15 nasopharyngeal carcinoma lymph node metastases were CXCR4 negative. These observations suggest that tumor cell populations are heterogeneous and factors other than CXCR4 may also contribute to tumor cell metastasis. In this context, studies of more homogeneous single nasopharyngeal carcinoma cell clones should provide valuable information.

The pathogenesis of nasopharyngeal carcinoma is closely related to EBV infection with up to 70% of patients with nasopharyngeal carcinoma were EBV latent membrane protein-1 (LMP-1) positive. It has been reported that EBV LMP-1 has the capacity to cause the activation of nuclear factor-κB (NF-κB), a potent transcription factor, thus may alter cell phenotype (32, 33). It is relevant that activation of NF-κB has been reported to enhance the expression of CXCR4 in breast cancer cells therefore may promote tumor cell migration and metastasis (34). In our study, both metastatic and nonmetastatic nasopharyngeal carcinoma cell lines are LMP-1 positive4 and both express CXCR4 at the mRNA and protein levels, yet with functional CXCR4 only in cell lines with metastatic property. However, at this stage, a direct LMP-1-NF-κB-CXCR4 linkage has yet to be established and further study is under way to more fully address the issue of CXCR4 regulation in human nasopharyngeal carcinoma. Nevertheless, a prominent role for CXCR4 in mediating the metastasis of nasopharyngeal carcinoma cells via both blood and lymph vessels as shown in our study suggests that CXCR4 should be considered as a molecular target for the design of novel anti-nasopharyngeal carcinoma therapy.

Acknowledgments

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4 Cao et al., unpublished observation.
References


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