SPANDIDOS PUBLICATIONS

ONCOLOGY LETTERS 10: 1227-1232, 2015

C-X-C motif receptor 7 in gastrointestinal cancer (Review)

HWAN-JUNG YUN[1,2*], HYEWON RYU[1*], YOON SEOK CHOI[1], IK-CHAN SONG[1], DEOG-YEON JO[1,2], SAMYONG KIM[1,2] and HYO JIN LEE[1,2]

[1]Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University Hospital, Daejeon 301-721; [2]Cancer Research Institute, Chungnam National University School of Medicine, Daejeon 301-747, Republic of Korea

Received November 5, 2014; Accepted May 22, 2015

DOI: 10.3892/ol.2015.3407

Abstract. Chemokine receptors are key mediators of normal physiology and numerous pathological conditions, including inflammation and cancer. This receptor family is an emerging target for anticancer drug development. C-X-C motif receptor 7 (CXCR7) is an atypical chemokine receptor that was first cloned from a canine cDNA library as an orphan receptor and was initially named receptor dog cDNA 1 (RDC1). Shortly after demonstrating that RDC1 binds with its ligand, stromal cell-derived factor-1α and interferon-inducible T-cell α chemoattractant, RDC1 was officially deorphanized and renamed CXCR7, as the seventh receptor in the CXC class of the chemokine receptor family. Recent accumulating evidence has demonstrated that CXCR7 expression is augmented in the majority of tumor cells compared with their normal counterparts and is involved in cell proliferation, survival, migration, invasion and angiogenesis during the initiation and progression of breast, lung and prostate cancer. In the present review, the expression and role of CXCR7, as well as its clinical relevance in cancer of the gastrointestinal system, were investigated. In addition, the potential of this chemokine receptor as a therapeutic target in the treatment of gastrointestinal cancer was discussed.

Contents

Correspondence to: Professor Hyo Jin Lee, Division of Hematology/Oncology, Department of Internal Medicine, Chungnam National University Hospital, 640 Daesa-dong, Jung-gu, Daejeon 301-721, Republic of Korea
E-mail: cymed@cnu.ac.kr

*Contributed equally

Key words: chemokine receptor, gastrointestinal neoplasm, C-X-C motif receptor 7, tumorigenesis, therapeutic target

1. Introduction

Chemokines and their binding receptors comprise the chemokine signaling systems, which are involved in organ development, host immune response and other physiological processes that direct cells to specific locations throughout the body. Since they first appeared in teleost fish, chemokines have become the most extensive family of cytokines (1-4). Chemokine receptors constitute the largest branch of the γ subfamily of rhodopsin-like seven-transmembrane receptors (4). Chemokine receptors are differentially expressed by all leukocytes and other nonhematopoietic cells, including cancer cells, and are classified into two categories: G protein-coupled receptors (GPCRs) and atypical chemokine receptors (ACKRs). This classification was recently introduced and approved by the Nomenclature Committee of the International Union of Pharmacology and the Human Genome Nomenclature Committee (1). A key structural determinant that distinguishes these two groups is the sequence motif Asp-Arg-Tyr-Leu-Ala-Ile-Val (also known as DRYLAIV), which is located at the end of transmembrane domain 3 and is conserved in the majority of GPCRs, but poorly conserved in ACKRs (1).

C-X-C motif receptor 7 (CXCR7), recently termed ACKR3, is an atypical chemokine receptor that was first cloned from a canine thyroid cDNA library as an orphan receptor and initially named receptor dog cDNA 1 (RDC1) (1,5). Shortly thereafter, the human and mouse RDC1 orthologs were identified and their amino acid sequences were found to have >90% similarity. The human and mouse *RDC1* genes were mapped to chromosome regions 2q37.3 and 1 55.6 cM, respectively. Notably, these are the same chromosomes that encode the *CXCR4* genes in the two species (6). Similar to CXCR4, RDC1 binds to stromal cell-derived factor-1α (SDF-1α; also known as CXCL12); however, unlike CXCR4, RDC1 is not monogamous since it can also bind to interferon-inducible T-cell α chemoattractant (I-TAC; also known as CXCL11) (1). Subsequent to demonstrating that SDF-1α and I-TAC bind with high affinity to RDC1, RDC1 was officially deorphanized and renamed CXCR7, as the seventh receptor of the CXC class of the chemokine receptor family (7). However, I-TAC is also able to bind to CXCR3. Therefore, any biological effects of I-TAC through the activation of CXCR7 should be distinguished from possible involvement of this cytokine with CXCR3, in cases where this receptor is also expressed on the target cells (8).

In addition, I-TAC can compete with SDF-1α for binding to CXCR7 and hinder the SDF-1α and CXCR7 interaction (8,9).

The physiological role of CXCR7 depends on its expression in tissues, as well as its ability to induce appropriate signaling cascades. Depending on cell type, CXCR7 is a signaling or non-signaling receptor (7,9-13). In normal tissues, CXCR7 is expressed in the heart, brain, spleen, kidney, lungs, testis, ovary, thyroid, placenta, liver and thymus, as well as in hematopoietic cells, including lymphocytes, granulocytes and monocytes (7,14-17). Therefore, CXCR7 has diverse roles in various organs, although its role in adult tissues remains unclear. CXCR7 expression is tightly regulated by many factors such as hypoxia and hormones, and is induced during pathological processes, including inflammation and cancer. In these conditions, CXCR7 expression is increased on immune cells and endothelial cells in the periphery; however, expression is decreased on leukocytes following their move into the tissues. CXCR7 expression is also augmented in the majority of tumor cells compared with their normal nontransformed counterparts (6,9). This overexpression may be involved in the increased proliferative and survival capacities of tumor cells, and provide an advantage for tumor development and dissemination (6,9,18,19). Signaling via CXCR7 has been demonstrated to enhance the proliferation of cancer cells on fibroblasts, promote tumor growth in nude mice and exert pro-survival and anti-apoptotic effects, supporting the hypothesis that CXCR7 facilitates the expansion and progression of certain tumor types and may be a potential prognostic marker (9,11,12,20). Accordingly, Miao *et al* (21) reported that CXCR7 promotes the growth of tumors formed from breast and lung cancer cells, and enhances experimental lung metastasis in immunodeficient and immunocompetent mouse models. The authors also demonstrated increased CXCR7 expression in human breast and lung cancer, where it is highly expressed in the majority of tumor-associated blood vessels and malignant cells, but not expressed in the normal vasculature (21). Wang *et al* (22) also demonstrated that, in prostate cancer, the level of CXCR7 expression increases as the tumors become aggressive. In addition, CXCR7 expression has been associated with enhanced adhesive and invasive activities, as well as increased proliferation in *in vitro* and *in vivo* studies. Furthermore, CXCR7 regulates the expression of the proangiogenic factors, interleukin-8 and vascular endothelial growth factor (VEGF), which likely participates in the regulation of tumor angiogenesis (22). CXCR7 is also expressed in tumors of hematopoietic origin (such as lymphomas) and mesenchymal origin (including sarcomas and gliomas), suggesting its potential role in tumorigenesis and tumor dissemination (10,11,13,20,23-28). However, the function of the receptor requires further clarification.

Regarding gastrointestinal cancer, increasing evidence suggests that CXCR7 is involved in tumor biology. The present review focuses on the expression and role of CXCR7 in gastrointestinal cancer, and discusses its prognostic and therapeutic potential.

2. CXCR7 in cancer of the gastrointestinal system

Cancer of the oral cavity. Squamous cell carcinomas of the head and neck are a heterogeneous group of malignancies involving the oral cavity, oropharynx, larynx and hypopharynx, and account for >90% of malignant tumors in the oral cavity (29,30). The biological properties of squamous cell carcinoma are intimately regulated by various cytokines and growth factors. Recent studies in the field of chemokine systems as mediators of tumor development and progression have demonstrated that chemokine receptors play an important role in head and neck squamous cell carcinomas (31,32). Xia *et al* (32) reported that the expression of CXCR7 mRNA in oral leukoplakia, which is a premalignant lesion of oral squamous cell carcinoma, was increased by >2-fold compared with normal tissues as observed by microarray analysis. CXCR7 was also expressed in 85% of oral leukoplakia and 86% of oral squamous cell carcinoma, whereas only 8% of normal tissues displayed CXCR7 immunostaining at the protein level. In addition, CXCR7 was concomitantly expressed with its ligands SDF-1α and I-TAC in all oral leukoplakia and oral squamous cell carcinoma tissues, suggesting that the CXCR7-SDF-1α/I-TAC axis is important in oral carcinogenesis (32). Recently, Maussang *et al* (33) demonstrated a high CXCR7 expression in head-and-neck cancer biopsies, highlighting a potential novel tumorigenic role of CXCR7 in these types of cancer. The authors also confirmed the expression of CXCR7 in head-and-neck cancer cell lines at the transcript and protein levels, and generated a patient-derived CXCR7-expressing head-and-neck cancer xenograft model in nude mice (33). Furthermore, CXCR7-targeting therapy inhibited the secretion of the angiogenic factor, resulting in the inhibition of tumor growth and angiogenesis *in vivo*.

Esophageal cancer. The expression and role of CXCR7 in esophageal cancer have not been studied intensively. Ge *et al* (34) reported that the long non-coding RNA, HOX transcript antisense RNA (HOTAIR), is involved in the molecular mechanism of esophageal squamous cell carcinoma metastasis. They detected CXCR7 in cells overexpressing HOTAIR using microarrays and quantitative polymerase chain reaction, which suggests the contribution of CXCR7 to esophageal squamous cell cancer progression (34). In addition, Tachezy *et al* (35) investigated the expression of CXCR7 in primary tumors, lymph nodes and distant metastases of 299 patients with esophageal cancer and its association with clinicopathological parameters. CXCR7 expression was rarely detected in esophageal adenocarcinoma tissues; however, CXCR7 was overexpressed in almost half of the esophageal squamous cell carcinoma cases investigated, underlining the different mechanisms and backgrounds of the two histologies. In contrast to other cancer types, such as breast, prostate and lung cancer (21,22,36), no significant correlation was observed between CXCR7 expression and histopathological data or patient survival rates in esophageal cancer.

Gastric and small bowel cancer. The role of CXCR7 in gastric and small bowel cancer is poorly understood. CXCR7 transcripts have been detected in gastric cancer cells, including MGC-803, SGC-7901 and BGC-823 cells (37). In a previous study, Lee *et al* (2) reported that CXCR7 was differentially expressed in gastric adenocarcinoma tissues. Increased expression levels of CXCR7 and its ligand SDF-1α in tumor cells was associated with aggressive tumor biology and a poor

prognosis (2), suggesting that further investigation is required to decipher the role of CXCR7 in these tumors.

Colorectal cancer. Previous studies have demonstrated that CXCR7 is differentially expressed in colorectal cancer at the transcriptional and protein levels, as well as in the cell membrane (38-43). CXCR7 expression increased following lipopolysaccharide treatment in the SW480 and COLO 205 colorectal carcinoma cell lines, which express Toll-like receptor 4 (TLR4)/myeloid differential protein-2. CXCR7 expression, which was mediated by TLR4, promoted tumor cell proliferation and migration in human colorectal carcinoma (38). In addition, higher rates of CXCR7 expression were confirmed in colorectal carcinoma tissues compared with those in normal tissues, and the high CXCR7 expression was associated with aggressive tumor behavior, including large tumor size, high TNM stage, high histological grade, and lymph node metastasis (38,42). Guillemot *et al* (39) also demonstrated that CXCR7 and its ligands were overexpressed in human colorectal cancer and that CXCR7 facilitated the progression of colon cancer in the lungs of a pulmonary metastasis mouse model. However, certain studies obtained contradicting results. For instance, Kheirelseid *et al* (44) identified no significant difference in CXCR7 expression between paired tumor and tumor-associated normal samples using gene expression profiling. In addition, they demonstrated that patients with a high *CXCR7* expression in the tumor cells exhibited longer survival rates compared with patients with a lower *CXCR7* gene expression (44).

Liver cancer. Several studies have demonstrated that CXCR7 was differentially expressed in hepatocellular carcinoma and its expression was significantly higher in tumor tissues compared with normal liver control tissues (45-50). For instance, Monnier *et al* (49) reported that in hepatocellular carcinoma, transcripts of CXCR7 and its ligand I-TAC are significantly overexpressed. They also identified that CXCR7 protein is expressed in endothelial cells within hepatocellular carcinoma, as well as in the adjacent fibrotic liver (49). By contrast, other studies detected CXCR7 protein expression in the membranes and cytoplasm of tumor cells (45-48,50). CXCR7 expression was upregulated by hypoxic and low pH conditions, which are well-known characteristics of the hepatocellular carcinoma microenvironment, as well as by VEGF (48,49). In addition, in a mouse model of hepatocarcinogenesis, a strong induction of CXCR7 and I-TAC transcripts was observed (49). Furthermore, SDF-1α induced invasion, adhesion, tube formation and VEGF secretion in hepatocellular carcinoma cells via CXCR7, and these biological effects were inhibited by abrogating CXCR7 (48). High CXCR7 expression in patients with hepatocellular carcinoma has been found to be associated with an increased tendency to develop distant metastases and poorer survival compared with patients with low CXCR7 expression following hepatic resection (46,47,51). Xue *et al* (52) also reported that a high CXCR7 expression was a risk factor for extrahepatic metastasis subsequent to hepatectomy in patients with hepatocellular carcinoma. In addition, CXCR7 expression correlated well with the expression of osteopontin in hepatocellular carcinoma *in vivo*, while knockdown of CXCR7 induced the downregulation of osteopontin, suggesting that the effect of CXCR7 is mediated through osteopontin upregulation (52). Therefore, these findings imply that CXCR7 and its ligand system play a prominent role in hepatocellular carcinoma.

Pancreatic cancer. CXCR7 expression has been identified in pancreatic adenocarcinoma *in vitro* and *in vivo*, along with upregulation of the *CXCR7* gene on oligonucleotide microarrays (53-59). The expression of CXCR7 was found to be associated with tumor grade and inversely correlated with tumor size in patients with pancreatic adenocarcinoma (56). In addition, stromal expression of CXCR7 was associated with significantly worse survival outcomes in pancreatic cancer patients that were treated with neoadjuvant chemoradiotherapy followed by surgery and adjuvant gemcitabine treatment (53). These observations suggest that CXCR7 has a potential role in the tumorigenesis of pancreatic adenocarcinoma, and that CXCR7 is involved in cell migration and invasion in pancreatic cancer. In the human pancreatic cell lines, PANC-1 and Su86.86, knockdown of CXCR7 resulted in decreased migration and invasion when compared with control cells (55). In addition, signaling via CXCR7 facilitated cell proliferation in pancreatic cancer cells (54).

Biliary tract cancer. The expression and role of CXCR7 in biliary tract cancer have not yet been investigated extensively. Only Yao *et al* (60) assessed the expression of CXCR7 in gallbladder cancer specimens from 72 patients and investigated its association with the clinicopathological characteristics and survival of patients. CXCR7 was detected in the cytoplasm, and its expression was associated with tumor stage and TNM (60). Furthermore, the CXCR7 expression was an independent risk factor for worse postoperative survival, collectively suggesting the potential role of CXCR7 in gallbladder cancer development and progression, and its possible application as a therapeutic target (60). However, further research is required to decipher how CXCR7 and its ligand contribute to tumorigenesis of gallbladder and other biliary tract cancer types.

3. CXCR7 as a therapeutic target

CXCR7 and its ligand system are currently considered as novel potential therapeutic targets, although the role of this system in tumor biology is not yet fully understood. Several agents are currently being developed to target CXCR7. Small molecular inhibitors of CXCR7 have been manufactured by ChemoCentryx, Inc. (Mountain View, CA, USA), including CCX771, CCX754, CCX733 and CCX2066 (1,61-63). CCX662 is in preclinical development for the treatment of glioblastoma multiforme (1). In gastrointestinal tract cancer, several preclinical studies have demonstrated that targeting the CXCR7 pathway had an antitumor activity *in vitro* and *in vivo* (33,39,42,45,46,48,54,55). Maussang *et al* (33) reported that CXCR7-targeting nanobodies reduced the secretion of the anti-angiogenic factor and inhibited tumor growth in head-and-neck cancer. In addition, Guillemot *et al* (39) evaluated the effects of CCX754 and CCX771 on mouse experimental models of metastasis using mouse C26 and human HT29 colon cancer cell lines, which were previously demonstrated to express CXCR7. In an *in vivo* study (39), animals with verified experimental micrometastasis were treated with

specific CXCR7 antagonists. Upon examination of the lungs, the CXCR7 antagonist-treated mice had fewer pulmonary metastases compared with vehicle-treated mice in the C26 and HT29 models. The treatment of mice with CXCR7 antagonists significantly reduced the number of metastases in the lungs of C26-injected mice [reduced by 40%; 77±6 (treated) vs. 129±5 (untreated)] and HT29-injected mice [reduced by 56%; 2.6±0.8 (treated) vs. 5.9±1.4 (untreated)]. CCX771 also blocked the proliferative and migratory effects of CXCR7 in CXCR7-positive SW480 colorectal carcinoma cells (38). In addition, Heckmann *et al* (42) demonstrated that CXCR7-expressing colon cancer cell lines were more chemoresistant compared with control cells. The authors also analyzed the cytotoxicity in a stroma-dependent cell kill assay subsequent to treatment with 5-fluorouracil (4, 8 and 16 mg/ml), which is a standard chemotherapeutic drug in colorectal cancer treatment (42). The stromal environment was mimicked using murine SDF-1α-producing stromal FBMD-1 cells in a co-culture with CXCR7-expressing SW480 (SW480CXCR7) and control cells [wild-type SW480 (SW480WT) or enhanced green fluorescent protein (EGFP)-expressing SW480 (SW480EGFP) cells] (42). The two control cell lines demonstrated similar chemosensitivity. However, SW480CXCR7 cells presented increased chemoresistance compared with the control cells following exposure to 5-fluorouracil (42).

In hepatocellular carcinoma, several studies demonstrated that targeting CXCR7 had an antitumor activity *in vitro* and *in vivo*. CXCR7 knockdown significantly inhibited the proliferation, migration, invasion and adhesion of hepatocellular carcinoma cells (45,46,48,64). In addition, silencing CXCR7 markedly suppressed tumor cell-induced tube formation and VEGF secretion *in vitro*, and further inhibited tumor growth, angiogenesis and lung metastasis in a xenograft model of hepatocellular carcinoma (46,48). Furthermore, Xue *et al* (51) recently reported that CXCR7 correlated with the differentiation of hepatocellular carcinoma. CXCR7 was also demonstrated to suppress hepatocyte nuclear factor 4α through the activation of extracellular regulated protein kinase (ERK), which was inhibited by U0125, an inhibitor of mitogen-activated protein kinase/ERK 1 and 2. These observations suggest that the CXCR7-ERK-HNF4α cascade may be a novel target for the differentiation therapy of hepatocellular carcinoma. Collectively, these results indicate that CXCR7 is a potential molecular target for the treatment of hepatocellular carcinoma.

Regarding pancreatic adenocarcinoma, CXCR7 knockdown in human pancreatic cancer cell lines transfected with CXCR7 siRNA was found to inhibit cell proliferation, migration and invasion (54,55). In addition, Hong *et al* (53) reported that stromal CXCR7 expression was associated with poor survival outcomes in patients with resectable pancreatic adenocarcinoma who underwent preoperative chemoradiation with proton beam therapy and capecitabine followed by surgery and adjuvant gemcitabine. These findings suggest that CXCR7 is involved in the resistance to treatment strategies, such as radiation and chemotherapy. Furthermore, several researchers demonstrated that CXCR7 expression was associated with treatment resistance in several cancer types, including brain tumors and breast cancer. Therefore, targeting CXCR7 may be a reasonable approach to overcome this hurdle in cancer treatment (9,42,65-67).

In conclusion, the findings described in the present review suggest that CXCR7 is a potential therapeutic target in gastrointestinal cancer. Improving the understanding on CXCR7 and its role in tumorigenesis of the gastrointestinal system, as well as developing further clinical applications, is crucial.

4. Conclusion

CXCR7 is a chemokine receptor that may be involved in the initiation, progression and metastasis of various gastrointestinal tract cancer types, as well as in processes such as cell proliferation, migration, invasion, adhesion and angiogenesis. In addition, several studies have demonstrated that targeting CXCR7 using small molecular inhibitors, siRNA and nanobodies exhibited an antitumor activity *in vitro* and *in vivo* (33,39,54,55). Therefore, the CXCR7 pathway is a potential therapeutic target in the treatment of gastrointestinal cancer. However, extensive research is required to improve the understanding on the effect of CXCR7 and its ligand system in the tumorigenesis of the gastrointestinal system, in order to achieve its successful use in clinical applications.

Acknowledgements

This study was supported by a grant from the Basic Science Research Program through the National Research Foundation of Korea funded by the Ministry of Education, Science and Technology (no. NRF-2014R1A1A2059765).

References

1. Bachelerie F, Ben-Baruch A, Burkhardt AM, Combadiere C, Farber JM, Graham GJ, Horuk R, Sparre-Ulrich AH, Locati M, Luster AD, *et al*: International Union of Basic and Clinical Pharmacology. [corrected]. LXXXIX. Update on the extended family of chemokine receptors and introducing a new nomenclature for atypical chemokine receptors. Pharmacol Rev 66: 1-79, 2014.
2. Lee HJ, Song IC, Yun HJ, Jo DY and Kim S: CXC chemokines and chemokine receptors in gastric cancer: From basic findings towards therapeutic targeting. World J Gastroenterol 20: 1681-1693, 2014.
3. Balkwill FR: The chemokine system and cancer. J Pathol 226: 148-157, 2012.
4. Lee HJ and Jo DY: The role of the CXCR4/CXCL12 axis and its clinical implications in gastric cancer. Histol Histopathol 27: 1155-1161, 2012.
5. Libert F, Parmentier M, Lefort A, Dumont JE and Vassart G: Complete nucleotide sequence of a putative G protein coupled receptor: RDC1. Nucleic Acids Res 18: 1917, 1990.
6. Sánchez-Martín L, Sánchez-Mateos P and Cabañas C: CXCR7 impact on CXCL12 biology and disease. Trends Mol Med 19: 12-22, 2013.
7. Tarnowski M, Liu R, Wysoczynski M, Ratajczak J, Kucia M and Ratajczak MZ: CXCR7: A new SDF-1-binding receptor in contrast to normal CD34(+) progenitors is functional and is expressed at higher level in human malignant hematopoietic cells. Eur J Haematol 85: 472-483, 2010.
8. Cole KE, Strick CA, Paradis TJ, Ogborne KT, Loetscher M, Gladue RP, Lin W, Boyd JG, Moser B, Wood DE, *et al*: Interferon-inducible T cell alpha chemoattractant (I-TAC): A novel non-ELR CXC chemokine with potent activity on activated T cells through selective high affinity binding to CXCR3. J Exp Med 187: 2009-2021, 1998.
9. Maksym RB, Tarnowski M, Grymula K, Tarnowska J, Wysoczynski M, Liu R, Czerny B, Ratajczak J, Kucia M and Ratajczak MZ: The role of stromal-derived factor-1 - CXCR7 axis in development and cancer. Eur J Pharmacol 625: 31-40, 2009.

10. Hartmann TN, Grabovsky V, Pasvolsky R, Shulman Z, Buss EC, Spiegel A, Nagler A, Lapidot T, Thelen M and Alon R: A crosstalk between intracellular CXCR7 and CXCR4 involved in rapid CXCL12-triggered integrin activation but not in chemokine-triggered motility of human T lymphocytes and CD34$^+$ cells. J Leukoc Biol 84: 1130-1140, 2008.
11. Infantino S, Moepps B and Thelen M: Expression and regulation of the orphan receptor RDC1 and its putative ligand in human dendritic and B cells. J Immunol 176: 2197-2207, 2006.
12. Mazzinghi B, Ronconi E, Lazzeri E, Sagrinati C, Ballerini L, Angelotti ML, Parente E, Mancina R, Netti GS, Becherucci F, *et al*: Essential but differential role for CXCR4 and CXCR7 in the therapeutic homing of human renal progenitor cells. J Exp Med 205: 479-490, 2008.
13. Naumann U, Cameroni E, Pruenster M, Mahabaleshwar H, Raz E, Zerwes HG, Rot A and Thelen M: CXCR7 functions as a scavenger for CXCL12 and CXCL11. PLoS One 5: e9175, 2010.
14. Burns JM, Summers BC, Wang Y, Melikian A, Berahovich R, Miao Z, Penfold ME, Sunshine MJ, Littman DR, Kuo CJ, *et al*: A novel chemokine receptor for SDF-1 and I-TAC involved in cell survival, cell adhesion, and tumor development. J Exp Med 203: 2201-2213, 2006.
15. Eva C and Sprengel R: A novel putative G protein-coupled receptor highly expressed in lung and testis. DNA Cell Biol 12: 393-399, 1993.
16. Libert F, Parmentier M, Lefort A, Dinsart C, Van Sande J, Maenhaut C, Simons MJ, Dumont JE and Vassart G: Selective amplification and cloning of four new members of the G protein-coupled receptor family. Science 244: 569-572, 1989.
17. Tripathi V, Verma R, Dinda A, Malhotra N, Kaur J and Luthra K: Differential expression of RDC1/CXCR7 in the human placenta. J Clin Immunol 29: 379-386, 2009.
18. Sun X, Cheng G, Hao M, Zheng J, Zhou X, Zhang J, Taichman RS, Pienta KJ and Wang J: CXCL12/CXCR4/CXCR7 chemokine axis and cancer progression. Cancer Metastasis Rev 29: 709-722, 2010.
19. Keeley EC, Mehrad B and Strieter RM: CXC chemokines in cancer angiogenesis and metastases. Adv Cancer Res 106: 91-111, 2010.
20. Raggo C, Ruhl R, McAllister S, Koon H, Dezube BJ, Früh K and Moses AV: Novel cellular genes essential for transformation of endothelial cells by Kaposi's sarcoma-associated herpesvirus. Cancer Res 65: 5084-5095, 2005.
21. Miao Z, Luker KE, Summers BC, Berahovich R, Bhojani MS, Rehemtulla A, Kleer CG, Essner JJ, Nasevicius A, Luker GD, *et al*: CXCR7 (RDC1) promotes breast and lung tumor growth in vivo and is expressed on tumor-associated vasculature. Proc Natl Acad Sci USA 104: 15735-15740, 2007.
22. Wang J, Shiozawa Y, Wang J, Wang Y, Jung Y, Pienta KJ, Mehra R, Loberg R and Taichman RS: The role of CXCR7/RDC1 as a chemokine receptor for CXCL12/SDF-1 in prostate cancer. J Biol Chem 283: 4283-4294, 2008.
23. Berahovich RD, Zabel BA, Penfold ME, Lewén S, Wang Y, Miao Z, Gan L, Pereda J, Dias J, Slukvin II, *et al*: CXCR7 protein is not expressed on human or mouse leukocytes. J Immunol 185: 5130-5139, 2010.
24. Bennani-Baiti IM, Cooper A, Lawlor ER, Kauer M, Ban J, Aryee DN and Kovar H: Intercohort gene expression co-analysis reveals chemokine receptors as prognostic indicators in Ewing's sarcoma. Clin Cancer Res 16: 3769-3778, 2010.
25. Tarnowski M, Grymula K, Reca R, Jankowski K, Maksym R, Tarnowska J, Przybylski G, Barr FG, Kucia M and Ratajczak MZ: Regulation of expression of stromal-derived factor-1 receptors: CXCR4 and CXCR7 in human rhabdomyosarcomas. Mol Cancer Res 8: 1-14, 2010.
26. Van Rechem C, Rood BR, Touka M, Pinte S, Jenal M, Guérardel C, Ramsey K, Monté D, Bégue A, Tschan MP, *et al*: Scavenger chemokine (CXC motif) receptor 7 (CXCR7) is a direct target gene of HIC1 (hypermethylated in cancer 1). J Biol Chem 284: 20927-20935, 2009.
27. Calatozzolo C, Canazza A, Pollo B, Di Pierro E, Ciusani E, Maderna E, Salce E, Sponza V, Frigerio S, Di Meco F, *et al*: Expression of the new CXCL12 receptor, CXCR7, in gliomas. Cancer Biol Ther 11: 242-253, 2011.
28. Hattermann K, Held-Feindt J, Lucius R, Müerköster SS, Penfold ME, Schall TJ and Mentlein R: The chemokine receptor CXCR7 is highly expressed in human glioma cells and mediates antiapoptotic effects. Cancer Res 70: 3299-3308, 2010.
29. Mehra R, Serebriiskii IG, Burtness B, Astsaturov I and Golemis EA: Aurora kinases in head and neck cancer. Lancet Oncol 14: e425-e435, 2013.
30. Miyazaki H, Takabe K and Yeudall WA: Chemokines, chemokine receptors and the gastrointestinal system. World J Gastroenterol 19: 2847-2863, 2013.
31. Yeudall WA and Miyazaki H: Chemokines and squamous cancer of the head and neck: Targets for therapeutic intervention? Expert Rev Anticancer Ther 7: 351-360, 2007.
32. Xia J, Wang J, Chen N, Dai Y, Hong Y, Chen X and Cheng B: Expressions of CXCR7/ligands may be involved in oral carcinogenesis. J Mol Histol 42: 175-180, 2011.
33. Maussang D, Mujić-Delić A, Descamps FJ, Stortelers C, Vanlandschoot P, Stigter-van Walsum M, Vischer HF, van Roy M, Vosjan M, Gonzalez-Pajuelo M, *et al*: Llama-derived single variable domains (nanobodies) directed against chemokine receptor CXCR7 reduce head and neck cancer cell growth in vivo. J Biol Chem 288: 29562-29572, 2013.
34. Ge XS, Ma HJ, Zheng XH, Ruan HL, Liao XY, Xue WQ, Chen YB, Zhang Y and Jia WH: HOTAIR, a prognostic factor in esophageal squamous cell carcinoma, inhibits WIF-1 expression and activates Wnt pathway. Cancer Sci 104: 1675-1682, 2013.
35. Tachezy M, Zander H, Gebauer F, von Loga K, Pantel K, Izbicki JR and Bockhorn M: CXCR7 expression in esophageal cancer. J Transl Med 11: 238, 2013.
36. Iwakiri S, Mino N, Takahashi T, Sonobe M, Nagai S, Okubo K, Wada H, Date H and Miyahara R: Higher expression of chemokine receptor CXCR7 is linked to early and metastatic recurrence in pathological stage I nonsmall cell lung cancer. Cancer 115: 2580-2593, 2009.
37. Zhi Y, Chen J, Zhang S, Chang X, Ma J and Dai D: Down-regulation of CXCL12 by DNA hypermethylation and its involvement in gastric cancer metastatic progression. Dig Dis Sci 57: 650-659, 2012.
38. Xu H, Wu Q, Dang S, Jin M, Xu J, Cheng Y, Pan M, Wu Y, Zhang C and Zhang Y: Alteration of CXCR7 expression mediated by TLR4 promotes tumor cell proliferation and migration in human colorectal carcinoma. PLoS One 6: e27399, 2011.
39. Guillemot E, Karimdjee-Soilihi B, Pradelli E, Benchetrit M, Goguet-Surmenian E, Millet MA, Larbret F, Michiels JF, Birnbaum D, Alemanno P, *et al*: CXCR7 receptors facilitate the progression of colon carcinoma within lung not within liver. Br J Cancer 107: 1944-1949, 2012.
40. Romain B, Hachet-Haas M, Rohr S, Brigand C, Galzi JL, Gaub MP, Pencreach E and Guenot D: Hypoxia differentially regulated CXCR4 and CXCR7 signaling in colon cancer. Mol Cancer 13: 58, 2014.
41. Rupertus K, Sinistra J, Scheuer C, Nickels RM, Schilling MK, Menger MD and Kollmar O: Interaction of the chemokines I-TAC (CXCL11) and SDF-1 (CXCL12) in the regulation of tumor angiogenesis of colorectal cancer. Clin Exp Metastasis 31: 447-459, 2014.
42. Heckmann D, Maier P, Laufs S, Li L, Sleeman JP, Trunk MJ, Leupold JH, Wenz F, Zeller WJ, Fruehauf S, *et al*: The disparate twins: A comparative study of CXCR4 and CXCR7 in SDF-1α-induced gene expression, invasion and chemosensitivity of colon cancer. Clin Cancer Res 20: 604-616, 2014.
43. D'Alterio C, Avallone A, Tatangelo F, Delrio P, Pecori B, Cella L, Pelella A, D'Armiento FP, Carlomagno C, Bianco F, *et al*: A prognostic model comprising pT stage, N status, and the chemokine receptors CXCR4 and CXCR7 powerfully predicts outcome in neoadjuvant resistant rectal cancer patients. Int J Cancer 135: 379-390, 2014.
44. Kheirelseid EA, Miller N, Chang KH, Nugent M and Kerin MJ: Clinical applications of gene expression in colorectal cancer. J Gastrointest Oncol 4: 144-157, 2013.
45. Wang L, Zhang X, Jia LT, Hu SJ, Zhao J, Yang JD, Wen WH, Wang Z, Wang T, Zhao J, *et al*: c-Myc-mediated epigenetic silencing of MicroRNA-101 contributes to dysregulation of multiple pathways in hepatocellular carcinoma. Hepatology 59: 1850-1863, 2014.
46. Xue TC, Chen RX, Han D, Chen J, Xue Q, Gao DM, Sun RX, Tang ZY and Ye SL: Down-regulation of CXCR7 inhibits the growth and lung metastasis of human hepatocellular carcinoma cells with highly metastatic potential. Exp Ther Med 3: 117-123, 2012.
47. Xue TC, Han D, Chen RX, Zou JH, Wang Y, Tang ZY and Ye SL: High expression of CXCR7 combined with Alpha fetoprotein in hepatocellular carcinoma correlates with extra-hepatic metastasis to lung after hepatectomy. Asian Pac J Cancer Prev 12: 657-663, 2011.
48. Zheng K, Li HY, Su XL, Wang XY, Tian T, Li F and Ren GS: Chemokine receptor CXCR7 regulates the invasion, angiogenesis and tumor growth of human hepatocellular carcinoma cells. J Exp Clin Cancer Res 29: 31, 2010.

49. Monnier J, Boissan M, L'Helgoualc'h A, Lacombe ML, Turlin B, Zucman-Rossi J, Théret N, Piquet-Pellorce C and Samson M: CXCR7 is up-regulated in human and murine hepatocellular carcinoma and is specifically expressed by endothelial cells. Eur J Cancer 48: 138-148, 2012.
50. Ghanem I, Riveiro ME, Paradis V, Faivre S, de Parga PM and Raymond E: Insights on the CXCL12-CXCR4 axis in hepatocellular carcinoma carcinogenesis. Am J Transl Res 6: 340-352, 2014.
51. Xue TC, Jia QA, Bu Y, Chen RX, Cui JF, Tang ZY and Ye SL: CXCR7 correlates with the differentiation of hepatocellular carcinoma and suppresses HNF4α expression through the ERK pathway. Oncol Rep 32: 2387-2396, 2014.
52. Xue TC, Chen RX, Ren ZG, Zou JH, Tang ZY and Ye SL: Transmembrane receptor CXCR7 increases the risk of extrahepatic metastasis of relatively well-differentiated hepatocellular carcinoma through upregulation of osteopontin. Oncol Rep 30: 105-110, 2013.
53. Hong TS, Ryan DP, Borger DR, Blaszkowsky LS, Yeap BY, Ancukiewicz M, Deshpande V, Shinagare S, Wo JY, Boucher Y, *et al*: A phase 1/2 and biomarker study of preoperative short course chemoradiation with proton beam therapy and capecitabine followed by early surgery for resectable pancreatic ductal adenocarcinoma. Int J Radiat Oncol Biol Phys 89: 830-838, 2014.
54. Heinrich EL, Lee W, Lu J, Lowy AM and Kim J: Chemokine CXCL12 activates dual CXCR4 and CXCR7-mediated signaling pathways in pancreatic cancer cells. J Transl Med 10: 68, 2012.
55. Guo JC, Li J, Yang YC, Zhou L, Zhang TP and Zhao YP: Oligonucleotide microarray identifies genes differentially expressed during tumorigenesis of DMBA-induced pancreatic cancer in rats. PLoS One 8: e82910, 2013.
56. Gebauer F, Tachezy M, Effenberger K, von Loga K, Zander H, Marx A, Kaifi JT, Sauter G, Izbicki JR and Bockhorn M: Prognostic impact of CXCR4 and CXCR7 expression in pancreatic adenocarcinoma. J Surg Oncol 104: 140-145, 2011.
57. Weekes CD, Song D, Arcaroli J, Wilson LA, Rubio-Viqueira B, Cusatis G, Garrett-Mayer E, Messersmith WA, Winn RA and Hidalgo M: Stromal cell-derived factor 1α mediates resistance to mTOR-directed therapy in pancreatic cancer. Neoplasia 14: 690-701, 2012.
58. Roy I, Zimmerman NP, Mackinnon AC, Tsai S, Evans DB and Dwinell MB: CXCL12 chemokine expression suppresses human pancreatic cancer growth and metastasis. PLoS One 9: e90400, 2014.
59. Maréchal R, Demetter P, Nagy N, Berton A, Decaestecker C, Polus M, Closset J, Devière J, Salmon I and Van Laethem JL: High expression of CXCR4 may predict poor survival in resected pancreatic adenocarcinoma. Br J Cancer 100: 1444-1451, 2009.
60. Yao X, Zhou L, Han S and Chen Y: High expression of CXCR4 and CXCR7 predicts poor survival in gallbladder cancer. J Int Med Res 39: 1253-1264, 2011.
61. Zabel BA, Wang Y, Lewén S, Berahovich RD, Penfold ME, Zhang P, Powers J, Summers BC, Miao Z, Zhao B, *et al*: Elucidation of CXCR7-mediated signaling events and inhibition of CXCR4-mediated tumor cell transendothelial migration by CXCR7 ligands. J Immunol 183: 3204-3211, 2009.
62. Luker KE, Gupta M and Luker GD: Imaging chemokine receptor dimerization with firefly luciferase complementation. FASEB J 23: 823-834, 2009.
63. Duda DG, Kozin SV, Kirkpatrick ND, Xu L, Fukumura D and Jain RK: CXCL12 (SDF1alpha)-CXCR4/CXCR7 pathway inhibition: An emerging sensitizer for anticancer therapies? Clin Cancer Res 17: 2074-2080, 2011.
64. Dai X, Xiong X, Wang L, Pan K, He L and Li H: Effects of CXCR7-shRNA lentiviral vector on the growth and invasiveness of human hepatoma carcinoma cells in vitro. Nan Fang Yi Ke Da Xue Xue Bao 33: 994-998, 2013 (In Chinese).
65. Ribas R, Ghazoui Z, Gao Q, Pancholi S, Rani A, Dunbier A, Dowsett M and Martin LA: Identification of chemokine receptors as potential modulators of endocrine resistance in oestrogen receptor-positive breast cancers. Breast Cancer Res 16: 447, 2014.
66. Walters MJ, Ebsworth K, Berahovich RD, Penfold ME, Liu SC, Al Omran R, Kioi M, Chernikova SB, Tseng D, Mulkearns-Hubert EE, *et al*: Inhibition of CXCR7 extends survival following irradiation of brain tumours in mice and rats. Br J Cancer 110: 1179-1188, 2014.
67. Hou KL, Hao MG, Bo JJ and Wang JH: CXCR7 in tumorigenesis and progression. Chin J Cancer 29: 456-459, 2010.