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## Functions and mechanisms of chemokine receptor 7 in tumors of the digestive system

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### Abstract

Chemokine (C-X-C motif) receptor 7 (CXCR7), recently termed ACKR3, belongs to the G protein-coupled cell surface receptor family, binds to stromal cell-derived factor-1 [SDF-1, or chemokine (C-X-C motif) ligand 12] or chemokine (C-X-C motif) ligand 11, and is the most common chemokine receptor expressed in a variety of cancer cells. SDF-1 binds to its receptor chemokine (C-X-C motif) receptor 4 (CXCR4) and regulates cell proliferation, survival, angiogenesis and migration. In recent years, another new receptor for SDF-1, CXCR7, has been discovered, and CXCR7 has also been found to be expressed in a variety of tumor cells and tumor-related vascular endothelial cells. Many studies have shown that CXCR7 can promote the growth and metastasis of a variety of malignant tumor cells. Unlike CXCR4, CXCR7 exhibits a slight modification in the DRYLAIV motif and does not induce intracellular Ca<sup>2+</sup> release following ligand binding, which is essential for recruiting and activating G proteins. CXCR7 is generally thought to work in three ways: (1) Recruiting β-arrestin 2; (2) Heterodimerizing with CXCR4; and (3) Acting as a “scavenger” of SDF-1, thus lowering the level of SDF-1 to weaken the activity of CXCR4. In the present review, the expression and role of CXCR7, as well as its prognosis in cancers of the digestive system, were investigated.

**Key words:** Stromal cell-derived factor-1; Chemokine (C-X-C motif) receptor 7; Chemokine (C-X-C motif) receptor 4; Carcinoma; Digestive system

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**Core tip:** Digestive tract tumors are one of the most important tumors in the whole body. As a newly discovered receptor of stromal cell-derived factor-1, chemokine (C-X-C motif) receptor 7 (CXCR7) has attracted increasing attention from researchers. Over the years, studies have found that CXCR7 is expressed in a variety of malignant tumors of the digestive system and plays an important role in the occurrence, development and metastasis of tumors. Many studies have also shown that CXCR7 can serve as a prognostic factor for a variety of tumors and may be a target for the treatment of a variety of tumors. Here, we summarized all the manifestations and functions of CXCR7 in various gastrointestinal tumors and compared the research status of CXCR7 in different types of gastrointestinal tumors.

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## INTRODUCTION

Chemokines are an almost 50-member group of small peptide proteins secreted by various cell types after induction, and they bind to chemokine receptors<sup>[1]</sup>. Chemokines play crucial roles in many physiological and pathological processes. They also play an important role in the tumorigenesis, migration, proliferation, angiogenesis, survival and progression of tumors. The configuration of the two cysteines closest to the N-terminus allows chemokines to be split into four subfamilies: CC, CXC, CX3C and XC. Chemokines have a highly conserved tertiary structure that consists of a free N-terminus followed by a three-stranded  $\beta$ -sheet with an embedded C-terminal  $\alpha$ -helix. Chemokines work by binding to the specifically paired G protein-coupled 7 transmembrane domain receptor, causing phosphorylation of serine and threonine residues at the C-terminal of the intracellular receptor and causing intracellular signal transduction.

Stromal cell-derived factor-1 (SDF-1) is a member of the CXC chemokine subfamily and is secreted by bone marrow stromal cells, endothelial cells, stromal fibroblasts and hepatic stellate cells<sup>[2]</sup>. SDF-1 plays an important role in hematopoietic, cardiovascular, nervous system and other physiological states, and regulates a variety of cellular functions in the immune system, including differentiation, distribution, activation, immune synapse formation, effector function, proliferation and survival. In addition to playing an important role in physiological processes, SDF-1 is also involved in pathological processes involved in the occurrence of disease development. This process is known to promote tumor growth and metastasis in at least 20 malignancies<sup>[3-5]</sup>. The G protein-coupled receptor chemokine (C-X-C motif) receptor 4 (CXCR4) has been considered for many years as the only receptor for SDF-1. Chemokine (C-X-C motif) receptor 7 (CXCR7), which belongs to the G protein-coupled cell surface receptor family, binds to SDF-1 with even higher affinity than CXCR4 and is the most common chemokine receptor expressed in a variety of cancer cells. Unlike CXCR4, CXCR7 exhibits a slight modification in the DRYLAIV motif and does not induce intracellular  $Ca^{2+}$  release following ligand binding, which is essential for recruiting and activating G proteins<sup>[6]</sup>. CXCR7 is a nonclassical G protein coupled receptor that is unable to activate G proteins. Early work suggested that CXCR7 is a scavenger receptor that creates gradients of SDF-1 to influence cell migration through SDF-1-CXCR7 internalization<sup>[7]</sup>. After binding with CXCR7, SDF-1 is internalized into the cytoplasm to cause signal transduction. After that, SDF-1 is transported to lysosomes for degradation, causing the difference in the concentration of SDF-1 inside and outside the cell, and CXCR7 is circulated to the cell membrane again<sup>[8,9]</sup>. Like CXCR4, CXCR7 is constitutively internalized and recycled between the cell membrane and endosomes in the cytoplasm, leading to higher intracellular concentrations than what is expressed on the plasma membrane, a dynamic and periodic process of regulating the levels of extracellular SDF-1 and the expression of CXCR4. The endosomal recycling of CXCR7 is less affected by SDF-1 concentrations than by CXCR4 concentrations; however, CXCR4 cell surface expression decreases by up to 50% under higher SDF-1 conditions. Further research into CXCR7 alternative

signaling has challenged this thinking. Evidence has shown that CXCR7 binding of SDF-1 causes non-G protein-mediated  $\beta$ -arrestin accumulation and subsequent extracellular regulated protein kinases (ERK) activation *via* mitogen-activated protein kinases (MAPK), which potentiate SDF-1-mediated downstream signaling<sup>[10]</sup>. CXCR7 is not expressed or weakly expressed in most normal tissues, but it is highly expressed in many cancer tissues, including cancers of the prostate, lung, liver, colon and pancreas<sup>[11-13]</sup>. More importantly, the presence of CXCR7 is necessary for cancer cell survival, migration, adhesion, angiogenesis and metastasis<sup>[14,15]</sup>. The interaction between SDF-1 and CXCR7 was shown to induce cellular adhesion, proliferation and survival *in vitro* and *in vivo*<sup>[16]</sup>. Because CXCR7 expression has been associated with tumor aggressiveness, our previous studies showed that high expression of CXCR7 can promote lymph node and liver metastasis of gastric cancer<sup>[17]</sup> and also predict a poor prognosis<sup>[3,18]</sup>.

In different types of tumor cells, affected by differentiation and microenvironment, CXCR4 and CXCR7 can be expressed uniquely or in combination<sup>[19]</sup>. When only CXCR7 is expressed in cells, SDF-1 binds to CXCR7 to activate intracellular signals by recruiting  $\beta$ -arrestin<sup>[20]</sup>. When CXCR4 and CXCR7 are co-expressed, CXCR4 and CXCR7 can form homodimers or heterodimers<sup>[21,22]</sup>. Previous literature along with our forthcoming research results show that in the process of tumor development, heterodimers seems to play a more important role, especially in regulating the signaling cascade downstream of cancer cells<sup>[23]</sup>. Whether CXCR4 or CXCR7 is expressed alone, it results in little activation of the p38 MAPK and stress-activated protein kinase (SAPK) pathways. However, cells co-expressing both CXCR4 and CXCR7 showed increased levels of phosphorylated p38 MAPK and SAPK upon SDF-1 stimulation<sup>[22]</sup>. With heterodimerization, Gai signaling is modified, intracellular calcium release is decreased and  $\beta$ -arrestin signaling is increased<sup>[21]</sup>. CXCR4/CXCR7 forms heterodimers and recruits  $\beta$ -arrestin to form CXCR4/CXCR7/ $\beta$ -arrestin complex<sup>[21]</sup>. More downstream effects of the CXCR4/CXCR7/ $\beta$ -arrestin complex include prolonged ERK1/2 and p38 MAPK signaling and increased chemotaxis towards SDF-1<sup>[22]</sup>. Co-expression of CXCR7 and CXCR4 not only can synergistically enhance the recruitment of  $\beta$ -arrestin and activate ERK1/2 MAPK pathway to cause invasion and metastasis but can also inhibit CXCR4-mediated phosphatidylinositol-3-phosphate (PI3K)/MAPK signaling pathway through CXCR7 competitively binding SDF-1<sup>[22,24]</sup>. There may also be crosstalk between CXCR4 and CXCR7 upon ligand binding that is mediated by intracellular signaling effectors<sup>[25]</sup>. CXCR7 is generally thought to work in three ways: (1) Recruiting  $\beta$ -arrestin 2<sup>[10]</sup>; (2) Heterodimerizing with CXCR4<sup>[21]</sup>; and (3) Acting as a "scavenger" of SDF-1, thus lowering the level of SDF-1 to weaken the activity of CXCR4<sup>[26,27]</sup>.

CXCR7 also binds to CXCL11, another chemokine family member; CXCR7 may also recruit CXCR4 when it has bound CXCL11 or different CXCR4 ligands or vice versa<sup>[19]</sup>. However, the results from a large number of studies show that SDF-1/CXCR7 signaling plays an important role in many physiological and pathological processes. Herein, we will review the effects of CXCR7 in digestive tract tumor development and progression as well as the potential of targeting this pathway for cancer therapy. Considerable efforts have been made in recent years to elucidate the biological function of chemokine receptors in cancer development and metastasis. So far, the role of CXCR7 in various types of tumors of the digestive system remains unclear. Even in the same type of tumors, the results of different studies vary. Table 1<sup>[28-60]</sup> provides a 10-year literature review of CXCR7 in digestive tumors.

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## ESOPHAGEAL CANCER

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### **Expression in tumor tissue**

CXCR7 is expressed in the cytoplasm and membrane of esophageal cancer cells<sup>[29]</sup>, and CXCR7 expression is rarely found in esophageal adenocarcinomas but is overexpressed in almost half of esophageal squamous cell carcinomas (ESCC)<sup>[30,61]</sup>. CXCR7 expression was significantly higher in ESCC tissues than in paired noncancerous tissues. In addition, the expression of CXCR7 in chemotherapy-sensitive ESCC patients is significantly lower than that in patients with chemotherapy-resistance<sup>[32]</sup>.

### **CXCR7 in the development and metastasis**

The high expression of CXCR7 was closely associated with higher histological grade and advanced clinical stage in patients with ESCC<sup>[29]</sup>. However, there was also a finding that the expression of CXCR7 in ESCC was unrelated to growth and metastasis<sup>[30]</sup>. After silencing CXCR7 in esophageal cancer cell lines (TE-1, EC9706 and

**Table 1** Stromal cell-derived factor-1/chemokine (C-X-C motif) receptor 7 impact in digestive tract tumor

Cancer	Biological/clinical effects	Ref.
Esophageal cancer	Proliferation, metastasis, prognosis	Wu <i>et al.</i> <sup>[28]</sup> ; Van Rechem <i>et al.</i> <sup>[29]</sup> ; Qiao <i>et al.</i> <sup>[30]</sup>
Gastric cancer	Proliferation, metastasis, prognosis, angiogenesis	Ma <i>et al.</i> <sup>[4]</sup> ; Xin <i>et al.</i> <sup>[17]</sup> ; Shi <i>et al.</i> <sup>[31]</sup> ; Nambara <i>et al.</i> <sup>[32]</sup> ; Kim <i>et al.</i> <sup>[33]</sup> ; Cao <i>et al.</i> <sup>[34]</sup> ; Li <i>et al.</i> <sup>[35]</sup>
Colorectal	Proliferation, metastasis, angiogenesis	Wang <i>et al.</i> <sup>[5]</sup> ; Li <i>et al.</i> <sup>[13]</sup> ; Heckmann <i>et al.</i> <sup>[20]</sup> ; Song <i>et al.</i> <sup>[23]</sup> ; Rupertus <i>et al.</i> <sup>[36]</sup> ; Romain <i>et al.</i> <sup>[37]</sup> ; Wang <i>et al.</i> <sup>[38]</sup> ; Xu <i>et al.</i> <sup>[39]</sup> ; Li <i>et al.</i> <sup>[40]</sup> ; Kollmar <i>et al.</i> <sup>[41]</sup> ; Yang <i>et al.</i> <sup>[42]</sup> ; Wang <i>et al.</i> <sup>[43]</sup> ; Guillemot <i>et al.</i> <sup>[44]</sup> ; D'Alterio <i>et al.</i> <sup>[45]</sup> ; Dambly-Chaudière <i>et al.</i> <sup>[46]</sup> ; Kheirleiseid <i>et al.</i> <sup>[47]</sup>
Hepatocellular carcinoma	Proliferation, metastasis, prognosis, angiogenesis, differentiation	Chen <i>et al.</i> <sup>[11]</sup> ; Zhao <i>et al.</i> <sup>[15]</sup> ; Xue <i>et al.</i> <sup>[48]</sup> ; Lin <i>et al.</i> <sup>[49]</sup> ; Neve Polimeno <i>et al.</i> <sup>[50]</sup> ; Xue <i>et al.</i> <sup>[51]</sup> ; Monnier <i>et al.</i> <sup>[52]</sup> ; Zheng <i>et al.</i> <sup>[53]</sup> ; Xue <i>et al.</i> <sup>[54]</sup> ; Xue <i>et al.</i> <sup>[55]</sup> ; Wang <i>et al.</i> <sup>[56]</sup> ; Wu <i>et al.</i> <sup>[57]</sup>
Pancreatic adenocarcinoma	Proliferation, metastasis, prognosis	Guo <i>et al.</i> <sup>[3]</sup> ; Roy <i>et al.</i> <sup>[58]</sup> ; Gebauer <i>et al.</i> <sup>[59]</sup> ; Liu <i>et al.</i> <sup>[60]</sup>
Cholangiocarcinoma	Proliferation, angiogenesis	Gentilini <i>et al.</i> <sup>[12]</sup>

EC109), it was found that silencing CXCR7 inhibited the apoptosis and chemotaxis of esophageal cancer cells, and *in vivo* animal experiments showed that CXCR7 could promote the growth of esophageal cancer through, and ERK1/2 pathway activation<sup>[29]</sup>. Interleukin (IL)-6 is an upstream regulator of CXCR7. By upregulating the expression of CXCR7, promoting the proliferation of tumor cells and drug resistance is an important way for it to interfere with tumors<sup>[32]</sup>. Hypermethylated in cancer 1 (HIC1) is a direct repressor of the CXCR7 gene. In esophageal cancer patients lacking HIC1 expression, overexpressed CXCR7 can promote tumor growth<sup>[61]</sup>.

### Role of CXCR7 in tumor prognosis

So far, there is substantial evidence that CXCR7 plays a crucial role in indicating poor prognosis of cancer patients. Patients with esophageal squamous cell carcinoma with high expression of CXCR7 have significantly worse overall survival (OS) and progression-free survival (PFS) after cisplatin chemotherapy than patients with low expression of CXCR7<sup>[29,32]</sup>. However, it remains controversial because contradictory evidence has also been reported. For example, the expression of CXCR7 had no effect on the survival and prognosis of patients with esophageal squamous cell carcinoma or adenocarcinoma<sup>[30]</sup>.

## GASTRIC CANCER

### Expression in tumor tissue

CXCR7 expression was detected at the mRNA and protein levels in five types of gastric cancer cell lines (HGC-27, MGC-803, BGC-823, SGC-7901 and MKN-28) by reverse transcription-polymerase chain reaction and Western blotting<sup>[4]</sup>. The mRNA and protein expression levels of CXCR7 were the most obvious in SGC-7901 cells, which had higher levels of CXCR7 than CXCR4<sup>[31]</sup> (Table 2)<sup>[62]</sup>.

CXCR7 is expressed in the cell membrane or cytoplasm in gastric cancer cells<sup>[17,31]</sup>. Our team's previous research found that the expression of CXCR7 in gastric cancer tissues was significantly higher than that in surrounding non-tumor tissues, and it was also expressed in some mesenchymal cells and inflammatory cells of tumor tissues<sup>[17]</sup>. Our previous studies showed that CXCR7 expression was seen in tumor-associated blood vessels in gastric cancer tissues, and CXCR7 expression was not seen in normal vascular endothelium at non-tumor sites. In addition, the expression of CXCR7 in cancer cells in metastatic vessels is significantly stronger than that in primary gastric cancer cells<sup>[17]</sup>.

### CXCR7 in the development and metastasis

CXCR7 promotes the proliferation, adhesion, migration, invasion and metastasis of gastric cancer cells through  $\beta$ -arrestin-dependent downstream signaling<sup>[31]</sup>, Akt (PKB, also known as including protein kinase B), ERK1/2, p38 MAPK, just another kinase/serial advanced technology attachment/cellular-myelocytomatosis (JAK2/STAT3/c-Myc) and SAPK pathways, by combining with SDF-1<sup>[4,17,34]</sup>. CXCR7 inhibits the processing of poly ADP-ribose polymerase and caspase-3 and induces an

**Table 2** Expression of chemokine (C-X-C motif) receptor 7 in different cancer cell lines

Cancer	Cell lines	Ref.
Gastric cancer	HGC-27, MGC-803, BGC-823, SGC-7901, MKN-28	Ma <i>et al</i> <sup>[4]</sup> ; Shi <i>et al</i> <sup>[31]</sup>
Colorectal cancer	RKO, HCT116, SW480, CT26, HT-29, Caco-2	Li <i>et al</i> <sup>[13]</sup> ; Heckmann <i>et al</i> <sup>[20]</sup> ; Rupertus <i>et al</i> <sup>[36]</sup> ; Wang <i>et al</i> <sup>[38]</sup> ; Romain <i>et al</i> <sup>[37]</sup> ; Xu <i>et al</i> <sup>[39]</sup> ; Li <i>et al</i> <sup>[40]</sup>
Hepatocellular carcinoma	HCCLM3, L02, QSG7701, QGY-7703, Hep3B, SMMC7721, MHCC97L, HepG2, Huh7, 97H, LM3, LM6, SNU449, SNU475	Chen <i>et al</i> <sup>[11]</sup> ; Xue <i>et al</i> <sup>[48]</sup> ; Lin <i>et al</i> <sup>[49]</sup> ; Neve Polimeno <i>et al</i> <sup>[50]</sup> ; Zheng <i>et al</i> <sup>[53]</sup>
Cholangiocarcinoma	HuCC1-1, SG231, CCLP1, MzCha, TFK1	Gentilini <i>et al</i> <sup>[12]</sup>
Pancreatic cancer	AsPC-1, MiaPaCa-2, PANC-1, SU86.86, HS-766 T, BxPC-3, FG, T3M4	Guo <i>et al</i> <sup>[3]</sup> ; Roy <i>et al</i> <sup>[58]</sup> ; Heinrich <i>et al</i> <sup>[62]</sup>

anti-apoptotic effect<sup>[34]</sup>. CXCR7 promotes the proliferation of gastric cancer BGC803 cells by being negatively regulated by miR-100<sup>[63]</sup>. Downregulation of CXCR7 significantly inhibits tumor growth *in vivo*<sup>[31]</sup>. Gastric cancer cells with high expression of CXCR7 are directed to specific target organs along the concentration gradient formed by SDF-1, and CXCR7 can promote the lymph node and liver metastasis of gastric cancer<sup>[17]</sup>. CXCR7 may also be associated with peritoneal metastasis in gastric cancer; high CXCR7 mRNA expression is associated with a high risk of peritoneal metastasis<sup>[31]</sup>. Lipopolysaccharide (LPS) is a toxic component of the outermost dermis of *Helicobacter pylori* cells, which can cause long-term inflammatory damage to the gastric mucosa<sup>[35]</sup>. The expression of Toll-like receptor 4 (TLR4) and CXCR7 is related to the growth and metastatic potential of gastric cancer, because LPS can upregulate the expression of CXCR7 through TLR4 signal and promote the proliferation and migration of gastric cancer cells. Myeloid differentiation factor 2 (MD-2) is a receptor molecule necessary for LPS-mediated activation of the TLR4 transmembrane signaling pathway and an important regulator of innate immune recognition. In LPS-induced gastric cancer, CXCR7 regulates downstream molecules through TLR4/MD-2 signaling to promote tumor development<sup>[35]</sup>. CXCR7 can serve as a factor in the regulation of vascular endothelial growth factor (VEGF) secretion and induce angiogenesis in gastric cancer<sup>[4,31]</sup>. Elevated CXCR7 expression levels are related to peritoneal metastasis and worse prognosis in gastric tumor patients<sup>[32]</sup>. The mechanism of CXCR7 in gastric cancer cell is shown in **Figure 1**.

## HEPATOCELLULAR CARCINOMA

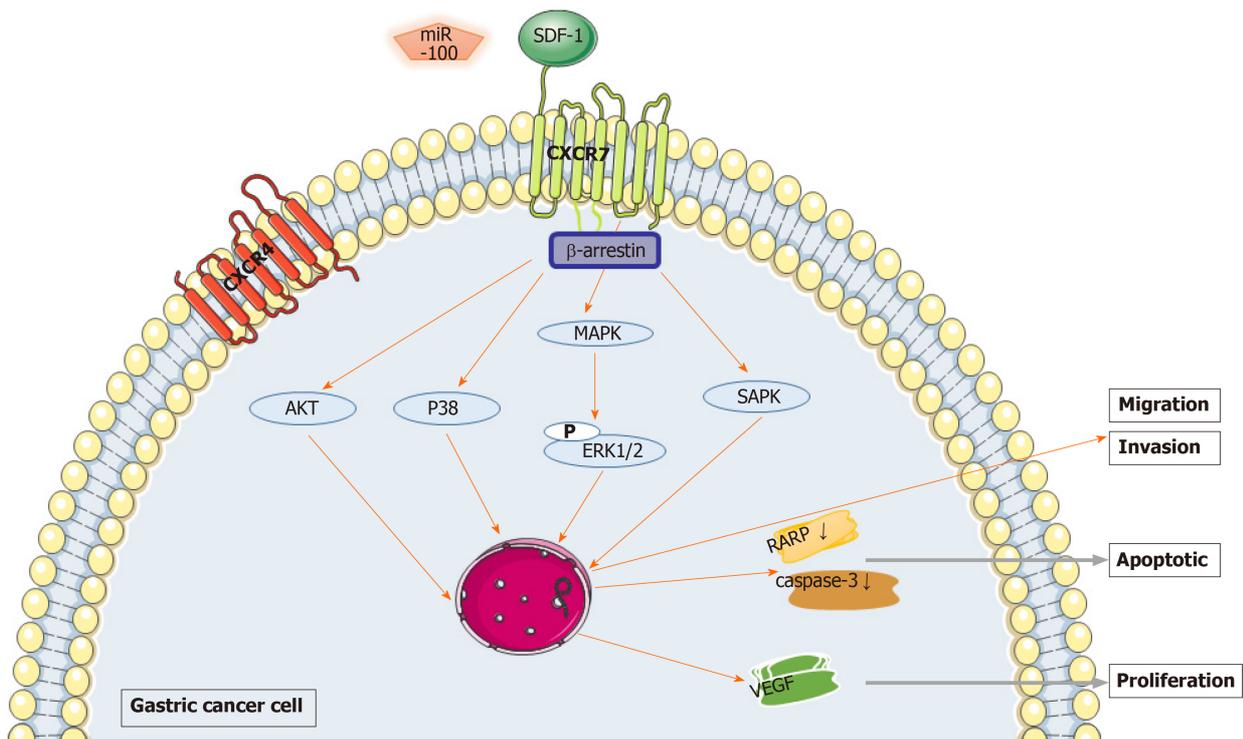
### Expression in tumor tissue

Hepatocellular carcinoma (HCC) cells (HCCLM3, SMMC7721, L02, QSG7701, MHCC97L, HepG2, Huh7, SNU449, 97H, LM3, QGY-7703, Hep3B, LM6 and SNU475) expressed CXCR7<sup>[48,49,53]</sup>, and highly metastatic cells (MHCC97L, 97H, LM3 and LM6) expressed much higher levels of CXCR7 than low-metastasis cells, including QGY-7703, HepG2 and Hep3B<sup>[53]</sup>. Moreover, CXCR7 was more markedly unregulated in the HCCLM3 cell line than in the MHCC97-L and SMMC7721 cell lines<sup>[49]</sup> (**Table 2**).

CXCR7 is stained mainly in the membrane and cytoplasm of HCC, with a positivity rate of 63%-85% by immunohistochemistry<sup>[52,54]</sup>. In the HCC group, CXCR7 levels were five times higher than those in normal hepatocytes<sup>[49,53]</sup>. High CXCR7 expression has been found in metastatic HCC samples and in the majority of tumor-associated vessels and is related to tumor neovascularization<sup>[49]</sup>. CXCR7 expression can be seen in almost all vascular endothelium in HCC, but CXCR7 expression is hardly seen in the vascular endothelium of normal liver tissues adjacent to the cancer. Very interestingly, in addition to the strong positive expression of CXCR7 on HCC, the expression of CXCR7 can also be seen in the vascular endothelium of liver cirrhosis around the cancer tissue<sup>[52]</sup>.

### CXCR7 in the development and metastasis

CXCR7 can promote tumorigenesis, growth and metastasis of HCC<sup>[15,49,53]</sup>. The knockdown of CXCR7 inhibits HCC growth in mice after transcatheter hepatic arterial chemoembolization (TACE)<sup>[15]</sup>. Elevated CXCR7 promotes cell proliferation by serving as a cell cycle priming factor in that it induces the G0/G1 to S phase transition in HCC<sup>[53]</sup>. CXCR7 contributes to HCC growth by regulating phosphorylation on ERK1/2 at Thr202/Tyr203, p38 at Thr180/Tyr183 and SAPK/Jun kinase enzyme at Thr183/Tyr185 and invasiveness *via* the promotion of matrix metalloproteinase (MMP) 2 expression<sup>[15]</sup>. Treatment with the CXCR7 antagonist CCX771 significantly



**Figure 1 Mechanism of chemokine (C-X-C motif) receptor 7 promoting the growth and metastasis of gastric cancer.** Chemokine (C-X-C motif) receptor 7 (CXCR7) affects disease progression by stimulating proliferation, invasion, migration and adhesion of gastric cancer through  $\beta$ -arrestin dependent downstream signaling, including also known as Protein Kinase B, extracellular regulated protein kinases 1/2, p38 mitogen-activated protein kinases, just another kinase 2/ serial advanced technology attachment 3/ cellular-myelocytomatosis, and stress-activated protein kinase pathways by combining with the stromal cell-derived factor-1. CXCR7 inhibits the processing of poly ADP-ribose polymerase and caspase-3 and induces an anti-apoptotic effect. Stromal cell-derived factor-1 promotes the secretion of vascular endothelial growth factor in gastric cancer cells by binding CXCR7, thus causing angiogenesis in gastric cancer. CXCR7: Chemokine (C-X-C motif) receptor 7; Akt: Also known as Protein Kinase B, PKB; ERK1/2: Extracellular regulated protein kinases 1/2; MAPK: Mitogen-activated protein kinases; JAK2: Just another kinase 2; STAT3: Serial advanced technology attachment 3; c-Myc: Cellular-myelocytomatosis; SAPK: Stress-activated protein kinase; SDF-1: Stromal cell-derived factor-1; PARP: Poly ADP-ribose polymerase; VEGF: Vascular endothelial growth factor.

reduces the formation of phosphorylated ERK<sup>[53]</sup>. The orthotopic transplantation model found that CXCR7 affects lymphocytes entering the liver or intestine, and CXCR7 downregulation reduces SDF-1 levels in the bloodstream of mice, indicating that CXCR7 can regulate SDF-1 levels and have proinflammatory effects<sup>[53]</sup>. CXCR7 is closely associated with the differentiation of HCC. Activated CXCR7 can inhibit the transcription factor hepatocyte nuclear factor 4 by activating the ERK signaling pathway, thus causing the dedifferentiation of HCC. The CXCR7-MAPK-hepatocyte nuclear factor 4 $\alpha$  cascade is the main pathway for the differentiation of HCC cells<sup>[51]</sup>.

The lung is the most common site of distant metastasis of HCC. CXCR7 is a potential prognostic factor for lung metastasis of HCC, and a group with high expression of CXCR7 had a 1.6 times greater chance of lung metastasis than a group with low expression of CXCR7<sup>[49,52]</sup>. The group with high expression of CXCR7 showed a prominent short-term development of lung metastasis compared with the group with low expression of CXCR7, especially during the early stage of follow-up. The knockdown of CXCR7 inhibited lung metastasis of HCC in mice after TACE<sup>[15]</sup>. Although metastasis was unlikely to occur in well-differentiated HCC patients, metastasis was also likely to occur if CXCR7 was highly expressed in tumor tissues of well-differentiated HCC patients. The mechanism may be that activated transmembrane CXCR7 activates the Wnt signaling pathway through  $\beta$ -arrestin, causing osteopontin expression, which in turn stimulates the ability of tumor cells to metastasize<sup>[56]</sup>. In poorly differentiated tumors, CXCR7 was epigenetically controlled by recombinant suppressor of zeste 12 homolog. Studies have shown in liver cancer cells that the potential upstream regulators of CXCR7 are mainly tumor protein 53, IL-6 and IL-1 $\beta$ <sup>[53]</sup>. CXCR7 is the target protein of miR-101, and miR101 binds to polycomb repressive complex 2 to form a complex that promotes HCC migration and invasion by regulating CXCR7<sup>[64]</sup>. Forkhead box P3 silencing may inhibit the expression of SDF-1/CXCR7 and CXCL11/CXCR7 and may be associated with the inhibition of cell proliferation and migration as well as the induction of apoptosis<sup>[65]</sup>. Plumbagin can abolish SDF-1/CXCR4-CXCR7 activation and inhibit HCC cell proliferation,

differentiation, and invasion<sup>[65]</sup>. The mechanism of CXCR7 in HCC cell is shown in [Figure 2](#).

### **Angiogenesis of CXCR7 in tumor**

CXCR7 has a potential role in microvascular invasion in HCC, similar to observations in breast and lung tumors<sup>[52]</sup>. CXCR7 plays an important role in HCC migration and invasion of tumor endothelial cells. Chen *et al*<sup>[11]</sup> found that overexpressed CXCR7 could induce human umbilical vein endothelial cell luminal formation and migration and significantly induced the increase in the number of the chicken chorioallantoic membrane secondary and tertiary blood vessels. CXCR7 activation promotes angiogenesis by regulating VEGFA and galectin-3 in HCC *via* the MAPK signaling pathway<sup>[53]</sup>. CXCR7 promotes angiogenesis, and the expression of CXCR7 can induce the secretion of VEGF. VEGF can positively feedback to enhance further the expression of CXCR7. This process occurs through activating the AKT signaling pathway, and the expression of AKT target proteins, including human tumor necrosis factor- $\alpha$ , IL-6 and IL-8, is also induced by CXCR7<sup>[41]</sup>. Silencing CXCR7 can reduce tumor endothelial cell migration and invasion in HCC by inhibiting phosphorylated STAT3 at Tyr705 to influence the signaling pathway and its downstream genes MMP-2 and VEGF<sup>[66]</sup>. Plumbagin can inhibit the angiogenesis of HCC by blocking the PI3K/Akt signaling pathway to act on the biological axis of SDF-1/CXCR4-CXCR7<sup>[65]</sup>. The knockdown of CXCR7 significantly inhibits the elevation of VEGF and CD31 induced by TACE, thereby reducing tumor angiogenesis and preventing the growth of HCC<sup>[15]</sup>. The mechanism is shown in [Figure 3](#).

### **Role of CXCR7 in tumor prognosis**

However, for HCC, although *in vitro* experiments confirmed that both CXCR4 and CXCR7 can cause liver cancer cell lines to migrate under the action of SDF-1, there is no significant correlation between the expression of CXCR7 and the OS of cancer patients<sup>[50]</sup>. CXCR4 affects the prognosis of HCC patients, but CXCR7 does not<sup>[50]</sup>. The median survival time of the CXCR4<sup>+</sup>CXCR7<sup>+</sup> group, however, was significantly lower than that of the CXCR4<sup>+</sup>CXCR7<sup>-</sup> group of HCC patients after hepatectomy, especially during the early stage of follow-up<sup>[54]</sup>. However, CXCR7, particularly combined with alpha-fetoprotein level, was a valuable prognostic indicator for poor prognosis of HCC after hepatectomy, and elevated alpha-fetoprotein levels enhanced the prognostic roles of CXCR7 in time-to-lung metastasis and OS<sup>[54]</sup>. Silencing CXCR7 with RNA interference improved the efficiency of TACE treatment of HCC by extending the survival time of rats<sup>[15]</sup>.

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## **COLORECTAL CANCER**

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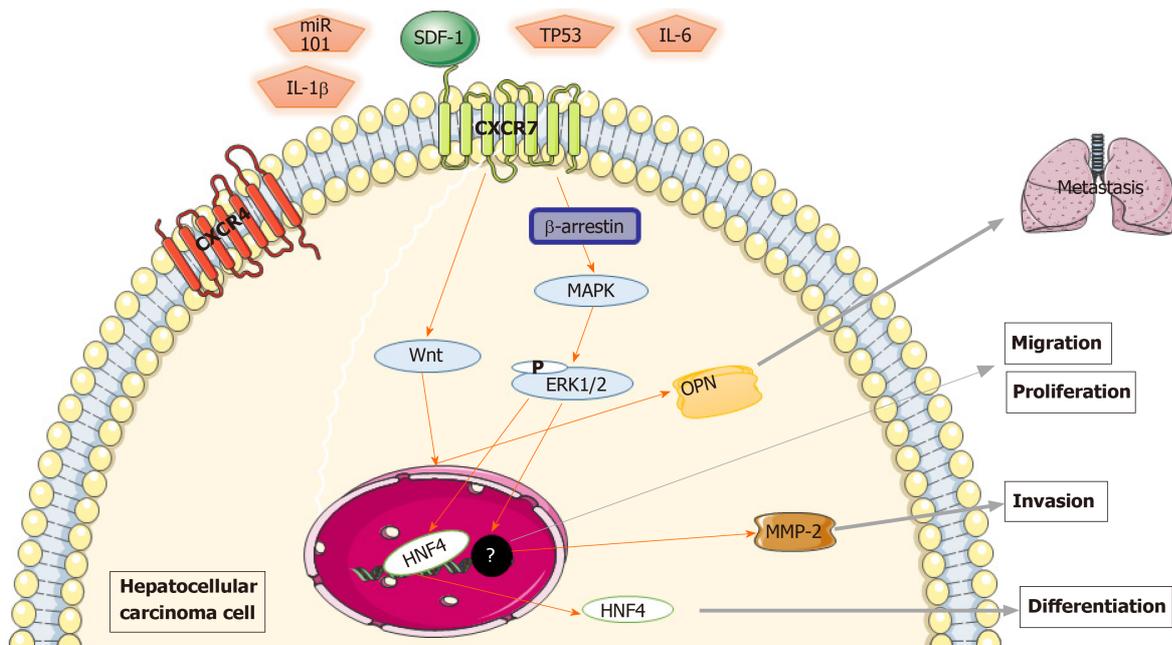
### **Expression in tumor tissue**

The expression of CXCR7 was evaluated in RKO, HCT116, SW480, CT26<sup>[36]</sup>, HT-29 and Caco-2 colorectal cancer (CRC) cells<sup>[13,37,38]</sup>, and CXCR7 localized to the cytomembrane in HT29 cells<sup>[38]</sup>; however, other researchers have found that CXCR7 is absent in HCT116 and HT-29 cells<sup>[37,39]</sup>. There was a significant upregulation of genes involved in lipid and fatty acid metabolism (*e.g.*, AKR1C3) in SW480-overexpressing CXCR7 cells<sup>[20]</sup> ([Table 2](#)).

CXCR7 is expressed in the cytoplasm of CRC cells<sup>[19]</sup>, but in HT-29 cells, CXCR7 localized to the cytomembrane<sup>[33]</sup>. The expression of CXCR7 in CRC cells was 4.2 times higher than that in healthy samples<sup>[19]</sup>. Analysis of a group of colonic polyps and chromosomal unstable cancers showed that the early expression of CXCR7 is similar to normal mucosa, but the cancer increases significantly from early to late stage<sup>[36]</sup>. The lower expression levels of CXCR7 in the proximal colon may indicate the role of CXCR7 in microsatellite instability, because colon cancer associated with microsatellite instability mainly occurs in the proximal colon<sup>[47]</sup>. The expression of CXCR7 protein can be detected near the relevant blood vessels of primary CRC and CRC with lung and liver metastases<sup>[52]</sup>.

### **CXCR7 in the development and metastasis**

CXCR7 is involved in the development, growth and metastasis of CRC<sup>[39]</sup>. When exposed to active oxygen method/dioctyl sodium sulfosuccinate, villin-CXCR7 mice showed more severe colitis and tumorigenesis than villin-CXCR4 mice<sup>[23]</sup>. The anti-apoptotic effect of CXCR7 was observed in human CRC, in which silencing the CXCR7 gene induced cell apoptosis and promoted CRC progression in CRC cells through ERK1/2 and  $\beta$ -arrestin pathway-mediated regulation of proliferating cell nuclear antigen, MMP-2 and caspase-3 expression<sup>[40]</sup>. CXCR7 regulates CRC growth independently of SDF-1<sup>[41]</sup> but binds to the ligand SDF-1 to participate in other CRC

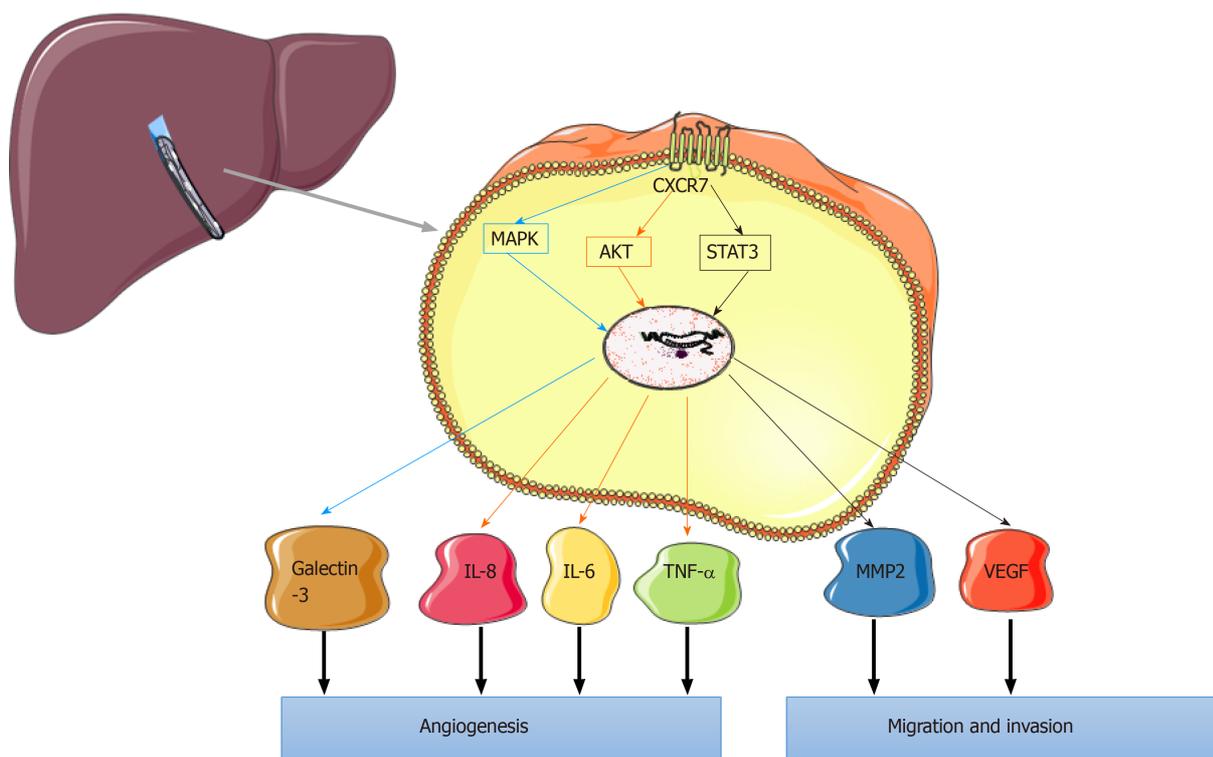


**Figure 2 Mechanism of chemokine (C-X-C motif) receptor 7 promoting the growth and metastasis of hepatocellular carcinoma.** Chemokine (C-X-C motif) receptor 7 (CXCR7) contributed to hepatocellular carcinoma growth, including extracellular regulated protein kinases 1/2, and invasiveness via the promotion of matrix metalloproteinase 2 expression; CXCR7- mitogen-activated protein kinases-hepatocyte nuclear factor 4 $\alpha$  cascade is the general pathway in the differentiation of hepatocellular carcinomas. Activated transmembrane CXCR7 activates the Wnt signaling pathway through  $\beta$ -arrestin, causing osteopontin expression, which in turn stimulates the ability of tumor cells to metastasize. Several regulators, including tumor protein 53, interleukin-6 and interleukin-1 $\beta$ , are potential upstream regulators of CXCR7-induced signaling. CXCR7: Chemokine (C-X-C motif) receptor 7; ERK1/2: Extracellular regulated protein kinases 1/2; MMP-2: Matrix metalloproteinase 2; MAPK: Mitogen-activated protein kinases; HNF4 $\alpha$ : Hepatocyte nuclear factor 4 $\alpha$ ; OPN: Osteopontin; TP53: Tumor protein 53; IL-6: Interleukin-6; IL-1 $\beta$ : Interleukin-1 $\beta$ .

processes, such as tumorigenesis and metastasis. CXCL11, another ligand of CXCR7, does not play a role in binding to CXCR7 during these CRC processes<sup>[20]</sup>. CXCR7 affected cell migration *in vitro* in colon cancer HT-29 cells and SW480 cells<sup>[38,39]</sup>, but silencing CXCR7 did not change the migration process nor activate PI3K/Akt or ERK/Ras signaling pathways. CXCR7 does not seem to directly induce cell migration but indirectly causes migration by enhancing cell adhesion<sup>[37]</sup>. In colon cancer, the proliferation of CXCR7 is greater than that of CXCR4, but there is no significant difference between CXCR7 and CXCR4 in migration<sup>[39]</sup>. Additionally, Zabel *et al*<sup>[25]</sup> showed that CXCR7, by mobilizing with  $\beta$ -arrestin instead of  $Ca^{2+}$ , regulated human CXCR7<sup>+</sup>/CXCR4<sup>+</sup> lymphoblastoid migration across endothelial monolayers.

When high concentrations of CXCR4 are expressed in circulating cells, it can help them to home to target organs with high expression of SDF-1, while the presence of CXCR7 helps extravasation of vascular endothelial cells, making these circulating cells easier to cross the endothelium, which is conducive to the occurrence of metastasis. In an animal model of CRC induced by LPS, TLR4 promotes the proliferation and migration of CRC cells by regulating the expression of CXCR7 instead of CXCR4<sup>[39]</sup>. Therefore, CXCR4 and CXCR7 seem to play different roles in colon cancer, and the role of CXCR7 in cell migration in colon cancer needs to be further studied.

Remote metastasis of liver and lungs is the main cause of death in CRC patients. CXCR7 expression is significantly associated with lymph nodal metastasis<sup>[39]</sup>, lung metastasis<sup>[5]</sup> and advanced Tumor Node Metastasis stage<sup>[42]</sup>. The expression level of CXCR7 in CRC with lymph node metastasis is significantly higher than that of CRC without lymph node metastasis. CXCR7 may be an important predictor of lymph node metastasis in CRC patients<sup>[43]</sup>. CXCR7 appears to be a key factor in the progression of colon cancer metastases in the lungs of mice. This systemic treatment with a CXCR7 antagonist strongly reduced tumor expansion within the lungs of both HT-29- and C26-inoculated mice<sup>[44]</sup>. In addition, in terms of distant metastasis, the expression level of CXCR7 mRNA in lung tissue is 12 times that of liver tissue<sup>[37,44]</sup>. CXCR7 ligands secreted by cancer cells such as SDF-1 can reach levels sufficient to cause paracrine in the lungs but not in the liver, which may further lead to the progression of tumor metastasis and/or worsening of the disease. The high expression of CXCR7 on the vascular endothelium can be seen in the lung tissue with colon cancer metastasis, so it can be explained that CXCR7 can directly and/or indirectly regulate the development of blood vessels in lung metastases after binding to ligand. Therefore, in lung metastases with colon cancer, unlike liver metastases, the



**Figure 3 Mechanism of chemokine (C-X-C motif) receptor 7 in angiogenesis of hepatocellular carcinoma.** Chemokine (C-X-C motif) receptor 7 (CXCR7) activation promotes angiogenesis by regulating vascular endothelial growth factor and galectin-3 in hepatocellular carcinoma via the mitogen-activated protein kinases signaling pathway. This process occurs through activating the also known as Protein Kinase B signaling pathway, and the expression of also known as Protein Kinase B target proteins, including human tumor necrosis factor- $\alpha$ , interleukin-6, and interleukin-8, is also induced by CXCR7; CXCR7 can promote tumor endothelial cells migration and invasion in hepatocellular carcinomas by phosphorylated serial advanced technology attachment 3 at Tyr705 to influence the signaling pathway and its downstream genes matrix metalloproteinase 2 and vascular endothelial growth factor. CXCR7: Chemokine (C-X-C motif) receptor 7; VEGF: Vascular endothelial growth factor; MAPK: Mitogen-activated protein kinases; Akt: Also known as Protein Kinase B, PKB; TNF $\alpha$ : Human tumor necrosis factor- $\alpha$ ; IL-6: Interleukin-6; IL-8: Interleukin-8; TEC: Tumor endothelial cells; STAT3: Serial advanced technology attachment 3; MMP-2: Matrix metalloproteinase 2; VEGF: Vascular endothelial growth factor.

level of SDF-1 is sufficient to trigger these synergistic effects, and the CXCR7 axis may mainly control tumor development in tissues with high expression of SDF-1<sup>[5]</sup>. CXCR7 antagonists have a good effect on lung metastasis of colon cancer but have no effect on liver metastasis<sup>[44]</sup>. However, there was also a correlation between CXCR7 and TLR2 expression in CRC liver metastasis patients, and *TLR2* and *CXCR7* are novel target genes repressed by HIC1<sup>[45]</sup>.

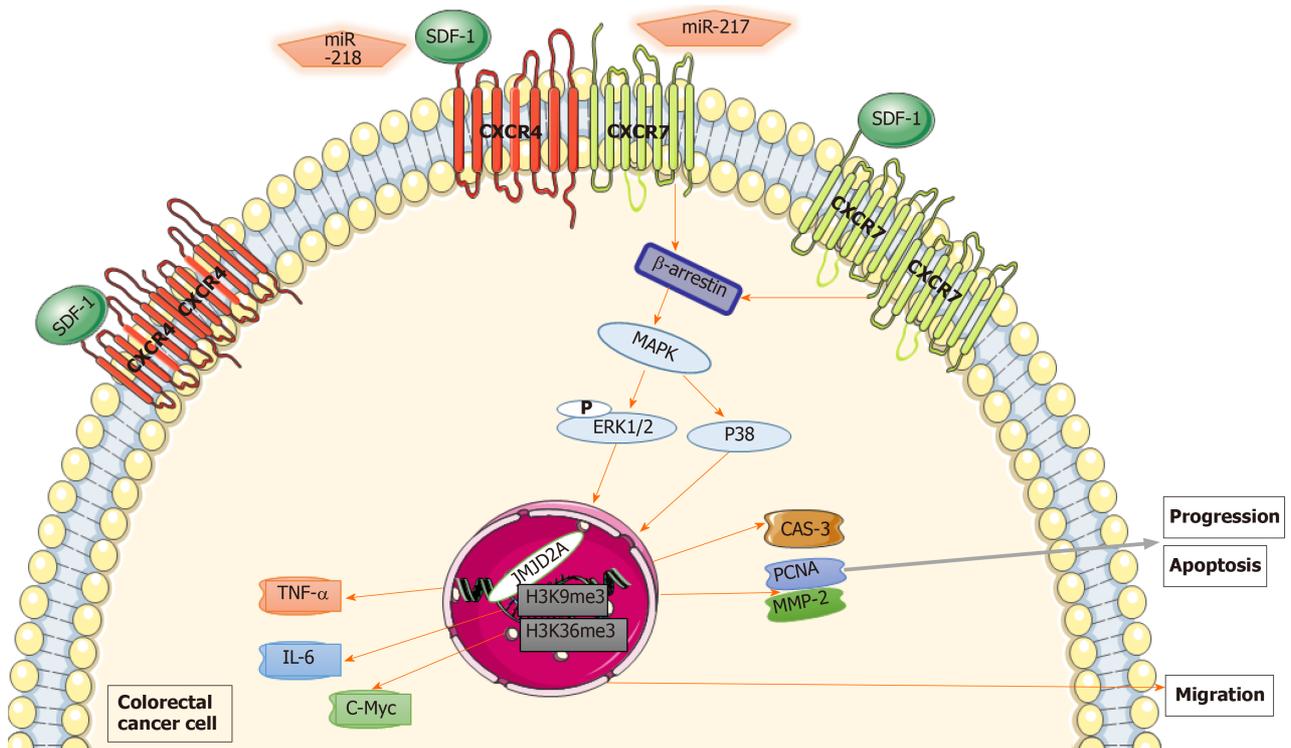
*AKR1C3* may be a potential downstream candidate regulatory gene for SDF-1/CXCR7 in the invasion pathway of colon cancer cells and might be a potential survival factor upon SDF-1 stimulation in CXCR7-overexpressing cells; miR-217, miR-218 and their targets may be regulatory molecules of CXCR4 or CXCR7<sup>[20]</sup>. Furthermore, combined expression of TLR4+MD-2+CXCR7 is more likely to result in lymph node metastasis and distant metastasis than each expression alone<sup>[39]</sup>. In the presence of SDF-1 secretion, although CXCR7-expressing colon cancer cell line SW480 was sensitive to 5-fluorouracil, CXCR4-expressing SW480 was more sensitive to 5-fluorouracil<sup>[20]</sup>. The mechanism of CXCR7 in colon cancer cell is shown in **Figure 4**.

### Angiogenesis of CXCR7 in tumor

CXCR7 regulates colon cancer angiogenesis by regulating the expression of VEGF through the AKT and ERK pathways<sup>[13]</sup>. CXCR7-silenced Caco-2 and SW480 cells, which were co-cultured with human umbilical vein endothelial cells, inhibited tube formation. CXCR7 regulates colon cancer angiogenesis independently of SDF-1<sup>[41]</sup>. In lung metastasis of CRC, CXCR7 has no regulatory effect on the expression of CXCL8 and VEGF at the transcription level, suggesting that CXCR7 directly regulates the growth of tumor blood vessels by binding to ligand<sup>[44]</sup>. CXCR7 was not modulated by hypoxia or HIF-1 $\alpha$  in colon carcinomas<sup>[37]</sup>.

### Role of CXCR7 in tumor prognosis

Patients with positive CXCR7 expression had worse OS and PFS than those with negative CXCR7 expression. Moreover, multivariate analysis with the Cox



**Figure 4 Mechanism of chemokine (C-X-C motif) receptor 7 promoting colorectal cancer growth and metastasis.** Chemokine (C-X-C motif) receptor 7 (*CXCR7*) gene induced cell anti-apoptosis and promoted colorectal cancer progression in colorectal cancer cells through extracellular regulated protein kinases 1/2 and  $\beta$ -arrestin pathway-mediated regulation of proliferating cell nuclear antigen, matrix metalloproteinase 2 and caspase-3 expression. miR-217, miR-218 and their targets may be regulatory molecules of Chemokine (C-X-C motif) receptor 4 (*CXCR4*) or *CXCR7*. The *CXCR7/CXCR4* heterodimer translocated much more  $\beta$ -arrestin 1 to the nucleus and then activated histone lysine demethylase to regulate *JMJD2A* expression via multiprotein complexes, selectively enriching the promoters of human tumor necrosis factor-alpha, interleukin-6, and cellular-myelocytomatosis, which might facilitate the recruitment of histone demethylases, resulting in enhanced local histone demethylation and transcription of these genes. The *CXCR7/CXCR4* heterodimer induced high levels of *JMJD2A*, leading to demethylation of histones H3K9me3 and H3K36me3 compared with the *CXCR7* monomer and *CXCR4* monomer. *CXCR7*: Chemokine (C-X-C motif) receptor 7; ERK1/2: Extracellular regulated protein kinases 1/2; PCNA: Proliferating cell nuclear antigen; MMP-2: Matrix metalloproteinase 2; CAS-3: Caspase-3; *CXCR4*: Chemokine (C-X-C motif) receptor 4; TNF $\alpha$ : Human tumor necrosis factor-alpha; IL-6: Interleukin-6; *c-Myc*: Cellular-myelocytomatosis.

proportional hazards model demonstrated that the status of *CXCR7* expression was an independent predictive factor for the OS and PFS of CRC patients<sup>[42]</sup>. Patients (neoadjuvant-treated CRC liver metastasis from a phase 2 clinical trial) overexpressing *CXCR7* displayed marginal significance with worse median PFS. *CXCR7* was not independent of PFS, but programmed death-ligand 1 T-helper cells and *CXCR4* were independently correlated with PFS<sup>[45]</sup>. Another study from Kheirleisid *et al*<sup>[47]</sup> showed that after a median follow-up of 15 mo, low *CXCR7* expression led to high mortality of CRC, with an average survival of 27 mo, while in CRC patients with high expression of *CXCR7*, the median survival time was 46 mo. Patients with high expression of *CXCR7* in tumor cells lived longer than those with low expression of *CXCR7*.

## CHOLANGIOCARCINOMA

### Expression in tumor tissue

*CXCR7* existed in many different cholangiocarcinoma (CCA) cell lines. All intrahepatic (HuCCT-1, SG231 and CCLP1) and extrahepatic (MzCha and TFK1) CCA cell lines expressed *CXCR7* at the protein level<sup>[12]</sup>. Its expression level was higher than that of untransformed bile epithelial cells. It is worth noting that the expression of *CXCR7* in all cell lines of intrahepatic CCA was higher than that of extrahepatic tumors or human intrahepatic biliary epithelial cells<sup>[12]</sup> (Table 2).

*CXCR7* is widely expressed in the cytoplasm of CCA cells<sup>[12]</sup>. The expression of *CXCR7* gene in tumor tissues was higher than that in surrounding non-tumor tissues, the expression level of *CXCR7* in larger tumors (> 50 mm) was higher than that in smaller tumors, and the expression of *CXCR7* in tumor tissues in moderate/poorly differentiation was higher than expression in well-differentiated tumors<sup>[12]</sup>.

### **CXCR7 in the development and metastasis**

The combination of CXCR7 and chemokine SDF-1 promotes many related phenotypic characteristics of CCA cells, potentially promoting cancer progression. CXCR7 contributes to SDF-1-induced migration, invasiveness, growth and survival of CCA cells<sup>[12]</sup>. CXCR7 mediates anti-apoptotic effects and induces CCA cell proliferation, and CXCR7 activation is necessary to maintain CCA cell survival.  $\beta$ -arrestin 2 is necessary for SDF-1-induced chemotaxis but dispensable for CXCR7-mediated CCA cell proliferation. Knockdown of CXCR7 expression results in reduced gene expression of MMP-2, MMP-9 and VEGF<sup>[12]</sup>. CXCR7 expression is associated with the maintenance of a stemness-like status in CCA cells. CXCR7 can serve as a factor in the regulation of VEGF secretion and induce angiogenesis in CCA<sup>[12]</sup>.

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## **PANCREATIC ADENOCARCINOMA**

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### **Expression in tumor tissue**

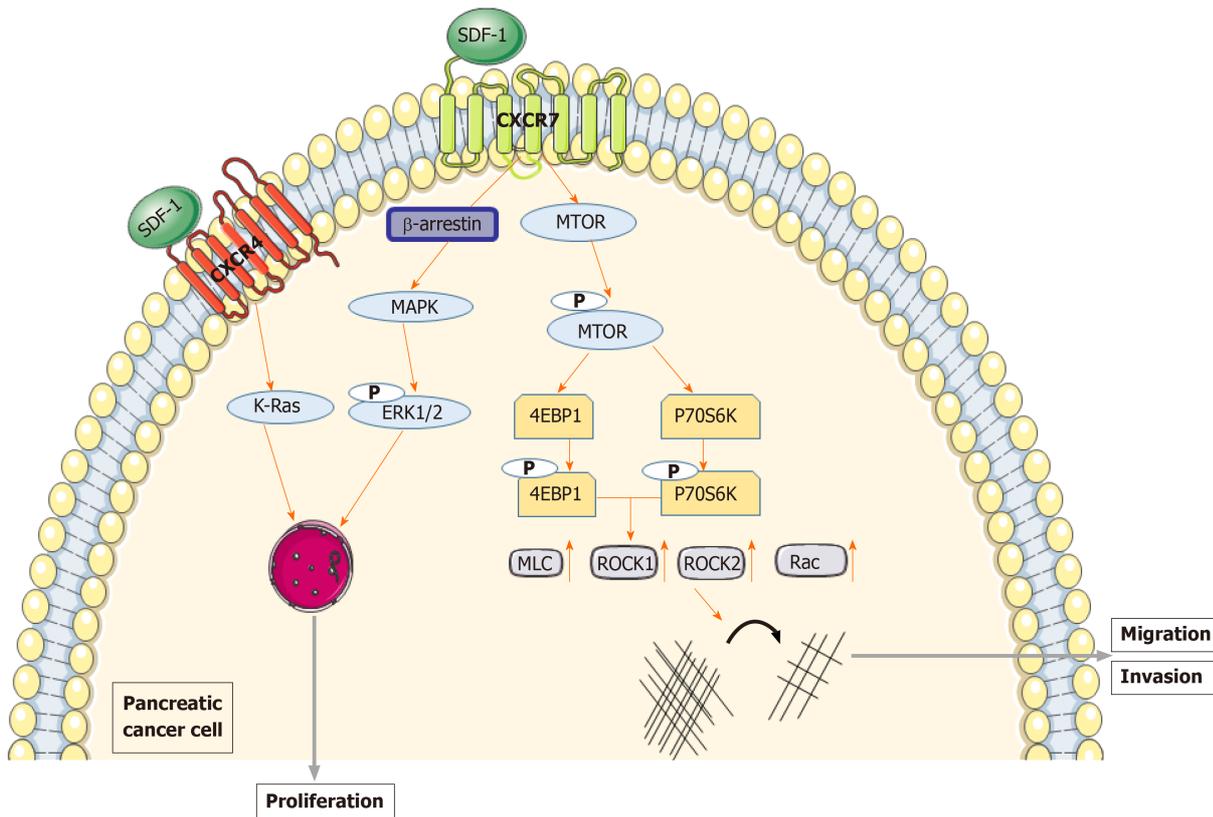
CXCR7 expression was detected in pancreatic cancer (PAC) cell lines (AsPC-1, MiaPaCa-2, FG, PANC-1, SU.86.86, HS-766 T and BxPC-3)<sup>[58,62]</sup> (Table 2). The expression of CXCR7 is cytoplasmic, but staining is also visible on the cell surface by immunohistochemistry in PAC<sup>[59]</sup>. In normal pancreatic tissues surrounding the pancreatic cancer, no expression of CXCR7 was seen in either pancreatic acinar or ductal cells. In PAC tissues, strong positive expression of CXCR7 was seen on tumor-associated vascular endothelial cells, but CXCR7 expression was not seen in the vascular endothelium of normal pancreatic tissue around the tumor. Co-expression of CXCR7 and CXCR4 was observed in PAC cells<sup>[62]</sup>.

### **CXCR7 in development and metastasis**

The CXCR7 receptor may be involved in the progression and metastasis of pancreatic adenocarcinoma and might be useful as an index for evaluating invasiveness<sup>[3,59,60]</sup>. The larger the tumor diameter and the lower the differentiation level, the higher the expression level of CXCR7. At the same time, CXCR4 also showed the same expression trend in PAC, suggesting that these two receptors have some functional connection in PAC<sup>[59]</sup>. CXCR7 is related to lymph node metastasis of PAC<sup>[60]</sup>. However, another study found that CXCR7 expression is not associated with tumor size, histological grade, Tumor Node Metastasis stage or distant metastasis in PAC<sup>[60]</sup>. After CXCR7 and SDF-1 activation,  $\beta$ -arrestin 2 induces ERK1/2 phosphorylation, leading to PAC cell proliferation<sup>[62]</sup>. CXCR7 binds to SDF-1 to enhance the migration and invasion of PAC cells by activating the mammalian target of rapamycin and Rho/Rho associated coiled-coil forming protein kinase signaling pathways<sup>[3]</sup>. Pancreatic stellate cells and transforming growth factor  $\beta$  play a role in this process, which also involves CXCR1/CXCL8 signaling<sup>[67]</sup>. Transforming growth factor receptor  $\beta$  upregulated the expression of CXCR4, CXCR4/CXCR7/SDF-1 biological axis activated Hedgehog pathway to activate tumor cells *in vitro* to achieve epithelial mesenchymal transformation<sup>[68]</sup>. The mechanism of CXCR7 in pancreatic adenocarcinoma cell is shown in Figure 5.

### **Role of CXCR7 in tumor prognosis**

Through statistical analysis of pancreatic adenocarcinoma, a single analysis showed that there is no relation between the expression of CXCR7 and OS or disease free survival<sup>[59]</sup>. Analysis of the relationship between SDF-1 and CXCR7 expression and prognosis found that the median survival time of the SDF-1<sup>+</sup>CXCR7<sup>+</sup> group was 6 mo, and the median survival time of the SDF-1<sup>+</sup>CXCR7<sup>-</sup>/SDF-1<sup>-</sup>CXCR7<sup>+</sup> group was 9 mo. The median survival time of the SDF-1<sup>-</sup>CXCR7<sup>-</sup> group was 10 mo. The survival time of the SDF-1<sup>+</sup>CXCR7<sup>+</sup> group was significantly shorter than that of the SDF-1<sup>+</sup>CXCR7<sup>-</sup>/SDF-1<sup>-</sup>CXCR7<sup>+</sup> group and the SDF-1<sup>-</sup>CXCR7<sup>-</sup> group<sup>[60]</sup>. However, several studies have also reported opposite results. Guo *et al.*<sup>[3]</sup> conducted a follow-up study on 429 patients with PAC and found that patients with high expression of CXCR7 had a worse prognosis, suggesting that CXCR7 was an independent prognostic factor affecting the survival of PAC patients. Therefore, in order to confirm the value of CXCR7 in the prognosis of pancreatic cancer, a larger, multi-center study involving patients at all stages is necessary. In addition, the specific role of SDF-1/CXCR4/CXCR7 axis in PAC and the relationship between them need to be further studied.



**Figure 5 Mechanism of chemokine (C-X-C motif) receptor 7 promoting the growth and metastasis of pancreatic cancer.** After chemokine (C-X-C motif) receptor 7 and stromal cell-derived factor-1 activation,  $\beta$ -arrestin 2 induces extracellular regulated protein kinases 1/2 phosphorylation, leading to pancreatic cancer cell proliferation. Chemokine (C-X-C motif) receptor 7 binds to stromal cell-derived factor-1 to enhance the migration and invasion of pancreatic cancer cells by activating the mammalian target of rapamycin and Rho/Rho associated coiled-coil forming protein kinase signaling pathways. CXCR7: Chemokine (C-X-C motif) receptor 7; SDF-1: Stromal cell-derived factor-1; ERK1/2: Extracellular regulated protein kinases 1/2; mTOR: Mammalian target of rapamycin; Rho/ROCK: Rho/Rho associated coiled-coil forming protein kinase.

## THE CHEMOKINE (C-X-C MOTIF) RECEPTOR 7 AND CHEMOKINE (C-X-C MOTIF) RECEPTOR 4 INTERACTIONS IN DIGESTIVE TRACT TUMORS

Whether the effects and dependence on CXCR4 and CXCR7 signaling in some tumors are reflective of individual differences and/or the presence of different subpopulations of tumor cells cannot be answered unequivocally at this point. CXCR7 and CXCR4 may be expressed in distinctive tumor cell populations, such as in breast cancer<sup>[69]</sup> and glioma<sup>[70]</sup>. Currently, in tumors of the digestive system, such as HCC, CRC and PAC, both receptors are expressed in the same cell<sup>[23,36,49,60]</sup>. CXCR4 and CXCR7 have been studied most thoroughly in terms of their presentation and function in colon cancer, and the existence and mechanism of CXCR4 and CXCR7 have not been reported in other digestive system tumors. Confocal live imaging results illustrated the colocalization of CXCR7 and CXCR4 upon SDF-1 internalization and endocytosis<sup>[23]</sup>. CXCR4/CXCR7 heterodimer is highly expressed in 65% of CRC patients, suggesting that this heterodimer may be widely expressed in cancer cells. The CXCR4/CXCR7 heterodimer could enhance SDF-1 mediated signaling; therefore the CXCR4/CXCR7 heterodimer played a stronger role than CXCR4 or CXCR7 homodimers in promoting the tumorigenesis. The CXCR7/CXCR4 heterodimer increased the infiltration of M-myeloid-derived suppressor cells and M2-like macrophages in colonic tissues<sup>[23]</sup>.

The CXCR7/CXCR4 heterodimer drove colorectal tumorigenesis by increasing histone demethylation by activating lysine demethylase. The CXCR7/CXCR4 heterodimer translocated much more  $\beta$ -arrestin 1 to the nucleus and then activated histone lysine demethylase to regulate *JMJD2A* expression *via* multiprotein complexes, selectively enriching the promoters of tumor necrosis factor-alpha, IL-6 and c-Myc, which might facilitate the recruitment of histone demethylases, resulting in enhanced local histone demethylation and transcription of these genes. The CXCR4/CXCR7 heterodimer induced elevated levels of *JMJD2A*, resulting in the

demethylation of histones H3K9me3 and H3K36me3. In this process, the role of heterodimer is stronger than that of CXCR7 monomer and CXCR4 monomer<sup>[23]</sup>.

Heckmann *et al*<sup>[20]</sup> found that differential expression in SW480-overexpressing CXCR4/CXCR7 cells was similar to that in SW480-CXCR4 cells, indicating that CXCR4 signaling dominates CXCR7 signaling. Very few genes (*e.g.*, troponin C type 1 and *RRAS*) showed SDF-1-dependent upregulation simultaneously in SW480 cells overexpressing CXCR7 and SW480 cells overexpressing CXCR4/CXCR7, with contrasting weak expression of recombinant troponin C type 1 or similar increased expression of *RRAS* in SW480 cells overexpressing<sup>[20]</sup>. In short, even in similar CRC studies, the research results of different research groups of CXCR4 and CXCR7 are inconsistent. In the future, scientists need to continue research in this field.

## TARGETING CXCR7 WITH ANTIBODIES

CXCR7 has become increasingly important in various diseases, especially in tumors, and many targeted drugs have been developed against it. Scientists from Chem-Centryx filed several patents to cover CCX733, CCX754 and CCX771 as SDF-1/CXCR7 ligands<sup>[70,71]</sup>. There are now three nanoantibodies targeting CXCR7, namely NB1-3, which all exhibit the substitution properties for SDF-1. NB1 can only partially inhibit the binding of SDF-1 and CXCR7, but NB2 and NB3 can completely inhibit the binding of SDF and CXCR7 by inhibiting the recruitment of SDF-1 to  $\beta$ -arrestin 2<sup>[72]</sup>. The use of small interfering RNA variant (siCXCR7) as well as CCX733 (a CXCR7 antagonist) suppressed the proliferation of long-term estrogen deprivation cells<sup>[73]</sup>. Because SDF-1/CXCR4 has been studied in various diseases for a long time, researchers have studied the role of SDF-1/CXCR4 in cancer cells thoroughly. The antagonist AMD3100 (Plerixafor) designed for the target of CXCR4 has been approved by the United States Food and Drug Administration for the treatment of lymphoma and multiple myeloma<sup>[74]</sup>. Sorafenib combined with AMD3100 prevented the increase of liver tumor fibrosis and improved the efficacy of sorafenib in the treatment of HCC patients<sup>[75]</sup>. The combination of three groups of immuncheckpoint inhibitor anti-programmed cell death protein-1 antibody in the treatment of AMD3100 and sorafenib enhanced the anti-tumor immune response by increasing lymphocyte immune cell infiltration in the necrotic area of HCC, leading to extensive tumor necrosis<sup>[76]</sup>. To our knowledge, no preclinical or clinical studies of therapeutic monoclonal antibody against CXCR7 have been reported.

## CONCLUSION

In the current review, we demonstrate that CXCR7 plays a key role in tumors of the digestive system. From these studies, we can see that the study of CXCR7 in the digestive system still needs to be continued and that the study of CXCR7 in digestive system tumors mainly focuses on HCC and CRC. CXCR7 has different roles and mechanisms in different organs. Even within the same organ, researchers disagree on the function and mechanism of CXCR7. The complex relationship of biological functions and mechanisms between SDF-1/CXCR4/CXCR7, the localization of CXCR4 and CXCR7 in cells and the functional role of CXCR7 in other types of cancer in digestive tract tumors except CRC have not been studied, so this should form the basis of future research.

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