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CXCR2: a target for pancreatic cancer treatment?

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Abstract

Introduction—Pancreatic cancer, a leading cause of cancer deaths worldwide, is very aggressive and has minimally effective treatment options. For those who have no surgical options, medical treatments are limited. The chemokine receptor CXCR2 has become the subject of much interest recently because of multiple studies indicating its involvement in cancer and inflammatory conditions. Research now indicates that CXCR2 and its ligands are intimately involved in tumor regulation and growth and that inhibition of its function shows promising results in multiple cancer types, including pancreatic cancer.

Areas covered—In this study, the authors review basic molecular and structural details of CXCR2, as well as the known functions of CXCR2 and several of its ligands in inflammation and cancer biology with specific attention to pancreatic cancer. Then the future possibilities and questions remaining for pharmacological intervention against CXCR2 in pancreatic cancer are explored.

Expert opinion—Many current inhibitory strategies already exist for targeting CXCR2 *in vitro* as well as *in vivo*. Clinically speaking, CXCR2 is an exciting potential target for pancreatic cancer; however, CXCR2 is functionally important for multiple processes and therapeutic options would benefit from further work toward understanding of these roles as well as structural and target specificity.

Keywords

chemokine receptor; CXCR2; inflammation; pancreatic cancer

1. Background

Pancreatic ductal adenocarcinoma (PDAC) is a lethal disease with few treatment options available from the field of oncology. At diagnosis, most patients have metastatic disease with a median survival of 6 months after diagnosis, and 5-year survival is ~ 5% [1]. Because the disease is often metastatic at the time of diagnosis, candidates for surgical resection are rare (15 – 20%), and PDAC is characterized by a phenotype that is relatively resistant to current chemotherapy and radiotherapy regimens. Even with successful resection, 5-year survival for patients with pancreatic cancer approaches only 35% because of early relapse and metastatic recurrence of the disease [2].

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Declaration of interest

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Current therapy includes surgical resection for local disease and chemotherapy with gemcitabine, a nucleoside analog first recognized to improve survival in pancreatic cancer patients in randomized trials in 1997 [3]. Standard of care for those with early disease is surgical resection followed by 6 months of adjuvant gemcitabine. Those patients with metastatic disease at discovery are started on palliative chemotherapy [4]. Patients with locally advanced disease and no obvious metastases may undergo chemotherapy or possibly chemoradiation with surgical resection after medical therapy. Many recent trials attempting to identify better chemotherapeutic regimens focus on combinations of gemcitabine with other cytotoxic agents with no clear significant benefit in overall survival except with platinum derivatives or fluoropyrimidines specifically in those patients with good performance status [5,6]. In addition, many targeted agents, including antiangiogenic drugs, such as bevacizumab (a vascular endothelial growth factor antibody), and multikinase inhibitors with antiangiogenic activity, have shown no benefits in clinical trials [7–9]. One bright spot on the horizon is FOLFIRINOX (a combination of leucovorin, fluorouracil, irinotecan and oxaliplatin). In a multicenter trial, this combination was recently shown to improve overall survival to 11.1 months as opposed to 6.8 months with gemcitabine alone in patients with metastatic pancreatic cancer and good performance status [10].

Current research toward better treatment of pancreatic cancer has focused on earlier detection and better chemotherapeutics. The failure of the chemotherapeutics now routinely involved in PDAC treatment necessitates alternative targets and the exploration of other mechanisms. As such, drug delivery has become an increasingly hot topic, as one hypothesis for poor chemotherapeutic response is that the desmoplastic stroma encircling the tumor blocks entry of currently used drugs. Alternatively, much attention has also been focused on new targets, including downstream signaling cascades, tumor vasculature and immune response modulators.

Tumor biology has increasingly begun to include immunology as an important factor in growth, development and metastasis. Indeed, chronic inflammation has been linked to multiple disease processes, including cardiovascular, diabetes, rheumatoid arthritis, Alzheimer's disease (AD), and autoimmune diseases in addition to cancer. Inflammation has been associated with carcinogenesis with several types of cancer by multiple epidemiological studies and is linked with an estimated 15 – 20% of all cancer deaths worldwide [11]. Ulcerative colitis increases colorectal cancer risk by 20-fold; a risk that is reduced by 50% with NSAIDs [12,13]. Patients with a history of pancreatitis have a sevenfold increased risk for PDAC [14]. Prostatitis is associated with prostate cancer. Inflammatory diseases increase the risk of many other types of cancer, including bladder, cervical, gastric, intestinal, esophageal, ovarian and thyroid cancer. There is increasing molecular evidence that the tumor microenvironment and inflammation go hand in hand. Inflammatory cells and markers have been identified in the microenvironments of most tumors. This inflammation is characterized by leukocyte infiltration, including tumor-associated macrophages, mast cells, dendritic cells, natural killer (NK) cells, neutrophils, eosinophils and lymphocytes [15]. Chronic inflammation can drive tumorigenesis, and leukocytes are thought to be critical for tumor maintenance/progression [16,17]. Macrophages are believed to be an important contributor to this environment and tumor promotion. Crosstalk between tumor cells and macrophages encourages a trophic role facilitating angiogenesis, matrix breakdown and tumor cell mobility and is a source of possibly mutagenic compounds. In addition, tumors are significantly altered by non-malignant cells, and inflammatory mediators are not alone in this role as adipocytes and fibroblasts also populate this environment [18]. Molecules important for inflammatory tumorigenesis have considerable potential for understanding and targeting this pathological process. Also of interest to tumor biology is the role of inflammatory cells, including myeloid-derived suppressor cells (often referred to as CD11b⁺Gr1⁺ cells in mice). These

cells were first described ~ 20 years ago and are a heterogeneous population that encompass progenitors and precursors of myeloid cells with upregulated immune suppressive activity that can rapidly expand in pathological states, including cancer. There are many subsets and roles for these cells that are beyond the scope of this review. However, the importance of these myeloid cells lies in their contribution to tumor progression by suppressing the antitumor functions of T cells and NK cells and, once recruited, by encouraging angiogenesis [19–21].

As can be imagined, the vast breadth and depth of the immune system leads to multiple potential roles and therapeutic targets. One target of intense interest is the chemokine receptor family member, CXCR2. Multiple studies to date have shown that CXCR2 participates in chronic inflammation, sepsis, lung pathology, atherosclerosis, neuroinflammation and critical roles in angiogenesis, tumorigenesis and metastasis of colorectal cancer, melanoma, lung cancer, prostate cancer, pancreatic cancer as well as head and neck cancers [22–38]. Because of its potentially powerful applications and because of the current poor treatment modalities, there has been a flurry of activity toward a better understanding of the role of CXCR2 in pancreatic cancer.

CXCR2 is a G-protein-coupled cell surface chemokine receptor commonly found on neutrophils. The chemokine receptors are subcategorized based on binding capacities for specific chemokines and are thus named according to the type of chemokines they bind. Chemokine nomenclature refers to the number of cysteine residues as well as their position. The chemokine subfamilies include C, CC, CXC and CX₃C chemokines. For example, for the CC chemokine family, the first two cysteines are adjacent, whereas in the CXC chemokine family, the first two cysteines are separated by one non-conserved amino acid residue [39,40]. Thus, CXC chemokines bind to CXC chemokine receptor proteins. The chemokine receptor superfamily contains at least 19 known family members (including C, CC, CXC and CX₃C receptors) [23,41]. CXCR2 is one of seven known CXC receptors and was cloned in 1991 from a human neutrophil cell line as a binding partner for IL-8 (CXCL8). CXCL8, a chemokine first described by Matsushima *et al.* in 1988, and its cleavage products are some of the most potent ligands for CXCR2 [42,43]. However, multiple other high-affinity binding partners have now been identified, including CXCL1, 2, 3, 5, 6 and 7 [44].

Classically, CXCR2 is a key regulator in recruitment and response of the immune system and has been shown to mediate neutrophil migration to sites of inflammation [45,46]. In addition to being expressed on neutrophils, CXCR2 has also been found on mast cells, monocytes and macrophages. Furthermore, CXCR2 has been found on endothelial cells where it mediates angiogenesis, epithelial cells and multiple tumor cells and can be induced by activated oncogenes [47–49]. Expression of CXCR2 has been characterized in the normal tissues of the pituitary gland, the adrenal medulla, pancreatic islets cells, thyroid C cells, scattered Kulchitsky cells of the bronchi, as well as neuroendocrine cells in the stomach, small bowel, colon and appendix [50].

2. CXCR2 structure

Chemokine receptors, such as CXCR2, are composed of ~ 350 amino acids and share 25 – 80% identity [44]. These proteins are G-protein-coupled receptors (GPCRs) with seven transmembrane domains comprised of three extracellular and three intracellular domains (Figure 1). The N-terminal domain is extracellular and is involved in chemokine binding. It is also important for receptor triggering via a tyrosine sulfation motif [41,44]. The C-terminal segment of the receptor is intracellular. Other important domains include an aspartate residue in the second extracellular loop and a LLKIL motif within the C terminus,

both required for rapid receptor internalization. The G-protein docking site, which is within the second intracellular loop is composed of a DRY motif and is responsible for intracellular downstream signaling [51,52]. In addition, the second intracellular loop contains a conserved 10 amino acid sequence and each extracellular domain contains a characteristic cysteine residue. Multiple studies have contributed a wealth of structural information beginning with the first crystallized GPCR, rhodopsin, in 2000 [53]. Since then, other GPCR structures have been solved, including adrenergic, adenosine and the CXCR4 and CXCR1 chemokine receptors, with some structures complexed to ligands [54]. However, the crystal structure of CXCR2 has not yet been solved.

3. CXCR2 ligands: the CXC chemokines

Chemokines are low molecular weight chemotactic cytokines and classically function as chemoattractants for leukocytes. They are of particular interest in cancer biology as they are thought to play roles in the development of tumors and metastases by modifying the tumor immune response, controlling leukocyte infiltration, serving as growth factors and regulating angiogenesis [55–57]. As previously mentioned, classification of these molecules into subfamilies is based on the first two conserved cysteine residues. Further classification of the CXC chemokines is typically based on the presence or absence of the ELR motif of the 8 – 14 kD peptide [58,59]. This motif is a three amino acid (Glu-Leu-Arg) segment located in the N terminus. The ELR⁺ chemokines (including CXCL1, 2, 3, 4, 5, 6, 7 and 8) tend to be angiogenic and often act through the CXCR2 receptor, whereas the ELR⁻ chemokines (CXCL 9, 10, 11, 12, 13, 14 and 16) tend to be inhibitors of angiogenesis and often, though not always, act through the CXCR3 receptor. For example, CXCL12 has been implicated in angiogenesis through CXCR4 [60]. Specifically CXCL1, 2, 3, 5, 6, 7, and 8 have been extensively studied and are known to be proangiogenic through CXCR2 in several types of cancer. The ELR⁺ CXC ligands appear to have equal CXCR2 binding properties and neutrophil attractant properties [61]. They are not expressed in normal pancreatic tissue. However, in instances of inflammation, the pancreas has been shown to express CXC chemokines (CXCL5, CXCL8, as well as CXCL9) [62]. Of note, researchers have shown that pancreatic cancer cell lines, as well as other cancer cell lines, secrete chemokines, such as CXCL8 and CXCL1, which have mitogenic effects *in vitro* [40,63]. In addition, several chemokines are overexpressed in human pancreatic cancers and have been associated with poor survival [36,37]. Also of potential interest is macrophage migration inhibitory factor (MIF), an inflammatory cytokine and binding partner of both CXCR2 and CXCR4. MIF has been implicated in neutrophil recruitment, T-cell recruitment, fibroblast migration and tumor angiogenesis in a mouse melanoma model.

4. CXCR2 signaling pathways

Signaling pathways regulated by chemokines lead to a variety of different cellular responses, including adhesion, migration, chemotaxis, change in cell morphology, cytoskeletal rearrangement and integrin expression upregulation or activation [64]. The molecular aspects leading to the downstream signaling cascade stem from the activation of the associated G protein whereby the α -subunit and $\beta\gamma$ -complex dissociate and activate or inhibit downstream targets (adenylyl cyclase, cAMP-dependent protein kinase, other GTPases, PI3K, phospholipase C and so forth) (Figure 2) [65–67]. Chemokine receptors are activated first by binding by their ligands (reviewed above). Although no studies are yet available showing the interaction of CXCR2 with its chemokine binding partners, information does exist regarding modeling studies of CCR2 and structural studies of CXCR4 as well as other chemokine receptors [68,69]. Binding of the chemokine to the GPCR involves interaction of the N terminus of the chemokine with the N terminus of the receptor. The ELR⁺ motif is thought to interact with the second and third extra-cellular loops

of the receptor. The N-terminal domain of the receptor is important for receptor selectivity and affinity and the ELR⁺ motif allows for stabilization of the binding interaction and further activation downstream [70,71]. Once ligand binding has occurred, the associated G-protein is activated and dissociates leading to downstream activation of phospholipase C and a number of other signaling pathways depending on the chemokine and the chemokine receptor involved. After ligand binding, the receptor itself is internalized, a process that is dependent on the N terminus of the chemokine and the N terminus of the chemokine receptor [72]. Efficiency of internalization and determination of the downstream signaling pathway relies on the C terminus of the receptor [73]. The specific signaling pathway of CXCR2 has been elucidated in neutrophils by Wu *et al.* who showed that CXCR2 forms a macromolecular complex with the PDZ scaffold protein NHERF1 and its downstream effector phospholipase C (PLC)- β 2 leading to intracellular calcium mobilization [74]. Responses to receptor activation can lead to chemotaxis and degranulation as well as transcriptional activation [58,75]. CXCR2 (as well as closely related receptor CXCR1) have been implicated in Rho, Rac and mitogen-activated protein (MAP) kinase signaling pathways which in turn are linked to cell growth and migration [76–81].

5. CXCR2 in normal physiology

In normal physiology, CXCR2 is known to regulate neutrophil homeostasis as well as recruitment and release from the bone marrow as part of a response to acute inflammation and injury [82–84]. Blocking CXCR2 leads to reduced leukocyte recruitment, tissue damage and mortality. Germline knockouts of CXCR2 (Cxc2^{-/-}) have a profound defect in neutrophil mobilization to sites of inflammation during acute injury as well as neutrophilia [46]. CXCR2 is also thought to be important for wound healing in the periphery via neutrophil recruitment and there is evidence that CXCR2 may have differing functions depending on location as Cxc2^{-/-} mice can still localize neutrophils to the CNS in response to inflammatory demyelination similar to wild-type mice [85,86].

6. CXCR2 in disease

It is difficult to consider all of the functional roles of CXCR2 in cancer without first recognizing the effects of CXCR2 signaling in other disease processes, especially as understanding these processes may allow us to clarify the role of CXCR2 in cancer. CXCR2 has been implicated in many disease systems and has been considered as a therapeutic target for multiple pathologies. CXCR2 has been accepted as important in acute lung injury (ALI), asthma, chronic obstructive pulmonary disease (COPD) and cystic fibrosis (CF). In at least several of these conditions, CXC chemokines and CXCR2 expression are increased and important roles have been identified. For example, in animal models of ALI, exposure to hyperoxic gas/ventilator-induced injury leads to neutrophil recruitment, increased airway microvascular leakage and lung edema [87–90]. Animals treated with a CXCR2 neutralizing antibody leads to reversal of these changes in ALI. In an animal model of COPD, inhibition of CXCR2 leads to decreased mucous secretion as well as decreased goblet cell hyperplasia [91–93]. In asthma, CXCR2 has been shown to be important in the response to viral and bacterial infections during asthma exacerbations and may play a role in the development of bronchial hyperresponsiveness and increased vascularity. In CF, where decreased lung clearance is a clear cause of pathology and recurrent lung infections with bacterial pathogens are common, studies indicate that CXCR2 may be involved in mucous hypersecretion as well as proliferation of mucous-secreting cells.

CXCR2 is also believed to play an important role in sepsis. In severe sepsis, the immune system may contribute to organ dysfunction via the inappropriate activation and migration of neutrophils. When compared to control donor neutrophils, investigators have found that

septic patients had decreased expression of CXCR2, and that these neutrophils also displayed reduced migratory activity in response to CXCR2 ligands than healthy controls [94]. However, blocking CXCR2 in sepsis led to decreased liver injury and mortality in a mouse model, but did not affect bacterial clearance [95].

Ischemia-reperfusion injury is of particular importance to multiple diseases and transplantation biology. Decreased metabolic supply leads to tissue hypoxia, microvascular dysfunction and the accumulation of inflammatory cells (predominantly neutrophils) as well as tissue injury. Blocking neutrophil recruitment or neutrophil depletion leads to positive effects and decreased tissue injury [96–99]. Specifically CXCR2-deficient mice showed decrease in myocardial infarct size in mice [100]. Inhibiting CXCR2 in a kidney transplant model reduces neutrophil accumulation and maintains function of the graft in ischemia/reperfusion models [101].

Neuroinflammation is also within the domain of CXCR2. Multiple sclerosis, traumatic brain injury (TBI) and AD are all associated with presence of chemokines and chemokine receptors [23]. The role of CXCR2 in neuroinflammation appears to be mostly harmful, as CXCR2 and associated chemokines may be associated with plaque deposition and may enhance pathology in AD. In addition, in a TBI model with *Cxcr2*^{-/-} mice, neuronal loss and tissue damage is attenuated [102–104].

7. CXCR2 in cancer

Demonstration of a potential role of CXCR2 ligands in cancer was established early on with extraction of CXCL1, 2, and 3 from tumor-derived human melanoma cells, and the discovery of evidence of their involvement in melanoma cell growth [105]. At this time, many CXCR2 ligands have been implicated in growth, blood vessel formation and proliferation of tumors as well as in neutrophil recruitment to the site of the tumor [106,107]. In addition, high expression of CXCR2 has been noted within neuroendocrine neoplasms, such as primary carcinoids in stomach, small bowel, colon, appendix, fallopian tube, ovary, lung, as well as atypical carcinoids of the lung, metastatic carcinoids, pituitary adenomas, pheochromocytomas and medullary carcinomas of thyroid of human tissue [50]. IL-8 (CXCL8) and/or CXCR2 overexpression either by molecular quantification or immunohistochemistry has been noted in other cancers, including renal (localizing to vascular endothelial cells), prostate (localizing to prostate cancer cells), pancreatic (localizing to pancreatic epithelial cancer structures), and nasopharyngeal (localizing to tumor and stromal cells) cancers [30,37,108,109].

Beyond expression patterns, there is clear evidence that CXCR2 and its associated ligands are important for multiple disease processes and multiple cancers. CXCR2 has also been found to be involved in primary brain tumor growth and development [110]. In addition, in a mammary gland tumor model of breast cancer, it has been shown that macrophages have increased expression of inflammatory chemokines that bind CXCR2 and that macrophages are capable of promoting epithelial and tumor cell migration as well as invasion through the activation of CXCR2 [111]. CXCR2 is required for optimal growth of Ras-transformed keratinocytes *in vivo* and stimulates tumor cell growth, survival and motility in multiple model systems [31,112–114]. In addition, blockade of ELR⁺ CXC chemokines and CXCR2 reduces tumorigenesis/angiogenesis in lung, esophageal, renal cell, colon and pancreatic cancers [30,31,56,57,115–118]. Studies in non-small-cell lung cancer (NSCLC) show a clear role for CXCR2 in tumor growth and angiogenesis in mice and high expression of CXCR2-associated ligands. Inhibition of CXCR2 or its ligands in NSCLC shows reduction in tumorigenesis in mice [115,116,119].

Furthermore, in inflammation-driven and spontaneous mouse models of intestinal and skin neoplasia, CXCR2 deficiency and/or inhibition by pepducin (one of a class of cell-penetrating lipopeptides based on the third intracellular loop of GPCRs that target chemokine receptors and selectively inhibits signaling) led to suppression of tumorigenesis, thus, further indicating that CXCR2 may be a good pharmacological target. Interestingly, these experiments bring up a fascinating issue that links CXCR2 and other chemokines and possibly chemokine receptors to the importance of the tumor environment and myeloid cells in the promotion of tumor development, as the dominant cell type of CXCR2 expression in the blood in these experiments were shown to be Ly6G⁺ neutrophils and that deficiency of CXCR2 attenuated neutrophil recruitment and decreased tumor-associated leukocytes [120].

Clearly, multiple studies indicate that CXCR2 and its associated ligands have universally important roles in cancer cell biology (Figure 3). However, induction of CXCR2 and ligands by Kras reinforces senescence *in vitro* and CXCR2 and its associated ligands are thought to be protective in early stages of tumorigenesis complicating the role of CXCR2 in cancer formation and progression [121,122].

8. CXCR2 and its role in pancreatic cancer

CXCR2 (as well as CXCR1) expression has been noted on both surgically resected pancreatic cancer tissue from human pancreatic cancer patients (55 – 65% of specimens according to one study) as well as several different lines of pancreatic cancer cells, including PANC-1, MiaPaCa-2, Capan-2 and Capan-1 cells as seen by immunohistochemistry, but not on ASPC-1 and BxPC-3 cells by RT-PCR [63,123,124]. Furthermore, ELR⁺ CXC chemokines in human pancreatic cancer cell lines have angiogenic activity and mediate their functions through CXCR2 [37]. As ELR⁺ CXC chemokine levels are higher in pancreatic cancer cell lines and pancreatic secretions of pancreatic cancer patients, this pathway clearly becomes important as a possible target. Indeed, levels of multiple cytokines and chemokines are elevated in pancreatic cancer [125]. Along with this data is the clear evidence that indicates that higher expression of many of the CXC chemokines can indicate a worse prognosis as well as increased cancer cachexia and decreased performance status. For example, CXCL5 is associated with poor tumor differentiation, advanced clinical stage and shorter patient survival [36,37]. Blockade of CXCL5 or CXCR2 attenuated human pancreatic cancer growth in a nude mice model. This pathway included protein kinase B (Akt), extracellular signal-regulated kinase (Erk) and activator of transcription (STAT) in human endothelial cells [36].

Furthermore, other recombinant chemokines (including CXCL1, 5 and 8) have been shown to enhance proliferation, invasion and tube formation of human umbilical vein endothelial cells (HUVEC) and treatment of pancreatic cancer cell lines with IL-8/CXCL8 enhanced cell invasiveness into matrigel and increased activity of matrix metalloproteinase (MMP2) in PANC-1 cells [32,123]. This process can be inhibited with CXCR2 antibodies, resulting in reduced tumor volume and inhibited microvessel formation [32]. However, increase in chemokine expression is not specific to carcinogenesis. Not surprisingly, elevated chemokines are also correlated with increased symptom severity of pancreatitis [126].

It appears that one important role of CXCR2 in pancreatic cancer and that of most cancers is that of a regulator of tumor angiogenesis or vasculogenesis, as well as enhancing invasiveness. However, in pancreatic cancer, this role may be complicated by the involvement of the desmoplastic stroma and the tumor microenvironment. Perhaps, the purpose of CXCR2 and its chemokines also involves the surrounding tumor microenvironment as well as the tumor itself by regulating tumor–stromal interaction. Using a pancreatic cancer model based on transgenic mice harboring a pancreas epithelium-

specific knockout of transcription growth factor beta (TGF β) type II receptor in the context of active Kras expression (Kras+Tgfr2^{-KO}) Ijichi *et al.* recently showed that CXCL1, 2, 5 and 16 are produced and secreted at higher levels in PDAC cells of these transgenic mice than in mPanIN cells (mouse pancreatic intraepithelial neoplasia) derived from Kras-activated transgenic mice and that CXCR2 inhibition could reduce tumor progression in these mouse models. However CXCR2 inhibition did not affect *in vitro* proliferation of PDAC cells in further experiments by Ijichi *et al.* They found that fibroblasts representative of PDAC stroma had higher CXCR2 expression, indicating that PDAC expression of CXCR2 ligands may be important for stroma formation and/or maintenance. Indeed, in a subcutaneous tumor grafting model, mixed cell tumors injected with PDAC cells and pancreatic fibroblasts had faster growth than PDAC cells alone. This growth was delayed when treated with CXCR2 inhibitor or when CXCR2 was knocked down in fibroblasts via shRNA. These data indicate that the role of chemokines and CXCR2 may be specifically in signaling between tumor and stroma. Further supporting this theory are experiments that showed that connective tissue growth factor, a profibrotic and tumor-promoting factor, was found to be highly expressed at border of tumor/stroma in PDAC tissue of Kras+Tgfr2^{-KO} mice. Its expression could be induced with chemokine incubation or conditioned culture media from PDAC cells, something that was dependent on the CXCL/CXCR2 axis and TGF β . Furthermore, inhibition of CXCR2 in addition to gemcitabine treatment also showed evidence of increase in overall survival with decreased tumor volume via inhibition of angiogenesis along with decreased macrophage and neutrophil migration into PDAC tissues, although with no advantage over CXCR inhibition or gemcitabine treatment alone [127]. Further evidence regarding the importance of the pancreatic cancer stroma is that ELR⁺ CXC chemokine expression increases in pancreatic cancer cells when cocultured with stromal cells [32].

The Ijichi paper broaches an interesting aspect of pancreatic cancer biology in regard to CXCR2 and the chemokines it binds. This paper highlights the role of the stroma in particular in a mouse pancreatic cancer model. Does CXCR2 primarily influence tumor–stroma interactions via expression on the stroma of pancreatic cancer, while pancreatic cancer cells upregulate chemokine production? It would be interesting to examine whether this sort of stroma–tumor interaction is paralleled in human pancreatic cancer. In addition, it seems that the localization and expression patterns of CXCR2 can be heterogeneous. As mentioned above, 55 – 65% of human pancreatic cancer specimens had CXCR1 or CXCR2 expression, whereas in the above experiments Ijichi *et al.* found CXCR2 at the tumor–stroma interface.

It is clear that CXCR2 and its chemokines are an intriguing target for preventing angiogenesis as blockade of CXCR2 with either broad spectrum GPCR antagonist or CXCR2 antibody blocks pancreatic cancer angiogenesis, but the mechanism by which this axis encourages angiogenesis and cancer progression remains unclear [37,38]. Recent studies have shown that the CXCR2 axis may also be involved in the mobilization of endothelial progenitor cells (EPCs) that contribute to new blood vessel formation particularly in tumors. Li *et al.* showed that EPC mobilization was impaired in CXCR2 knockout mice with pancreatic cancers and that circulating levels of EPCs were also decreased in blood and bone marrow in tumor-bearing CXCR2 knockout mice. Proliferation, differentiation and vasculogenesis (blood vessel formation *de novo*) *in vitro* was also decreased in these mice [128]. In addition, in endothelial cells, there is evidence that downstream signaling involves Erk 1/2 kinase [129].

Although clearly CXCR2 and the CXC chemokines are upregulated, what leads to this activation? Some information related to this question may come from signaling downstream of the *Kras* oncogene as activated *Kras* mutations enhance production of angiogenic factors

(including CXC chemokines and VEGF) in immortalized pancreatic epithelial cell systems, and blocking of MEK signaling inhibits production of chemokines. Triggering of these pathways leads to invasion and tube formation of HUVEC in coculture systems [130]. These data are especially intriguing given that activating point mutations of this gene are among the most common alterations in pancreatic cancer.

However, despite all of the evidence that indicates that CXCR2 and its ligands are cancer and angiogenesis promoting agents, it is interesting to note that in mouse heterozygote knockouts of CXCR2 injected with pancreatic cancer cells that these animals exhibited larger tumors than CXCR2^{+/+} mice (our unpublished data). These data further support the possibility that CXCR2 and its ligands play multiple roles in initiation versus progression of pancreatic cancer.

9. Conclusions: CXCR2 as a therapeutic target?

When discussing CXCR2 as a possible target, it is important to consider the CXCR/CXCL axis as a whole. Therapeutic targets can include the CXCR2 receptor as well as particular chemokines that are clearly involved in activating the receptor. Though multiple targets broaden our possibilities in drug designs, they also lead to the necessity for molecular as well as tissue specificity, given the number of CXCR2 ligands and the multiple locations and roles of CXCR2 in the normal inflammatory response.

As previously mentioned, one powerful role of the CXCR2/CXCL axis in tumorigenesis is its involvement in angiogenesis. This is a complex multistep process involving the extracellular matrix, endothelial migration, proliferation and capillary tube formation [131]. Angiogenesis in cancer is dependent on production of proangiogenic factors by both cancer and stromal cells [132]. Interestingly, recent studies indicate that CXCL1 and CXCL2, through CXCR2, may also play a role in metastasis and chemoresistance as a part of a paracrine network. Research by Acharyya *et al.* showed that CXCL1/2 is hyperactivated in breast cancer cell lines by chemotherapy and that blocking CXCR2 in conjunction with chemotherapeutic agents could markedly reduce lung metastases in xenograft-implanted mice (using metastatic breast cancer cell lines) [133]. These data indicate that there may be multiple roles for CXCR2 and that its therapeutic potential is likely multifactorial. Indeed, likely the most potent benefit for CXCR2 antagonist therapy would be in combination with current chemotherapeutic agents which will differ depending on the type of cancer addressed.

At this point in time, there are multiple options for CXCR2 inhibition. The first described low molecular weight CXCR2 antagonist (SB 225002), which was identified via high-throughput chemical screening, inhibited IL-8/CXCL8-dependent neutrophil chemotaxis in rabbits and IL-8/CXCL8 and Gro- α -dependent neutrophil chemotaxis *in vitro* [134]. Multiple CXCR2 antagonists have been identified and several trials for other disease processes are in the works. Recent trials of an oral CXCR2 antagonist (SB 656933) have been completed in patients with CF and results indicate that the compound was well tolerated and showed some beneficial pulmonary effects for these patients [135].

Other current strategies for CXCR2 antagonists include N-terminally modified chemokines, antibodies and other small-molecule inhibitors. Certain allosteric inhibitors of CXCR2, such as NSAIDs such as ketoprofen and ibuprofen block receptor signaling, and are potent inhibitors of CXCL8-dependent neutrophil chemotaxis [136]. However, although NSAIDs have been reported to be associated with a reduced risk for multiple malignancies, pancreatic cancer was not among them [137]. Reparixin (also previously known as repertaxin), is an inhibitor of both CXCR1- and CXCR2-mediated neutrophil migration *in vitro* and has been used in pancreatic cancer studies with some positive results. It was first

characterized in a model of ischemia and reperfusion injury by Bertini *et al.* in 2004 and has since been seen to mediate beneficial effects in bacteria-induced peritonitis, venom-induced lung injury as well as other models of ischemia reperfusion, to attenuate ALI by reducing neutrophil recruitment and vascular permeability and to promote recovery in traumatic spinal cord lesions [101,138–143]. In our study, we have found that reparixin inhibits CXCL5 and CXCL8-stimulated HUVEC growth in a dose-dependent manner and also decreased HUVEC growth stimulated by conditioned media from MiaPaCa-2 cell cultures. However, in an orthotopic rodent xenograft model, mice treated with reparixin grew larger tumors, complicating the understanding of its future possibility as a therapeutic agent (our unpublished data).

Other inhibitors include AZD-8309 (a pyrimidine series-based CXCR2 antagonist) that has been shown to reduce LPS-induced neutrophil recruitment and elastase activity in a lower airway LPS model. GlaxoSmithKline has published CXCR2 antagonists that are reported to inhibit chemokine binding to CXCR2. For these antagonists, there is decreased migration in response to CXCL1, 5 and 7, and they have been shown to inhibit CD11b upregulation and shape changes of neutrophil activation after stimulation with CXCL1 of neutrophils of COPD patients [144,145]. Many of these inhibitors have been assayed in inflammatory models but not in cancer systems.

Curcumin, a natural product found in the spice turmeric, is potent inhibitor of tumor progression in a variety of tumors and reduces the activity of IL-8/CXCL8, but increases expression of CXCR2 and CXCR1 (likely through inhibited internalization of receptors) [146]. Finally, in many studies, antibodies of IL-8/CXCL8 and Gro- α or CXCR2 have been shown to inhibit growth of Capan-1 cells or to inhibit tumor growth in other studies [63].

10. Expert opinion

As above-described, multiple studies have indicated that CXCR2 is involved in tumor progression, including growth, invasion and mediation with the tumor environment (Figure 4). Clearly there is plenty of therapeutic promise within the CXCR2/CXCL axis, but further biological understanding specific to pancreatic cancer is necessary since CXCR2 and its ligands are involved in so many other processes as described above. Indeed along with the current interest in CXCR2, CXCR4, another member of this family of chemokine receptors, and its ligand CXCL12 show promise of targeting pancreatic cancer as well. In addition to work showing its promise for future pancreatic cancer treatment, this chemokine receptor has the advantage of a previously solved crystal structure leading to recent studies of structure-based drug design [147]. Other receptors which complicate this picture include CXCR1, another chemokine receptor family member with 78% sequence identity to CXCR2. The structure of CXCR1 has been determined recently by nuclear magnetic resonance spectroscopy within a phospholipid bilayer [148]. Several studies regarding pancreatic cancer and chemokine receptors also include data on CXCR1 and indicate that its role may be similar to that of CXCR2. CXCR1 shares chemokine binding partners with CXCR2; however, it does not appear to be involved in ELR⁺ chemokine-promoted angiogenesis [115,149,150]. It would be beneficial to determine if there are roles specific to CXCR1 rather than CXCR2. Another chemokine receptor of interest is Duffy antigen/chemokine receptor (DARC) whose function may be important to differentiate from CXCR2 as these receptors share multiple binding partners. DARC is an atypical and promiscuous chemokine receptor, in that it has been found to bind at least 20 different CC and CXC chemokines. There is little data regarding DARC and pancreatic cancer; however, it is expressed most prominently on vascular endothelial cells and has been described as a

chemokine reservoir potentially functioning to negatively regulate chemokine-induced angiogenesis [151–153].

CXCR2 antagonists can easily be applied to many other pathologies and such a broad spectrum agent would benefit from further modification that will specifically target one system. In addition, it is important to remember that there is evidence that CXCR2 is involved in early tumor surveillance and, of course, normal immune system physiology. These functions will need to be protected in any antagonist, although this feat may be difficult to obtain. CXCR2 and its ligands induce cellular senescence during early tumorigenesis, such that further understanding of at which point of tumorigenesis CXCR2 and its ligands become cancer-promoting rather than cancer-inhibiting warrants investigation [122]. Moreover, this means that some focus in research and drug design will likely need to be on targeting of specific tissues or potentially specific ligands most important in PDAC or other cancers of interest. The question then becomes, when are we ready for trials with CXCR2 antagonists in pancreatic cancer patients?

Before clinical trials commence, understanding of CXCR2 may be furthered by answering several pending questions. Although there is a plethora of CXCR2 inhibitors, without a doubt it would be beneficial for the specificity drug design to have structural data of CXCR2, although current structural work of GPCRs includes the related receptors CXCR1. It has also been proposed that single nucleotide polymorphisms (SNP) of CXCR2 may play a role in pancreatic cancer, and although none have been yet identified in pancreatic cancer patients, this possibility introduces the intriguing idea that some as yet unknown alteration of CXCR2 may also be implicated in its role in pancreatic cancer growth as SNP have been identified in CF patients that are correlated with lung dysfunction [154,155]. It is also of importance to understand the biology of the receptor and its ligands specifically in PDAC tissue and its stroma at multiple stages. What is the role of the receptor and its ligands prior to tumorigenesis and how does the biological role change during the initiation and after the establishment of carcinogenesis? Also important is tissue specificity. What is the true therapeutic target: the stroma or the cancer, or both? In addition, if CXCR2 and its ligands are involved primarily in pathways involving angiogenesis, why are inhibitors of angiogenesis poor chemotherapeutics for pancreatic cancer? Although many questions still require answers, the future of pancreatic cancer research and the possibilities of new clinical therapies involving CXCR2 and its ligands holds a great deal of promise.

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Article highlights

- CXCR2 is a GPCR important for the normal physiology of neutrophil migration in response to acute inflammation.
- CXCR2 participates in chronic inflammation, sepsis, lung pathology, atherosclerosis and neuroinflammation.
- CXCR2 and chemokine overexpression detected in multiple human cancers has been implicated in promoting migration, invasion and angiogenesis.
- Multiple CXCR2 inhibitors are available and have been shown to modulate disease progression.
- Inhibition of the CXCR2 axis leads to decreased angiogenesis, attenuates pancreatic cancer progression and reduces tumor volume in mouse models.

This box summarizes key points contained in the article.

Figure 1. CXCR2 receptor

These proteins are GPCRs with seven transmembrane domains comprising three extracellular and three intracellular domains. The N-terminal domain is extracellular and is involved in chemokine binding. It is also important for receptor triggering via a tyrosine sulfation motif. The C-terminal segment of the receptor is intracellular. Other important domains include an aspartate residue (A) in the second extracellular loop and a LLKIL motif within the C terminus, both required for rapid receptor internalization. The G-protein docking site, which is within the second intracellular loop is composed of a DRY motif and is responsible for intracellular downstream signaling. In addition, the second intracellular loop contains a conserved 10 amino acid sequence and each extracellular domain contains a characteristic cysteine residue (C).

Figure 2. CXCR2 signalling pathway

Binding of the chemokine (red) to the GPCR involves interaction of the N terminus of the chemokine with the N terminus of the receptor. Once ligand binding has occurred, the associated G-protein is activated and dissociates leading to downstream activation of PLC, MAPK or a number of other signaling pathways depending on the chemokine involved, each leading to different downstream pathways responsible for actions, such as calcium mobilization, proliferation or migration, leading to chemotaxis.

Figure 3. The roles of CXCR2 in cancer

The various roles of CXCR2 are indicated with respect to multiple cancer types.

Figure 4. Pancreatic adenocarcinoma and CXCR2

CXCL5 is thought to act on CXCR2 to stimulate Akt, Erk and STAT to effect tumor growth. CXCL8 has been shown to act on CXCR2 to increase matrix metalloproteinase 2 (MMP2), enabling tumor invasion. Finally, research has shown the transcription growth factor beta (TGFβ) interacts with CXCR2 to promote tumor-stroma communication.