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Emerging roles of the CXCL12/CXCR4 axis in pancreatic cancer progression and therapy☆

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ABSTRACT

Chemokine networks regulate a variety of cellular, physiological, and immune processes. These normal functions can become appropriated by cancer cells to facilitate a more hospitable niche for aberrant cells by enhancing growth, proliferation, and metastasis. This is especially true in pancreatic cancer, where chemokine signaling is a vital component in the development of the supportive tumor microenvironment and the signaling between the cancer cells and surrounding stromal cells. Although expression patterns vary among cancer types, the chemokine receptor CXCR4 has been implicated in nearly every major malignancy and plays a prominent role in pancreatic cancer development and progression. This receptor, in conjunction with its primary chemokine ligand CXCL12, promotes pancreatic cancer development, invasion, and metastasis through the management of the tumor microenvironment via complex crosstalk with other pathways. Thus, CXCR4 likely contributes to the poor prognoses observed in patients afflicted with this malignancy. Recent exploration of combination therapies with CXCR4 antagonists have demonstrated improved outcomes, and abolishing the contribution of this pathway may prove crucial to effectively treat pancreatic cancer at both the primary tumor and metastases.

Contents

Abbreviations: CAFs, cancer-associated fibroblasts; CIS, carcinoma in situ; CSCs, cancer stem cells; CXCL12, CXC ligand 12; CXCR4, CXC chemokine receptor 4; EMT, epithelial mesenchymal transition; HMGB1, high mobility group box 1; MDSCs, myeloid-derived suppressor cells; MIF, macrophage migration inhibitory factor; PanIN, pancreatic intraepithelial neoplasia; PAUF, pancreatic adenocarcinoma upregulated factor; PC, pancreatic cancer; PDAC, pancreatic ductal adenocarcinoma; PSCs, pancreatic stellate cells; ROS, reactive oxygen species; SDF-1, stromal derived factor 1; SHH, Sonic Hedgehog; TAMs, tumor-associated macrophages; TME, tumor microenvironment; Tregs, T-regulatory cells.

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1. Introduction

Pancreatic cancer (PC) is the third leading cause of cancer related mortalities and second most common gastrointestinal cancer in the US (Bilimoria et al., 2007; Siegel, Miller, & Jemal, 2016), with pancreatic ductal adenocarcinoma (PDAC) comprising 90% of all PC cases (Biankin et al., 2012). Despite continued research efforts to counter or slow this trend, the incidence of PC is on the rise, which is in stark contrast to most other cancers, whose rates remain stable or are declining (Siegel, Ma, Zou, & Jemal, 2014). Moreover, PC has overtaken breast cancer for the third highest annual death rate (Siegel, Miller, & Jemal, 2015), and it is predicted that by 2030, PC will become the second leading cause of cancer-related mortalities (Rahib et al., 2014). The American Cancer Society estimated that in 2016 there would be about 53,000 new cases of PC with nearly 42,000 patients deaths, which equates to 80% of the incidence (Siegel et al., 2015). This high mortality can be partially attributed to the fact that 80–90% of patients present with either locally advanced or metastatic disease. Treatment for PC includes surgical excision, radiation, and chemotherapeutic approaches. Surgery remains the only potentially curative intervention, yet only affords a modest improvement in 5-year survival (Bilimoria et al., 2007). Unfortunately, only 10–20% of patients qualify as surgical candidates due to the high incidence of local invasion and metastatic spread prior to diagnosis (Garcea et al., 2008; Verbeke, 2008). Thus, chemotherapeutic approaches are the foundation for treatment of PC in a large majority of patients. FOLFIRINOX, a combination of folinic acid (leucovorin), 5-fluorouracil, irinotecan, and oxaliplatin, has resulted in the best improvement in PC patient outcomes to date, but the median survival still remains less than a year, and the overall five-year survival is only 6% (Conroy et al., 2011; Goldstein et al., 2015). In addition, the toxicity of FOLFIRINOX can be so severe that most patients are forced to revert to a less toxic, but less effective, nab-paclitaxel and gemcitabine regimen.

Our inability to effectively treat PDAC stems in part from the atypical tumor microenvironment (TME) found within these tumors (Fig. 1) (Neesse et al., 2011). Whereas most cancers display abundant and irregular networks of vasculature, the hypovascular nature of PDAC tumors reduces tissue perfusion and mitigates delivery of chemotherapeutics to cancerous cells (Komar et al., 2009). Moreover, the dense stromal composition of pancreatic tumors creates a physical barrier, rendering what little perfused tumor tissue there is, impermeable to drug diffusion (Olive et al., 2009). This desmoplastic reaction is a direct consequence of immune cell infiltration and subsequent inflammation. The resulting desmoplasia in the TME of PC is one of the most extensive of all cancers (Feig et al., 2012; Whatcott, Han, Posner, & Von Hoff, 2013). In many cases, a majority of the mass of pancreatic tumors is stroma, and nearly 50% of the cellular components can be accounted for by immune cells, including macrophages, myeloid-derived suppressor cells (MDSCs), and regulatory T cells (Tregs), which do more to protect cancer cells than harm them (Clark et al., 2007). Through paracrine signaling, tumor-associated macrophages (TAMs) increase levels of cytidine deaminase in PDAC cells and thus promote gemcitabine resistance by enhancing its metabolism (Weizman et al., 2014). Furthermore, TAMs along with MDSCs and Tregs promote the evasion of tumor cells from the immune system (Balkwill, 2012; Neesse, Algul, Tuveson, & Gress, 2015). The desmoplastic reaction also recruits and enhances proliferation of non-cancerous components of the stroma such as bone marrow-derived dendritic cells (BMDCs), cancer-associated fibroblasts (CAFs), and pancreatic stellate cells (PSCs). These cells display a nurturing role through the production of growth factors, chemokines, and other signaling molecules. In short, the body's attempts to wall off and manage the growing neoplasm create a unique environment that accelerates tumor growth and counterproductively reduces our ability to treat PDAC.

The unique TME in PC is governed in part by reciprocal signaling networks between cancerous and normal cells (Lippitz, 2013; Sarvaiya, Guo, Ulasov, Gabikian, & Lesniak, 2013). Although many signaling molecules play a substantial role in tumor biology, cytokines, specifically chemokines, are arguably among the most influential mediators in establishing and maintaining the TME (Egeblad, Nakasone, & Werb, 2010). Chemokines are responsible for the recruitment of macrophages to the tumor, which subsequently inhibits CD8 T-cell immune surveillance and promotes tumor immunity (Balkwill, 2012). Chemokines also facilitate Treg (Tan et al., 2009; Wei, Kryczek, & Zou, 2006) and MDSC (Mace et al., 2013) infiltration into tumors, aiding in immune evasion. Furthermore, chemokines recruit bone-marrow-derived fibroblasts to tumor sites (Katoh et al., 2010). Upon maturation to PSCs and

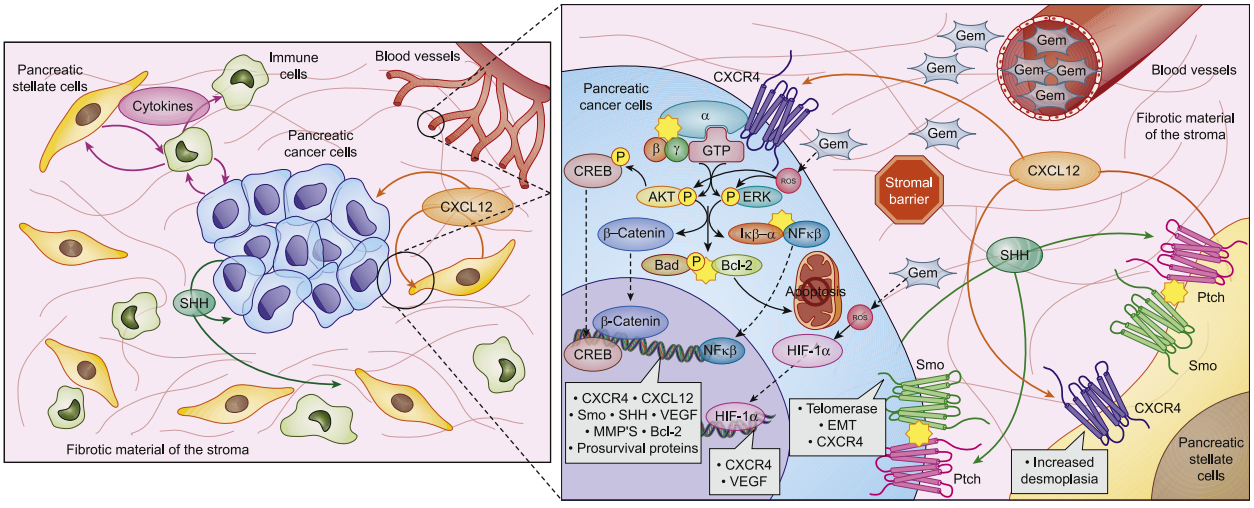

Fig. 1. (Left) Schematic depiction of pancreatic tumor microenvironment. PDAC tumor (blue) is surrounded by dense stromal deposition as a result of stromal cells (orange) desmoplastic reaction (pink lines). The desmoplastic barrier contributes to the hypovascular nature of PDAC tumors and poor ability to deliver imaging and therapeutic agents to PDAC. A large cellular proportion of these tumors can be accounting for by infiltrating immune cells (green) that ultimately hinder immune-cell surveillance of cancer cells and help to further promote tumor growth through various cytokine signaling. (Right) Model of CXCR4 autocrine and paracrine signaling between stromal cells and tumor cells. CXCL12/CXCR4 axis increases proliferation and survival of PDAC cells via several mechanisms. Through Akt and ERK activation, $NF_{\kappa}\beta$, CREB, and β-catenin accumulate in the nucleus and lead to transcription of oncologically relevant proteins. Additionally, phosphorylation of Bad causes its dissociation from Bcl-2 allowing for blockade of the apoptotic pathway. CXCR4 activation also leads to SHH production in PDAC cells, enhancing their own survival by: 1) autocrine activation of HH pathway and 2) paracrine activation of stromal cells to enhance desmoplasia and prevent chemotherapy diffusion. Gemcitabine (Gem in blue) permeates the stromal barrier and diffuses into PDAC cells, which causes cell killing but may also cause upregulation of CXCR4 via a reactive oxygen species (ROS in red) mediated process. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

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