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Chronic Pancreatitis and the Development of Pancreatic Cancer

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Abstract

Pancreatitis is a fibro-inflammatory disorder of the pancreas that can occur acutely or chronically as a result of the activation of digestive enzymes that damage pancreatic cells, which promotes inflammation. Chronic pancreatitis with persistent fibro-inflammation of the pancreas progresses to pancreatic cancer, which is the fourth leading cause of cancer deaths across the globe. Pancreatic cancer involves cross-talk of inflammatory, proliferative, migratory, and fibrotic mechanisms. In this review, we discuss the role of cytokines in the inflammatory cell storm in pancreatitis and pancreatic cancer and their role in the activation of SDF1α/CXCR4, SOCS3, inflammasome, and NF-κB signaling. The aberrant immune reactions contribute to pathological damage of acinar and ductal cells, and the activation of pancreatic stellate cells to a myofibroblast-like phenotype. We summarize several aspects involved in the promotion of pancreatic cancer by inflammation and include a number of regulatory molecules that inhibit that process.

Keywords

Pancreatitis; pancreatic cancer; cytokines; chemokines; immune cell infiltration; inflammation signaling

1. INTRODUCTION

The pancreas produces a variety of digestive enzymes, including trypsin and chymotrypsin which digest proteins, amylase which digests carbohydrates, and lipase, which breaks down fats. Islet cells supply the endocrine component of pancreatic function by releasing insulin and glucagon to maintain sugar balance in the body.

Pancreatic cancer (PC) is the third leading cause of cancer deaths and poses a severe health burden globally. The median survival rate of PC is six months to a maximum of five years in less than 5% of patients. The histological futures of pancreatic cancer involve a progression from dysplasia to invasive carcinoma. The major genetic changes in carcinogenesis of the

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pancreas include the activation of KRAS and inactivation of TP53, CDKN2A, SMAD4. Less frequently, mutations in ARID1A, GL13, MLL3, DNAH11, SYNE1, HMCN1, LRP1B, MUC16, FLG, OBSCN, FAT3, DNAH14, ZNF559, WDFY4, ASTN1, RNF43, TGFBR2, ZNF568, MLL2, PXDN, PREX2, PCDH15, COL6A5 occur in pancreatic cancer [1]. Although prevention may be an effective strategy, early diagnosis is essential for successful therapy. Further research is required to design treatments to reduce the mortality rate of this devastating disease.

Cytokines are diverse group of molecules produced by nucleated cells that play essential roles in regulating cell growth, inflammation, and metastasis [2, 3]. Uncontrolled inflammation of the pancreas, chronic pancreatitis, is one of the risk factors for the development of various malignancies. Activation and recruitment of immune cells produce a cytokine- and chemokine-enriched environment, which promotes cancer development and impairs immune detection of the tumor. Chronic pancreatitis leads to changes in endocrine and exocrine functions of the pancreas and may lead to obesity, diabetes mellitus, calcification of the pancreatic parenchyma, dilatation, distortion, and stricturing of the pancreatic ducts [4–8]. The immune system has enormous potential to destroy tumors; however, immune dysregulation leads to the expansion of the tumor, metastasis, and poor survival of individuals [9].

In the present review, we discuss the role of cytokine-mediated immune cell infiltration and SDF-1α/CXCL12-CXCR4, SOCS, NLRP3, and NF-κB inflammation signaling that contributes to pancreatic acinar, stellate and ductal cell pathology in pancreatitis and progression to pancreatic cancer. Further, we discuss the role of cytokine inhibitors/inducers and chemokines, immune cells, and inflammation signaling inhibitors in combating pancreatitis and pancreatic cancer.

2. PANCREATITIS

Activation of digestive enzymes in the pancreas before release into the small intestine causes injures to pancreatic cells, leading to inflammation with abdominal pain. Acute or chronic pancreatitis may be related to autoimmunity or hyperlipidemia. A low-fat diet and avoiding alcohol consumption and smoking are key to controlling the progression of acute to chronic pancreatitis [10].

2.1. Acute Pancreatitis (AP)

Acute pancreatitis is the leading cause of hospitalization for gastrointestinal disorders accompanied by epigastric pain. The diagnosis of the disease involves the detection of serum amylase or lipase ≥3 times the upper limit of normal levels. Severe acute pancreatitis is accompanied by organ failure with peri-pancreatic fluid collection, pancreatic and peri-pancreatic necrosis, pseudocyst formation, and walled-off necrosis [11]. Acute pancreatitis can be diagnosed by computed tomography or magnetic resonance cholangiopancreatography identification of retained common bile duct stones. Endoscopic retrograde cholangiopancreatography for patients with suspected gallstone pancreatitis and magnetic resonance imaging helps in distinguishing walled-off necrosis from a pseudocyst. Endoscopic ultrasonography is a highly sensitive test for detecting cholelithiasis and chole-

docholithiasis in acute pancreatitis [12]. Patients with acute pancreatitis can recover completely; however, risk factors like smoking, alcohol consumption, and pancreatic necrosis in those patients can lead to the development of recurrent or chronic pancreatitis after the first episode [13].

2.2. Chronic Pancreatitis (CP)

Chronic pancreatitis is a progressive fibro-inflammatory disease frequently related to excessive consumption of alcohol, cigarette smoking, exposure to industrial chemicals, or analgesics. Genetic mutations in a trypsin-controlling gene or the cystic fibrosis transmembrane conductance regulator account for hereditary forms of the disease [14]. Pancreatitis begins as pancreastasis or the prevention of apical exocytosis in pancreatic acinar cells. Consequently, newly synthesized and stored digestive enzymes are released *via* the basolateral membrane into lymphatics by way of the interstitium into the bloodstream, which causes inflammation [15–17].

2.3. Autoimmune Pancreatitis (AIP)

AIP is chronic inflammation due to the self-reactivity of the pancreas by the immune system, which leads to calcification and obstruction characteristic of chronic pancreatitis. Medication for AIP involves immune suppression by steroidal therapy. Type 1 AIP, also called lymphoplasmacytic sclerosing pancreatitis, is characterized by abundant infiltration with immunoglobulin G4 (IgG4)-positive plasma cells, whereas Type II AIP is characterized by granulocytic epithelial lesions in the pancreas without systemic involvement and is duct-centric [18]. The symptoms of AIP include dark urine, pale or floating stools, jaundice, pain in the upper abdomen, nausea, vomiting, weakness, loss of appetite, and weight loss. Pancreatic complications in AIP include pancreatic insufficiency/inability to make pancreatic enzymes, diabetes, and pancreatic calcifications.

2.4. Hyperlipidemia-Hypertriglyceridemia Pancreatitis (HTGP-AP)

Severe hypertriglyceridemia (HTG) is a common cause of acute pancreatitis. HTGP-AP occurs in approximately 15–20% of subjects referred to lipid clinics. Pathophysiology of HTGP-AP includes hydrolysis of triglycerides by pancreatic lipase and excessive formation of free fatty acids with inflammatory changes that promote capillary injury. Therapeutic measures in HTG-AP include dietary modifications, use of antihyperlipidemic agents, insulin, and heparin treatment [19]. Women with abnormal lipid metabolism are also at risk of developing hyperlipidemic gestational pancreatitis [20].

2.5. Obesity-Induced Pancreatitis (OIP)

Obesity, a risk factor for acute pancreatitis, aggravates the disease severity by damaging the intestinal mucosal barrier and changing the microbiota composition [21]. Adipose tissue produces adipokines, including adiponectin, leptin, visfatin, and resistin. In addition, adipose tissue-related MCP-1, TNF-α, and IL-6 enhance inflammation to worsen the severity of acute pancreatitis in diabetes patients [5]. Another comorbidity of chronic pancreatitis associated with obesity is an increased lifetime risk of developing pancreatic cancer. Upregulation of cytokines, chemokines, and other inflammatory mediators contributes to

disease severity in pancreatitis and pancreatic cancer in obesity through activation of transcription factors such as NF-κB, AP-1, NFAT, STAT3 with immune suppression and a decrease in NK, i-NKT cells and immune surveillance function of $CD8^+$ T cells [22].

2.6. Diabetes-Induced Pancreatitis (DIP)

There is a correlation between diabetes and pancreatitis and vice versa. Chronic pancreatitis is observed in type 1 diabetes patients with pancreatic ductal hyperplasia/dysplasia with a reduction in pancreas weight [23]. Animal studies showed that diabetes aggravates pancreatitis and suppresses regeneration of the pancreas [24]. Type 2 diabetes mellitus increased the risk of developing pancreatitis [6, 25]. Girman *et al.* [25] demonstrated that T2DM is a high-risk factor for acute pancreatitis compared with patients without diabetes. Chronic pancreatitis patients also develop Type 2 diabetes [26]. Diabetes mellitus secondary to chronic pancreatitis is accompanied by pancreatic exocrine dysfunction with deficient insulin secretion and classified as type 3c diabetes. In patients with chronic calcified or alcoholic pancreatitis, the incidence of retinopathy and neuropathy is high [27].

3. CHRONIC PANCREATITIS AND THE DEVELOPMENT OF PANCREATIC CANCER

Chronic pancreatitis is linked with an increased risk of pancreatic cancer. The incidence of pancreatic cancer is higher in chronic pancreatitis patients at an older age, and the prevalence increases with smoking and alcohol consumption. Diabetes, obesity, and an age >60 years also contribute to pancreatic cancer risk [28]. Metaplasia of pancreatic acinar cells is observed in chronic pancreatitis progression to pancreatic ductal adenocarcinoma. Oxido-nitrosative stress and fibro-inflammatory signals contribute to the development of pancreatitis and cooperate with oncogenic KRAS mutations and loss of tumor suppressor barriers p16/INK4A/CDKN2A, TP53 and SMAD4/DPC4 and subsequent progression to pancreatic intraepithelial neoplasias. The pathological progression increases from PanIN-1A, PanIN-1B, and PanIN 2/3 lesions and, ultimately, to invasive ductal adenocarcinoma [29].

4. CYTOKINES AND THEIR ROLE IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

Cytokines are released in the systemic circulation in response to various stimuli to defend against attacks of antigens and pathogens in the biological system. The pro-inflammatory response is opposed by an anti-inflammatory response, and an imbalance between these two systems leads to localized tissue destruction and organ damage [30]. In pancreatitis, the excessive release of cytokines stimulates various inflammatory signals and cytokine release, which in turn induces accumulation of inflammatory cells and depletes T cell response. These events cause acinar cell injury accompanied by fibrosis with the activation of quiescent pancreatic stellate cells to activated myofibroblast-like phenotype and pancreatic damage [31] (Fig. 1). Likewise, in pancreatic cancer, the response to inflammatory cytokines leads to acinar, ductal, and stellate cell proliferation with epithelial to mesenchymal transition and progressive tumorigenesis. Treatment for pancreatic cancer requires a portion of the organ to be removed if detected early or complete removal of the pancreas if detected

in later stages, and life expectancy reduces to less than five years in most cases [32]. Hence, understanding the role of cytokines in pancreatitis and its progression to pancreatic cancer will delineate new avenues for the discovery of anti-inflammatory and cytokine and chemokine inhibitory therapies in these disease states to reduce disease progression and to increase quality of life and survival. Cytokine inhibitors/inducers for pancreatitis and pancreatic cancer are listed in Table 1. Further, we describe some of the cytokines that play a crucial role in pancreatitis and pancreatic cancer.

4.1. IL-4

IL-4 is a Th2 cytokine that regulates cell proliferation and apoptosis and plays a role in inflammation [54, 55]. IL-4 levels are upregulated in cerulein-induced pancreatitis in mice, and IL-4 stimulates macrophages and activates pancreatic stellate cells. Blocking IL-4/IL-13 in the cerulein model using a peptide antagonist inhibits pancreatic damage and disease progression [34]. Pancreatic cancer cells and tissues express high levels of IL-4 and IL-4 receptors, and IL-4 acts as a growth factor in pancreatic cancer cells, facilitating pancreatic tumor growth and metastasis. Neutralizing IL-4 antibodies inhibits the growth of pancreatic cell lines [56]. IL-4 receptor-targeted cytotoxin is a potent target for pancreatic cancer therapy. Intra-tumoral injections of IL-4-Pseudomonas exotoxin exhibit antitumor activity against human pancreatic tumors implanted subcutaneously in immunodeficient animals [57].

4.2. IL-5

IL-5 is a proinflammatory cytokine that plays a critical role in eosinophil initiation, development, migration, and recruitment to the tissues in allergy and inflammation [58]. GATA-1 and IL-5 deficiency inhibits the induction of eosinophil active chemokines and profibrotic cytokines, and protects mice from an experimental model of pancreatitis induced fibro-inflammatory pathology of the pancreas as described in Fig. (2) [59]. The role of IL-5 has been demonstrated in bladder cancer cells where it enhances the migration and invasion *via* activation of ERK1/2, MMP-9, NF-κB, AP-1, and p21WAF1 [60]. Eosinophils play an active role in tumor immune surveillance and kill methylcholanthrene-induced fibrosarcoma in IL-5 transgenic mice [61].

4.3. IL-6

IL-6 signaling plays a pivotal role in chronic inflammation, autoimmunity, and inflammation-associated cancer. IL-6 signaling controls the differentiation and activation of T lymphocytes *via* induction of the Jak/STAT-3 and Ras/Erk/C/EBP pathways and regulates the balance between Treg cells and Th17 cells [62]. Pancreatitis is associated with elevated IL-6 levels, which promotes acinar cell damage in mice. In humans, IL-6 levels are a prognostic indicator in acute pancreatitis [59]. Acute lung injury (ALI) is associated with severe acute pancreatitis. IL-6 KO mice had a lower death rate compared with wild-type mice with acute pancreatitis; however, mice challenged with IL-6 developed lethal ALI *via* phosphorylation of STAT3 and production of neutrophil attractant CXCL1. Therapeutic inhibition of IL-6 may prevent severe acute pancreatitis associated with acute lung injury [62]. IL-6 plays a role in tumor progression in pancreatic cancer, and its expression is localized to the stroma of tumors. IL-6 and PD-L1 blockade showed antitumor activity in

mice bearing orthotopic KPC-luc tumors and inhibited tumor progression increased overall survival in KPC-Brca2 mice [63].

4.4. IL-13

IL-13 is produced by Th2 cells and plays a critical role in allergic diseases [64, 65]. Activation of macrophages is dependent on IL-4 and IL-13 signaling, and mice lacking IL4Ra and IL-4/IL-13 are less susceptible to cerulein-induced pancreatic fibrosis [34]. IL-13 is produced by PanIN and Tuft cells in the development of pancreatic cancer, and promotes macrophage polarization and contributes to PanIN cell proliferation and fibrosis. IL-13 neutralizing antibody decreases activated macrophages in ADM/PanIN lesions and reduces fibrosis and pancreatic lesion growth [66].

4.5. IL-15

IL-15 shares structural similarity with IL-2, and it activates NK cell proliferation, cytotoxicity, and cytokine production and regulates NK cell/macrophage interaction. IL-15 plays an anti-inflammatory role against asthma and eosinophil-mediated allergic diseases [65, 67]. IL-15 treatment produces an increase of interferon-γ-responsive invariant natural killer T (iNKT) cells in the blood. In the tissue, it protects against cerulein-induced pancreatic fibro-inflammation in mice, as illustrated in Fig. (3). [59]. IL-15 promotes NK cell-mediated cytotoxicity as a treatment for pancreatic cancer and stellate cells [47].

4.6. IL-17

IL-17 is a pro-inflammatory Th17 cytokine that plays a role in host defense, promoting inflammatory pathology and inducing eosinophil-mediated allergic diseases [68]. Stimulator of interferon genes (STING) activation worsens acute pancreatitis; however, it is protective in chronic pancreatitis and limits fibrosis. STING deficiency leads to IL-17 polarization, which is possibly inhibited by STING activation. IL-17A neutralization inhibits STING deficiency-mediated chronic pancreatitis [69]. Immune cell-derived IL-17 regulates the development of tuft cells and stem cell features of pancreatic cancer cells *via* increased expression of DCLK1, POU2F3, ALDH1A1, and IL-17RC and promotes pancreatic tumor growth and progression in mice and humans [70].

4.7. IL-18

IL-18, also called IFN-γ-inducing factor, is a proinflammatory cytokine that is converted to an active form by IL-1 p converting enzyme caspase-1. IL-18 plays a central role in inflammation and contributes to the pathogenesis and pathophysiology of inflammation and eosinophil-mediated allergic diseases [67, 71–73]. An increase in IL-18 levels was observed in chronic pancreatitis in mouse and human samples and served as a prognostic marker [39, 74]. IL-18 is increased in the blood and tissues of most cancer patients, including pancreatic cancer, and is associated with disease progression, metastatic recurrence risk, and reduced survival [75].

4.8. IFN-γ

IFN-γ plays a crucial role in host defense in innate and acquired immunity and exhibits both pro- and anti-tumorogenic roles [76]. Cerulein-induced pancreatitis is exacerbated in IFN-γ −/− mice with increased neutrophil recruitment. IFN-γ administration induced anti-inflammatory effects and attenuated cerulein-induced acute pancreatitis in both WT and IFN-γ−/− mice, with a reduction in NF-κB activation and COX-2 expression [77]. NKT cells are the source of IFN-γ, and recently we showed that cerulein induces a decrease in IFN-γ in a mouse chronic pancreatitis model. However, IL-15 administration induces IFN-γ and protects pancreatic pathology *via* NKT cell recruitment [59]. Interferon-γ released in the tumor microenvironment inhibits human pancreatic carcinoma cell growth *via* caspase-1 dependent induction of apoptosis [53].

4.9. TNF-α

TNF α is a proinflammatory cytokine that contributes to oxidative stress at sites of inflammation, participates in vasodilatation and edema formation, and plays a role in malignancy and inhibition of pancreatic cancer [78, 79]. TNFα directly induces premature protease activation and necrosis in pancreatic acinar cells *via* calcium and cathepsin-B activity. Genetic deletion of TNFα and neutralizing antibodies against TNFα prevented neutrophil- and macrophage-induced trypsin activity and necrosis in pancreatic acini treated with phorbol-12-myristate-13-acetate, cerulein, or TNFα, and prevented cerulein-induced experimental pancreatitis in mice [80]. Anti TNF-α reduces desmoplasia and the inflammatory microenvironment in pancreatic ductal adenocarcinoma, and anti-TNFα combined with chemotherapy killed tumor cells [81].

5. CHEMOKINES AND THEIR ROLE IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

Chemokines are secondary pro-inflammatory mediators induced by cytokines that stimulate the recruitment of leukocytes. The major chemokine sub-families based upon the position of cysteine residues are CXC and CC chemokines [82]. Chemokines and their receptors are critical mediators of cell migration during immune surveillance. Chemokines promote the tumorigenesis, proliferation, metastasis, and angiogenesis of a variety of cancers [83, 84]. In an earlier study, Yubero *et al.* [85] reported that oxidant-mediated MAPK, NF-κB, and STAT3 activation triggers chemokine expression in pancreatic acinar cells in pancreatitis in rats [85]. Chemokine receptor antagonists are a favorable therapeutic approach for the treatment of inflammatory diseases and cancer. Chemokine inhibitors for pancreatitis and pancreatic cancer are listed in Table 2.

5.1. The CC Family of Chemokines

CC chemokines influence allergic inflammation and progression of cancer [97, 98]. The following CC family chemokines are well reported in pancreatitis and pancreatic cancer and are reviewed in brief.

5.1.1. CCL2—Monocyte chemoattractant protein-1 (MCP-1/CCL2) regulates migration and infiltration of monocytes/macrophages [99]. MCP-1 upregulation is seen in acute and chronic pancreatitis in animal models and human tissues and contributes to the pathogenesis of mononuclear infiltration [100, 101]. Mutant MCP-1 inhibited intrapancreatic cytokine and chemokine expression and suppressed the development of pancreatic fibrosis in chronic pancreatitis induced by dibutyltin dichloride in rats [102]. Induction of pancreatitis by cerulein in mice involves the migration of CD11b high CD11c–Gr-1 low macrophages from the bone marrow mediated by CCL2 *via* CCR2 and SOCS-3 dependent activation. CCL2−/− mice exhibited less infiltration of CD11b high CD11c–Gr-1 low macrophages with less severe pancreatitis upon cerulein-induced pancreatitis [103]. Monocyte recruitment is critical to pancreatic cancer progression and increased monocyte prevalence in the peripheral blood, and its decrease in bone marrow correlates inversely with survival. Human pancreatic tumors express CCL2, and immunosuppressive $CCR2^{+}$ macrophages infiltrate these tumors with low CD8 T-cells. CCR2 blockade depletes inflammatory monocytes and macrophages from cancer and exhibits antitumor immunity, decreased tumor growth, and reduced metastasis in mice [104].

5.1.2. CCL5—CCL5, also known as RANTES, is expressed in various immune cells such as macrophages, dendritic cells, and memory T cells. The receptor for CCL5 is CCR5. CCL5 plays an essential role in inflammatory diseases and promotes carcinogenesis and stroma genesis [105]. In chronic pancreatitis, CCR5, CCL5, and MIP-1α mRNA levels were increased 12.9, 13.3, and 9.2-fold, respectively. Most CCR5-positive cells were also CD68-positive macrophages, and the study demonstrated that CCR5 is most likely involved in the attraction and activation of CD68-positive macrophages in chronic pancreatitis [106]. CCR5 and CCL5 interaction increased pancreatic cancer cell invasion through F-actin polymerization. Pancreatic cancer metastases showed elevated epithelial staining for CCR5 and CCL5. Pancreatic cancer cell lines (AsPc-1, BxPc-3, and MIA PaCa-2) showed higher expression levels of CCR5 and invasive potential. Treatment with the CCR5 inhibitor maraviroc appeared beneficial in preventing metastasis and may serve as a therapeutic strategy to control pancreatic cancer progression [107].

5.1.3. CCL18—CCL18, also called macrophage inflammatory protein 4, is expressed in monocytes, macrophages, and immature dendritic cells. The chemokine plays a crucial role in immune and inflammation responses and attracts lymphocytes and immature dendritic cells. CCL18 induces collagen deposition by fibroblasts and plays a role in the progression of malignant tumors [108]. Serum CCL18 levels were higher in patients with pancreatic ductal adenocarcinoma. Cancer epithelial cells and macrophages in pancreatic ductal adenocarcinoma tissues expressed CCL 18 that correlated with lymph node metastasis. Treatment with recombinant human CCL18 promoted the migration and invasion of pancreatic cancer cells and induced EMT by upregulation of SNAIL1 [109].

5.1.4. CCL20—CCL20, a direct target gene of RelA-containing NF-κB dimers, attracts immune cells to the site of the tumor and modulates the resistance of the cancer cells through their interaction with immune cells. The receptor for CCL20, CCR6, is expressed on a variety of immune cells, including macrophages, dendritic cells, and T-cells, as well as on

different tumor cells. The TRAIL-RelA-CCL20 signaling pathway in pancreatic ductal adenocarcinoma cells leads to paracrine immune cell modulation and resistance towards TRAIL-induced apoptosis in pancreatic ductal adenocarcinoma cell lines. Dissection of the CCL20-CCR6 cancer-immune cell interaction is required for anti-tumor therapy [110]. CCL20 and CCR6 levels are increased in pancreatic carcinoma and play a role in the development and progression of the tumor. Inhibition of CCR6 signaling or neutralization of CCL20 or inhibition of its production and activity may be useful in preventing further progression of pancreatic carcinoma [111]. Aberrant expression of CCL20 is observed in tumor-associated macrophages of pancreatic cancer tissue. CCL20 secreted by IL-4-challenged M2 macrophages promotes the migration and epithelial-mesenchymal transition [112]. Expression of CCL20 was significantly higher in pancreatic cancer than in chronic pancreatitis and adjacent normal tissue, and may therefore be a new parameter for histological diagnosis and discrimination between pancreatic cancer and chronic pancreatitis [113].

5.1.5. CCL21—CCL21, an efficient chemoattractant for lymphocytes, is found on endothelial venules and within the T cell zones of both spleen and lymph nodes. It is selective in its recruitment of naive T cells and dendritic cells, and it influences integrin-mediated dendritic cell transmigration [114–117]. In the lymph nodes, CCL21 plays a role in the initiation of an immune response by colocalizing naive T cells with dendritic cells presenting antigens [118, 119]. CCR7 is a receptor for CCL21 that is expressed on all naive T cells, memory T cells, B cells, and mature dendritic cells. CCR7 plays a central role in lymphocyte infiltration and homing to lymph nodes [120, 121]. CCL21/CCR7 signaling is involved in regulating inflammation, development and progression of several types of cancer [122]. CCL21 expression is associated with microvessel density, while CCR7 expression is associated with microlymphatic vessel density. CCR7 and its ligand, CCL21, are critical in the progression of pancreatic cancer, and induction of angiogenesis and lymphangiogenesis by chemotactic interaction [123]. CCL21/CCR7 promotes migration and survival of CD133+ pancreatic cancer stem cells *via* activation of ERK/NF-κB signaling and promoting EMT and lymph node metastasis markers E-cadherin, N-cadherin, and LYVE-1 [124].

5.2. The CXC Family of Chemokines

CXC chemokines regulate tumor-associated angiogenesis, as well as cancer cell metastases [125]. Here we discuss the role of the following CXC chemokines in pancreatitis and pancreatic cancer.

5.2.1. CXCL1—CXCL1, also known as neutrophil-activating protein 3 and melanoma growth stimulating activity α, signals *via* CXCR2 on neutrophils, which mediates mammary tumor growth and lung metastasis [126, 127]. An experimental model of cerulein-induced pancreatitis and acute lung injury in C57BL/6 mice activated IL-6 and induced phosphorylation of STAT3, which elevated CXCL1 in the serum, BALF and pancreatic acinar cells [62]. RelA activation promotes oncogene-induced senescence *via* elevation of CXCL1, which activates CXCR2 during pancreatic carcinogenesis. In Kras mice, pancreas-specific inactivation of CXCR2 prevented oncogene-induced senescence, which correlated with increased tumor proliferation and decreased survival. In human tissues, reductions in

CXCR2 levels were associated with advanced neoplastic lesions, which demonstrates that the RelA/CXCL1/CXCR2 axis is an essential mechanism of tumor surveillance in pancreatic ductal adenocarcinoma [128]. CXCL1 is highly expressed in mouse and human pancreatic ductal adenocarcinoma. High RIP3 (a critical regulator of programmed necrosis/necroptosis/inflammatory cell death) expression correlated with higher expression of CXCL1, and RIP3 deletion reduced *in vivo* and *in vitro* expression of CXCL1. Macrophage inducible $Ca2^{+}$-dependent lectin receptor (Mincle) deletion also slowed the rate of oncogenesis. Targeting these networks represents a therapeutic approach for pancreatic ductal adenocarcinoma [129].

5.2.2. CXCL4—CXCL4, also called platelet factor 4, drives inflammation-mediated cancer aggravation and angiogenesis and promotes antitumor immunity [130]. CXCL4 secreted from platelets is a stimulator of neutrophil infiltration and subsequent pancreatic tissue damage *via* CXCL2 activation that also mediates cancer regrowth after chemotherapy [131]. Taurocholate infusion into the pancreatic duct or by intraperitoneal administration of L-arginine induced pancreatitis in C57BL/6 mice with increased plasma levels of CXCL4, whereas depletion of platelets markedly reduced CXCL4 plasma levels, demonstrating that circulating levels of CXCL4 are derived from platelets in acute pancreatitis. CXCL4 inhibition decreased taurocholate-induced neutrophil recruitment, IL-6 secretion, edema formation, amylase release, and tissue damage in the pancreas. CXCL4 reduction also diminished plasma and lung levels of CXCL2 and neutrophil infiltration and tissue damage in the inflamed pancreas [132]. CXCL4 levels are also elevated in mild and severe acute pancreatitis, which directs CXCL4 inhibition as a therapy for the treatment of pancreatitis. A paralog of CXCL4, CXCL4L1, hindered cell proliferation and migration in patient tumors, tumor cell lines, and murine xenografts and increased substantially in primary and metastatic pancreatic ductal adenocarcinoma. Myofibroblasts induce CXCL4L1 in tumor cells. Administration of a monoclonal antibody (mAb) against CXCL4L1 blocked the growth of tumors positive for CXCR3, a receptor for CXCL4, and inhibited pancreatic ductal adenocarcinoma development *via* the antiangiogenic function [130].

5.2.3. CXCL8—CXCL8, also called monocyte-derived neutrophil chemotactic factor or neutrophil-activating protein 1 or IL-8 in humans, is a pro-inflammatory chemokine. Leukocytes and tumor cells secrete CXCL8, which plays a role in immune surveillance, inflammation, and angiogenesis and modulates endothelial cell proliferation and migration. The cellular response to CXCL8 is affected by CXCR1 and CXCR2, which cross-link with CXCL8 and exert biological function. IL-8 levels increased in human subjects with pancreatitis, and Pooran *et al.* [133] recommend IL-8 as a marker for the evaluation of pancreatitis. Pancreatic cancer cell-derived CXCL8 and fibroblast-derived CXCL12 promote HUVEC proliferation, migration, and invasion. CXCL12 enhanced CXCL8 production by pancreatic cancer cells, and drugs targeting CXCR4 and CXCR2 block metastasis and angiogenesis in pancreatic cancer [134]. Chen *et al.* [135] found that IL-8 levels were increased in the serum of patients with pancreatic adenocarcinoma and recommend IL-8 as a serum marker for predicting the prognosis.

5.2.4. CXCL10—CXCL10, also called 10 KDa interferon gamma-induced protein, binds to its receptor CXCR3 to exert biological effects such as chemotaxis, induction of apoptosis, regulation of cell growth, and mediation of angiostatic effects. CXCL10 correlates with inflammation, immune dysfunction, tumor development, and metastasis [136]. In response to inflammation, immune cells like neutrophils, eosinophils, monocytes, and other cells such as epithelial cells, endothelial cells, and stromal cells secrete CXCL10 [137–139]. CXCL10 was elevated in human pancreatic ductal adenocarcinoma specimens and cocultures of pancreatic cancer cells with pancreatic stellate cells and correlated with high stroma content and decreased median survival in patients with pancreatic cancer. CXCL10 and its receptor CXCR3 are associated with the intratumoral presence of T reg cells, and CXCL10 stimulated the *ex vivo* recruitment of $CXCR3^+$ effector T cells as well as $CXCR3^+$ T reg cells leading to immunosuppressive and tumor-promoting effects [140].

5.2.5. CXCL16—CXCL16, a transmembrane and soluble chemokine, plays a role in inflammation, and its expression promotes tumor growth, proliferation, metastasis, NF-κB regulation, and angiogenesis [141, 142]. Increased levels of CXCL16 are observed in humans with severe pancreatitis and confirmed bacterial infection, and in mice challenged with sodium taurocholate and *Escherichia coli*-mediated necrotizing pancreatitis [143]. CXCL16 and CXCR6 are induced in chronic pancreatitis and pancreatic ductal adenocarcinoma tissues. Proinflammatory cytokines increase CXCL16 and silencing of ADAM10 inhibits CXCL16 [144]. sst2+/− mice showed PI3K/AKT activation, whereas KRASG12D sst2+/− mice showed premalignant lesions, tumors, and lymph node metastases and activation of PI3K signaling *via* AKT, NF-κB activation, and CXCL16 production, which prompted neoplastic lesions. Pancreatic ductal adenocarcinoma tissues and surrounding acini from mice and humans expressed higher CXCL16 and its receptor CXCR6 in pancreatic tissues. Neutralizing CXCL16 in KRASG12D mice reduced PI3K/AKT/NF-κB signaling and blocked carcinogenesis. sst2 is progressively lost in mouse lesions that expressed KRASG12D with PI3K activation that progressed to pancreatic ductal adenocarcinoma [145].

6. THE IMMUNE CELLS ACTIVATED IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

Host immune cells defend against microbial and foreign substances in the tumor environment. Reports demonstrate that acute pancreatitis provoked after the consumption of food products like mustard, milk, egg, banana, fish, and kiwi fruits and food allergies are a possible cause for the initiation of pancreatitis associated with cytokine release and activation and release of immune cells [146]. In pancreatic cancer-immune cell infiltration like pan-macrophages, M2, Neu, or the ratio of T reg cells to $CD4^+$T cells associated with shorter survival [147]. Proper activation of immune cells when required, and inhibition of aberrant infiltration of immune cells, are key to countering pancreatitis progression and development to pancreatic cancer. Immune cell inhibitors/inducers for pancreatitis and pancreatic cancer are listed in Table 3.

6.1. Dendritic Cells

Dendritic cells protect against cell stress and are required for pancreatic viability in mice with acute pancreatitis. Major histocompatibility complex II+CD11c+ DCs are increased in pancreata of mice with acute pancreatitis along with increased IL-6 and TNF-α. With the depletion of dendritic cells, mice died upon challenge with cerulean or L-arginine and exhibited acinar cell death and neutrophil infiltration [151]. Blockade of the MyD88-independent TRIF pathway is protective against pancreatic cancer neoplastic transformation by augmenting the DC–Th2 axis, whereas blockade of the MyD88-dependent pathway exacerbates pancreatic inflammation and malignant progression. The protumorigenic and fibroinflammatory effects of MyD88 inhibition are mediated by dendritic cells (DCs), which induce pancreatic antigen-restricted Th2-deviated $CD4^+$ T cells and promote the transition from pancreatitis to carcinoma [152].

6.2. Macrophages

Macrophages execute a critical role in disease progression in pancreatitis in mice and human tissues. M1 macrophages are predominant in acute pancreatitis. In contrast, macrophages are alternatively activated in chronic pancreatitis, promote proliferation and activation of PSCs and express high levels of TIMP2 and MMP9, which regulate ECM turnover. Alternatively, enabled macrophages are dependent on IL-4 and IL-13 signaling, and mice lacking IL-4Rα, and IL-4/IL-13 were less susceptible to pancreatic fibrosis. Pharmacologic inhibition of IL-4/IL-13 decreases alternatively activated macrophages and fibrosis in the pancreas [34]. Macrophages play an essential role in mediating tumor progression. M2-polarized tumor-associated macrophages induce epithelial-mesenchymal transition in the progression to metastasis. Activation of TLR4 on M2-polarized TAMs stimulates an increase in the cytokine IL-10 and increased EMT of pancreatic cancer cells [153]. PI3Kγ, an essential macrophage lipid kinase, regulates macrophage transcriptional programming, leading to stimulation of $CD8^+$ T-cell–mediated tumor suppression, desmoplasia, tumor cell invasion, and metastasis in pancreatic adenocarcinoma. Genetic or pharmacologic inhibition of PI3Kγ restores antitumor immune responses and improves responsiveness to standard-of-care chemotherapy in animal models of pancreatic ductal adenocarcinoma. [154].

6.3. Mast Cells

Mast cell number and IgE-dependent mast cell activation are higher in chronic pancreatitis than in the healthy pancreas and localized in the fibrotic areas and the residual acinar parenchyma [155]. Perineural mast cells are enriched in pancreatic neuritis, a histopathological hallmark of pancreatic neuropathy in chronic pancreatitis and pancreatic adenocarcinoma [156]. Mast cell degranulation is observed in the pancreas with sodium taurodeoxycholate-induced pancreatitis in rats [157]. Mast cells are critical components of the tumor-stromal microenvironment in several solid and hematological malignancies. Mast cell infiltration increases in pancreatic cancer and plays a role in promoting angiogenesis and tumor growth [158]. In contrast to mast cells in acute pancreatitis, the mast cells in pancreatic ductal adenocarcinoma were found degranulated [159]. Mast cells contribute to the aggressiveness of pancreatic ductal adenocarcinoma, enhancing the expression of several

pro-angiogenic factors such as VEGF, FGF-2, PDGF, and angiopoietin-1 as well as stimulating the pancreatic cancer cell proliferation by IL-13 and tryptase activity [160].

6.4. Neutrophils

Neutrophils are critical in mediating pancreatic and lung tissue damage in severe acute pancreatitis in taurocholate-induced pancreatitis in mice. Trypsinogen activation is dependent on neutrophil activation in the pancreas [161]. Neutrophils make use of histone citrullination, an epigenetic post-translational modification of histone arginine to citrulline by peptidyl arginine deiminase-4 (PADI4), upon contact with particulate agents to extrude decondensed chromatin as neutrophil extracellular traps (NETs) and form macroscopically visible aggregates. PADI4 is critical for intraductal aggregate formation, and PADI4-deficiency abrogates disease progression. Components of pancreatic juice, such as bicarbonate ions and calcium carbonate crystals, induce aggregated NET formation. Ductal occlusion by aggregated NETs emerges as a pathomechanism with relevance in a plethora of inflammatory conditions involving secretory ducts with IL-17A/cerulean challenge [162]. Neutrophil gelatinase-associated lipocalin secreted by neutrophils and other cell types is a prognostic marker in pancreatitis and pancreatic cancer [163, 164]. The transition of epithelial to mesenchymal phenotype in pancreatic cancers coincides with the polymorphonuclear infiltrate, a contribution of the inflammatory response in tumor progression [165].

6.5. Basophils

Basophils are proinflammatory granulocytes released in response to allergy and inflammation that infiltrate the tumor microenvironment [166]. Basophils activated by TLR2/TLR4 stimulation in type 1 AIP were significantly higher than those in healthy subjects and showed an essential role in the pathophysiology of type 1 AIP [167]. Mouse models of pancreatic cancer demonstrate the functional role of basophils during tumor progression. Basophils expressing IL-4 are enriched in tumor-draining lymph nodes of patients with pancreatic ductal adenocarcinoma. Basophils rely on the release of CCL7/MCP3 by “alternatively activated” monocytes, whereas basophil activation is induced by T-cell-derived IL-3. Basophils present in TDLNs correlate with the Th2/Th1 cell ratio in tumors [168].

6.6. Monocytes

Monocytes can differentiate into macrophages and dendritic cells and play a role in host defense against microorganisms and dead cells. Monocyte infiltration in pancreatitis, and increased numbers of CD14+CD163- and CD14+CD163-MAC387+ monocytes were detected in mild acute pancreatitis patients [169]. An increase in monocytes in the blood and decrease in the bone marrow correlates with poor survival in pancreatic cancer. The chemokine CCL2 and $CCR2^{+}$ macrophages infiltration with low CD8T cells are observed in pancreatic tumor patients. CCR2 blockade augments antitumor immunity, decreases tumor growth, and reduces metastasis with depletion of inflammatory monocytes and macrophages from the primary tumor and premetastatic liver in mice [104].

6.7. Eosinophils

Eosinophils are a type of leukocyte that are released in response to allergic stimuli and play a critical role in allergic disease. An increase in eosinophils is observed in mouse and human pancreatitis [39, 71]. Eosinophilic pancreatitis is a rare form of recurrent acute and/or chronic pancreatitis characterized by localized or diffuse periductal, acinar, and septal inflammatory eosinophilic infiltration of the pancreas and elevated serum immunoglobulin E levels [170, 171]. Eosinophil accumulation and degranulation were observed in human and mouse pancreatitis and may have a critical role in promoting pancreatitis pathogenesis and fibrosis [39]. Eosinophilia in pancreatic cancer is rare [172]. In a human study of pancreatic adenocarcinoma, eosinophilia was observed with infiltration of the duodenal wall characterized by multiple eosinophilic extracellular deposits consistent with non-calcified psammoma bodies [172].

6.8. T Cells

The pancreatic ductal adenocarcinoma microenvironment is predominantly infiltrated with immune suppressive cells. The checkpoint inhibitors such as cytotoxic T lymphocyte antigen-4 (CTLA-4), programmed death 1 (PD-1), and its ligand PD-L1 have failed to demonstrate responses given as single agents to PDA patients [173]. The combination of αCD40/chemotherapy plus αPD-1 and αCTLA-4 induced regression of subcutaneous tumors, and improved overall survival by priming T-cell response in pancreatic ductal adenocarcinoma [174]. PD-1 blockade increased effector CD8+ T lymphocytes and tumor-specific interferon-γ production of CD8+ T cells in the tumor microenvironment for pancreatic ductal adenocarcinoma [173].

6.8.1. $CD4^+$T Cells—$CD4^+CD25$high Tregs cells are observed in autoimmune pancreatitis patients and influence IgG4 production, and decreased T reg cells are involved in the pathogenesis of autoimmune pancreatitis [175]. The severity of cerulein-induced acute pancreatitis is also reduced by *in vivo* $CD4^+$ (but not $CD8^+$) T-cell depletion, and Fas ligand-targeted mutant mice display a decrease in histological lesions, serum hydroxylase and IFN-γ, IL-12, and FasL gene transcription [176].

6.8.2. $CD8^+$T Cells—Tumor-derived GM-CSF is an essential regulator of inflammation and immune suppression within the tumor microenvironment. GM-CSF drives the development of Gr-1^+ $CD11b^+$ cells that suppress antigen-specific T cells in the KPC mouse model of spontaneous pancreatic ductal adenocarcinoma in which expression of oncogenic KrasG12D and mutant p53R172H are targeted to the pancreas. Abrogation of tumor-derived GM-CSF inhibited the recruitment of Gr-1^+ $CD11b^+$ cells to the tumor microenvironment and blocked tumor development dependent on $CD8^+$ T cells to rescue the tumor growth [177].

6.8.3. NK Cells—Pancreatic tissue of chronic pancreatitis patients shows an increase in activated $CD56^+$ NK cells, which mediate HLA-independent cytotoxicity [178]. NK cells constitutively express receptors for several cytokines, including IL-21, which promotes the maturation of NK cells. IL-21 enhances NK cell-mediated effector functions against

cetuximab-coated pancreatic tumor cells irrespective of KRAS mutation status and reduced pancreatic tumor burden *in vivo* [49].

6.8.4. NKT Cells—The absence of NKT cells leads to aggressive development of pancreatic cancer, with an increase in pancreatic intraepithelial neoplasia lesions and 5-LOX and mPGES-1 expression in M2-type macrophages, and cancer stem-like cells in pancreatic tumors of CD1d−/− mice deficient in both invariant and variant NKT cells with the KrasG12D mice [179].

6.8.5. i-NKT Cells—Reduction in i-NKT cells is observed in human chronic pancreatitis and cerulean-induced chronic pancreatitis in mice, whereas IL-15 treatment mediates an increase in the interferon-γ-responsive invariant natural killer T cells in the blood and tissue and protects against cerulein-induced pancreatic pathology in mice [59].

6.8.6. T Regulatory Cells—Type 1 autoimmune pancreatitis patients show an increase in T reg cells and IgG4-sclerosing cholangitis (IgG4-SC) in the pancreas, and the numbers of infiltrated T reg cells correlate with IgG4-positive plasma cells. The increase in the inducible costimulatory molecule $(ICOS)^+$ and IL-10^+ T reg cells influence IgG4 production *via* IL-10 in Type 1 autoimmune pancreatitis [180]. T reg cell infiltration constitutes an immunosuppressive phenotype on tumor-associated $CD11c^+$ DCs that then fail to activate a cytotoxic $CD8^+$ T cell-mediated delay in tumor growth by suppressing the expression of costimulatory ligands. Targeting this interaction is a therapeutic strategy for the treatment of PDA and dependent on $CD8^+$ T cell activation [181].

6.9. B Cells

Pancreatic neoplasms harboring oncogenic Kras are pointedly compromised in B-cell–deficient mice. B cells elicit a pro-tumorigenic effect *via* IL-35-mediated tumor cell proliferation released by CD1dhi$CD5^+$ B cells in pancreatic cancer pathogenesis [182]. Hif1α deletion promotes pancreatic ductal adenocarcinoma initiation with increased intrapancreatic accumulation of B cells, B1b” B-cell subtype in $Kras^{G12D}$-driven pancreatic neoplasia. B-cell depletion by αCD20 monoclonal antibodies suppresses pancreatic tumorigenesis [183]. $CD19^+$CD24high$CD27^+$ regulatory B cells are involved in the development of type 1 autoimmune pancreatitis and increase conquers the severity of disease activity [184]. IgG4-related autoimmune pancreatitis mimicking acute pancreatitis is observed in humans [185].

7. THE ROLE OF THE COMPLEMENT SYSTEM

The complement system is made of plasma proteins that defend the host by opsonizing pathogens and inducing inflammatory responses that help fight infections. Loss of complement component 5 (C5) or injection of a C5a-receptor antagonist reduces the level of fibrosis in cerulein-induced chronic pancreatitis in mice, and C5a induces activation of primary stellate cells delineating its antifibrotic effects in chronic pancreatitis [186]. The expression levels of complement C3, complement C4b1, and apoE were higher in pancreatic cancer. Complement C4b1 and apoE markedly correlated with tumor staging and lymph node metastasis. Complement C3 may be used as a marker for the diagnosis of early-stage

pancreatic cancer, while C4b1 and apoE might be used as diagnostic markers of advanced pancreatic cancer [187].

8. INFLAMMATORY MECHANISMS IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

Chronic pancreatitis increases the risk of pancreatic cancer by 10 to 20-fold, and inflammatory mediators play a crucial role in disease progression. Although the exact inflammatory mechanisms are not yet determined, disease initiation and progression is due to a combined effect of several inflammatory mechanisms in response to cytokine and chemokine infiltration in pancreatitis and pancreatic stroma (Fig. 4). Understanding these inflammatory pathways and development of inhibitors that inhibit aberrant activation of inflammatory signals is a key for pancreatitis and pancreatic cancer therapy [188]. Some of the inflammation signaling inhibitors for pancreatitis and pancreatic cancer are listed in Table 4.

8.1. Stromal-Derived Factor-1α/CXCL12-CXCR4 Signaling

SDF-1α/CXCR4 plays a role in the proliferation and maturation of human fetal pancreatic endocrine progenitor cells, where its increased expression is associated with inflammation [199]. Mice with experimental acute pancreatitis exhibit enhanced pancreatic SDF-1 α expression. The SDF-1α/CXCR4 axis promotes the migration of transplanted bone marrow mesenchymal stem cells towards the injured pancreas to facilitate a reparative process to combat the progression of acute pancreatitis [200]. CXCR4 upregulated on the surface of tumor cells of epithelial origin and CXCR4-positive tumor cells could migrate toward distant organs in response to an SDF-1α gradient [201]. SDF-1α /CXCR4 are expressed at higher levels in pancreatic cancer cells, and the expression level influences the clinical outcome of pancreatic ductal adenocarcinoma patients [202, 203]. Survival was lower in patients positive for CXCR4 expression than in patients negative for CXCR4 expression. Abrogation of SDF1α/CXCR4 influences the pancreatic cancer cell phenotype, including cell proliferation, colony formation, and cell invasion. Inhibition of Wnt targets genes and the mesenchymal markers vimentin and Slug, and may be a promising therapeutic target to delay pancreatic cancer progression [204].

8.2. SOCS Signaling

The suppressor of cytokine signaling (SOCS) proteins are inhibitors of activation of the JAK-STAT pathway, and studies demonstrated critical roles for SOCS1 and SOCS3 in inflammation and the development and progression of cancers [205]. Abnormal expression of SOCS1 and SOCS3 is associated with dysregulation of signals from cytokine receptors, Toll-like receptors (TLRs), and hormone receptors, resulting in inflammation and malignancies in cancer cells and human carcinomas including pancreatic cancer [206]. Inhibition of SOCs can exert protective effects against severe acute pancreatitis-associated acute lung injury, and this effect could be partially mediated by restraining mitochondrial-associated apoptosis of pulmonary microvascular endothelial cells [207]. SOCS3 suppresses the IL-6-mediated STAT3 activation that mediates the suppression of TLR/NF-κB signaling in macrophages, and the lack of the SOCS3 signaling pathway can accelerate STAT3

activation and amelioration of pancreatitis [103]. Activated IL-6/STAT3 signaling induces SOCS3 methylation *via* DNA methyltransferase 1 (DNMT1), which leads to pancreatic cancer growth and metastasis, whereas inhibitors of STAT3 or DNMT1 are therapeutics for treating pancreatic cancer [208].

8.3. NLRP3 Inflammasome Signaling

The db/db mice with diabetes are susceptible to acute pancreatitis, and the pancreatic tissues showed NLRP3 inflammasome activation [209]. NLRP3 signaling in macrophages drives the differentiation of $CD4^+$ T cells into tumor-promoting Th2, Th17, and regulatory T cell populations and suppresses Th1 cell polarization and cytotoxic $CD8^+$ T cell activation, while the transfer of PDA-entrained macrophages or T cells from NLRP3−/− mice was protective, and targeting NLRP3 is immunotherapy for PDA [196]. Caspase-1, ASC, and NLRP3 are required for inflammation in acute pancreatitis. TLR9 and P2X7 are important DAMP receptors upstream of inflammasome activation. Genetic deletion of TLR9 and pretreatment with the TLR9 antagonist IRS954 reduced pancreatic edema, inflammation, and pro–IL-1β expression in pancreatitis. IRS954 also decreased pancreatic necrosis and lung inflammation in taurolithocholic acid 3-sulfate-induced acute pancreatitis and is a therapeutic strategy for treating acute pancreatitis [210].

8.4. NF-κB Signaling

NF-κB is activated in the early stages of pancreatitis and regulates genes that control inflammation, survival, proliferation, and migration [211–212]. Huang *et al.* [213] demonstrated that acute pancreatitis by cerulein challenge to p65 transgenic mice showed higher levels of NF-κB activity in acinar cells and inflammation. Constitutive expression of IKK2 increased the activity of NF-κB in acinar cells and induced pancreatitis, and prolonged action of IKK2 for three months activated stellate cells, loss of acinar cells, and fibrosis with characteristic chronic pancreatitis. Co-expression of IKK2 and p65 also increased the inflammatory mediators and the severity of pancreatitis in mice. Activation of NF-κB is observed in pancreatic cancer, and its inhibition reduces pancreatic tumors. Blocking NF-κB by BAY11- 7082, an NF-κB pathway inhibitor, and recombinant IL-18 improved survival in a murine pancreatic cancer model [214].

9. PANCREATIC CELLS IN CHRONIC PANCREATITIS AND PANCREATIC CANCER

The pancreas, located in the upper left area of the abdomen behind the stomach near the duodenum, has endocrine and exocrine compartments. The exocrine compartment consists of acinar, ductal, and centroacinar cells that produce enzymes essential to digestion. The pancreatic juices and bile that release into the duodenum help digest fats, carbohydrates, and proteins. The endocrine compartment of the pancreas consists of islets of Langerhans cells α, β, δ, e, and pancreatic polypeptide cells that release hormones directly into the bloodstream. The primary pancreatic hormone insulin acts to lower blood sugar, and glucagon works to raise blood sugar, maintaining proper blood sugar level balance in the body for vital functioning of organs [215].

9.1. Pancreatic Acinar Cells

The pancreatic acinar cell is the functional unit for pancreas exocrine function. Premature activation of digestive enzymes in pancreatic acinar cells initiates pancreatitis [216]. In pancreatitis and pancreatic cancer, acinar cells may undergo redifferentiation into ductal cells and blockade of the ductal system [217]. Reducing Ca^{2+} influx and inhibition of amylase secretion reduced cellular damage in cerulean-induced pancreatitis in mice [218]. Defective lysosomal function, resulting in impaired autophagy, leads to pancreatitis. LAMP-2 deficient mice exhibit lysosomal/autophagic dysfunction, show a decrease in pancreatic digestive enzyme content, and inhibit cholecystokinin-induced amylase secretion by acinar cells and mimic the genetic model of human pancreatitis, explaining the homeostatic role of LAMP2 in pancreatic acinar cell health [219]. Cerulein-induced pancreatitis in mice revealed inflammation-associated death of acinar cells with pancreas-specific RelA/p65 truncation [220]. Kras activation itself is not enough to drive pancreatic carcinogenesis beyond the level of premalignancy. A secondary stimulus, such as inflammation-induced signaling, is required for tumor formation. Inflammatory transcription factor NFATc4 is highly induced and localizes to the nucleus in response to inflammation-induced EGFR signaling, and drives acinar-to-ductal conversion and pancreatic ductal adenocarcinoma initiation through direct transcriptional induction of Sox9 [221].

9.2. Pancreatic Ductal Cells

In pancreatic injury due to KRAS hyperactivity and increased inflammatory signaling with the loss of cell-cell and cell-matrix contacts, loss of polarity can drive acinar cells to transdifferentiate to a duct-like phenotype with acinar-to-ductal metaplasia and initiate further progression to low-grade precancerous lesions [222]. Chronic stimulation and proliferation of the pancreatic duct gland in response to islet inflammation in type 2 diabetes mellitus (T2DM) is linked with increased risk for pancreatitis in T2DM [223]. Pancreatic ductal adenocarcinoma is a type of exocrine pancreatic cancer, and account for 95% of all pancreatic cancers. It is an aggressive malignancy, and surgical removal of the tumor is a possible cure. However, 90% of patients possess a high grade of the disease and are surgically incurable at the time of clinical presentation [224]. LCN2 is upregulated in patients with pancreatic ductal adenocarcinoma and obesity. Depletion of LCN2 diminished ECM deposition, immune cell infiltration, PanIN formation, tumor growth and increased survival in both obesity-driven and syngeneic orthotopic pancreatic ductal adenocarcinoma mouse models *via* modulation of proinflammatory cytokines secreted by pancreatic stellate cells [225]. TNF-α expression is elevated in the pancreatic ductal adenocarcinoma initiation process, and anti-TNF-α antibodies have shown promising effects in pancreatic ductal adenocarcinoma in preclinical models *via* killing tumor cells and diminishing desmoplasia and inflammation in the pancreatic ductal adenocarcinoma tumor stroma [81].

9.3. Pancreatic Stellate Cells (PSCs)

Pancreatic stellate cells, which comprise about 4-7% of the pancreas, are normally quiescent and play a role in standard tissue architecture by regulating extracellular matrix turnover [226]. PSCs can synthesize and secrete acetylcholine and play a role in mediating exocrine secretion from acinar cells [227]. PSCs transition to activated myofibroblast-like cells in

response to inflammation. These cells play a vital role in ECM production, migration, and proliferation, and foster progression of chronic pancreatitis to pancreatic cancer [228]. PSCs respond to pro-inflammatory cytokines in acute pancreatitis and may exacerbate the disease to chronic pancreatitis with pancreatic injury and fibrosis [229]. TLR9 ligation induces pancreatic stellate cells to secrete chemokines and become fibrogenic and proliferative, and mediate pro-tumorogenic effects *via* CCL11 [230]. Understanding the biology of the pancreas and its cell types could provide avenues to treat pancreatic pathology in disease states.

CONCLUSION AND FUTURE THERAPEUTIC PERSPECTIVES

Understanding of the mechanisms of pancreatitis and progression of pancreatic cancer has advanced but much remains unclear. Inflammation and fibrosis with epithelial to mesenchymal transition are critical factors in pancreatic carcinogenesis, and hence novel anti-fibrotic agents in combination with those anti-inflammatory effects might be therapeutic in targeting acinar to ductal metaplasia and pancreatic ductal adenocarcinoma. A multitude of molecular, fibrotic, stress, and signal transduction pathways and factors that determine progression remains the main obstacle to combating this aggressive disease. Targeting multiple pathways may be effective in the treatment of pancreatitis and inhibiting its progression to pancreatic cancer.

Complementary and combinational therapeutics such as immunogenic, signal transduction targeted agents, chemotherapeutics, and therapies aimed against the tumor microenvironment will hopefully be a beneficial treatment. Targeted therapies towards the control of pro-inflammatory cytokines and chemokines, to inhibit immune cell infiltration and aberrant inflammatory signals and to enhance T cell activation that contributes to the disease pathology in pancreatitis and pancreatic cancer, might be helpful to inhibit pancreatitis progression to pancreatic cancer and metastasis.

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LIST OF ABBREVIATIONS

ADM	Acinar-ductal metaplasia
AIP	Autoimmune pancreatitis
ALDH1A1	Aldehyde Dehydrogenase 1 Family Member A1
ALI	acute lung injury

AP-1	Activator protein 1
ARID1A	AT-Rich Interaction Domain 1A
AsPC-1	Human pancreatic adenocarcinoma cells
ASTN1	Astrotactin 1
BAY11-7082	irreversible inhibitor of IKK α and phosphorylation of cytokine-inducible IκBα
Brca2	Breast Cancer Type 2 Susceptibility Protein
BxPC-3	Human pancreas adenocarcinoma cell line
C/EBP	CCAAT Enhancer Binding Protein Beta
Cap43	N-Myc Downstream Regulated 1
Capan-1	Human pancreatic ductal adenocarcinoma cell line
Capan-2	Human pancreatic ductal adenocarcinoma cell line
CC Chemokine	C-C motif chemokine
CCL18	C-C Motif Chemokine Ligand 18
CCL2	C-C Motif Chemokine Ligand 2
CCL20	C-C Motif Chemokine Ligand 20
CCL5	C-C Motif Chemokine Ligand 5
CCR2	C-C Motif Chemokine Receptor 2
CCR6	C-C Motif Chemokine Receptor 6
CD11b	CD11 Antigen-Like Family Member B
CD11c	CD11 Antigen-Like Family Member C
CD18	Integrin beta chain-2
CD206	Cluster of Differentiation 206
$CD4^+T$	Cluster of differentiation 4 T cells
$CD8^+T$	Cluster of differentiation 8 T cells
CDKN2A	Cyclin Dependent Kinase Inhibitor 2A
CFPAC-1	Pancreatic ductal adenocarcinoma cell line
COL6A5	Collagen Type VI Alpha 5 Chain
COX-2	Cyclooxygenase-2

CXCL1	C-X-C Motif Chemokine Ligand 1
CXCR2	C-X-C Motif Chemokine Receptor 2
CXCR4	C-X-C Motif Chemokine Receptor 4
DAMPS	Damage-associated molecular patterns
Dan-G cells	Human Pancreas cancer cell line
DCLK1	Doublecortin Like Kinase 1
DNAH11	Dynein Axonemal Heavy Chain 11
DNAH14	Dynein Axonemal Heavy Chain 11
DNMT1	DNA methyltransferase 1
DPC4	Deletion Target In Pancreatic Carcinoma 4
ED-B	Extra-domain B
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial–mesenchymal transition
ERK1/2	Extracellular signal-regulated kinases1/2
FAT3	FAT Atypical Cadherin 3
FLG	Filaggrin
GATA-1	GATA Binding Protein 1
GL13	Glioma-Associated Oncogene Family Zinc Finger 3
Gr-1	Ly-6G/Ly-6C
HMCN1	Hemicentin 1
HPAC	Homo sapiens pancreas adenocarcinoma
HPAF-II	Human pancreatic adenocarcinoma cell line
HTGP-AP	Hyperlipidemia/ hypertriglyceridemia pancreatitis
ICE	Ac-Tyr-Val-Ala-Asp-2,6-dimethylbenzoyloxymethylketone
IFN-γ	Interferon Gamma
IgG4	immunoglobulin G4
IKK2	I-Kappa-B Kinase 2
IKKβ	Inhibitor Of Nuclear Factor Kappa B Kinase Subunit Beta
IL-10	Interleukin-10

IL-11	Interleukin-11
IL-13	Interleukin-13
IL-13-PE	Pseudomonas exotoxin
IL-15	Interleukin-15
IL-17B	Interleukin-17B
IL-17RB	Interleukin-17 receptor B
IL-17RC	Interleukin 17 Receptor C
IL-1β	Interleukin-1β
IL-2	Interleukin-2
IL-21	Interleukin-21
IL-22	Interleukin-22
IL-23	Interleukin-23
IL-27	Interleukin-27
IL-4	Interleukin-4
IL-4Rα	Interleukin-4 receptor α
IL-6	Interleukin-6
IL-8	Interleukin-8
INK4A	Cyclin Dependent Kinase Inhibitor 2A
i-NKT	Invariant natural killer T
IRS954	TLR9 inhibitor
JAK	Janus Kinase
KPC mouse	PdxCretg/+ mouse
KRAS	Kirsten Rat Sarcoma Viral Proto-Oncogene
L19-IL2	L19-Interleukin-2
LAMP2	Lysosomal Associated Membrane Protein 2
LRP1B	Low-density lipoprotein receptor-related protein 1B
Ly-6C	Lymphocyte antigen 6 complex locus C1
Ly-6G	Lymphocyte antigen 6 complex locus G6D
MAPK	Mitogen-activated protein kinase

MCP-1	Monocyte chemoattractant protein-1
MIA PaCa-2	pancreatic carcinoma
MIP-1α	Macrophage Inflammatory Protein 1-Alpha
MIP-2	Macrophage Inflammatory Protein 2-Alpha
MLL2	Myeloid/Lymphoid Or Mixed-Lineage Leukemia 2
MLL3	Myeloid/Lymphoid Or Mixed-Lineage Leukemia 3
MMP-9	Matrix Metallopeptidase 9
MUC16	Mucin 16 Cell Surface Associated
NDRG1	N-Myc Downstream Regulated 1
NFATc4	Nuclear Factor Of Activated T Cells 4
NF-IL6	Nuclear Factor Of Interleukin 6
NF-κB	Nuclear Factor Kappa B Subunit 1 Nuclear Factor Kappa B Subunit 1
NK	Natural killer
NLRP3	NLR Family Pyrin Domain Containing 3
NOD	Nucleotide Binding Oligomerization Domain
OBSCN	Obscurin
p16	CDK4 Inhibitor P16-INK4
p21WAF1	Wild-Type P53-Activated Fragment 1
P2X7	Purinergic Receptor P2X 7
p65	NF-Kappa-B Transcription Factor P65
PAMPS	Pathogen-associated molecular patterns
PANC-1	Human pancreas duct epithelioid carcinoma
PANC-28	Human Pancreatic adenocarcinoma cell line
PanIN-1A	Pancreatic Intraepithelial Neoplasia 1A
PanIN-1B	Pancreatic Intraepithelial Neoplasia 1B
PanIN-2/3	Pancreatic Intraepithelial Neoplasia 2/3
PARP	Poly (ADP-Ribose) Polymerase 1
PCC	Pancreatic cancer cells

PCDH15	Protocadherin Related 15
PDA/PDAC	Pancreatic Ductal Adenocarcinoma
PD-L1	Programmed Cell Death 1 Ligand 1
PDTC	Pyrrolidine derivative of dithiocarbamate
POU2F3	POU Class 2 Homeobox 3
PREX2	Phosphatidylinositol-3,4,5-Trisphosphate Dependent Rac Exchange Factor 2
PSC	Pancreatic stellate cells
PXDN	Peroxidasin
RANTES	Regulated Upon Activation Normally T-Expressed And Presumably Secreted
Ras	Rat Sarcoma Viral Oncogene Homolog
RelA	Nuclear Factor NF-Kappa-B P65 Subunit
RNF43	Ring Finger Protein 43
SAP	Severe acute pancreatitis
SCIDγ mice	Severe Combined Immunodeficiency
SDF1α	Stromal Cell-Derived Factor 1
SMAD4	SMAD Mothers Against DPP Homolog 4
SNAIL-1	Snail Family Transcriptional Repressor 1
SOCS	Suppressor of cytokine signaling
SOX9	SRY-Box 9
STAT3	Signal transducer and activator of transcription 3
STING	Stimulator of interferon genes
SU.86.86	Human pancreatic adenosarcoma cell line
SYNE1	Spectrin Repeat Containing Nuclear Envelope Protein 1
T Reg cell	Regulatory T cell
T2DM	Type 2 diabetes
TGFBR2	Transforming Growth Factor Beta Receptor 2
Th1	Type 1 T helper
TLRs	Toll-like receptors

TNF-α	Tumor necrosis factor alpha
TP53	Tumor Protein P53
TPCK	Tosylphe-chloromethyl ketone
TRAIL	TNF-Related Apoptosis Inducing Ligand
U937	Human myeloid leukaemia cell line
WDFY4	WD Repeat- And FYVE Domain-Containing Protein 4
Wnt	Wingless/Integrated
WS-4	Anti-IL 8 antibody
ZNF559	Zinc Finger Protein 559
α-SMA	α-smooth muscle actin

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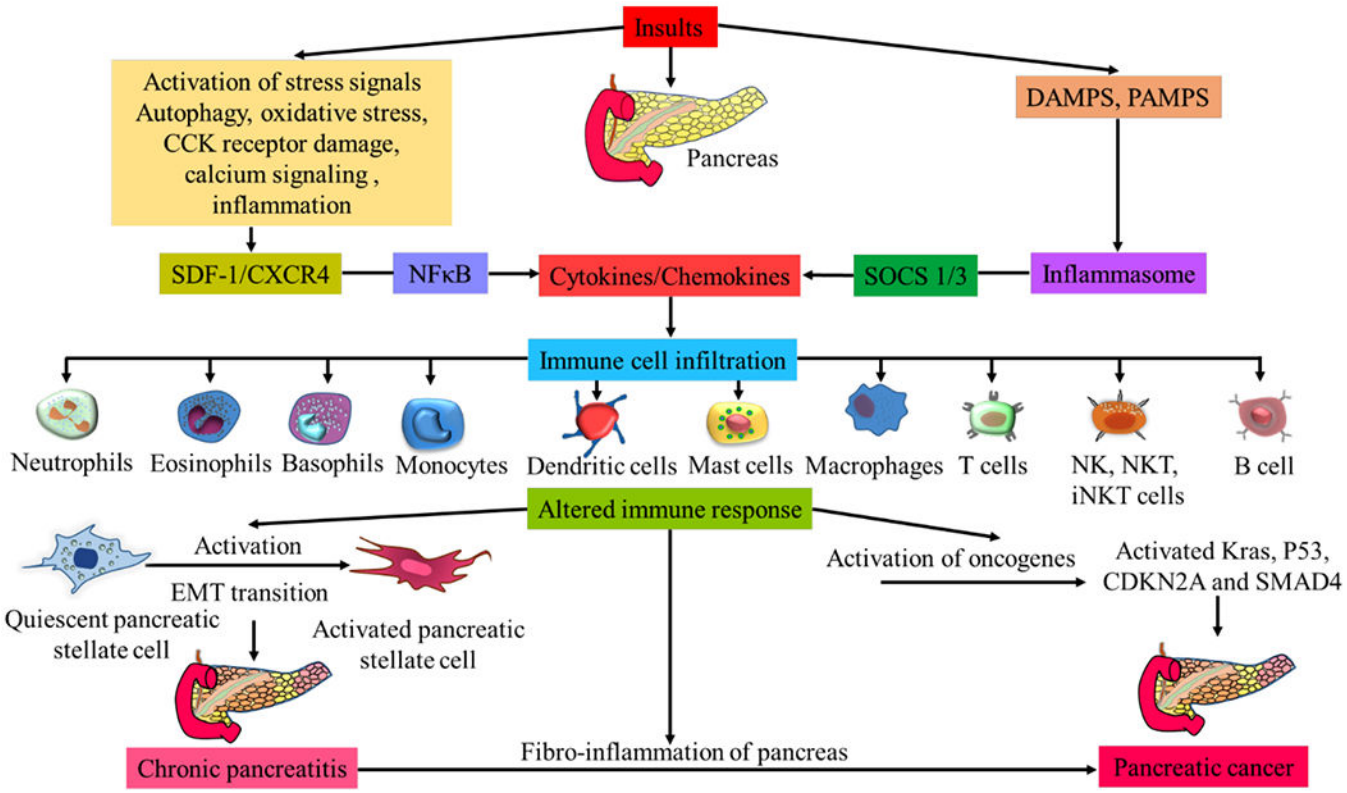

Fig. (1).

Activation of cytokines and chemokines, induction of inflammatory signaling mechanisms, immune cell infiltration, and fibro-inflammation in pancreatitis and progression to pancreatic cancer. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

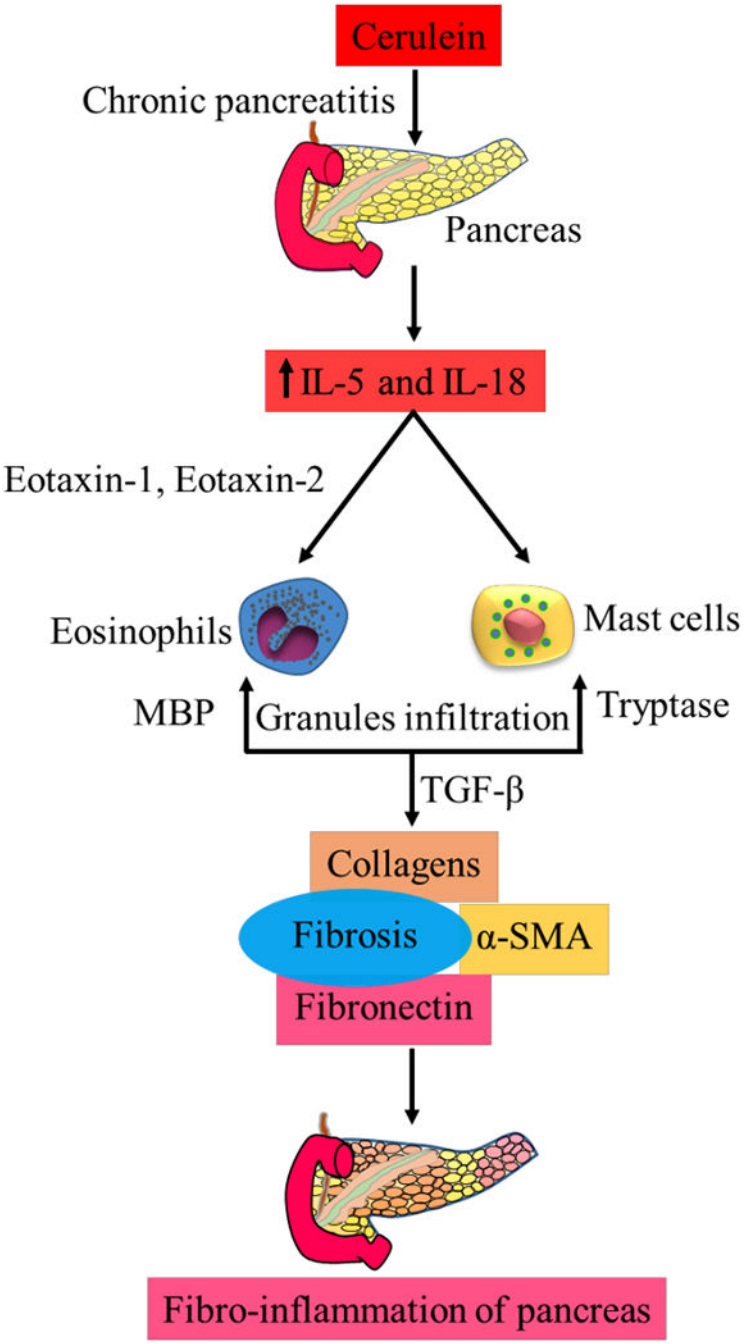

Fig. (2).

Role of eosinophils and mast cells in the initiation and progression of pancreatitis pathogenesis *via* induction of IL-5, IL-18 and fibrosis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

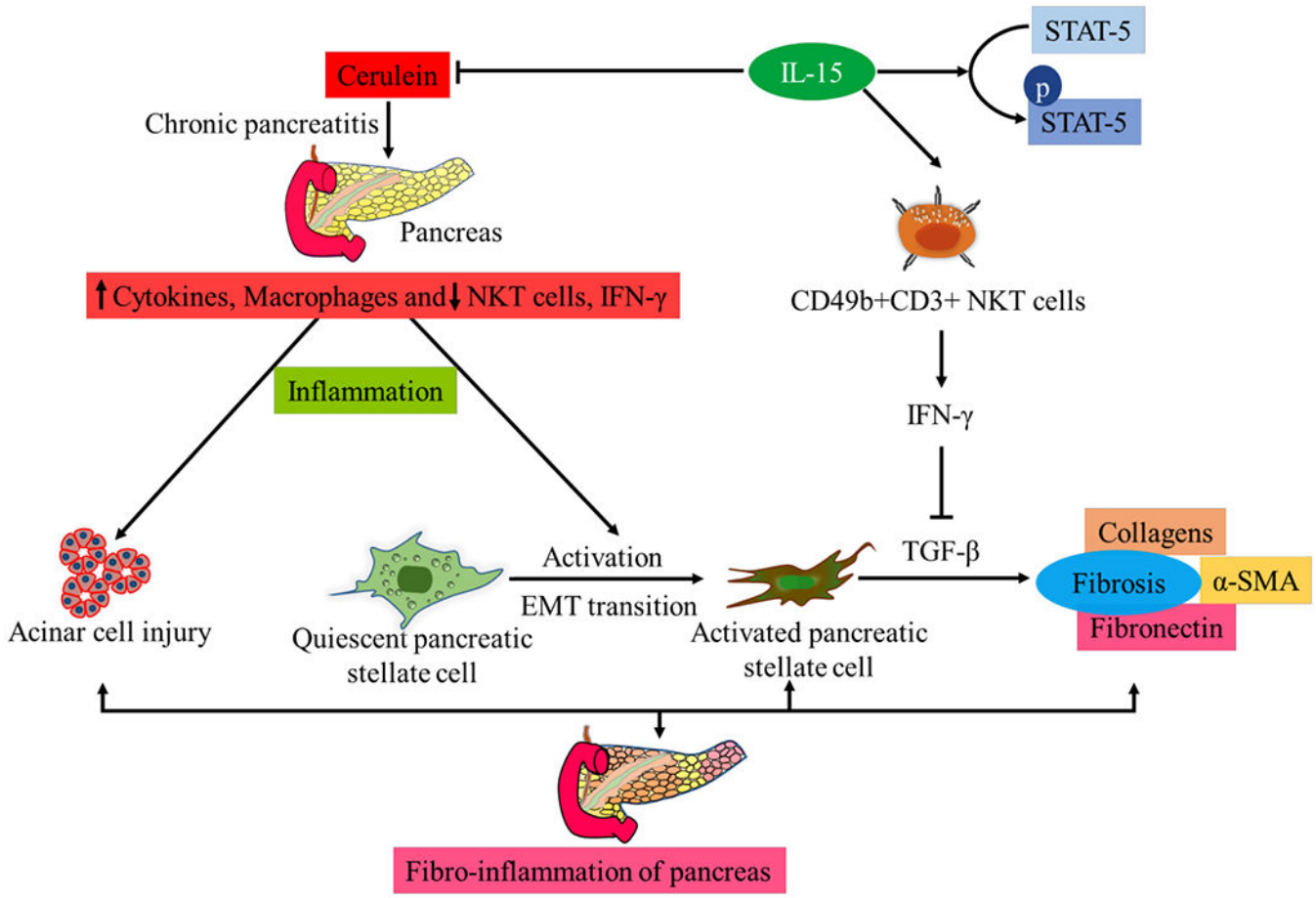

Fig. (3).

IL-15 treatment mitigates cerulein induced pancreatitis *via* induction of i-NKT cells, IFN-γ and inhibits pancreatic inflammation and fibrosis. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

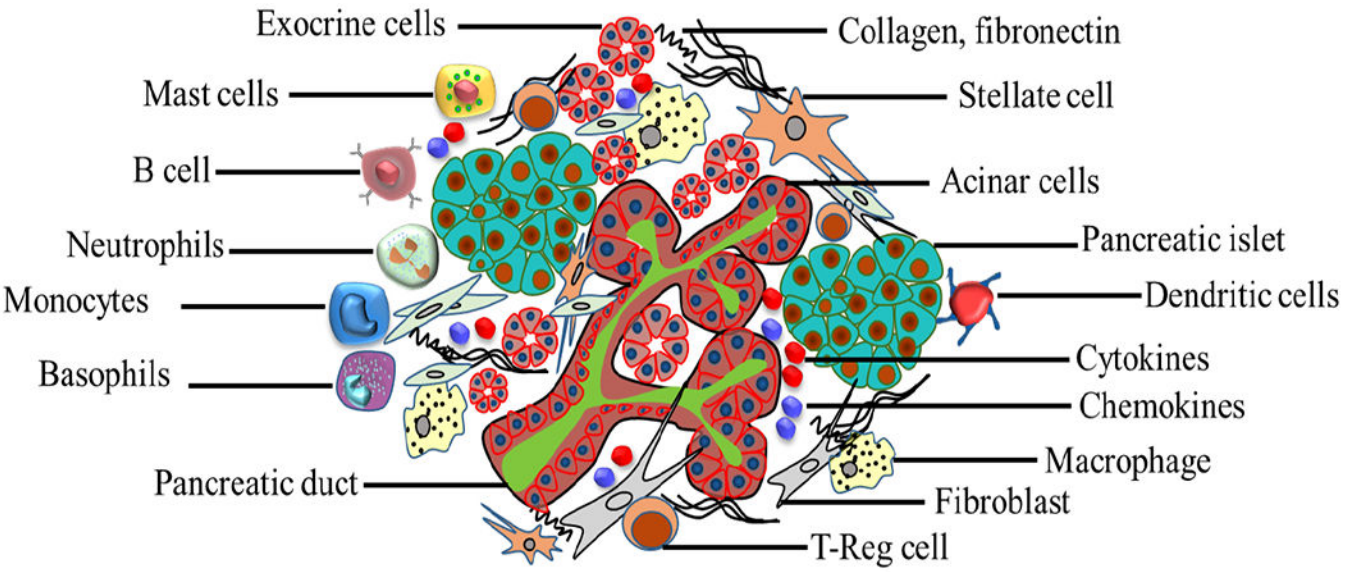

Fig. (4).

Pancreatic cancer microenvironment. (*A higher resolution / colour version of this figure is available in the electronic copy of the article*).

Table 1.

Cytokine inhibitors/ inducers for pancreatitis and pancreatic cancer.

Cytokine Inhibition/Induction for Pancreatitis Therapy						
S.NO	**Cytokine**	**Cytokine Inhibitor/Inducer**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	IL-1β	Ac-Tyr-Val-Ala-Asp-2,6-dimethylbenzoyloxymethylketone (ICE)	Male Wistar rats	Pancreatitis by retrograde infusion of 0.1 ml/100 g body weight; 5% sodium taurocholate solution into the biliopancreatic duct	Myeloperoxidase inhibition, neutrophils, lymphocytes, and monocytes were attenuated	[33]
2.	IL-4Rα	IL-4Rα signaling blockade peptide (a potent cyclic peptide ~1.5 kD) (50 μg per mouse, 100 μl daily for 5 days per week x 2 weeks)	C57BL/6 mice	Chronic pancreatitis by caerulein (50-μg kg^{-1} bodyweight) administration	The inhibitor (1μM) decreased mouse IL-4/IL-13-induced M2 polarization and CD206 expression, pancreas size, and α-SMA expression, pancreas fibrosis, blockade of alternative activation of pancreatic macrophages, and inhibited hPSC-mediated M2 polarization of human macrophages	[34]
3.	IL-8	Anti-IL 8 antibody (WS-4)	Rabbits	Pancreatitis by retrograde injection of 5% chenodeoxycholic acid into the pancreatic duct and duct ligation	Reduced the acute lung injury, via inhibition of circulating IL-8 and TNF-α, and CD11b/CD18 in lung tissue	[35]
4.	IL-10	Recombinant IL-10	Mice	Acute pancreatitis by cerulein (50 μg/kg body weight) administration	reduction of TNF α and acinar cell necrosis	[36]
		intraperitoneal IL-10	Sprague-Dawley rats	Acute pancreatitis induced by intravenous cerulein (8.5 μg x kg(−1) administration	Reduction in serum amylase, TNF-α levels, and pancreatic edema	[37]
5.	IL-11	Recombinant human Interleukin-11	Male BALB/c mice	cerulein (50 μg/kg) induced Acute necrotizing pancreatitis	Decreased amylase and lipase levels, serum and intrapancreatic TNF-α, pancreatic injury including edema, inflammatory cell infiltration, and hemorrhage	[38]
6.	IL-15	Recombinant IL-15 (5μg /mice)	Balb/c mice	Chronic pancreatitis by cerulein (50 μg/kg body weight) administration	Negotiated IFN-γ-responsive iNKT cells in the blood and tissue and protects cerulein-induced pancreatic fibro-inflammation in mice	[39]
7.	IL-22	Recombinant IL-22 or adenovirus IL-22	C57BL/6 mice and IL-22 TG mice	Cerulein-induced acute and chronic pancreatitis	IL-22 treatment ameliorates cerulein-induced pancreatitis by inhibiting autophagy	[40]
8.	TNF-α	CNI-1493 10mg/kg	NIH Swiss mice	Pancreatitis by cerulein (50 μg/kg body weight) administration	Inhibited serum amylase, lipase, and pancreatic necrosis	[41]
Cytokine Inhibitor/Inducer for Pancreatic Cancer Therapy						
S.NO	**Cytokine**	**Cytokine Inhibitor/Inducer**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	IL-2	L19-Interleukin-2 (L19-IL2), consisting of the human singlechain Fv antibodyL19, highly specific for the extra-domain B (ED-B) of fibronectin, and the human cytokine IL-2	Female NMRI nude mice and human pancreatic carcinoma tissues	Orthotropic mouse models for pancreatic cancer	Inhibited tumor growth, metastasis, long-term tumor control with the induction tumor necrosis and inhibition of tumor cell	[42]

Cytokine Inhibition/Induction for Pancreatitis Therapy						
S.NO	**Cytokine**	**Cytokine Inhibitor/Inducer**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
					proliferation, increase of macrophages and NK cells in the tumor tissue	
2.	IL-6	LLL12, a nonpeptide, cell-permeable small molecule	Pancreatic cancer cell lines	PANC-1 and ASPC-1 pancreatic cancer cell lines	Blocked exogenous IL-6-induced STAT3 phosphorylation and nuclear translocation in both PANC-1 and ASPC-1 pancreatic cancer cell lines	[43]
		Anti-IL-6-receptor antibody tocilizumab; fusion protein sgp130Fc	An orthotopic model of human Colo357 cells in SCID/bg mice	Blocks IL-6 classical and trans-signaling	Reduced primary tumor weight metastases and tumor reoccurrence	[44]
3.	IL-12	IL-12 cDNA	Female BALB/c nu/nu and BALB/c scid/scid mice	Retrovirally transduced with IL-12 cDNA into nude mice	In IL-12-mediated antitumor effect, granulocytes are candidate cells and impaired tumorigenicity of human pancreatic cancer cells	[45]
4.	IL-13	Recombinant immunotoxin, a fusion of IL-13 and Pseudomonas exotoxin (IL-13-PE) and gemcitabine	Pancreatic cell lines and mouse model human pancreatic ductal cancer	Targeting IL-13Rα2 in pancreatic cell lines and an orthotopic mouse model of human PDA	Cytotoxicity to two pancreatic cancer cell lines, complete eradication of tumors and enhanced survival rate of mice	[46]
5.	IL-15	recombinant human IL-15 (10 ng/ml)	Pancreatic cancer cells (PCC) and pancreatic stellate cells (PSC)	NK cell-mediated killing of PCC and PSC cell lines	Pancreatic cancer cells and pancreatic stellate cells killing via upregulation of TIM-3 and NKG2D	[47]
6.	IL-17	Anti-IL-17RB antibody	NOD/SCIDγ mice, HPAF-II, BxPC3, Capan2, CFPAC-1, HPAC, SU.86.86, and MIA PaCa-2 human pancreatic cancer cells	Targeting IL-17B–IL-17RB signaling	Blocked tumor metastasis and promote survival in a mouse xenograft model	[48]
7.	IL-21	Cetuximab treatment in combination with mouse IL-21 adjuvant therapy	Human pancreatic cells and mouse tumor model	NK cells from normal donors or with pancreatic cancer, human pancreatic cancer cells, mouse subcutaneous and intraperitoneal model of pancreatic cancer	NK cell activation and inhibition of tumor growth	[49]
8.	IL-23	The murine IL-23 cDNA transfected Dendritic cell vaccine	Mouse	β-elemene combined with interleukin-23 gene-modified dendritic cells on murine pancreatic carcinoma	IL-23 increased the antigen-presenting ability of DCs specific Th1-type and CTL response against pancreatic carcinoma cells induced auto-immunity against pancreatic carcinoma	[50]
9.	IL-24	Adenovirus-mediated human IL-24 gene therapy	Human pancreatic carcinoma cell line, patu8988, nude mice bearing patu8988 tumors	Adenovirus (AdV)-mediated IL-24 gene therapy on human pancreatic carcinoma	Inhibited pancreatic carcinoma growth, tumor suppression by downregulating the vascular endothelial growth factor, CD34, and Bcl-2, and inhibiting tumor angiogenesis.	[51]
10.	IL-27	IL-27 (20 ng/ml)	Human pancreatic cell lines PANC-1, MiaPaCa-2, U937 cells, and M2 macrophages	IL-27 in the regulation of phenotypes and functions of tumor-associated macrophages	IL-27 decreased M2-polarized tumor-associated macrophages (TAM) and increased M1-polarized TAMs. IL-27	[52]

Cytokine Inhibition/Induction for Pancreatitis Therapy						
S.NO	**Cytokine**	**Cytokine Inhibitor/Inducer**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
					inhibits proliferation, migration, and invasion of pancreatic cancer cells	
11.	IFN-γ	Recombinant human IFN-γ	Human pancreatic carcinoma cells AsPc-1, Capan-1, and Capan-2, Dan-G cells	IFN-γ effects on growth and survival in human pancreatic cancer cells.	Inhibited pancreatic cancer cells growth, showed apoptosis by DNA fragmentation and PARP cleavage, and upregulation of procaspase-1 accompanied by proteolytic activation.	[53]

Table 2.

Chemokine inhibitors for pancreatitis and pancreatic cancer.

Chemokine Inhibition for Pancreatitis Therapy						
S.NO	**Chemokine**	**Chemokine Inhibitor**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	CXCR2	Antileukinate (52.63 mg/kg, s.c.)	Swiss mice	Caerulein (50 μg/kg/h) induced acute pancreatitis mediated pancreatic and lung injury	Reduced plasma amylase, pancreatic water content, pancreatic myeloperoxidase activity, pancreatic MIP-2 levels pancreas, and lung myeloperoxidase activity	[86]
2.	CCL2/MCP-1	Pepducin	BALB/c mice	Acute and chronic pancreatitis induced by intraperitoneal administration of (0.2 mg/kg body weight) caerulein	The decrease in pancreatitis induced neutrophils, macrophages, and acinar cell damage	[87]
		Bindarit; inhibitor of MCP-1,	A rat model of severe acute pancreatitis (SAP)	SAP model was induced by retrograde infusion of (4%) sodium taurocholate into the biliopancreatic duct	Bindarit ameliorates SAP by inhibiting serum amylase MCP-1, levels, and pancreatic damage	[88]
Chemokine Inhibitors for Pancreatic Cancer Therapy						
S.NO	**Chemokine**	**Chemokine Inhibitor**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	CXCR2	Anti-CXCR2 antibody	BxPC-3 cell line	Secreted CXC protein levels	Inhibition of neovascularization	[89]
		CCR2 inhibitor PF-04136309 in combination with Folfirinox chemotherapy (oxaliplatin and irinote-can plus leucovorin and fluorouracil)	Human subjects with borderline resectable and locally advanced pancreatic cancer	Single-centre, open-label, dose-finding, non-randomised, phase 1b trial	Objective tumor response, with local tumor control in 32 (97%) patients.	[90]
		AZ13381758 is a potent inhibitor of both murine and human CXCR2	KPC mice	Immunotherapy by CXCR2 Inhibition in pancreatic ductal adenocarcinoma	Cxcr2 deficiency in KPC mice, Ly6G+ cell depletion, or CXCR2 inhibition suppresses metastasis in PDAC and enhance response to chemotherapeutics and immunotherapy to prolong survival.	[87]
		CXCR2 inhibitor repertaxin and SB225002	Mice bearing autochthonous PDAC. Ptf1acre/+; LSL-KrasG12D/+; Tgfbr2flox/flox	NF-κB inhibitor SC-514 (an IκB kinase-2 inhibitor) showed significant suppression of the CXCL1 and −5 expression	CXCR2 inhibitors repertaxin inhibited the PDAC–induced CTGF upregulation and tumor growth and exhibited antitumor effects in Ptf1acre/+; LSL-KrasG12D/+; Tgfbr2flox/flox PDAC mice	[91]
2.	CCR5	-	Human and mouse	Human pancreatic adenocarcinoma and a murine pancreatic tumor model (Pan02)	Reduction of T reg cells migration to tumors	[92]
3.	CXCL12	AMD3100, an inhibitor of chemokine (C-X-C motif) receptor 4, a CXCL12 receptor,	KPCD (LSL-KrasG12D/+; LSL-Tp53R172H/+; Pdx-1-Cre; FAP-DTR) mice, pancreatic cancer cell lines derived from tumors arising	Targeting CXCL12 with anti–PD-L1 immunotherapy in pancreatic cancer	Revealed antitumor effects and greatly diminished cancer cells	[93]

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Chemokine Inhibition for Pancreatitis Therapy						
S.NO	**Chemokine**	**Chemokine Inhibitor**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
			in KPC mice (TB32964, K8484), LL2 cell line expressing chicken OVA (LL2/OVA)			
4.	CXCR4	Zerumbone inhibitor of CXCR4	PANC-1 (pancreatic duct cell carcinoma), PANC-28 (pancreatic carcinoma), MIA PaCa-2 (pancreatic carcinoma), AsPC-1 (pancreatic adenocarcinoma)	Zerumbone, a component of subtropical ginger (Zingiber zerumbet), as a regulator of CXCR4 expression leading to inhibition of CXCL12-induced invasion of pancreatic tumor Cells	Suppression of CXCR4 NF-κB, inhibition of CXCL12-induced invasion of pancreatic cancer cells	[94]
5.	CCL21	Recombinant murine CCL21	C57BL/6	CCL21 mediated anti-tumor cellular immunity	Intratumoral injection of CCL21 into pancreatic tumors reduced the growth of distant tumors and treated tumors, immune cell infiltration of the tumor mass, delayed growth of treated tumors, and generate a tumor-specific cellular immune response	[95]
6.	CXCL2	Triptonide	Patu8988 and Panc1 cancer cells and *in vivo* mouse model of matrigel assay	Pancreatic cancer cell-mediated vasculogenesis	Inhibition of CXCL2 via reduction of gene promoter activity and suppresses pancreatic cancer cell-mediated tumor vasculogenic mimicry by reducing tumor cell migration and invasion and inhibiting expression of VE-cadherin and CXCL2	[96]

Table 3.

Immune cell inhibitors/ inducers for pancreatitis and pancreatic cancer.

Immune cell inhibitors/inducers for pancreatitis therapy						
S.NO	**Immune Cells**	**Immune Cell Inhibitors**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	Neutrophils	Neutrophil–depleting anti–Ly6G antibody	BALB/c mice	Acute and chronic pancreatitis induced by intraperitoneal administration of caerulein (0.2 mg/kg body weight)	A decrease in pancreatitis induced neutrophils, macrophages, and acinar cell damage	[87]
		Anti-mouse lymphocyte function antigen–1 antibody (5mg·g-1; i.p.)	C57BL/6 male mice	Pancreatitis was induced by retrograde infusion of sodium taurocholate into the pancreatic duct in mice	Reduced taurocholate-induced amylase levels, accumulation of neutrophils, production of CXC chemokines and tissue damage in the pancreas, leucocyte adhesion in postcapillary venules of the pancreas, attenuation of pulmonary infiltration of neutrophils	[148]
2.	i-NKT cells	Recombinant IL-15 (5ug/ mice)	Balb/c mice	Chronic pancreatitis by cerulein administration (50 μg/kg body weight)	Negotiated an increase of IFN-γ-responsive iNKT cells in the blood and tissue and protected cerulein-induced pancreatic fibro-inflammation in mice	[59]
Immune Cell Inhibitors for Pancreatic Cancer Therapy						
S.NO	**Immune Cells**	**Immune Cell Inhibitors**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	Dendritic cells	Dendritic cell vaccine modified with tumor lysate and IL-18 gene	BALB/C	Pancreatic carcinoma induced with Dimethylbenzanthracene	Induced tumor cell death and promoted NK and T cells to secrete IFN-γ and produced a specific and effective immune response against pancreatic carcinoma cells	[50]
2.	Macrophages	Liposomal clodronate	LSL-KrasG12D/+;LSL-Trp53R172H/+;Pdx-1-Cre; CD11b-DTR (KPCD) mice	A genetic model of pancreatic cancer	Reduced CD11b-positive macrophages, tumor incidence, and growth slightly reduced, metastasis formation in the liver and lungs were significantly diminished after macrophage depletion, significantly impaired angiogenesis, reduced circulating vascular endothelial growth factor levels and circulating CD4+CD25+ T cells	[149]
3.	T reg cells	Low-dose gemcitabine	Pancreatic carcinoma cells were injected orthotopically in C57Bl/6 mice	Orthotopic Panc02 model of pancreatic cancer	Selectively diminishes Treg prevalence at the tumor site and improves survival in pancreatic cancer	[150]

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Table 4.

Inflammation signaling inhibitors for pancreatitis and pancreatic cancer.

Inflammation Signaling Inhibitors for Pancreatitis						
S.NO	**Immune Cells**	**Inflammation Signaling Inhibitors**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	NLRP3	INF-39 (50 mg/kg body weight)	C57BL/6 mice	Mouse model of severe acute pancreatitis by cerulean administration for 12 hours (50 μg), followed by one administration of LPS (10 mg/kg)	Reduce serum, amylase, IL-1β, TNFα, IL-6, and severity of severe acute pancreatitis	[189]
2.	NF-κB	NF-κB essential modifier-binding domain peptide	Swiss Webster mice	Cerulein (50 μg/kg) induced acute pancreatitis	Decreased inflammation in the pancreas, hemorrhage in the lungs, and myeloperoxidase activity in pancreas and lungs.	[190]
		Pyrrolidine derivative of dithiocarbamate (PDTC)	Rats	Taurocholate induced pancreatitis	Attenuated NF-κB activation and improved survival of the rats	[191]
		Withaferin A, an inhibitor of NFκB	C57BL/6 mice	Acute and chronic pancreatitis by cerulein (50 μg/kg) administration	Blocks translocation of the p65 subunit and prevents caspase 3, IL-6, nitric oxide synthase 2, TNF-α; Inhibition of the ER stress pathway, PERK, ATF6, ATF4, ERN1, CHOP, Xbp1, HMGB1, Pycard and inflammasome signaling IL-18, IL-1β, NLRP3,	[192]
Inflammation Signaling Inhibitors for Pancreatic Cancer						
S.NO	**Immune Cells**	**Inflammation Signaling Inhibitors**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
1.	SDF-1α/ CXCL12-CXCR4	CXCR4 antagonist, AMD3100	Human pancreatic cancer cell lines Colo357, SW1990, AsPc1, BxPc3, CaPan1, HPAF II, CFPAC1, Panc1, MiaPaCa, Panc10. 05, Panc03.27, Panc02.03	Rescue effect of activated CXCL12–CXCR4 signaling	Halted CXCL12-induced pancreatic cancer cell growth and drug resistance	[193]
		CXCR4 antagonist, TN14003	Human pancreatic cancer cell lines (CFPAC-1, Capan-2, AsPC-1, PANC-1, BxPC-3, and SUIT-2	CXCR4 antagonist for SDF1 induced migration and invasion of human pancreatic cancer	Blocked SDF-1-induced migration and invasion of cancer cells via the alteration in phosphorylation of MAPK and reduction of actin polymerization.	[194]
		Chloroquine	Tumor tissues resected from patients with PDAC before any neoadjuvant radiation or chemotherapy were implanted into immunocompromised mice, to establish low passage tissue xenografts, human pancreatic cancer cell lines Panc1, BxPC3, and 8988 T	Targeting pancreatic cancer stem cells via inhibition of CXCR4	Inhibitory effect of chloroquine by inhibition of CXCL12/CXCR4 signaling, resulting in reduced phosphorylation of ERK and STAT3, reduction in sonic hedgehog-induced chemotaxis and down-regulation of downstream targets in highly tumorigenic and metastatic cancer stem cells	[195]
2.	NLRP3	CRID3 blocks ASC oligomerization in the NLRP3 inflammasome	WT, ASC−/−, and caspase-1−/− mice	Orthotopically implanted with KPC-derived tumor cells in mice	CRID3 offered synergistic efficacy when combined with TLR9 inhibition and reduced	[196]

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Inflammation Signaling Inhibitors for Pancreatitis						
S.NO	**Immune Cells**	**Inflammation Signaling Inhibitors**	**Study Organism**	**Experimental Study**	**Biological Effects**	**References**
					PANIN lesions in pancreatic ductal adenocarcinoma.	
3.	NF-κB	Pyrrolidine derivative of dithiocarbamate (PDTC), Tosylphe-chloromethyl ketone (TPCK)	Human pancreatic periacinar myofibroblasts	Assessed IL-8, MCP-1, RANTES, and MIP1α, activation of NF-κB and NF-IL-6	Reduced the IL-1β– or TNFα– induced chemokine gene expression	[197]
		Inhibitor of κB kinase (IKK) β	Pancreatic cancer cell lines, male athymic nu/nu mice	NDRG1/Cap43-induced reduction of tumor growth and angiogenesis	Reduced IKKμ expression in cells overexpressing NDRG1/Cap43, resulted in a reduction of both nuclear translocation of p65 and p50 and their binding to the NF-κB motif and reduced tumor growth and angiogenesis of pancreatic cancer	[198]