Inflammation and pancreatic cancer: An updated review

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Abstract
Pancreatic cancer is a devastating disease with poor prognosis in the modern era. Inflammatory processes have emerged as key mediators of pancreatic cancer development and progression. Recently, studies have been carried out to investigate the underlying mechanisms that contribute to tumorigenesis induced by inflammation. In this review, the role of inflammation in the initiation and progression of pancreatic cancer is discussed.

Keywords: Inflammation, pancreatic cancer, tumorigenesis

INTRODUCTION
Pancreatic cancer, particularly pancreatic adenocarcinoma, is the fourth leading cause of cancer deaths in the Western world, and prediction curves predict that it will be the second most common cause around 2030 just after lung cancer.11 Initiation and progression of this disease results from the interaction of genetic events combined.2,3 The existence of a link between chronic inflammation and cancer has been recognized for more than 150 years, because of the pioneering work of Rudolf Virchow, particularly recognized in the context of pancreatic ductal adenocarcinoma (PDAC).4,5 Many human cancers result directly from chronic inflammation. However, even in cancers with no preceding inflammation, tumor-elicited inflammation, inflammatory secretions, and infiltrating immune cells play critical roles in cancer initiation, promotion and progression to malignant metastasis. The mechanisms involved in inflammation associated with cancer are not completely understood. This review sheds light on the relationship between pancreatitis and pancreatic cancer [Table 1].

NUCLEAR FACTOR-κB (NF-κB)
NF-κB is constitutively activated in pancreatic cancer,6-8 and there is substantial evidence in pancreatic cancer that supports the involvement of a dense stroma with infiltration of innate immune cells.9,10 NF-κB is a transcription factor known to participate in the communication between tumor and immune cells.11 The NF-κB subunit p65 is ubiquitously expressed in mammalian cells, and when constitutively activated, it is associated with cellular transformation.12 The abnormal activation of NF-κB contributes to significant cell proliferation and migration in pancreatic cancer.13-15 There are two distinct pathways involved in the regulation of NF-κB activation: the canonical and noncanonical pathways. The canonical pathway is controlled by IkB kinase (IKK) complex, which comprises IKKa, IKKb, and IKKc. The noncanonical pathway is regulated by IKKa and the NF-κB-inducing kinase.16 In preneoplastic cells, the p65 subunit of NF-κB functions as a tumor suppressor by maintaining cells in senescence.17 Furthermore, following loss of tumor suppressors and

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Table 1: A summary of inflammation and pancreatic cancer

| Inflammatory factors | Role |
|----------------------|------|
| NF-κB                | Switches from tumor suppressor to tumor promoter during an early phase of tumorigenesis |
| IL-6                 | Promotes pancreatic intraepithelial neoplasia |
| TLRs                 | TLR4 promotes angiogenesis and TLR9-induced epithelial cell proliferation |
| TGF-β                | Plays tumor promoter through genomic instability, neo-angiogenesis, immune evasion, cell motility, and metastasis |
| TNF-α                | Activates transcription factor NF-κB |
| IL-1-α               | Favors metastatic and invasive behavior of pancreatic cells by inducing k63-linked polyubiquitination of TRAF6 leading to activation of NF-κB |
| IL-4                 | Increases expression of antiapoptotic proteins and mediates the downregulation of cell adhesion molecules |
| IL-8                 | Mimics VEGF and promotes angiogenesis |
| IL-1-β               | Stimulates autophagy and induces endoplasmic reticulum stress |
| COX-2                | A key enzyme responding to various cytokines and growth factor |
| SPINK-1              | Mutations lead to premature trypsinogen activation and resultant hereditary pancreatitis |
| ROS                  | Induces oxidative damage to DNA, lipids, and proteins |
| CP                   | KRAS mutations are found in patients with CP |
| Autophagy            | Cleaning of damaged organelles to guarantee pancreatic cell survival |
| CXCL-12              | Enhances growth and restricts immune surveillance through local autocrine and paracrine mechanisms |

NF-κB: Nuclear factor-κB; IL-6: Interleukin-6; TLR: Toll-like receptor; TGF: Transforming growth factor; TRAF6: TNF-receptor-associated factor 6; TNF: Tumor necrosis factor; VEGF: Vascular endothelial growth factor; COX: Cyclooxygenase-2; SPINK1: Serine protease inhibitor Kazal type-1; ROS: Reactive oxygen species; CP: Chronic pancreatitis

escape from senescence, expression of oncogenic Ras causes p65 to switch its function to a tumor promoter, to protect transformed cells against immune surveillance. This concept of NF-κB switching from a tumor suppressor to tumor promoter during an early phase of tumorigenesis was recently supported in genetically engineered mouse model of pancreatic cancer. Ongoing research did indicate that NF-κB is able to modulate inflammatory macrophages through direct regulation of GDF-15. GDF-15 is highly expressed in pancreatic cancer compared with other cancers. Growth and differentiation factor 15 (GDF-15), also known as macrophage inhibitory cytokine 1 (Mic-1), is an NF-κB-regulated gene whose production by tumor cells and signaling in macrophages serve as an important promoter of early cancer development. Secreted GDF-15 inactivates tumor infiltrating macrophages by negatively regulating transforming growth factor (TGF)-B-activated kinase 1 (TAK1), which in turn causes NF-κB activity to be downregulated expression of NF-κB target genes Tnf and iNOS. In the absence of TNF and NO, macrophages are no longer able to eliminate tumor cells, thus allowing the expansion of a developing tumor. GDF-15 is limited to pancreatic cancer, because immune surveillance is considered a general feature of tumorigenesis.

INTERLEUKIN-6 (IL-6)

Chronic inflammation can lead to production of cytokines that upregulate proinflammatory cytokines, such as interleukin-6 (IL-6), and affects progression of pancreatic cancer. IL-6 activates certain intrinsic molecular pathways through specific receptors, ligands and enzymes, with biologic response of cell and tissue, for example, Janus-Kinase-Signal Transducer and Activator of Translation3 (JAK-STAT3), Mitogen-activated protein kinase (MAPK), and androgen receptor. IL-6 promotes pancreatic intraepithelial neoplasia (PanIN). The myofibroblast-like pancreatic stellate cells (PSCs) reside in a quiescent state in the normal pancreas, but transition to an activated state under pathological conditions such as inflammation or cancer. PSC secretion contains high levels of IL-6, which can promote pancreatic cancer cell proliferation through Nrf2-mediated metabolic reprogramming. IL-6-JAK2-STAT3 promotes pancreatic growth and progression. This is inhibited naturally by SOCS3 which downregulates the molecular pathway and overall prevents cell proliferation. During oncogenesis, IL6/STAT3 controls restraining action of SOCS3 through hypermethylation of its promoter by increasing DNA methyltransferase1. IL-6 can independently activate Pim-1-kinase, a proto-oncogene target of the STAT3. The serine/threonine kinase activation is closely related to pancreatic cancer oncogenesis and tumor transformation. Associated with the progression of cell cycle and linked to the G1/S and G2/M checkpoints, Pim-1-kinase is required in cell proliferation. Moreover, the enzymes are implicated in the synthesis of certain transcription factors, cell survival by apoptosis avoidance, drug resistance by producing gemcitabine and erlotinib, and intrinsic irradiation resistance in pancreatic cancer. IL-6 through STAT3 activation confers PC cells’ anokis resistance, which finally enhances metastasis. Furthermore, the proinflammatory cytokine inhibits radiation-induced apoptosis along with the increasing expression of antiapoptotic proteins B-cell lymphoma (Bcl-2).

TOLL-LIKE RECEPTORS (TLRs)

Toll-like receptors (TLRs) are type I membrane receptors, pattern recognition receptors of the innate immune system. There is evidence of TLR involvement in pancreatic cancer. Inflammation of pancreas results in damage-associated molecular patterns (DAMPs) and growth factors such as vascular endothelial growth
factor (VEGF) during subsequent healing. DAMPs that arise from inflammation and cellular injury can stimulate TLRs and consequently induce TLR signaling that supports an inflammatory microenvironment. Enhanced expression of TLRs has been described in a variety of different tumor entities, and depending on the cancer type, it could be linked to either favorable or poor prognosis. TLR ligands are known to promote cancer cell survival, migration, and tumor progression. For example, TLR agonists have shown to induce tumor cell viability and metastasis in human lung cancer. It has been shown that TLR7 or -8 expression is associated with UICC stage in pancreatic cancer, and stimulation increases tumor cell proliferation and resistance to the cytostatic agent 5-fluorouracil in pancreatic cancer cells. Endogenous ligands, such as heat-shock proteins, fibrinogen, hyaluronic acid fragments, and high-mobility group box 1, arising from damaging events promoted through inflammatory processes, are known to induce TLR2, -4, and -9 which play a role in inflammation linked to pancreatic cancer. TLR4 signaling activates the PI3K-AKT pathway thereby inducing cancer cells to secrete multiple inflammatory mediators and cytokines. TLR4 promotes angiogenesis of pancreatic cancer through upregulating VEGF through PI3K-AKT. TLR9 ligation induced epithelial cell proliferation in PSCs. So far, single studies have shown that TLR2 is expressed in pancreatic cancer tissue and has been suggested as potential target for immunotherapy.

**TRANSFORMING GROWTH FACTOR-β (TGF-β)**

TGF-β signaling is one of the 12 core signaling pathways involved in pancreatic cancer. Mutation is at least one of the TGF-β signaling genes which occurs in 100% of the pancreatic cancer. TGF-β plays a tumor suppressor in early-stage pancreatic cancer by promoting apoptosis and inhibiting epithelial cell cycle progression but plays a tumor promoter in late stage by genomic instability, neangiogenesis, immune evasion, cell motility, and metastasis. TGF-β is a cytokine with a dichotomous role in oncogenesis. In normal tissue development and early oncogenesis, the TGF-β signaling complex is a cell cycle regulator and induces apoptosis. The canonical pathway of TGF-β signaling starts with binding two TGF-β receptor type II (TGF-β RII) to two TGF-β receptor type I (TGF-β RI) to activate SMAD pathway. The receptors dimerize, when the ligand binds, triggering the activation of TGF-β RI kinase activity and switching it to a docking site for SMAD proteins. SMAD2 and SMAD3 are activated by the TGF-β RI. Once phosphorylated by TGF-β RI, SMAD2 and -3 dimerize forming the SMAD 2/3 complex. The SMAD 2/3 dimer joins with SMAD4, creating a hetero-hexameric complex. TGF-β/SMAD4 signaling pathway controls the signal transduction from cell membrane to nucleus and is responsible for a wide range of cellular processes, including proliferation, differentiation, apoptosis, migration, as well as cancer initiation and progression. Therefore, as the core mediator of canonical TGF-β signaling pathway, SMAD4 plays a pivotal role in the switch of TGF-β function on tumorigenesis.

**TUMOR NECROSIS FACTOR-α (TNF-α)**

Tumor necrosis factor-α (TNF-α) is a master regulator of inflammation and a key player in the cytokine network. TNF-α is a type II transmembrane protein with signaling potential as a membrane-integrated protein or a soluble cytokine released by proteolytic cleavage. There are several reports emphasizing the detrimental functions of TNF-α in pancreatic cancer. Previsouly, it has been shown that TNF-related apoptosis ligand (TRAIL) could promote tumor growth in murine pancreatic cancer by editing the tumor’s immunological environment. There are two specific reports for TNF-α: TNFR1 and TNFR2. TNFR1 is associated with inflammation by activation of the transcription factor NF-kB, JNK, and p38-MAPK. TNFR1 activation causes formation of caspase-containing complexes and through multiple complex pathways including activation of the proapoptotic Bcl-2 family proteins and reactive oxygen species (ROS)—inducing apoptosis. TNFR2 mediates anti-inflammatory signaling. Egberts et al. have shown that for human pancreas cell lines, stimulation with TNF-α strongly increased invasiveness with only a moderate antiproliferative effect. TNF-α can be produced by tumor cells, and its presence in the tumor microenvironment further stimulates the production of other cytokines and chemokines. This results in the enhancement of primary tumor growth and metastases, angiogenesis, and chemoresistance, and the immune evasive tumor microenvironment is established.

**INTERLEUKIN-1-α (IL-1-α)**

IL-1-α is abundantly present in the tumor microenvironment and exerts multiple effects in the tumor stroma, including tumor-promoting effects. In pancreatic cancer, IL-1-α is expressed exclusively by the malignant cells of the tumor and is immunohistochemically detected in most tumors. IL-1-α-positive pancreatic cancer cell lines were shown to induce a specific inflammatory profile of the PSCs, and under IL-1-α stimulation, PSCs induce migration of PDAC cells in vitro. Moreover, induction of IL-α expression
in pancreatic cancer cell lines has shown to promote metastatic and invasive behavior in an orthotopic mouse model.\[82\] In the presence of IL-1-α, a specific expression profile was induced in PSCs, which was characterized by increased expression of MMP1 and MMP3 as well as reduced levels of MMP2, TIMP2 and TIMP3. TIMP3 has previously been found to preferentially inhibit the activity of MMP1 and MMP3,\[83\] and reduced expression of TIMP3 could enhance their proteolytic activity, resulting in remodeling of the tumor stroma. Induction of IL-1-α expression in pancreas cell lines has shown to favor their metastatic and invasive behavior in vitro and in preclinical models.\[82\] IL-1-α has been detected in a majority of pancreatic cancers, and high expression is associated with poor clinical outcome.\[89\] Moreover, binding of IL-1-α to its receptor induces k63-linked polyubiquitination of TNF-receptor-associated factor 6 and activates TAK1, which induces activation of IKK2/B, c-Jun N-terminal kinase, and p38 MAPK to activate NF-κB.\[86\]

**INTERLEUKIN-4 (IL-4)**

The immune-modulatory cytokine interleukin-4 (IL-4) and its associated receptor chains interleukin-4-receptor-α (IL-4-R-α) have been shown to be overexpressed in pancreatic cancer.\[85,86\] IL-4 is mainly produced by CD4+ T cells\[87\] and binds to its transmembrane receptor chain (IL-4Rα), a 140-kDa protein. The subsequent association with the common γ chain (γc) forms the type-I-IL-4-receptor (γc). On nonhematopoietic cells, the type-II-IL-4-receptor (IL-4/IL-4Rα) represents the predominant IL-4 receptor.\[88\] IL-4 can exert growth-stimulating and proinvasive effects in several cancer cells including the pancreas.\[80,91\] It is found abundantly in the surroundings of tumor cells, secreted by infiltrating lymphocytes\[82\] as well as by the tumor cells themselves.\[80,91\] The presence and biological responsiveness of the IL-4 receptor in pancreatic cancer cells by growth inhibition is by Pseudomonas exotoxin coupled to IL-4, as well as growth promotion by exogenous IL-4 in pancreatic cancer cells.\[86,91\] One of its receptor chains, IL-4Rα, was shown to be overexpressed in several solid human tumors and was associated with locally advanced tumor staging, increased propensity for metastases, and poor overall survival.\[93-96\] In pancreatic cancer, exogenous IL-4 increased the growth of cultural cancer cells, possibly by stimulating growth-promoting pathways such as MAPKs.\[91\] Besides, previous studies have demonstrated an increased risk for lymph node metastases in a human pancreatic cancer specimen with high IL-4 receptor expression.\[86\] Furthermore, IL-4 increased the expression of antiapoptotic proteins leading to promoted cell survival\[89\] and mediated the downregulation of cell adhesion molecules, promoting invasiveness.\[89\] On nonhematopoietic cells, IL-4 will activate STAT3 through type-II-IL-4-receptor.\[97\] Activated STAT3 can stimulate pro-oncogenic pathways in cell survival, apoptosis, invasion and tumor immune surveillance.\[98,99\]

**INTERLEUKIN-8 (IL-8)**

Interleukin-8 (IL-8) is a proinflammatory factor, belonging to CXC chemokine family.\[100,101\] Many studies have revealed that pancreatic cancer produces IL-8, which can promote angiogenesis and invasion of tumors.\[102\] It has been found that IL-8 can mimic the role of VEGF, transactivate VEGFR2, and promote angiogenesis.\[103\] In acute pancreatitis, IL-8 is even higher and is considered a reliable indicator in evaluating the severity of inflammation and necrosis.\[104\] Investigation has proved that pancreatic cancer cell lines have high levels of IL-8 in supernatant and high level of its mRNA expression.\[105\] Nomura et al.\[106\] demonstrated that high IL-8 expression was closely correlated with the aggressive behavior of pancreatic cancer cells.

**INTERLEUKIN-1β (IL-1β)**

A considerable body of evidence has shown a key role for interleukin-1β (IL-1β) in acute pancreatitis.\[107,108\] IL-1β can stimulate autophagy in macrophages and induce endoplasmic reticulum stress\[109,111\] which causes the release of Ca2+ in the cytoplasm.\[112\] This causes subsequent activation of trypsinogen through impaired autophagy in acute pancreatitis. Lee et al.\[113\] proposed that autophagy inhibits IL-1β signaling by downregulating the expression of p62, which is an important scaffold in the IL-1β pathway whose increased expression promotes IL-1β production. Exogenous IL-1β could induce endogenous IL-1β mRNA expression and protein production. Moreover, IL-1β plays an important role in neuroendocrine tumors because it directs cancer cells to either neuroendocrine differentiation or to development of adenocarcinoma and increase in carcinoembryonic antigen.\[114\] Barber et al.\[115\] reported that the +3954C/T polymorphism of IL-1β gene predisposes to pancreatic cancer, and Čigrovski et al.\[116\] suggested that there is an association between IL-1β-511 C/T genotype and the susceptibility to pNET, especially functional pNETs.

**CYCLOOXYGENASE-2 (COX-2)**

Cyclooxygenase-2 (COX-2) is a key enzyme implicated in inflammation and has been reported to be elevated in pancreatic cancer.\[117\] High levels of COX-2 is correlated with poor prognosis.\[118-120\] As an inducible isoform of
COX, COX-2 could respond to various cytokines and growth factors. Multiple binding elements had been identified within the COX-2 promoter for TP53, NF-κB, and other transcription factors. Structural analysis of this promoter suggested a high affinity for Sp1, as multiple GC sequences were identified within the promoter. An Sp1/COX-2 signaling axis can be formed by Sp1 which transcriptionally activates COX-2 expression, which has significance to pancreatic cancer.

SERINE PROTEASE INHIBITOR KAZAL TYPE-1 (SPINK-1)

Mutation in the serine protease inhibitor Kazal type-1 (SPINK-1 gene) increases the chance of an individual in developing chronic pancreatitis (CP) 12-fold. The incidence is autosomal recessive because of the need for mutations in both copies of the SPINK-1 gene, thus one mutant copy is inherited from each parent who are unaffected carriers. Mutations in the SPINK-1 gene lead to premature trypsinogen activation and resultant pancreatitis. SPINK-mutation-associated pancreatitis is extremely rare, with less than 1% of carriers proceeding to develop pancreatitis. Hereditary pancreatitis significantly increases the risk of pancreatic malignancy. While up to 2% of the general population carry SPINK1 mutations, the actual number of individuals with SPINK-1-associated pancreatitis is extremely rare, with less than 1% of carriers going on to developing pancreatitis. The prevalence of SPINK1 mutations in patients with idiopathic CP has been reported to be between 16% and 23% with a case series reporting that SPINK1 mutations were 16.9% more common in patients with chronic and recurrent acute pancreatitis than controls. SPINK1 encodes a pancreatitis secretory trypsin inhibitor which is released by pancreatic acinar cells when there is inflammation. Mutation in the SPINK1 gene leads to trypsin uninhibited which increases the risk of pancreatitis. Most patients have heterozygous SPINK1 mutations leading to complex inheritance patterns, although SPINK1 variants have also been associated with autosomal recessive familial pancreatitis, alcoholic pancreatitis and tropic pancreatitis.

REACTIVE OXYGEN SPECIES

Reactive oxygen species (ROS), natural by-products from mitochondrial respiration and other cellular processes, play important roles as second messengers in cell signaling. However, when present at high concentration, ROS can be detrimental to cells by inducing oxidative damage to DNA, lipids and proteins. Cells eliminate excess intracellular ROS through expression of antioxidant genes regulated by the ROS-detoxifying machine. In tumor cells, antioxidant enzymes are often induced because of elevated levels of intrinsic ROS. Expression of mutant oncogenic KrasG12D, commonly present in PDAC, keeps the master transcription factor NRF2 elevated at the basal rate to mount an antioxidant response. There is a shift in the redox-induced oxidative stress, overwhelming their adaptive antioxidant capacity and promoting ROS-mediated cell death.

CHRONIC PANCREATITIS

CP is a well-known risk factor for pancreatic malignancy, including PDAC. A large, retrospective cohort study found a 14-fold increased risk of pancreatic cancer in patients with CP. A point mutation in the KRAS oncogene, which leads to its constitutive activation, is considered the initial event in pancreatic carcinogenesis. This is followed by mutations in tumor suppressor genes p16, p53 and DPC4. It has been shown previously that KRAS mutations are found in CP only after a disease duration of more than 3 years. A hypothesis has been proposed by Real et al, in which KRAS mutation might favor the appearance of dysplasia only when occurring in initiated pancreatic cells harboring allelic loss in a crucial tumor suppressor gene, such as INK4A or TP53, while halting progression when occurring in a truly normal cell. In pancreatic cancer tissue, the frequency of point mutation in the 12th codon of KRAS genes ranges from 72% to 95% and from 50% to 90% in pancreatic juice. Many studies have also shown that this mutation is detectable in circulating DNA of patients with pancreatic cancer, though at a lower frequency.

AUTOPHAGY

Pancreatitis facilitates and accelerates the transformation of pancreatic cells if the oncogene KRAS is mutated. A fundamental question which remains without clear answers in the field of pancreatology is the mechanisms by which pancreatitis promotes the formation of preneoplastic lesions (PanIN). A part of the answer to this question is provided by studies that show autophagy is systematically activated during pancreatitis, often to participate in the protection of pancreatic cells, to curb the progression of the disease, and to help during its recovery phase. In pancreatic acinar cells, induction of autophagy is accomplished by the activation of gene expression Vacuole Membrane Protein 1 (VMP1). VMP1 encodes a transmembrane protein that was identified and cloned in 2002 precisely because of its extraordinary activation during the acute phase of the pancreatitis. Overexpression
of VMP1 can trigger autophagy in many cells.\textsuperscript{161-164} VMP1 is involved in the formation of the phagophore\textsuperscript{164} after its direct interaction with the autophagic protein beclin-1,\textsuperscript{162} the protein tumor protein p53-inducible nuclear protein 2 (TP53INP2),\textsuperscript{163} and possibly its counterpart TP53INP1.\textsuperscript{166} During pancreatitis, the physiological role of autophagy consists mainly of cleaning the organelles damaged to maintain homeostasis of the cell guaranteeing better pancreatic cell survival.\textsuperscript{167} It is likely that at least one part of the protective effect of autophagy during the acute phase of the disease is related to sequestration of zymogen grains that contain the enzymes' digestive organs responsible for self-digestion during pancreatitis. This effect would have a dual mission for pancreatic cell: on one hand, zymophagia (autophagy zymogen granules) would reduce the availability of digestive enzymes, and, on the other hand, these organelles could satisfy the exceptional need of metabolism that accompanies cell growth during the regeneration phase.\textsuperscript{168} The expression of VMP1 protein triggers autophagy which is induced and maintained by the mutation of oncogene KRAS. This is strongly strengthened during pancreatitis. A hypothesis states that autophagy is more likely to be induced by pancreatitis, based on the overexpression of VMP1, ensuring the energetic need of cells presenting an active mutation of oncogene KRAS, thus allowing their transformation.\textsuperscript{169} The use of chloroquine, an inhibitor of the autophagic flow,\textsuperscript{170} reverses the effects of VMP1 on pancreatic cancer initiation induced by oncogene KRAS.\textsuperscript{169} Such observations reinforce the idea that the pathways that regulate autophagy are activated by pancreatitis and can later contribute to the process of pancreatic carcinogenesis. The concept that inhibition of autophagy could be used to prevent progression of preneoplastic lesions to pancreatic cancer is further supported in the study and more studies are required to shed light on this.

In addition, Yang et al.\textsuperscript{171} showed that when autophagy was inhibited in tumor itself, tumor regression was observed and there was partial mediation by macrophages. Further studies are required to show benefits of combining macrophages' modulators with autophagy inhibitors.\textsuperscript{172,173} As shown previously,\textsuperscript{174} in the study by Yang et al., it was found that autophagy could regulate macrophage infiltration by degradation of inflammation regulators by directly affecting cytokine secretion. However, the limitation of the study by Yang et al.\textsuperscript{171} is that the impact of autophagy inhibition was shown only in stellate cells other than different host cell types in pancreatic cancer microenvironment.\textsuperscript{175} More studies are required to guide trials with newer autophagy inhibitors.

**CXCL-12**

CXCL-12 is a chemokine also known as stromal-derived factor 1 alpha (SDF-1 alpha). It is known to be the ligand of CXCR4 receptors.\textsuperscript{176,177} High expression of CXCL-12 and CXCR4 receptor activation in tumors enhances growth and restricts immune surveillance in the tumor through local autocrine and paracrine mechanisms.\textsuperscript{178} This axis promotes epithelial–mesenchymal transition (EMT) and increases the invasive phenotype of pancreatic cancer cells.\textsuperscript{179,180} It has been shown that CXCL-12/CXCR4 interactions enhance metastatic spread to sites of high CXCL-12 expression by providing chemotactic survival and proliferative signals that guide implantation and support growth.\textsuperscript{178,181} The activation of CXCR4 in pancreatic cancer leads to increased expression of Smoothened, Gli1, and EMT markers.\textsuperscript{179} There is also production and release of sonic hedgehog (SHH) to potentiate paracrine signaling interactions with stromal cells.\textsuperscript{179,182} This CXCR4 and SHH interaction contributes to extensive stromal deposition and creates a physical barrier that may explain the lack of vasculature in pancreatic tumors even with increased expression of VEGF. In addition, peripheral and central CXCL-12-mediated signaling exert contrasting effects for nociception, that is, CXCL-12-mediating analgesia through modulation of Schwann cells. This explains decreased pain sensation among patients with pancreatic cancer who bear increased pancreatic gliosis with cellular hypertrophy of pancreatic glia.\textsuperscript{183}

**IMMUNE CHECKPOINT INHIBITION**

Recently, checkpoint inhibitors have been investigated as a novel mode of cancer treatment as tumor cells often take advantage of immune checkpoints to avoid detection and being under attack.\textsuperscript{184} The potential advantage of immunotherapy is its ability to detect specific tumor cells, creating a durable response and much better survival-prognosis.\textsuperscript{185} Royal et al.\textsuperscript{186} noted delayed progression in one patient with 3 mg/kg of ipilimumab, and Le et al.\textsuperscript{187} reported an overall survival of 5.7 months in patients treated with ipilimumab and GVAX vaccine. Moreover, Aglietta et al.\textsuperscript{188} observed a median overall survival of 7.4 months with tremelimumab. However, immunotherapy has little success with pancreatic cancer because it is a highly aggressive malignancy, characterized by delayed diagnosis and treatment resistance.\textsuperscript{189} The tumor microenvironment is composed of a dense fibrotic stroma of extracellular matrix components and a variety of inflammatory cells.\textsuperscript{190} This gives the ability of pancreatic cancer to evade host immune surveillance\textsuperscript{191} and accounts for one of the reasons for poor effect of immunotherapy.
CONCLUSION
Pancreatic cancer is a deadly cancer worldwide. Inflammation has emerged to be a key mediator of pancreatic cancer development. Further research is needed to elucidate the mechanisms through which inflammation contributes to tumor initiation and progression.

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