Review Article

Inflammation and pancreatic cancer: An updated review

Kamleshsingh Shadhu[1,2,3], Chunhua Xi[1,2]

[1]Pancreas Center of The First Affiliated Hospital of Nanjing Medical University, [2]Pancreas Institute of Nanjing Medical University, [3]School of International Education of Nanjing Medical University, Nanjing, P.R. China

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

Address for correspondence: Dr. Kamleshsingh Shadhu, School of International Education, Nanjing Medical University, Hanzhong Road, 140, Gulou, Nanjing, Jiangsu 210029, P.R. China.
E-mail: kamlesh3012@yahoo.co.uk

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.[1] 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 preceeding 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].

Access this article online	
Quick Response Code:	Website: www.saudijgastro.com
	DOI: 10.4103/sjg.SJG_390_18

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 cona 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

How to cite this article: Shadhu K, Xi C. Inflammation and pancreatic cancer: An updated review. Saudi J Gastroenterol 2019;25:3-13.

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; SPINK-1: 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.[18] 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.[19] 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.[20] 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.[16]

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.[4,5,21-24] 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.[25-29] IL-6 promotes pancreatic intraepithelial neoplasia (PanIN).[21] 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.[30-33] PSC secretion contains high levels of IL-6, which can promote pancreatic cancer cell proliferation through Nrf2-mediated metabolic reprogramming.[34] 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.[35] 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.[36,37] IL-6 through STAT3 activation confers PC cells' aniokis resistance, which finally enhances metastasis.[38,39] Furthermore, the proinflammatory cytokine inhibits radiation-induced apoptosis along with the increasing expression of antiapoptotic proteins B-cell lymphoma (Bcl-2).[40]

TOLL-LIKE RECEPTORS (TLRS)

Toll-like receptors (TLRs) are type I membrane receptors, pattern recognition receptors of the innate immune system.[41] There is evidence of TLR involvement in pancreatic cancer.[42] Inflammation of pancreas results in damage-associated molecular patterns (DAMPs) and growth factors such as vascular endothelial growth

factor (VEGF) during subsequent healing.[43,44] DAMPs that arise from inflammation and cellular injury can stimulate TLRs and consequently induce TLR signaling that supports an inflammatory microenvironment.[45,46] 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.[47-51] 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.[52] 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.[48] 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.[43,53] TLR4 signaling activates the PI3K-AKT pathway thereby inducing cancer cells to secrete multiple inflammatory mediators and cytokines.[54-56] TLR4 promotes angiogenesis of pancreatic cancer through upregulating VEGF through PI3K-AKT.[57-59] TLR9 ligation induced epithelial cell proliferation in PSCs.[60] So far, single studies have shown that TLR2 is expressed in pancreatic cancer tissue and has been suggested as potential target for immunotherapy.[61]

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, neoangiogenesis, immune evasion, cell motility, and metastasis.[62] 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.[63,64] 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.[65] SMAD2 and SMAD3 are activated by the TGF-β RI.[66] Once phosphorylated by TGF-β RI, SMAD2 and -3 dimerize forming the SMAD 2/3 complex.[67] The SMAD 2/3 dimer joins with SMAD4, creating a hetero-hexameric complex.[67] 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.[65] 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.[68,69] TNF-α is a type II transmembrane protein with signaling potential as a membrane-integrated protein or a soluble cytokine released by proteolytic cleavage.[70] There are several reports emphasizing the detrimental functions of TNF-α in pancreatic cancer.[71-73] Previously, 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.[74] There are two specific reports for TNF-α: TNFR1 and TNFR2. TNFR1 is associated with inflammation by activation of the transcription factor NF-κB, JNK, and p38-MAPK.[75] 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.[76] TNFR2 mediates anti-inflammatory signaling. Egberts *et al.*[77] 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.[68,69]

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.[78,79] In pancreatic cancer, IL-1-α is expressed exclusively by the malignant cells of the tumor and is immunohistochemically detected in most tumors.[80,81] 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*.[58,80] 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.[80] 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.[84]

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).[88] 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.[89-91] It is found abundantly in the surroundings of tumor cells, secreted by infiltrating lymphocytes[92] as well as by the tumor cells themselves.[90,91] 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.[93-95] 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.[96] Furthermore, IL-4 increased the expression of antiapoptotic proteins leading to promoted cell survival[90] 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-1-β (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-β 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 Cigrovski *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.[121,122] 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.[123]

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.[124] 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.[125-127] SPINK-mutation-associated pancreatitis is extremely rare, with less than 1% of carriers proceeding to develop pancreatitis.[128] Hereditary pancreatitis significantly increases the risk of pancreatic malignancy.[125-128] 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.[129] 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.[124,128,130] 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.[131] Most patients have heterozygous SPINK1 mutations leading to complex inheritance patterns, although SPINK1 variants have also been associated with autosomal recessive familiar pancreatitis, alcoholic pancreatitis and tropic pancreatitis.[132]

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.[133] However, when present at high concentration, ROS can be detrimental to cells by inducing oxidative damage to DNA, lipids and proteins.[134] 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.[135] 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.[136-138] There is a shift in the redox-induced oxidative stress, overwhelming their adaptive antioxidant capacity and promoting ROS-mediated cell death.[139,140]

CHRONIC PANCREATITIS

CP is a well-known risk factor for pancreatic malignancy, including PDAC.[141-143] A large, retrospective cohort study found a 14-fold increased risk of pancreatic cancer in patients with CP.[141] 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.[144] A hypothesis has been proposed by Real *et al*.[145] 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%[146-149] and from 50% to 90% in pancreatic juice.[150-154] Many studies have also shown that this mutation is detectable in circulating DNA of patients with pancreatic cancer, though at a lower frequency.[155-157]

AUTOPHAGY

Pancreatitis facilitates and accelerates the transformation of pancreatic cells if the oncogene KRAS is mutated.[158] 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.[159,160] In pancreatic acinar cells, induction of autophagy is accompanied 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.[161] Overexpression

of VMP1 can trigger autophagy in many cells.[161-164] VMP1 is involved in the formation of the phagophore[164] after its direct interaction with the autophagic protein becline-1,[162] the protein tumor protein p53-inducible nuclear protein 2 (TP53INP2),[165] and possibly its counterpart TP53INP1.[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.[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.[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.[169] The use of chloroquine, an inhibitor of the autophagic flow,[170] reverses the effects of VMP1 on pancreatic cancer initiation induced by oncogene KRAS.[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 prepancreatic neoplastic 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.*[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.[172,173] As shown previously,[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.*[171] is that the impact of autophagy inhibition was shown only in stellate cells other than different host cell types in pancreatic cancer microenvironment.[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 α (SDF-1 α). It is known to be the ligand of CXCR4 receptors.[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.[178] This axis promotes epithelial–mesenchymal transition (EMT) and increases the invasive phenotype of pancreatic cancer cells.[179,180] It has been shown that CXCL-12/CXCR44 interactions enhance metastatic spread to sites of high CXCL-12 expression by providing chemotactic survival and proliferative signals that guide implantation and support growth.[178,181] The activation of CXCR4 in pancreatic cancer leads to increased expression of Smoothened, Gli1, and EMT markers.[179] There is also production and release of sonic hedgehog (SHH) to potentiate paracrine signaling interactions with stromal cells.[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.[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.[184] The potential advantage of immunotherapy is its ability to detect specific tumor cells, creating a durable response and much better survival-prognosis.[185] Royal *et al.*[186] noted delayed progression in one patient with 3 mg/kg of ipilimumab, and Le *et al.*[187] reported an overall survival of 5.7 months in patients treated with ipilimumab and GVAX vaccine. Moreover, Aglietta *et al.*[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.[189] The tumor microenvironment is composed of a dense fibrotic stroma of extracellular matrix components and a variety of inflammatory cells.[190] This gives the ability of pancreatic cancer to evade host immune surveillance[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.

Financial support and sponsorship
Nil.

Conflicts of interest
There are no conflicts of interest.

REFERENCES

1. Rahib L, Smith BD, Aizenberg R, Rosenzweig AB, Fleshman JM, Matrisian LM. Projecting cancer incidence and deaths to 2030: The unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
2. Iovanna JL, Marks DL, Fernandez-Zapico ME, Urrutia R. Mechanistic insights into self-reinforcing processes driving abnormal histogenesis during the development of pancreatic cancer. Am J Pathol 2013:182:1078-86.
3. Lomberk GA, Iovanna J, Urrutia R. The promise of epigenomic therapeutics in pancreatic cancer. Epigenomics 2016;8:831-42.
4. Bosetti C, Lucenteforte E, Silverman DT, Petersen G, Bracci PM, Ji BT, *et al*. Cigarette smoking and pancreatic cancer: An analysis from the International Pancreatic Cancer Case-Control Consortium (Panc4). Ann Oncol 2012;23:1880-8.
5. Masamune A, Watanabe T, Kikuta K, Shimosegawa T. Roles of pancreatic stellate cells in pancreatic inflammation and fibrosis. Clin Gastroenterol Hepatol 2009;7:S48-54.
6. Carbone C, Melisi D. NF-κB as a target for pancreatic cancer therapy. Expert Opin Ther Targets 2012;16(Suppl 2):S1.
7. Heike D, Geou-Yarh L, Peter S. Downregulation of TRAF2 mediates NIK-induced pancreatic cancer cell proliferation and tumorigenicity. PLoS One 2013;8:e53676.
8. Rd WW, Baldwin AS. Maintenance of constitutive IkappaB kinase activity by glycogen synthase kinase-3alpha/beta in pancreatic cancer. Cancer Res 2008;68:8156-63.
9. Hu H, Jiao F, Han T, Wang LW. Functional significance of macrophages in pancreatic cancer biology. Tumour Biol 2015;36:9119-26.
10. Habtezion A, Edderkaoui M, Pandol SJ. Macrophages and pancreatic ductal adenocarcinoma. Cancer Lett 2016;381:211-6.
11. Oh H, Ghosh S. NF-κB: Roles and regulation in different CD4(+) T-cell subsets. Immunol Rev 2013;252:41-51.
12. Hayden MS, Ghosh S. Shared principles in NF-κB signaling. Cell 2008;132:344-62.
13. Prabhu L, Mundade R, Korc M, Loehrer PJ, Lu T. Critical role of NF-κB in pancreatic cancer. Oncotarget 2014;5:10969-75.
14. Mansouri L, Sutton LA, Ljungström V, Bondza S, Arngården L, Bhoi S, *et al*. Functional loss of I kappa B epsilon leads to NF-kappa B deregulation in aggressive chronic lymphocytic leukemia. J Exp Med 2015;212:833:43.
15. Setia S, Nehru B, Sanyal SN. Activation of NF-κB: Bridging the gap between inflammation and cancer in colitis-mediated colon carcinogenesis. Biomed Pharmacother 2014;68:119-28.
16. Colotta F, Allavena P, Sica A, Garlanda C, Mantovani A. Cancer-related inflammation, the seventh hallmark of cancer: Links to genetic instability. Carcinogenesis 2009;30:1073-81.
17. Wang J, Jacob NK, Ladner KJ, Beg A, Perko JD, Tanner SM, *et al*. RelA/p65 functions to maintain cellular senescence by regulating genomic stability and DNA repair. EMBO Rep 2009;10:1272.
18. Wang DJ, Ratnam NM, Byrd JC, Guttridge DC. NF-κB functions in tumor initiation by suppressing the surveillance of both innate and adaptive immune cells. Cell Rep 2014;9:90-103.
19. Lesina M, Wörmann SM, Morton J, Diakopoulos KN, Korneeva O, Wimmer M, *et al*., RelA regulates CXCL1/CXCR2-dependent oncogene-induced senescence in murine Kras-driven pancreatic carcinogenesis. J Clin Invest 2016;126:2919.
20. Wang X, Li Y, Tian H, Qi J, Li M, Fu C, *et al*. Macrophage inhibitory cytokine 1 (MIC-1/GDF15) as a novel diagnostic serum biomarker in pancreatic ductal adenocarcinoma. BMC Cancer 2014;14:578.
21. Lesina M, Kurkowski MU, Ludes K, Rose-John S, Treiber M, Klöppel G, *et al*. Stat3/Socs3 activation by IL-6 transsignaling promotes progression of pancreatic intraepithelial neoplasia and development of pancreatic cancer. Cancer Cell 2011;19:456-69.
22. Fukuda A, Wang SC, Morris JP, Folias AE, Liou A, Kim GE, *et al*. Stat3 and MMP7 contribute to pancreatic ductal adenocarcinoma initiation and progression. Cancer Cell 2011;19:441-55.
23. Ikeda O, Egami H, Ishiko T, Ishikawa S, Kamohara H, Hidaka H, *et al*. Signal of proteinase-activated receptor-2 contributes to highly malignant potential of human pancreatic cancer by up-regulation of interleukin-8 release. Int J Oncol 2006;28:939-46.
24. Kuwada Y, Sasaki T, Morinaka K, Kitadai Y, Mukaida N, Chayama K. Potential involvement of IL-8 and its receptors in the invasiveness of pancreatic cancer cells. Int J Oncol 2003;22:765.
25. Chen J, Wang S, Su J, Chu G, You H, Chen Z, *et al*. Interleukin-32α inactivates JAK2/STAT3 signaling and reverses interleukin-6-induced epithelial–mesenchymal transition, invasion, and metastasis in pancreatic cancer cells. Onco Ther 2016;9:4225-37.
26. Muñoz-Cánoves P, Scheele C, Pedersen BK, Serrano AL. Interleukin-6 myokine signaling in skeletal muscle: A double-edged sword? FEBS J 2013;280:4131-48.
27. Okitsu K, Kanda T, Imazeki F, Yonemitsu Y, Ray RB, Chang C, *et al*. Involvement of interleukin-6 and androgen receptor signaling in pancreatic cancer. Genes Cancer 2010;1:859-67.
28. Lesina M, Wörmann SM, Neuhöfer P, Song L, Algül H. Interleukin-6 in inflammatory and malignant diseases of the pancreas. Semin Immunol 2014;26:80-7.
29. Feurino L W, Zhang Y, Bharadwaj U, Zhang R, Li F, Fisher WE, *et al*. IL-6 stimulates Th2 type cytokine secretion and upregulates VEGF and NRP-1 expression in pancreatic cancer cells. Cancer Biol Ther 2007;6:1096.
30. Omary MB, Lugea A, Lowe AW, Pandol SJ. The pancreatic stellate cell: A star on the rise in pancreatic diseases. J Clin Invest 2007;117:50-9.
31. Erkan M. Understanding the stroma of pancreatic cancer: Co-evolution of the microenvironment with epithelial carcinogenesis. J Pathol 2013;231:4-7.
32. Tang D, Wang D, Yuan Z, Xue X, Zhang Y, An Y, *et al*. Persistent activation of pancreatic stellate cells creates a microenvironment favorable for the malignant behavior of pancreatic ductal adenocarcinoma. Int J Cancer 2013;132:993-1003.
33. Apte MV, Pirola RC, Wilson JS. Pancreatic stellate cells: A starring role in normal and diseased pancreas. Front Physiol 2012;3:344.
34. Duluc C, Moatassim-Billah S, Chalabi-Dchar M, Perraud A, Samain R, Breibach F, *et al*., Pharmacological targeting of the protein synthesis mTOR/4E-BP1 pathway in cancer-associated fibroblasts abrogates pancreatic tumour chemoresistance. EMBO Mol Med 2015;7:735-53.
35. Huang L, Hu B, Ni J, Wu J, Jiang W, Chen C, *et al*. Transcriptional repression of SOCS3 mediated by IL-6/STAT3 signaling via DNMT1 promotes pancreatic cancer growth and metastasis. J Exp Clin Cancer Res 2016;35:27.
36. Block KM, Hanke NT, Maine EA, Baker AF. IL-6 stimulates STAT3 and Pim-1 kinase in pancreatic cancer cell lines. Pancreas 2012;41:773.
37. Xu J, Xiong G, Cao Z, Huang H, Wang T, You L, *et al*. PIM-1 contributes to the malignancy of pancreatic cancer and displays diagnostic and prognostic value. J Exp Clin Cancer Res 2016;35:133.

38. Fofaria NM, Srivastava SK. STAT3 induces anoikis resistance, promotes cell invasion and metastatic potential in pancreatic cancer cells. Carcinogenesis 2015;36:142-50.
39. Weidner N, Semple JP, Welch WR, Folkman J. Tumor angiogenesis and metastasis – Correlation in invasive breast carcinoma. N Engl J Med 1991;324:1-8.
40. Miyamoto Y, Hosotani R, Doi R, Wada M, Ida J, Tsuji S, *et al.* Interleukin-6 inhibits radiation induced apoptosis in pancreatic cancer cells. Anticancer Res 2001;21:2449-56.
41. Takeda K, Akira S. Toll - like receptors. Curr Protoc Immunol 2015;109:14.12.1-10.
42. Vaz J, Akbarshahi H, Andersson R. Controversial role of toll-like receptors in acute pancreatitis. World J Gastroenterol 2013;19:616-30.
43. Whitcomb DC. Inflammation and Cancer V. Chronic pancreatitis and pancreatic cancer. Am J Physiol Gastrointest Liver Physiol 2004;287:315-9.
44. Farrow B, Evers BM. Inflammation and the development of pancreatic cancer. Surg Oncol 2002;10:153-69.
45. Janeway CA Jr. Pillars article: Approaching the asymptote? Evolution and revolution in immunology. Cold spring harb symp quant biol. 1989. 54: 1-13. J Immunol 2013;191:4475.
46. Rubartelli A, Lotze MT. Inside, outside, upside down: Damage-associated molecular-pattern molecules (DAMPs) and redox. Trends Immunol 2007;28:429-36.
47. Grimm M, Kim M, Rosenwald A, Heemann U, Germer CT, Waaga-Gasser AM, *et al.* Toll-like receptor (TLR) 7 and TLR8 expression on CD133+ cells in colorectal cancer points to a specific role for inflammation-induced TLRs in tumourigenesis and tumour progression. Eur J Cancer 2010;135:2849-57.
48. Grimmig T, Matthes N, Hoeland K, Tripathi S, Chandraker A, Grimm M, *et al.* TLR7 and TLR8 expression increases tumor cell proliferation and promotes chemoresistance in human pancreatic cancer. Int J Oncol 2015;47:857-66.
49. Mai CW, Kang YB, Pichika MR. Should a Toll-like receptor 4 (TLR-4) agonist or antagonist be designed to treat cancer? TLR-4: Its expression and effects in the ten most common cancers. Onco Targets Ther 2013;6:1573-87.
50. Muccioli M, Benencia F. Toll-like receptors in ovarian cancer as targets for immunotherapies. Front Immunol 2014;5:341.
51. Dajon M, Iribarren K, Cremer I. Toll-like receptor stimulation in cancer: A pro- and anti-tumor double-edged sword. Immunobiology 2016;222:89.
52. Cherfils-Vicini J, Platonova S, Gillard M, Laurans L, Validire P, Caliandro R, *et al.* Triggering of TLR7 and TLR8 expressed by human lung cancer cells induces cell survival and chemoresistance. J Clin Invest 2010;120:1285-97.
53. Tsan MF, Gao B. Endogenous ligands of Toll-like receptors. J Leukoc Biol 2004;76:514-9.
54. Yuan X, Zhou Y, Wang W, Li J, Xie G, Zhao Y, *et al.* Activation of TLR4 signaling promotes gastric cancer progression by inducing mitochondrial ROS production. Cell Death Dis 2013;4:e794.
55. Hsu RY, Chan CH, Spicer JD, Rousseau MC, Giannias B, Rousseau S, *et al.* LPS-induced TLR4 signaling in human colorectal cancer cells increases beta1 integrin-mediated cell adhesion and liver metastasis. Cancer Res 2011;71:1989-98.
56. Li D., Jin Y, Sun Y, Lei J, Liu C. Knockdown of toll-like receptor 4 inhibits human NSCLC cancer cell growth and inflammatory cytokine secretion *in vitro* and *in vivo*. Int J Oncol 2014;45:813.
57. Ikebe M, Kitaura Y, Nakamura M, Tanaka H, Yamasaki A, Nagai S, *et al.* Lipopolysaccharide (LPS) increases the invasive ability of pancreatic cancer cells through the TLR4/MyD88 signaling pathway. J Surg Oncol 2009;100:725-31.
58. Tjomsland V, Bojmar L, Sandström P, Bratthäll C, Messmer D, Spångeus A, *et al.* IL-1α expression in pancreatic ductal adenocarcinoma affects the tumor cell migration and is regulated by the p38MAPK signaling pathway. PLoS One 2013;8:e70874.
59. Zhang JJ, Wu HS, Wang L, Tian Y, Zhang JH, Wu HL. Expression and significance of TLR4 and HIF-1alpha in pancreatic ductal adenocarcinoma. World J Gastroenterol 2010;16:2881-8.
60. Zambirinis CP, Levie E, Nguy S, Avanzi A, Barilla R, Xu Y, *et al.* TLR9 ligation in pancreatic stellate cells promotes tumorigenesis. J Exp Med 2015;212:2077-94.
61. Huynh AS, Chung WJ, Cho HI, Moberg VE, Celis E, Morse DL, *et al.* Novel toll-like receptor 2 ligands for targeted pancreatic cancer imaging and immunotherapy. J Med Chem 2012;55:9751-62.
62. Melzer C, Hass R, von der Ohe J, Lehnert H, Ungefroren H. The role of TGF-β and its crosstalk with RAC1/RAC1b signaling in breast and pancreas carcinoma. Cell Commun Signaling 2017;15:19.
63. Macíassilva M, Abdollah S, Hoodless PA, Pirone R, Attisano L, Wrana JL. MADR2 is a substrate of the tgfβ receptor and its phosphorylation is required for nuclear accumulation and signaling. Cell 1996;87:1215-24.
64. Zhang Y, Feng X, We R, Derynck R. Receptor-associated Mad homologues synergize as effectors of the TGF-|[beta]| response. Nature 1996;383:168-72.
65. Shi Y, Massagué J. Mechanisms of TGF-beta signaling from cell membrane to the nucleus. Cell 2003;113:685-700.
66. Souchelnytskyi S, Tamaki K, Engström U, Wernstedt C, ten Dijke P, Heldin CH. Phosphorylation of Ser465 and Ser467 in the C terminus of Smad2 mediates interaction with Smad4 and is required for transforming growth factor-beta signaling. J Biol Chem 1997;272:28107-15.
67. Katz LH, Li Y, Chen JS, Muñoz NM, Majumdar A, Chen J, *et al.* Targeting TGF-beta signaling in cancer. Expert Opin Ther Targets 2013;17:743-60.
68. Balkwill F. Tumour necrosis factor and cancer. Nat Rev Cancer 2009;9:121-37.
69. Waters JP, Pober JS, Bradley JR. Tumour necrosis factor and cancer. J Pathol 2013;230:241-8.
70. Tracey D, Klareskog L, Sasso EH, Salfeld JG, Tak PP. Tumor necrosis factor antagonist mechanisms of action: A comprehensive review. Pharmacol Ther 2008;117:244-79.
71. Alam MS, Gaida MM, Bergmann F, Lasitschka F, Giese T, Giese NA, *et al.* Selective inhibition of the p38 alternative activation pathway in infiltrating T cells inhibits pancreatic cancer progression. Nat Med 2015;21:1337-43.
72. Aida K, Miyakawa R, Suzuki K, Narumi K, Udagawa T, Yamamoto Y, *et al.* Suppression of Tregs by anti-glucocorticoid induced TNF receptor antibody enhances the antitumor immunity of interferon-α gene therapy for pancreatic cancer. Cancer Sci 2014;105:159-67.
73. Chopra M, Riedel SS, Biehl M, Krieger S, von Krosigk V, Bäuerlein CA, *et al.* Tumor necrosis factor receptor 2-dependent homeostasis of regulatory T cells as a player in TNF-induced experimental metastasis. Carcinogenesis 2013;34:1296-303.
74. Beyer K, Normann L, Sendler M, Käding A, Heidecke CD, Partecke LI, *et al.* TRAIL promotes tumor growth in a syngeneic murine orthotopic pancreatic cancer model and affects the host immune response. Pancreas 2016;45:401-8.
75. Dickens LS, Powley IR, Hughes MA, MacFarlane M. The "complexities" of life and death: Death receptor signalling platforms. Exp Cell Res 2012;318:1269-77.
76. Ding WX, Yin XM. Dissection of the multiple mechanisms of TNF-alpha-induced apoptosis in liver injury. J Cell Mol Med 2004;8:445-54.
77. Egberts JH, Cloosters V, Noack A, Schniewind B, Thon L, Klose S, *et al.* Anti-tumor necrosis factor therapy inhibits pancreatic tumor growth and metastasis. Cancer Res 2008;68:1443-50.
78. Apte RN, Dotan S, Elkabets M, White MR, Reich E, Carmi Y, *et al.* The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions. Cancer Metastasis Rev 2006;25:387-408.
79. Xu D, Matsuo Y, Ma J, Koide S, Ochi N, Yasuda A, *et al.* Cancer cell-derived IL-1α promotes HGF secretion by stromal cells and

enhances metastatic potential in pancreatic cancer cells. J Surg Oncol 2010;102:469-77.
80. Tjomsland V, Spångeus A, Välilä J, Sandström P, Borch K, Druid H, *et al*. Interleukin 1α sustains the expression of inflammatory factors in human pancreatic cancer microenvironment by targeting cancer-associated fibroblasts. Neoplasia 2011;13:664.
81. Ling J, Kang Y, Zhao R, Xia Q, Lee DF, Chang Z, *et al*. KrasG12D-induced IKK2/β/NF-κB activation by IL-1α and p62 feedforward loops is required for development of pancreatic ductal adenocarcinoma. Cancer Cell 2012;21:105-20.
82. Melisi D, Niu J, Chang Z, Xia Q, Peng B, Ishiyama S, *et al*. Secreted interleukin-1alpha induces a metastatic phenotype in pancreatic cancer by sustaining a constitutive activation of nuclear factor-kappaB. Mol Cancer Res 2009;7:624.
83. Amour A, Slocombe PM, Webster A, Butler M, Knight CG, Smith BJ, *et al*. TNF-alpha converting enzyme (TACE) is inhibited by TIMP-3. FEBS Lett 1998;435:39.
84. Skaug B, Jiang X, Chen ZJ. The role of ubiquitin in NF-kappaB regulatory pathways. Ann Rev Biochem 2009;78:769-96.
85. Kawakami K. *et al*. Targeting interleukin-4 receptors for effective pancreatic cancer therapy. Cancer Res 2002;62:3575.
86. Kornmann M, Kawakami M, Husain SR, Puri RK. Pancreatic cancer cells express interleukin-13 and -4 receptors, and their growth is inhibited by Pseudomonas exotoxin coupled to interleukin-13 and -4. Anticancer Res 1999;19:125-31.
87. Paul WE. Interleukin-4: A prototypic immunoregulatory lymphokine. Blood 1991;77:1859.
88. Murata T, Obiri NI, Puri RK. Structure of and signal transduction through interleukin-4 and interleukin-13 receptors (review). Int J Mol Med 1998;1:551.
89. Kanai T, Watanabe M, Hayashi A, Nakazawa A, Yajima T, Okazawa A, *et al*. Regulatory effect of interleukin-4 and interleukin-13 on colon cancer cell adhesion. Br J Cancer 2000;82:1717-23.
90. Todaro M, Lombardo Y, Francipane MG, Alea MP, Cammareri P, Iovino F, *et al*. Apoptosis resistance in epithelial tumors is mediated by tumor-cell-derived interleukin-4. Cell Death Differ 2008;15:762.
91. Prokopchuk O, Liu Y, Henne-Bruns D, Kornmann M. Interleukin - 4 enhances proliferation of human pancreatic cancer cells: Evidence for autocrine and paracrine actions. Br J Cancer 2005;92:921.
92. Yamamura M, Modlin RL, Ohmen JD, Moy RL. Local expression of antiinflammatory cytokines in cancer. J Clin Invest 1993;91:1005.
93. Joshi BH, Leland P, Lababidi S, Varrichio F, Puri RK. Interleukin - 4 receptor alpha overexpression in human bladder cancer correlates with the pathological grade and stage of the disease. Cancer Med 2015;3:1615-28.
94. Burt BM, Bader A, Winter D, Rodig SJ, Bueno R, Sugarbaker DJ. Expression of interleukin-4 receptor alpha in human pleural mesothelioma is associated with poor survival and promotion of tumor inflammation. Clin Cancer Res 2012;18:1568-77.
95. Venmar KT, Carter KJ, Hwang DG, Dozier EA, Fingleton B. IL-4 receptor ILR4α regulates metastatic colonization by mammary tumors through multiple signaling pathways. Cancer Res 2014;74:4329-40.
96. Formentini A, Prokopchuk O, Sträter J, Kleeff J, Grochola LF, Leder G, *et al*. Interleukin-13 exerts autocrine growth-promoting effects on human pancreatic cancer, and its expression correlates with a propensity for lymph node metastases. Int J Colorectal Dis 2009;24:57-67.
97. Akdis M, Burgler S, Crameri R, Eiwegger T, Fujita H, Gomez E, *et al*. Interleukins, from 1 to 37, and interferon-γ: Receptors, functions, and roles in diseases. J Allergy Clin Immunol 2011;127:701.
98. Carpenter RL, Lo HW. STAT3 target genes relevant to human cancers. Cancers 2014;6:897-925.
99. Johnston PA, Grandis JR. STAT3 signaling: Anticancer strategies and challenges. Mol Interv 2011;11:18.
100. Baggiolini M, Imboden P, Detmers P. Neutrophil activation and the effects of interleukin-8/neutrophil-activating peptide 1 (IL-8/NAP-1). Cytokines 1992;4:1.
101. Mukaida N, Harada A, Matsushima K. Interleukin-8 (IL-8) and monocyte chemotactic and activating factor (MCAF/MCP-1), chemokines essentially involved in inflammatory and immune reactions. Cytokine Growth Factor Rev 1998;9:9-23.
102. Matsuo Y, Ochi N, Sawai H, Yasuda A, Takahashi H, Funahashi H, *et al*. CXCL8/IL-8 and CXCL12/SDF-1alpha co-operatively promote invasiveness and angiogenesis in pancreatic cancer. Int J Cancer 2009;124:853-61.
103. Petreaca ML, Yao M, Liu Y, Defea K, Martins-Green M. Transactivation of vascular endothelial growth factor receptor-2 by interleukin-8 (IL-8/CXCL8) is required for IL-8/CXCL8-induced endothelial permeability. Mol Biol Cell 2007;18:5014.
104. Pooran N, Indaram A, Singh P, Bank S. Cytokines (IL-6, IL-8, TNF): Early and reliable predictors of severe acute pancreatitis. J Clin Gastroenterol 2003;37:263-6.
105. Bellone G, Smirne C, Mauri FA, Tonel E, Carbone A, Buffolino A, *et al*. Cytokine expression profile in human pancreatic carcinoma cells and in surgical specimens: Implications for survival. Cancer Immunol Immunother 2006;55:684-98.
106. Nomura H, Nishimori H, Yasoshima T, Hata F, Tanaka H, Nakajima F, *et al*. A new liver metastatic and peritoneal dissemination model established from the same human pancreatic cancer cell line: Analysis using cDNA macroarray. Clin Exp Metastasis 2002;19:391-9.
107. Gukovsky I, Li N, Todoric J, Gukovskaya A, Karin M. Inflammation, autophagy, and obesity: Common features in the pathogenesis of pancreatitis and pancreatic cancer. Gastroenterology 2013;144:1199.
108. Romac J, Shahid RA, Choi SS, Karaca GF, Westphalen CB, Wang TC, *et al*. Pancreatic secretory trypsin inhibitor 1 reduces the severity of chronic pancreatitis in mice over-expressing interleukin-1β in the pancreas. Gastroenterology 2011;140:535-41.
109. O'Neill CM, Lu C, Corbin KL, Sharma PR, Dula SB, Carter JD, *et al*. Circulating levels of IL-1B+IL-6 cause ER stress and dysfunction in islets from prediabetic male mice. Endocrinology 2013;154:3077-88.
110. Harris J. Autophagy and cytokines. Cytokines 2011;56:140-44.
111. Levine B, Mizushima N, Virgin HW. Autophagy in immunity and inflammation. Nature 2011;469:323-35.
112. Berridge MJ. The endoplasmic reticulum: A multifunctional signaling organelle. Cell Calcium 2002;32:235-49.
113. Lee J, Kim HR, Quinley C, Kim J, Gonzalez-Navajas J, Xavier R, *et al*. Autophagy suppresses interleukin-1β (IL-1β) signaling by activation of p62 degradation via lysosomal and proteasomal pathways. J Biol Chem 2012;287:4033-40.
114. Abdul M, Hoosein N. Relationship of the interleukin-1 system with neuroendocrine and exocrine markers in human colon cancer cell lines. Cytokine 2002;18:86-91.
115. Barber MD, Powell JJ, Lynch SF, Fearon KC, Ross JA. A polymorphism of the interleukin-1β gene influences survival in pancreatic cancer. Br J Cancer 2000;83:1443-7.
116. Cigrovski BM, Čačev T, Catela Ivković T, Marout J, Ulamec M, Zjačić-Rotkvić V, *et al*. High VEGF serum values are associated with locoregional spread of gastroenteropancreatic neuroendocrine tumors (GEP-NETs). Mol Cell Endocrinol 2016;425:61.
117. Wei D, Wang L, He Y, Xiong HQ, Abbruzzese JL, Xie K. Celecoxib inhibits vascular endothelial growth factor expression in and reduces angiogenesis and metastasis of human pancreatic cancer via suppression of Sp1 transcription factor activity. Cancer Res 2004;64:2030-8.
118. Ristimäki A, Sivula A, Lundin J, Lundin M, Salminen T, Haglund C, *et al*. Prognostic significance of elevated cyclooxygenase-2 expression in breast cancer. Cancer Res 2002;62:632.
119. Kondo M, Yamamoto H, Nagano H, Okami J, Ito Y, Shimizu J, *et al*. Increased expression of COX-2 in nontumor liver tissue is associated with shorter disease-free survival in patients with hepatocellular carcinoma. Clin Cancer Res 1999;5:4005.

120. Masunaga R, Kohno H, Dhar DK, Ohno S, Shibakita M, Kinugasa S, *et al.* Cyclooxygenase-2 expression correlates with tumor neovascularization and prognosis in human colorectal carcinoma patients. Clin Cancer Res 2000;6:4064-8.
121. Misra S, Sharma K. COX-2 signaling and cancer: New players in old arena. Curr Drug Targets 2014;15:347-59.
122. Dannenberg AJ, Altorki NK, Boyle JO, Dang C, Howe LR, Weksler BB, *et al.* Cyclo-oxygenase 2: A pharmacological target for the prevention of cancer. Lancet Oncol 2001;2:544-551.
123. Bennett CL, Lai SY, Sartor O, Georgantopoulos P, Hrushesky WJ, Henke M, *et al.* Consensus on the existence of functional erythropoietin receptors on cancer cells. JAMA Oncol 2015;2:1.
124. Teich N, Bauer N, Mössner J, Keim V. Mutational screening of patients with nonalcoholic chronic pancreatitis: Identification of further trypsinogen variants 1. Am J Gastroenterol 2002;97:341-6.
125. Truninger K, Ammann RW, Blum HE, Witt H. Genetic aspects of chronic pancreatitis: Insights into aetiopathogenesis and clinical implications. Swiss Med Wkly 2001;126:565-74.
126. Whitcomb DC, Preston RA, Aston CE, Sossenheimer MJ, Barua PS, Zhang Y, *et al.* A gene for hereditary pancreatitis maps to chromosome 7q35. Gastroenterology 1996;110:1975-80.
127. Sossenheimer MJ, Aston CE, Preston RA, Gates LK Jr, Ulrich CD, Martin SP, *et al.* Clinical characteristics of hereditary pancreatitis in a large family, based on high-risk haplotype. The Midwest Multicenter Pancreatic Study Group (MMPSG). Am J Gastroenterol 1997;92:1113-6.
128. Schneider A, *et al.* Combined bicarbonate conductance-impairing variants in CFTR and SPINK1 variants are associated with chronic pancreatitis in patients without cystic fibrosis. Gastroenterology 2011;140:162-71.
129. Pfützer RH, Barmada MM, Brunskill AP, Finch R, Hart PS, Neoptolemos J, *et al.* SPINK1/PSTI polymorphisms act as disease modifiers in familial and idiopathic chronic pancreatitis. Gastroenterology 2000;119:615-23.
130. Witt H, Luck W, Hennies HC, Classen M, Kage A, Lass U, *et al.* Mutations in the gene encoding the serine protease inhibitor, Kazal type 1 are associated with chronic pancreatitis. Nat Genet 2000;25:213-6.
131. Dimagno EP, Dimagno MJ. Chronic pancreatitis: Landmark papers, management decisions, and future. Pancreas 2016;45:641-50.
132. Aoun E, Chang CC, Greer JB, Papachristou GI, Barmada MM, Whitcomb DC. Pathways to injury in chronic pancreatitis: Decoding the role of the high-risk SPINK1 N34S haplotype using meta-analysis. PLoS One 2008;3:e2003.
133. Li X, Fang P, Mai J, Choi ET, Wang H, Yang XF. Targeting mitochondrial reactive oxygen species as novel therapy for inflammatory diseases and cancers. J Hematol Oncol 2013;6:19.
134. Iic C, Tuveson DA. ROS in cancer: The burning question. Trends Mol Med 2017;23:411.
135. Fruehauf JP, Meyskens FL. Reactive oxygen species: A breath of life or death? Clin Cancer Res 2007;13:789-94.
136. Kong B, Qia C, Erkan M, Kleeff J, Michalski CW. Overview on how oncogenic Kras promotes pancreatic carcinogenesis by inducing low intracellular ROS levels. Front Physiol 2013;4:246.
137. Storz P. KRas, ROS and the initiation of pancreatic cancer. Small GTPases 2017;8:38-42.
138. Zhang L, Li J, Ma J, Chen X, Chen K, Jiang Z, *et al.* The relevance of Nrf2 pathway and autophagy in pancreatic cancer cells upon stimulation of reactive oxygen species. Oxid Med Cell Longev 2016;2016:3897250.
139. Sabharwal SS, Schumacker PT. Mitochondrial ROS in cancer: Initiators, amplifiers or an Achilles' heel? Nat Rev Cancer 2014;14:709-21.
140. Durand N, Storz P. Targeting reactive oxygen species in development and progression of pancreatic cancer. Exp Rev Anticancer Ther 2017;17:19.
141. Wang F, Efird J, Holly EA. Pancreatitis and the risk of pancreatic cancer. Cancer Res 2005;65:1036.
142. Talamini G, Falconi M, Bassi C, Sartori N, Salvia R, Caldiron E, *et al.*, Incidence of cancer in the course of chronic pancreatitis. Am J Gastroenterol 1999;94:1253-60.
143. Malka D, Hammel P, Maire F, Rufat P, Madeira I, Pessione F, *et al.* Risk of pancreatic adenocarcinoma in chronic pancreatitis. Gut 2003;51:849-52.
144. Löhr M, Klöppel G, Maisonneuve P, Lowenfels AB, Lüttges J. Frequency of K-ras mutations in pancreatic intraductal neoplasias associated with pancreatic ductal adenocarcinoma and chronic pancreatitis: A meta-analysis. Neoplasia 2005;7:17.
145. Real FX, Cibriánuhalte E, Martinelli P. Pancreatic cancer development and progression: Remodeling the model. Gastroenterology 2008;135:724-8.
146. Kim J, Reber HA, Dry SM, Elashoff D, Chen SL, Umetani N, *et al.* Unfavourable prognosis associated with K-ras gene mutation in pancreatic cancer surgical margins. Gut 2006;55:1598.
147. Talar-Wojnarowska R, Gasiorowska A, Smolarz B, Romanowicz-Makowska H, Strzelczyk J, Janiak A, *et al.* Usefulness of p16 and K-ras mutation in pancreatic adenocarcinoma and chronic pancreatitis differential diagnosis. J Physiol Pharmacol 2004;55(Suppl 2):129.
148. Lemoine NR, Jain S, Hughes CM, Staddon SL, Maillet B, Hall PA, *et al.* Ki-ras oncogene activation in preinvasive pancreatic cancer. Gastroenterology 1992;102:230.
149. Finkelstein SD, Przygodzki R, Pricolo VE, Sayegh R, Bakker A, Swalsky PA, *et al.* K-ras-2 topographic genotyping of pancreatic adenocarcinoma. Arch Surg 1994;129:367.
150. Lu X, Xu T, Qian J, Wen X, Wu D. Detecting K-ras and p53 gene mutation from stool and pancreatic juice for diagnosis of early pancreatic cancer. Chin Med J (Engl) 2002;115:1632-6.
151. Sawabu N, Watanabe H, Yamaguchi Y, Ohtsubo K, Motoo Y. Serum tumor markers and molecular biological diagnosis in pancreatic cancer. Pancreas 2004;28:263-7.
152. Wang Y, Yamaguchi Y, Watanabe H, Ohtsubo K, Motoo Y, Sawabu N. Detection of p53 gene mutations in the supernatant of pancreatic juice and plasma from patients with pancreatic carcinomas. Pancreas 2004;28:13.
153. Yan L, McFaul C, Howes N, Leslie J, Lancaster G, Wong T, *et al.* Molecular analysis to detect pancreatic ductal adenocarcinoma in high-risk groups. Gastroenterology 2005;128:2124-30.
154. Shi C, Fukushima N, Abe T, Bian Y, Hua L, Wendelburg BJ, *et al.* Sensitive and quantitative detection of KRAS2 gene mutations in pancreatic duct juice differentiates patients with pancreatic cancer from chronic pancreatitis, potential for early detection. Cancer Biol Ther 2008;7:353-60.
155. Däbritz J, Preston R, Hänfler J, Oettle H. Follow-up study of K-ras mutations in the plasma of patients with pancreatic cancer: Correlation with clinical features and carbohydrate antigen 19-9. Pancreas 2009;38:534.
156. Chen H, Tu H, Meng ZQ, Chen Z, Wang P, Liu LM. K-ras mutational status predicts poor prognosis in unresectable pancreatic cancer. Eur J Surg Oncol 2010;36:657-62.
157. Uemura T, Hibi K, Kaneko T, Takeda S, Inoue S, Okochi O, *et al.* Detection of K-ras mutations in the plasma DNA of pancreatic cancer patients. J Gastroenterol 2004;39:56-60.
158. Guerra C, Schuhmacher AJ, Cañamero M, Grippo PJ, Verdaguer L, Pérez-Gallego L, *et al.* Chronic pancreatitis is essential for induction of pancreatic ductal adenocarcinoma by K-Ras oncogenes in adult mice. Cancer Cell 2007;11:291-302.
159. Diakopoulos KN, Lesina M, Wörmann S, Song L, Aichler M, Schild L, *et al.* Impaired autophagy induces chronic atrophic pancreatitis in mice via sex- and nutrition-dependent processes. Gastroenterology 2015;148:626-38.e17.
160. Gukovsky I, Gukovskaya AS. Impaired autophagy underlies key pathological responses of acute pancreatitis. Autophagy 2010;6:428-9.

161. Dusetti NJ, Jiang Y, Vaccaro MI, Tomasini R, Azizi Samir A, Calvo EL, *et al.* Cloning and expression of the rat vacuole membrane protein 1 (VMP1), a new gene activated in pancreas with acute pancreatitis, which promotes vacuole formation. Biochem Biophys Res Commun 2002;290:641.
162. Ropolo A, Grasso D, Pardo R, Sacchetti ML, Archange C, Lo Re A, *et al.* The pancreatitis-induced vacuole membrane protein 1 triggers autophagy in mammalian cells. J Biol Chem 2007;282:37124-33.
163. Calvo-Garrido J, King JS, Muñoz-Braceras S, Escalante R. Vmp1 regulates PtdIns3P signaling during autophagosome formation in Dictyostelium discoideum. Traffic 2015;15:1235-46.
164. Tian Y, Li Z, Hu W, Ren H, Tian E, Zhao Y, *et al.* C. elegans screen identifies autophagy genes specific to multicellular organisms. Cell 2010;141:1042-55.
165. Nowak J, Archange C, Tardivel-Lacombe J, Pontarotti P, Pébusque MJ, Vaccaro MI, *et al.* The TP53INP2 protein is required for autophagy in mammalian cells. Mol Biol Cell 2009;20:870-81.
166. Seillier M, Peuget S, Gayet O, Gauthier C, N'Guessan P, Monte M, *et al.* TP53INP1, a tumor suppressor, interacts with LC3 and ATG8-family proteins through the LC3-interacting region (LIR) and promotes autophagy-dependent cell death. Cell Death Differ 2012;19:1525-35.
167. Antonucci L, Fagman JB, Kim JY, Todoric J, Gukovsky I, Mackey M, *et al.* Basal autophagy maintains pancreatic acinar cell homeostasis and protein synthesis and prevents ER stress. Proc Natl Acad Sci U S A 2015;112:6166-74.
168. Grasso D, Ropolo A, Lo Ré A, Boggio V, Molejón MI, Iovanna JL, *et al.* Zymophagy, a novel selective autophagy pathway mediated by vmp1-usp9x-p62, prevents pancreatic cell death. J Biol Chem 2011;286:8308.
169. Loncle C, Molejon MI, Lac S, Tellechea JI, Lomberk G, Gramatica L, *et al.* The pancreatitis-associated protein VMP1, a key regulator of inducible autophagy, promotes Kras(G12D)-mediated pancreatic cancer initiation. Cell Death Dis 2016;7:e2295.
170. Klionsky D, Abdelmohsen K, Abe A, Abedin MJ, Abeliovich H, Acevedo Arozena A, *et al.* Guidelines for the use and interpretation of assays for monitoring autophagy (2nd edition). 2016;151-75.
171. Yang A, Herter-Sprie G, Zhang H, Lin EY, Biancur D, Wang X, *et al.* Autophagy sustains pancreatic cancer growth through both cell autonomous and non-autonomous mechanisms. Cancer Discov 2018;8:276-87.
172. Brown JM, Recht L, Strober S. The promise of targeting macrophages in cancer therapy. Clin Cancer Res 2017;23.
173. Beatty GL, Chiorean EG, Fishman MP, Saboury B, Teitelbaum UR, Sun W, *et al.* CD40 agonists alter tumor stroma and show efficacy against pancreatic carcinoma in mice and humans. Science 2011;331:1612-6.
174. Lock R, Kenific CM, Leidal AM, Salas E, Debnath J. Autophagy-dependent production of secreted factors facilitates oncogenic RAS-driven invasion. Cancer Discov 2014;4:466-79.
175. Sousa CM, Biancur DE, Wang X, Halbrook CJ, Sherman MH, Zhang L, *et al.* Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion. Nature 2016;536:479-83.
176. Sun X, Cheng G, Hao M, Zheng J, Zhou X, Zhang J, *et al.* CXCL12/CXCR4/CXCR7 chemokine axis and cancer progression. Cancer Metastasis Rev 2010;29:709-22.
177. Roy I, Zimmerman NP, Mackinnon AC, Tsai S, Evans DB, Dwinell MB. CXCL12 chemokine expression suppresses human pancreatic cancer growth and metastasis. PLoS One 2014;9:e90400.
178. Fearon DT. The carcinoma-associated fibroblast expressing fibroblast activation protein and escape from immune surveillance. Cancer Immunol Res 2014;2:187-93.
179. Li X, Ma Q, Xu Q, Liu H, Lei J, Duan W, *et al.* SDF-1/CXCR4 signaling induces pancreatic cancer cell invasion and epithelial-mesenchymal transition *in vitro* through non-canonical activation of Hedgehog pathway. Cancer Lett 2012;322:169-76.
180. Shen B, Zheng MQ, Lu JW, Jiang Q, Wang TH, Huang XE. CXCL12-CXCR4 promotes proliferation and invasion of pancreatic cancer cells. Asian Pac J Cancer Prev 2013;14:5403-8.
181. Ma Y, Hwang RF, Logsdon CD, Ullrich SE. Dynamic mast cell-stromal cell interactions promote growth of pancreatic cancer. Cancer Res 2013;73:3927-37.
182. Singh AP, Arora S, Bhardwaj A, Srivastava SK, Kadakia MP, Wang B, *et al.* CXCL12/CXCR4 protein signaling axis induces sonic hedgehog expression in pancreatic cancer cells via extracellular regulated kinase - and Akt kinase-mediated activation of nuclear factor κB: Implications for bidirectional tumor-stromal interactions. J Biol Chem 2012;287:39115-24.
183. Demir IE, Tieftrunk E, Schorn S, Saricaoglu ÖC, Pfitzinger PL, Teller S, *et al.* Activated Schwann cells in pancreatic cancer are linked to analgesia via suppression of spinal astroglia and microglia. Gut 2016;65:1001-14.
184. Mcgranahan N, Furness AJ, Rosenthal R, Ramskov S, Lyngaa R, Saini SK, *et al.* Clonal neoantigens elicit T cell immunoreactivity and sensitivity to immune checkpoint blockade. Science 2016;351:1463-9.
185. Pennock GK, Chow LQ. The evolving role of immune checkpoint inhibitors in cancer treatment. Oncologist 2015;20:812.
186. Royal RE, Levy C, Turner K, Mathur A, Hughes M, Kammula US, *et al.* Phase 2 trial of single agent ipilimumab (anti-ctla-4) for locally advanced or metastatic pancreatic adenocarcinoma. J Immunother 2010;33:828-33.
187. Le DT, Lutz E, Uram JN, Sugar EA, Onners B, Solt S, *et al.* Evaluation of ipilimumab in combination with allogeneic pancreatic tumor cells transfected with a GM-CSF gene in previously treated pancreatic cancer. J Immunother 2013;36:382-9.
188. Aglietta M, Barone C, Sawyer MB, Moore MJ, Miller WH Jr, Bagalà C, *et al.* A phase I dose escalation trial of tremelimumab (CP-675,206) in combination with gemcitabine in chemotherapy-naive patients with metastatic pancreatic cancer. Ann Oncol 2014;25:1750.
189. Bazhin AV, Shevchenko I, Umansky V, Werner J, Karakhanova S. Two immune faces of pancreatic adenocarcinoma: Possible implication for immunotherapy. Cancer Immunol Immunother 2014;63:59-65.
190. Ryan DP, Hong TS, Bardeesy N. Pancreatic adenocarcinoma. Curr Prob Surg 2016;53:107-54.
191. Sideras K, Braat H, Kwekkeboom J, van Eijck CH, Peppelenbosch MP, Sleijfer S, *et al.* Role of the immune system in pancreatic cancer progression and immune modulating treatment strategies. Cancer Treat Rev 2014;40:513-22.