Phosphatidylinositol 3-Kinase: A Link Between Inflammation and Pancreatic Cancer

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Abstract

Even though a strong association between inflammation and cancer has been widely accepted, the underlying precise molecular mechanisms are still largely unknown. A complex signaling network between tumor and stromal cells is responsible for the infiltration of inflammatory cells into the cancer micro-environment. Tumor stromal cells such as pancreatic stellate cells (PSCs) and immune cells create a microenvironment that protects cancer cells through a complex interaction, ultimately facilitating their local proliferation and their migration to different sites. Furthermore, PSCs have multiple functions related to local immunity, angiogenesis, inflammation and fibrosis. Recently, many studies have shown that members of the phosphoinositol-3-phosphate kinase (PI3K) family are activated in tumor cells, PSCs and tumor infiltrating inflammatory cells to promote cancer growth. Pro-inflammatory cytokines and chemokines secreted by immune cells and fibroblasts within the tumor environment can activate the PI3K pathway both in cancer and inflammatory cells. In this review, we focus on the central role of the PI3K pathway in regulating the cross-talk between immune/stromal cells and cancer cells. Understanding the role of the PI3K pathway in the development of chronic pancreatitis and cancer is crucial for the discovery of novel and efficacious treatment options.

Keywords

PI3K; pancreatic cancer; chronic pancreatitis; inflammation

Introduction

Pancreatic cancer continues to be one of the most lethal human malignancies with an overall 5-year survival of 6% or below. It is currently the 4th leading cause of cancer-related deaths in the US and its incidence is predicted to rise. Patients are usually diagnosed late in the disease process and often present with local and distant metastases, and only a small percentage of them are candidates for surgical resection. Even among this highly selected group of patients with resectable disease, the 5-year survival in centers of excellence reaches only 25%. In addition, pancreatic cancer is known to be largely resistant to common radio- and chemo-therapy adding to the dismal prognosis for patients[1,2].

It is well established that chronic inflammation represents a major risk factor for the development and progression of cancer, including pancreatic cancer. For example, inflammatory bowel disease[3], chronic prostatitis[4], and chronic obstructive pulmonary disease (COPD)[5] represent risk factors for development of cancer in the colon, prostate, and lung, respectively. Chronic pancreatitis, which is characterized by acinar loss, fibrosis, and immune cell infiltration, is the strongest identified risk factor for pancreatic cancer[6, 7]. Chronic inflammation usually is characterized by a recruitment and infiltration of inflammatory cells into the tissue with an increased production and secretion of chemokines and cytokines. There is a strong interplay between the malignant or premalignant cells and the stromal cells, including inflammatory cells. This inflammatory micro-environment is believed to be a major driver for cancer initiation and/or promotion[8]. Chronic inflammation also underlies, at least partially, the increased cancer risk by other risk factors, including alcohol abuse, smoking, obesity, and infections. Although today numerous studies link inflammation with cancer, the exact underlying molecular mechanisms and operative cross-talks between malignant and stromal cells are still largely unknown.

During acute and chronic inflammation and tumor development a host of immune cells are recruited to and infiltrate the tissue. The current concept of the role of immune cells during tumor development is called "immunoediting"[9] and includes three phases: first, attempt by the immune system to eliminate tumor cells; secondly, the establishment of an equilibrium between tumor cells and the immune system thereby preventing further tumor growth; and thirdly, an escape of a subset of tumor cells from the tumor-suppressive action of the immune system, which leads to development and cancer progression. In this last phase the tumor cells often "hijack" physiological processes of the immune system thereby creating a pro-tumorigenic environment[10].

The PI3K signaling cascade is critical in conditions of inflammation and cancer. The PI3K pathway is often activated in both tumor cells and tumor-infiltrating immune cells and is also involved in the cytokine-mediated cross-talk between cancer and inflammatory cells[11]. Based on the current evidence, targeting the PI3K and its signaling pathway is an intriguing concept for preventing inflammation-associated tumor development. This review will summarize our current understanding about the pancreatitis - pancreatic cancer continuum and will highlight the key role of the PI3K in this process.

Risk factors for pancreatitis and pancreatic cancer

The link between chronic inflammation and cancer is not new: more than 150 years ago, Virchow postulated chronic inflammation as the origin of cancer[12]. Today, it is well established that immune cells are regularly present in tumors and play a critical role in tumor development and progression[13]. However, the operative cross-talks between tumor and stromal cells as well as the precise underlying molecular mechanisms remain still largely unknown. Chronic inflammation is also a well-established risk factor for the development of pancreatic cancer and underlies to some extent many of the risk factors for this disease.

Chronic pancreatitis, the strongest identified risk factor for pancreatic cancer, has a high incidence in industrialized countries, ranging from 3.5 to 10 per 100,000 people[14]. The pathological hallmarks of chronic pancreatitis are inflammation, glandular atrophy, ductal changes, and fibrosis[6]. There are several hypotheses for the development of chronic pancreatitis. The necrosis-fibrosis hypothesis envisions the development of fibrosis from recurrent acute pancreatitis[15]. During the development of chronic pancreatitis inflammatory cells, e.g. macrophages, neutrophils, lymphocytes, and mast cells, are recruited into the pancreas leading to fibrosis and inflammation. The infiltrating inflammatory cells create a pro-inflammatory microenvironment by secreting chemokines, cytokines, and growth factors, potentially promoting genetic instability and thereby increasing the risk of malignant transformation[16,17]. Many risk factors of chronic pancreatitis, including alcohol abuse, cigarette smoking, and obesity also increase the risk of developing pancreatic cancer, thereby highlighting a common underlying pathophysiologic mechanism between these two diseases.

Alcohol abuse, the best characterized risk factor for chronic pancreatitis[18], can cause repeated episodes of acute pancreatitis often referred to as acute relapsing pancreatitis. It is accepted today that acute pancreatitis and acute relapsing pancreatitis can develop into chronic pancreatitis[19]. Takeyama, showed a significant risk of progression to chronic pancreatitis after the first episode of alcohol-related acute pancreatitis[20]. Recent studies have shown that about 60 g of ethanol (around 5 drinks per day) are needed to significantly increase the risk for developing pancreatitis[21]. It has been reported that ethanol metabolites damage and kill pancreatic acinar cells; acinar cells metabolize ethanol to ethanol fatty acid ethyl esters (FAEE), which can increase intracellular calcium levels causing acinar cells necrosis[22]. The resulting necrotic tissue generates a strong inflammatory reaction with recruitment and infiltration of inflammatory cells and the release of chemokines and cytokines. If persistent or recurrent, this process may ultimately lead to chronic inflammation and may promote the generation of fibrosis and development of neoplastic lesions[23].

Another risk factor for chronic pancreatitis is cigarette smoking. Studies have shown that N-nitrosamines, which are present in cigarette smoke, are directly secreted into the bile and may stimulate an inflammatory response in the pancreas[24]. As an alternative mechanism, nicotine metabolites can bind to receptors on the exocrine pancreas, thereby promoting pancreatitis and pancreatic cancer[25]. Importantly, cigarette smoking increases the risk of pancreatic cancer by 1.5 to 3 fold, depending on the duration and number of cigarette

smoked[26]. Recently, Jang and colleagues showed that the effect of tobacco smoking on increasing the risk of pancreatic cancer may depend on certain genetic variations[27]. Interestingly, the effects of cigarette smoke are additive to alcohol abuse in increasing the incidence of acute and chronic pancreatitis[28].

Many studies identified obesity, in particular visceral adiposity, as another risk factor that promotes the development of acute and chronic pancreatitis, and pancreatic cancer[29]. Obesity is now recognized as a chronic inflammatory state with increased systemic and tissue levels of cytokines and growth factors[30]. During the development of obesity, inflammatory cells, e.g. macrophages, are recruited to and infiltrate adipose tissue with subsequent secretion of pro-inflammatory cytokines. The adipose tissue inflammation during obesity is thought to be integral to the development of obesity-associated metabolic diseases[31]. Besides adipose tissue inflammation, obesity also leads to inflammation in other tissues and organs, including pancreas[32]. Again, obesity-induced inflammation of the pancreas may create a micro-environment that is conducive to the development of chronic pancreatitis and cancer[33]. In addition, obesity is often associated with insulin-resistance and frank diabetes mellitus. In that context, an increased risk of developing pancreatic cancer in diabetic patients has been reported[34,35].

Hereditary pancreatitis is a rare cause of chronic pancreatitis. The altered genes involved in the pathogenesis are the cationic trypsinogen gene (PRSS1) and the serine protease inhibitor Kazal type 1 (SPINK 1). These genetic mutations can lead to an auto-activation of trypsinogen in the pancreas that leads to necrosis and inflammation[36]. Importantly, patients with hereditary pancreatitis have a 40–60 fold higher risk to develop pancreatic cancer, and this occurs earlier when individuals are smokers or heavy drinkers[37]. Noteworthy, patients with hereditary pancreatitis and acute pancreatitis episodes who also drink alcohol and smoke showed a higher risk to progress to recurrent acute pancreatitis, chronic pancreatitis, and finally pancreatic cancer, highlighting the importance of recurrent and chronic inflammation and cancer.

Taken together, several factors are known to increase the risk of pancreatic cancer. Chronic inflammation with infiltration of inflammatory cells into the pancreas and subsequent secretion of numerous cytokines, thereby creating an inflammatory micro-environment, is thought to be an important mechanism of pancreatic cancer development and underlies most, if not all, of the risk factors for chronic pancreatitis and pancreatic cancer.

Pancreatic inflammation: the path to pancreatic cancer

Many factors can cause an acute inflammation in the pancreas (acute pancreatitis) that if persistent or recurrent can lead to the development of chronic pancreatitis with disturbances in exocrine pancreas function, the formation of desmoplasia, and an increased risk of pancreatic cancer. Several cell populations play a central role in acute and chronic pancreatic injury and inflammation, including pancreatic stellate cells, inflammatory cells, i.e. macrophages, and pancreatic acinar cells.

Pancreatic stellate cells (PSC) are myofibroblast-like cells in the pancreas, which are currently known to be responsible for the formation of the desmoplastic reaction in chronic pancreatitis and pancreatic cancer[38]. In healthy subjects with normal pancreatic tissue, PSCs are quiescent[39] while after pancreatic inflammation or injury they are activated and transformed into myofibroblast-like cells, which characteristically express alpha-smooth muscle actin (alpha-SMA)[38]. Once activated PSCs start to proliferate, migrate, produce extracellular matrix (ECM) and, importantly, display a pro-inflammatory phenotype, releasing chemokines, cytokines, and growth factors such as IL-1, IL-6, IL-8, TNF-alpha, TGF-beta, VEGF, and PDGF; all these factors can attract other inflammatory cells into the pancreas, thereby perpetuating the inflammatory reaction[40]. PSCs also express and secrete metalloproteinases, e.g. MMP-9, MMP-13, MMP-2, highlighting their role in the formation and modulation of the pancreatic stroma during the development of chronic pancreatitis and pancreatic cancer[41]. Thus, PSCs can create a microenvironment that favors cancer cells growth, survival and migration[42]. It has also been reported that PSCs can exhibit a macrophage-like phenotype, due to their capacity to phagocytize necrotic debris and foreign elements, similarly to Kupffer cells in the liver[43,44]. In addition, PSCs can promote angiogenesis by producing vascular endothelial growth factor (VEGF)[45]. A strong correlation between high levels of VEGF, angiogenesis, and fibrosis has been demonstrated in chronic pancreatitis and pancreatic cancer[46].

Among inflammatory cells, macrophages are considered to play a central and important role in chronic pancreatitis and pancreatic cancer. As discussed above, many factors contribute to an inflammatory and pro-carcinogenic environment in the pancreas with the recruitment and infiltration of inflammatory cells, including macrophages. Signals in the tumor environment lead to maturation of two types of macrophages: tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs)[47]. TAMs are the predominant leukocytes in solid tumors[48]: they produce cytokines and growth factors that can promote tumor cell growth[49]. MDSCs are activated immature cells with morphological and functional heterogeneous characteristics that play a key role in cancer immune evasion. Recently, Khaled and colleagues found high levels of MDSCs in the blood of patients with pancreatic cancer[50]. Thus, TAMs and MDSCs can be recruited by signals from the tumor and other inflammatory cells and secrete cytokines that may promote cancer progression and metastasis[51]. Similar to Th1 and Th2 lymphocytes, macrophages can be divided into two principal subtypes: M1 macrophages that produce cytokines with inhibitory function on cell proliferation and M2 macrophages that release cytokines that promote cell proliferation. It has been shown that pro-tumorigenic M2 macrophages can be recruited by signals from the tumor and other inflammatory cells[52].

Besides pancreatic stellate and inflammatory cells, pancreatic acinar cells are critical in the development of chronic pancreatitis and cancer[53]. Pancreatic acinar cells are the main component of the exocrine pancreas, constituting about 80% of the gland. After pancreatic injury, acinar cells can secrete cytokines, chemokines, and other pro-inflammatory molecules[54]. Acinar cell necrosis during pancreatitis can attract immune cells, which in turn produce pro-inflammatory molecules. The extrinsic factors lead to oxidative stress with the formation of reactive oxygen species (ROS) and reactive nitrogen species (RNS). ROS and RNS can promote DNA mutations and other genetic alterations. In addition, these reactive

molecules can lead to protein and lipid modifications and damage that can contribute to the development of chronic pancreatitis[55]. Interestingly, certain immune cells, e.g. MDSCs, can also produce ROS[56]. The role of acinar cell in pancreatic cancer development is less recognized. Some authors demonstrated that chronic pancreatitis promotes the development of PanIN lesions and pancreatic cancer in mice that express an oncogenic Kras in pancreatic acinar cells[57]. Furthermore, acinar cells have been recently demonstrated to be the cells of origin for pancreatic cancer in at least mouse models of the disease[58].

Taken together, several different cell populations play a central and important role during acute and chronic pancreatic inflammation. Injury to pancreatic acinar cells, activation of stellate cells, and recruitment and activation of inflammatory cells, i.e. macrophages, contribute and sustain an inflammatory environment in the pancreas, which ultimately can increase the risk for developing pancreatic cancer.

PI3K in chronic pancreatitis and pancreatic cancer

Many inflammatory molecules that are present and important during pancreatic inflammation and cancer activate the PI3K signaling pathway. In addition, activation of PI3K has been shown to be critical for inflammation and cancer development[59]. Furthermore, common mutations found in pancreatic cancer can activate PI3K, highlighting the central role of this signaling molecule.

PI3K belongs to the family of lipid kinases that phosphorylate the 3′-hydroxyl group of phosphoinositides[60]. This family of enzymes includes eight mammalian isoforms clustered in three classes (I–III) based on different structure and substrate selection. The class I PI3K has been divided in two subsets, IA and IB. PI3K IA is comprised of p110 alpha, p110 beta, p110 delta catalytic subunit, and the regulatory subunit p85. The only member of the class IB is p110 gamma[61]. The importance of PI3K in cancer in general has been described in many recent reviews[62]. P110 gamma is the principal isoform in leukocytes and it plays a crucial role in immunity by regulating cell proliferation, maturation and motility of neutrophils, macrophages, mast cells, natural killer cells and CD8+ T cells[63,64]. The p110 gamma isoform is essential for the activation and migration of macrophages and granulocytes in response to chemokines and cytokines released from cancer cells[65]. Upon activation, macrophages and neutrophilic granulocytes produce chemokines and cytokines that attract other immune cells, e.g. T- and mast cells to the inflammatory site[66]. Interestingly, Edling and colleagues demonstrated that p110 gamma is overexpressed in pancreatic ducts of patients with pancreatic cancer and chronic pancreatitis, suggesting an important role of this PI3K isoform in regulating proliferation and motility both in immune and tumor cells[67].

Among tumors, pancreatic cancer has one of the highest rates of genetic mutations and the most frequent (>90%) is the K-Ras mutation[68]. In addition, K-Ras mutations can also be found in patients with chronic pancreatitis[69]. Oncogenic RAS often leads to a pathological downstream activation of the PI3K pathway[70]. This process, in the presence of an inflammatory environment, leads to an over-activation of intracellular signals that promote permanent inflammation and consequently genetic mutations that can lead to development

and progression of cancer. Another frequent genetic alteration in pancreatic cancer is the loss of PTEN, either by mutation or deletion[71]. PTEN is a tumor suppressor gene that dephosphorylates PIP3, the principal product of PI3K, into PIP2 thereby counteracting the PI3K pathway activation[72]. The decreased PTEN expression and activity result in an over-activation of PI3K pathway, which has been showed in both chronic pancreatitis and pancreatic cancer[73].

Persistent overproduction of chemokines and cytokines, e.g. IL-1β, is critical for the development of chronic pancreatitis. Inflammatory cytokines can stimulate the expression of other inflammatory mediators, e.g. cyclooxygenase-2 (COX-2). Some authors showed that high levels of COX-2 are present both in pancreatitis and pancreatic cancer[74]. COX-2 is the inducible isoform of cyclooxygenases, enzymes responsible for the synthesis of prostaglandins, which are potent players in inflammation. COX-2 generated prostaglandins, which bind to their respective G-protein-coupled receptors, e.g. EP1-4 for PGE_2, may, in turn, activate the PI3K pathway[75]. Activation of the PI3K pathway leads to several phenotypic responses, including activation of cell survival programs (by expression of anti-apoptotic molecules, e.g. bcl-2), cell proliferation (by induction of cell cycle proteins), angiogenesis (via production of angiogenic factors, e.g. VEGF), and modulation of cellular metabolism (through activation of downstream mTORC1). High levels of COX-2 have been demonstrated in macrophages in patients with chronic pancreatitis and also in patients with pancreatic cancer and pancreatic intraepithelial neoplasia (PanIN), highlighting a possible role of COX-2 in linking chronic pancreatitis and pancreatic cancer[76]. This hypothesis is supported by the finding that inhibition of COX-2 leads to reduced fibrosis, inflammation and tumor lesions[77]. In addition, several growth factors, e.g. IGF, PDGF, and EGF that are present in chronic pancreatitis can activate RAS, which in turn can activate PI3K. This leads to the activation of the serine/threonine kinases AKT1, AKT2, and AKT3. AKT has many substrates, such as Bad, caspase 9, mTOR, GSK3 beta, and tuberin, which are involved in the regulation of cell proliferation, survival, metabolism, angiogenesis, and motility[78].

PI3K also regulates the expression of uPA (urokinase-type plasminogen activator), a serine protease that is secreted from leukocytes, macrophages, fibroblasts, and cancer cells. Normally, uPA is over-produced in inflammatory cells and in inflamed tissues[79,80]. Once bound to its receptor uPAR, the uPA/uPAR complex cleaves plasminogen to plasmin. In turn, plasmin promotes fibrinolysis and the degradation of ECM that is associated with the release of growth factors and other proteases, which in turn can activate the PI3K pathway[81]. In pancreatic cancer as well as in other tumors, there is an abnormal expression of uPA/uPAR that promotes cancer cells survival, angiogenesis, invasion, and migration. uPA/uPAR plays also a key role in the tumor microenvironment being expressed in tumor-associated inflammatory cells and stromal cells. Noteworthy, tumor-associated macrophages are more attracted to the inflammatory environment surrounding cancer cells when they expressed higher levels of uPAR[82]. Thus, inflammation and overexpression of PI3K can stimulate the uPA/uPAR system that, in turn, causes a release of growth factor and proteases that can promote the inflammatory environment.

Taken together, genetic alterations and inflammatory molecules that are present and secreted in chronic pancreatitis (inflammation) and pancreatic cancer can activate the PI3K signaling

pathway, which in turn can stimulate the inflammatory process and tumor development further (Table 1, Figure 1). Since PI3K is activated in both inflammatory and neoplastic diseases of the pancreas, it represents an intriguing therapeutic and preventive target for the pancreatic inflammation – pancreatic cancer progression.

PI3K: a common pathway in multiple cell lineages

Several cell populations are critically involved in the development of chronic pancreatitis and the progression to pancreatic cancer. The PI3K pathway has been shown to play a central and critical role in various cell lineages during this development and is involved in multiple cellular processes, such as proliferation, growth, survival, metabolism, and migration (Table 2).

PI3K and pancreatic stellate cells

Pancreatic stellate cells play a central role in the formation of the desmoplastic reaction by depositing extracellular matrix (ECM) proteins, in the promotion of angiogenesis, and in the local pancreatic immune response[83]. Activated pancreatic stellate cells can express cytokines, chemokines, and various growth factors that promote and sustain a persistent and chronic inflammation. Some authors showed that PDGF is one of the principal mitogens for PSCs. PDGF is produced after pancreatic injury and during inflammation by mononuclear cells, macrophages, and platelets. PDGF induces PI3K pathway activation in PSCs, which leads to their enhanced migration and proliferation. This mechanism is fundamental for the formation of the pancreatic fibrosis[84,85]. Besides TGF-β[86], CCK (cholecystokinin) and gastrin have also been shown to activate PSCs and stimulate collagen production. Interestingly, patients with chronic pancreatitis often have elevated levels of CCK[87]. After binding of CCK to their respective receptors on PSCs, the PI3K pathway is activated, which increases collagen synthesis and fibrosis. Noteworthy, PI3K activity in PSCs has also been implicated to promote the development of pancreatic cancer. Indeed, pancreatic cancer produces pro-mitogenic and pro-fibrotic factors like TGF-β and PDGF that activate PI3K in PSCs. In turn, PSCs release factors such as PDGF, IGF-1, and matrix metalloproteinases that can activate the PI3K pathway in cancer cells promoting tumor growth, survival, metastasis and resistance to chemotherapy[88]. Thus, this mechanism creates a positive loop between PSCs and pancreatic cancer cells.

PI3K and pancreatic acinar cells

Some studies have demonstrated a crucial role of the PI3K pathway in the regulation of Ca^{2+} signaling in pancreatic acinar cells. In particular, PI3K acts in two principal ways in regulating Ca^{2+} signaling: by regulating bile acid-induced Ca^{2+} responses and by acting directly on the sarcoendoplasmic reticulum Ca^{2+} ATPase (SERCA). Bile acids and PI3K cause an inhibition of SERCA that consequently leads to Ca^{2+} release from endoplasmic reticulum stores[89,90]. An increase in intracellular Ca^{2+} in pancreatic acinar cells has been shown to induce cell death, lead to trypsinogen activation, and induce the activation of pro-inflammatory transcription factors such as NF-kB, ultimately promoting pancreatitis[91,92]. PI3K activity in pancreatic acinar cells has been implicated in protein synthesis, cellular metabolism and as a mitogenic and anti-apoptotic factor[93]. Recent reports have described

that at least in animal models PanINs develop from acinar cells via acinar cell de-differentiation and acinar to ductal metaplasia[94]. The transformation from acinar cells into pre-cancerous and cancerous cells is at least partially governed by genetic alterations of the K-Ras oncogene with downstream PI3K activation[95,96]. Interestingly, macrophages have been demonstrated to contribute in promoting acinar cell de-differentiation[97].

PI3K and macrophages

Macrophages are thought to play an important and central role in the development of chronic pancreatitis and pancreatic cancer[98]. There is currently great interest in studying the role of macrophages and the conversion of M0/M1 macrophages into pro-tumorigenic M2 macrophages. Some authors have described how PI3K can convert macrophages into the immunosuppressive and pro-tumorigenic M2 type[99,100]. In macrophages the PI3K pathway is involved in cellular survival, adhesion, and motility[101–104]. Macrophages are present in chronic pancreatitis and pancreatic cancer and have been shown to play a fundamental role in pancreatic inflammation and tumor progression[105,106].

PI3K and neutrophils

Neutrophils are an important component of the innate immune system. They are recruited to sites of acute inflammation and into the tumor microenvironment. They are capable of inducing tumor growth and invasion through the production of proteases and reactive oxygen species (ROS). On the other hand, neutrophils have also been shown to be noxious for cancer cells[107]. Neutrophils are commonly present in chronic pancreatitis but are rarely found in pancreatic cancer[108]. PI3K plays a crucial role for neutrophil growth, survival, phagocytosis, adhesion, diapedesis, and chemotaxis[109–111].

PI3K and mast cells

Mast cells are fundamental in the initiation of an inflammatory response. Mast cells are recruited and activated during inflammation. They produce cytokines and chemokines, thereby maintaining the inflammatory reaction. Mast cells have been shown to promote pancreatic cancer growth and progression by releasing pro-inflammatory and pro-angiogenic factors[112]. The PI3K pathway plays a key role in regulating mast cell differentiation, degranulation, cytokine production, chemotaxis, adhesion, cellular growth, and survival, at least partially through regulation of intracellular calcium levels[113,114].

PI3K in CD8+ T Cells and Natural Killer Cells

T-Lymphocytes are the principal cells of acquired immunity. Several studies showed that PI3K is a crucial pathway involved in T cell activation, chemotaxis, development, and proliferation[115–117]. CD8+ T lymphocytes are the principal T cell subtype present in chronic pancreatitis and in the tumor stroma[118,119]. Some authors highlighted also the crucial role of the PI3K pathway in natural killer cells (NK), as a key factor for cellular development, function, chemotaxis, and cytokine production[120]. The exact role of NK cells in pancreatic cancer is complicated and multifaceted. It has been shown that NK cells are capable of promoting tumor cell lysis[121]. On the other hand, evidence suggests that although NK cells are recruited into the cancer, signals from the tumor microenvironment suppresses NK cell

cytotoxicity while increasing their cytokine production (split anergy)[122]. It has been reported that NK cells are increased in the pancreatic tissue of patients with chronic pancreatitis[123] and decreased in pancreatic cancer[124].

PI3K in pancreatic cancer cells

The central role of the PI3K pathway in pancreatic cancer cells in regulating critical cancer cell phenotypic processes is well documented[125,126]. Activation of PI3K has been linked to proliferation[127], inhibition of apoptosis, survival[128], invasion, migration, metastasis[11], angiogenesis[129], and altered tumor cell metabolism[130]. The PI3K pathway regulates G1-phase progression in cancer cells thereby promoting the S-phase of the cell cycle[131], and contributes to an increase in pancreatic cancer cell size[132]; PI3K favors an anaerobic environment through activation of glycolysis, thus creating a hypoxic state which may promote tumor growth and survival[133]. The PI3K pathway plays also a crucial role in angiogenesis and metastasis. It has been shown that epithelial-mesenchymal transition (EMT) is a critical step in the dissemination of (pancreatic) cancer cells. EMT is regulated by several transcription factors, e.g. twist. Reports have described an interplay between transcriptional regulators of EMT, like twist, and PI3K and downstream Akt[134,135]. The PI3K pathway is also involved in the promotion of tumor angiogenesis by regulating hypoxia-inducible factor (HIF)-1 alpha. HIF-1 alpha induces the transcription of VEGF, which plays a fundamental role in promoting angiogenesis[129,136,137].

Taken together, numerous reports described a central role of PI3K in various cell populations in the pancreas during the development of pancreatic inflammation (pancreatitis) and cancer. A complex reciprocal cross-talk exists between stromal, inflammatory, and pancreatic cells potentially leading to chronic pancreatitis. This resulting inflammatory micro-environment is conducive to pancreatic tumor development. Pancreatic pre-cancer and cancer cells in turn communicate with other cell types in the pancreatic micro-environment to sustain cell survival and further tumor growth. The crosstalk between various cell populations is maintained by molecules secreted by various cell types into the pancreatic stroma, which can activate PI3K and downstream events in an autocrine and/or paracrine manner. Activation of PI3K in turn can lead to the production of further inflammatory molecules, creating a complex communication network (Figure 2). Due to its central role in pancreatic inflammation and cancer, PI3K is an intriguing molecular target for cancer prevention and therapy. Targeting PI3K may reduce the risk of developing (inflammation-associated) pancreatic cancer and decrease tumor growth by affecting fibrosis, inflammation, immune responses, and cancer cell growth. The importance of PI3K as a molecular target in pancreatic cancer is reflected by ongoing clinical trials using various combination regimens (Table 3). In addition, PI3K is also one of the main targets of nutriceuticals underlying their health promoting effects[138].

Exosomes and PI3K pathway

Interestingly, a bidirectional crosstalk between inflammatory and cancer cells can cause a surrounding pro-tumorigenic microenvironment. Some authors showed that also release and exchange of secreted extracellular vesicles (EVs) can play a critical role in the intercellular

crosstalk between tumor and immune cells [139]. Exosomes are 50–150 nm CD9-positive nanovescicles, acting as natural shuttles of RNA and cargo of proteins, lipids and carbohydrates [140]. Recently, some authors demonstrated that exosomes play a fundamental role in the intercellular signaling, transfecting different molecules like IGF, EGF, VEGF, IL-6, leptin and insulin that can activate PI3K pathway[141].

Exosomes can be released from PSCs to other PSCs, transfecting connective tissue factor (CCN2) and microRNA-21 (miR-21) that lead to collagen production, playing thus a fundamental role in the development of chronic pancreatitis[142]. miR-21 is also up-regulated in several solid neoplasia, including pancreatic cancer[143] and inhibits PTEN expression, inducing in this way a PI3K pathway activation[144]. Tumor cells secrete more exosomes compared to normal cells and the amount of exosomes increases as the disease advances[145,146]. It was showed that through exosomes, pancreatic cancer cells can secrete several factors, like EGFR, leading to an up-regulation of PI3K in other cells[147]. Similarly, cancer cells can transfer cytokines, chemokines and growth factors to distant cells, promoting tumor metastasis[148].

Conclusion

Several risk factors can increase the development of chronic pancreatitis and pancreatic cancer. Inflammation is a critical mechanism underlying these risk factors. Pancreatic inflammation is characterized by a recruitment and infiltration of inflammatory cells that secrete cytokines, chemokines, and growth factors. Persistence of this inflammatory environment increases the risk of genetic instability and alterations promoting the development of tumors. There is plenty of evidence that the PI3K pathway is a critical signaling module in inflammatory pancreatic diseases, including chronic pancreatitis and pancreatic cancer. Numerous reports described activation of PI3K in stromal, immune, and pancreatic cancer cells. PI3K plays a key role in tumor-associated immune responses, tumor cell growth, survival, proliferation, angiogenesis and dissemination. Importantly, cytokines, chemokines, and growth factors represent a "common language", by which inflammatory and cancer cells can cross talk, thereby creating a positive feedback loop. In fact, many inflammatory molecules present in chronic pancreatic inflammation and cancer can activate the PI3K pathway. Thus, PI3K represents a common intracellular signaling pathway stimulated in pancreatic inflammatory and neoplastic diseases. Because of its central role in inflammatory and neoplastic pancreatic disease, PI3K is an intriguing target for therapy and prevention of pancreatic cancer. Several clinical trials are currently underway to evaluate targeting PI3K in pancreatic cancer patients.

Acknowledgments

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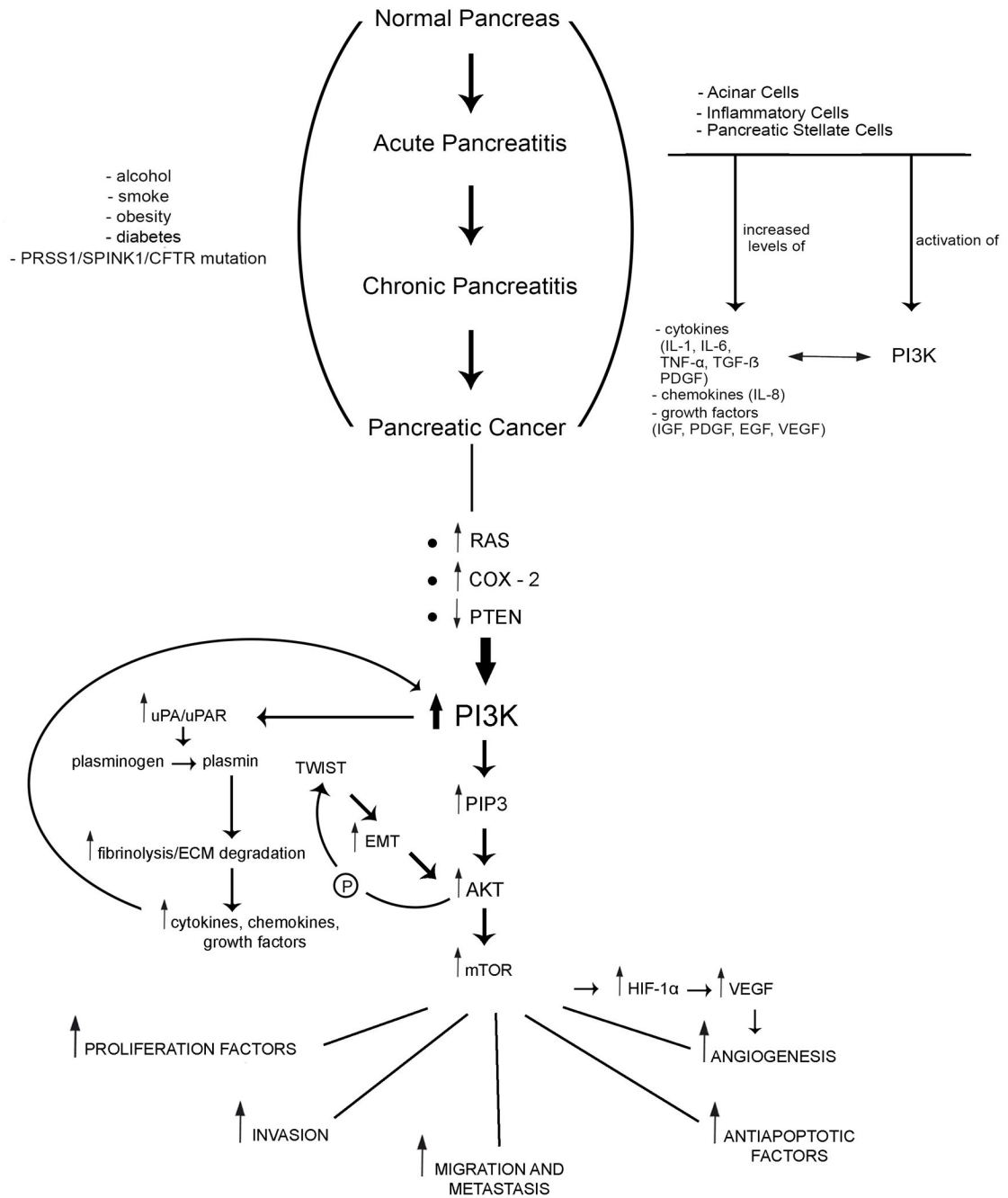
Figure 1.
The effects of alcohol, smoke, obesity, diabetes and hereditary factors on the development and progression of recurrent acute pancreatitis, chronic pancreatitis and pancreatic cancer through increased levels of inflammatory molecules mediated by the PI3K pathway.
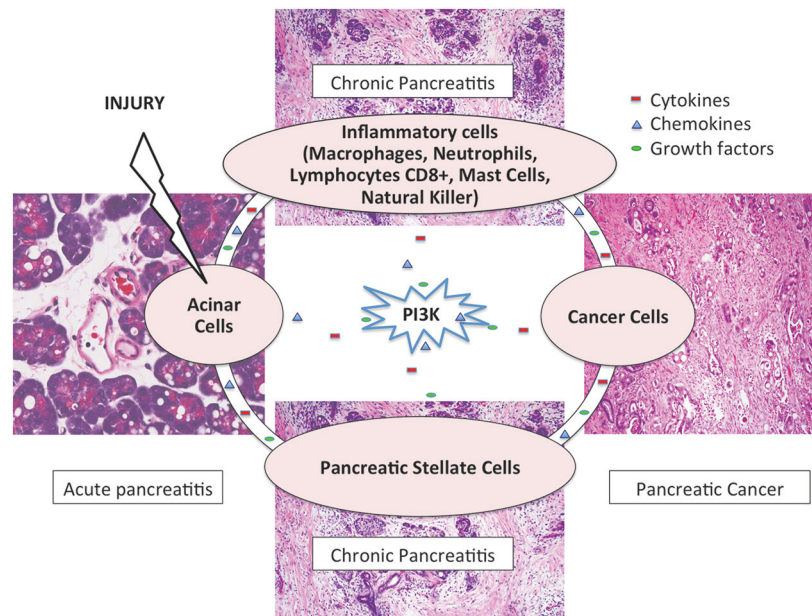
Figure 2.
Several cell types in the pancreatic microenvironment, including macrophages, stellate cells, contribute to the development of acute pancreatitis, chronic pancreatitis, and pancreatic cancer. PI3K plays a central role in mediating the communication between all these cell types.

Table 1

PI3K-related molecular factors in chronic pancreatitis and pancreatic cancer

Description of the genetic/cellular factors	Expression/activity in chronic pancreatitis	Expression/activity in pancreatic cancer	Ref.
PI3K Regulates the transcription of many anti-apoptotic factors (Bcl2), proliferation factors (c-myc, cyclin D1 and again COX-2) and angiogenesis factors (VEGF). The isoform p110 gamma is expressed in leukocytes and it controls the immune cells proliferation, maturation and motility	Increased activity	Increased activity	73, 74, 77
K-Ras Is an oncogene that determines the transcription of membrane-bound called RAS, which is crucial protein for the transmission of signals from extracellular to intracellular environment. This protein controls positively PI3K activity.	Overexpressed	Overexpressed	79, 135
PTEN Is a tumor suppressor gene that dephosphorylates PIP3, the main second messenger of PI3K. PTEN thus negatively regulates PI3K activity.	Down-regulated expression	Down-regulated expression	82, 83
AKT Is a serine/threonine kinase activated by PIP3 that regulates cell proliferation, survival and motility	Increased activity	Increased activity	135, 144, 144
mTOR Is a serine/threonine kinase activated by AKT that controls cell growth, proliferation and transcription	Increased activity	Increased activity	83
COX-2 Is a gene coding for an enzyme that synthesizes prostaglandins. It has a crucial role as inflammation inducer. COX2 increases activation of PI3K pathway.	Overexpressed	Overexpressed	85, 86
uPA/uPAR Is a serine protease regulated by PI3K and it is secreted from leukocytes, macrophages, fibroblasts and cancer cells. It promotes an overproduction of cytokines, chemokines and growth factor that stimulate, in turn, PI3K	Increased activity	Increased activity	89, 90, 91, 92

Table 2

PI3K: a common pathway in different cells in chronic pancreatitis and pancreatic cancer

Cell type	PI3K function	Chronic pancreatitis	Pancreatic cancer	Author, year
Pancreatic Stellate Cells (PSCs)	Activation; chemotaxis; migration in the damaged area; proliferation; increases collagen synthesis and fibrosis	Activated	Activated	94, 95, 96, 97, 98
Acinar cells	Trypsinogen activation, necrosis, transcription of pro-inflammatory factors; controls protein synthesis and metabolism; mitogenic and anti-apoptotic factor	Damaged	De-differentiated	101, 102, 103
Macrophages	Differentiation in different subtypes; survival, adhesion, motility	Present +++	Present +++	111, 112,113, 115, 116
Neutrophils	Growth, survival, phagocytosis, firm adhesion, diapedesis, chemotaxis	Present +++	Present +	119, 120, 121
Mast Cells	Differentiation, degranulation, cytokines production, chemotaxis, adhesion, cellular growth and survival	Present ++	Present ++	122, 123, 124
Lymphocytes T CD8+	Activation, chemotaxis, development, proliferation	Present ++	Present ++	125, 126, 127
Natural Killer Cells (NK)	Development, cellular function, chemotaxis, cytokines production	Present ++	Present +	130, 131, 133, 134

Table 3

Ongoing Clinical Trials in Patients with Pancreatic Cancer with Drugs Targeting the PI3K Pathway

NCT Number	Title	Phase	Drug targeting the PI3K pathway
NCT01155453	A Study to Investigate Safety, Pharmacokinetics (PK) and Pharmacodynamics (PD) of BKM120 Plus GSK1120212 in Selected Advanced Solid Tumor Patients	I	BKM120
NCT01363232	Safety, Pharmacokinetics and Pharmacodynamics of BKM120 Plus MEK162 in Selected Advanced Solid Tumor Patients	I	BKM120
NCT01576666	Phase Ib, Dose Escalation Study of Oral LDE225 in Combination With BKM120 in Patients With Advanced Solid Tumors	I	BKM120
NCT01096199	A Study of TS-1, Cisplatin (CDDP) and RAD001 (Everolimus)	I	Everolimus
NCT01077986	Everolimus, Cetuximab and Capecitabine in Patients With Metastatic Pancreatic Cancer	I–II	Everolimus
NCT01096199	A Study of TS-1, Cisplatin (CDDP) and RAD001 (Everolimus)	I	Everolimus
NCT00499486	Sirolimus in Treating Patients With Advanced Pancreatic Cancer	II	Sirolimus
NCT00075647	CCI-779 in Treating Patients With Locally Advanced or Metastatic Pancreatic Cancer	II	Temsirolimus
NCT01210911	Metformin Combined With Chemotherapy for Pancreatic Cancer	II	Metformin
NCT01347866	Clinical Study Of PI3K/mTOR Inhibitors In Combination With An Oral MEK Inhibitor Or Irinotecan In Patients With Advanced Cancer	I	PF-05212384
NCT01449058	A Phase Ib Study of MEK162 Plus BYL719 in Adult Patients With Selected Advanced Solid Tumors	I–II	BYL719
NCT00777699	Safety Study of XL765 (SAR245409) in Combination With Erlotinib in Adults With Solid Tumors	I	XL765
NCT00692640	Safety Study of XL147 (SAR245408) in Combination With Erlotinib in Adults With Solid Tumors	I	XL147