Clinical Insights Into the Biology and Treatment of Pancreatic Cancer

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Abstract

Pancreatic cancer is a devastating disease with a universally poor prognosis. In 2015, it is estimated that there will be 48,960 new cases of pancreatic cancer and that 40,560 people will die of the disease. The 5-year survival rate is 7.2% for all patients with pancreatic cancer; however, survival depends greatly on the stage at diagnosis. Unfortunately, 53% of patients already have metastatic disease at diagnosis, which corresponds to a 5-year survival rate of 2.4%. Even for the 9% of patients with localized disease confined to the pancreas, the 5-year survival is still modest at only 27.1%. These grim statistics highlight the need for ways to identify cohorts of individuals at highest risk, methods to screen those at highest risk to identify preinvasive pathologic precursors, and development of effective systemic therapies. Recent clinical and translational progress has emphasized the relationship with diabetes, the role of the stroma, and the interplay of each of these with inflammation in the pathobiology of pancreatic cancer. In this article, we will discuss these relationships and how they might translate into novel management strategies for the treatment of this disease.

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RELATIONSHIP BETWEEN DIABETES AND PANCREATIC CANCER

There are a number of risk factors for the development of pancreatic cancer, which may be classified into environmental causes (tobacco use, chronic pancreatitis), genetic factors (pancreatic cancer in families, hereditary syndromes), preinvasive lesions (mucinous cystic neoplasm, intraductal pancreatic mucinous neoplasm), and metabolic factors (obesity, diabetes). Obesity increases the risk of insulin resistance and overt diabetes, and, compared with normal-weight or overweight

ASSOCIATED CONTENT

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individuals, those with obesity have an earlier age of onset of pancreatic cancer and a worse prognosis.[2] Furthermore, long-standing diabetes modestly increases the risk of pancreatic cancer.[3] Compelling data also support the concept that pancreatic cancer itself can induce diabetes, which may precede the actual onset of pancreatic cancer symptoms by months.[4,5] The complexity of these relationships is outlined in Figure 1. Interestingly, antidiabetic therapy modulates the risk of developing pancreatic cancer; those treated with insulin or insulin secretagogues are at a higher risk, whereas patients treated with metformin have a significantly lower risk of pancreatic cancer.[6] These observations serve to emphasize the important relationship between whole-body energy metabolism and pancreatic carcinogenesis.

Obesity and diabetes represent states of nutritional excess. Classically, nutrients such as glucose and amino acids have been regarded as building blocks for the generation of high-energy molecules. However, there is also a clear role for these nutrients as signaling molecules that affect a number of different cell-signaling pathways. These pathways function together as a metabolic regulatory network that controls fuel and energy metabolism, linking the availability of nutrients to cell growth and proliferation.[7] The three nutrient-sensing pathways that comprise this network are the adenosine monophosphate–activated protein kinase α (AMPK), mammalian target of rapamycin (mTOR), and hexosamine pathways. In states of normoglycemia, glucose is converted to pyruvate, which leads to the reduction of nicotinamide adenine dinucleotide (NAD) to nicotinamide adenine dinucleotide hydrate (NADH) and the generation of adenosine triphosphate (ATP) via the mitochondrial oxidative phosphorylation pathway. However, in states of nutrient excess and hyperglycemia, such as obesity and diabetes, signaling through these nutrient-sensing pathways may be enhanced. The AMPK pathway serves to sense low ATP levels and restore them by stimulating catabolic pathways that generate ATP and by inhibiting anabolic pathways that consume ATP.[8] The mTOR pathway senses amino acid availability, regulates cell growth and proliferation, and modulates tissue and organ growth by stimulating protein synthesis and ribosomal biogenesis.[9] The hexosamine pathway senses glucose availability, regulates fuel metabolism, and conveys nutrient status to the central nervous system by regulating insulin responsiveness of the glucose transport system and by stimulating lipogenesis, glycogen synthesis, leptin and adiponectin secretion, and cytokine secretion.[7] These functions represent the normal nutrient-sensing functions of each of these pathways.

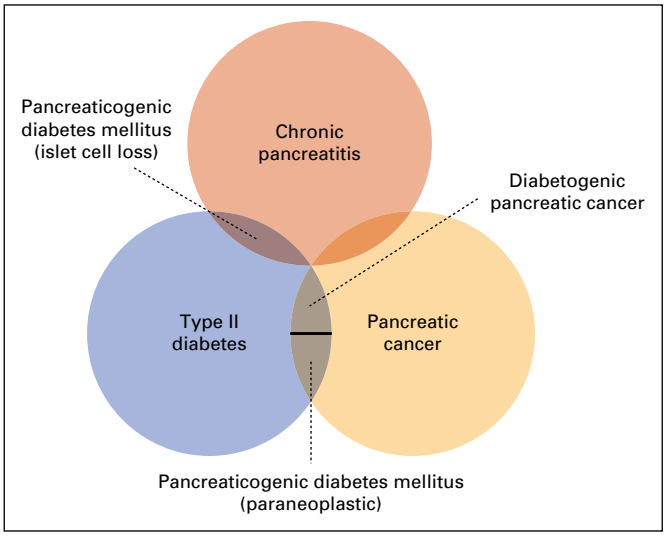

FIG 1. The complex relationships among chronic pancreatitis, type 2 diabetes, and pancreatic cancer.

However, under states of nutrient excess, there is increasing evidence that alterations in these nutrient-sensing pathways contribute to abnormal cell growth and oncogenesis. For example, adiponectin markedly promotes pancreatic tumorigenesis in vivo by inhibiting apoptosis of both human and mouse pancreatic cancer cells via enhanced signaling through an AMPK/sirtuin-1/peroxisome proliferator gamma coactivator 1-α mediated pathway.[10] Furthermore, loss of the tumor suppressor liver kinase B1 (LKB1) within the AMPK signaling pathway leads to defective acinar cell polarity, abnormal cytoskeletal organization, and inactivation of the AMPK family of kinases and is sufficient to drive early pancreatic carcinogenesis.[11,12] The mTOR pathway is a key mitogenic pathway that is suppressed by LKB1 and AMPK-mediated phosphorylation of the tuberous sclerosis complex (TSC)-2 and by the regulatory-associated protein of mTOR (raptor).[13] Deletion of TSC1 results in activation of the mTOR signaling pathway in pancreatic progenitor cells and the subsequent development of adenocarcinoma-like lesions.[14] Additional evidence that mTOR signaling is important to pancreatic carcinogenesis is suggested by studies that demonstrate that knockdown of the transmembrane mucin MUC16 in pancreatic cancer cells leads to inhibition of mTOR activity, reduced migration and invasive potential, and reduced expression of its downstream target c-MYC, which plays essential roles in cellular growth, proliferation, and metabolism.[15] Activating Kirsten rat sarcoma viral oncogene

homolog (*KRAS*) mutations turn on canonical cancer-related pathways but also contribute to extensive metabolic reprogramming of pancreatic cancer cells. *KRAS G12D,* a common mutation in pancreatic cancers, plays a vital role in the control of tumor metabolism by stimulating glucose uptake and directing these intermediates into the hexosamine biosynthesis and pentose phosphate pathways, which also demonstrates the interplay between nutrient excess, the genomic makeup of the pancreatic cancer, and nutrient-signaling pathway activation.[16] These relationships are depicted in Figure 2.

Nutrient excess also results in increased reactive oxidative stress, which leads to genomic instability in genes, including *KRAS*. It is well established that *KRAS* mutations initiate pancreatic carcinogenesis.[17] However, oncogenic *KRAS* mutations alone do not induce pancreatic intraepithelial neoplasia and metastatic pancreatic ductal adenocarcinoma, because adult acinar cells are resistant to oncogenic insults. Pancreatic inflammation induces pancreatic intraepithelial neoplasia and metastatic pancreatic ductal adenocarcinoma in mutant *KRAS*-expressing adult acinar cells by inhibiting oncogene-induced senescence.[18,19] It has been demonstrated that oncogenic *KRAS* promotes the initiation and progression of preinvasive pancreatic neoplasia through activation of an interleukin (IL)-17–dependent pathway. In the setting of *KRAS* mutation and inflammation, two distinct IL-17–secreting populations of lymphoid cells are recruited to the pancreas: T helper 17 (Th17) cells and γδT cells, both of which are normally rare in pancreatic tissue.[20,21] IL-17 helps to drive the initiation and progression of pancreatic carcinogenesis.[20] Besides recruitment of IL-17–secreting cell types, oncogenic *KRAS* (but not wild-type *KRAS*) also drives expression of the functional IL-17 receptor (IL-17R) on the pancreatic epithelium, and neutralization of IL-17 in vivo alters the downstream cell signaling–driven gene expression. This leads to a loss of signal transducer and activator of transcription (STAT)-3 phosphorylation and IL-6 expression, both of which are key regulators of pancreatic neoplastic progression. The prevalence of *KRAS* mutations in pancreatic cancer and the contribution of IL-17 as an inflammatory mediator that promotes carcinogenesis in the setting of oncogenic *KRAS* expression highlights the potential for translation into a therapeutic strategy, particularly because anti–IL-17 monoclonal antibodies are actively being developed for various inflammatory diseases. However, given the antitumor activity of Th17 cells in some models, an anti–IL-17 treatment approach would have to be carefully tested in preclinical models.[22]

ROLE OF THE STROMA

Pancreatic cancer results in a dense desmoplastic reaction, in which the stroma increases to greater than 50% of the tumor tissue.[23] The stroma in pancreatic tumors is characterized by an extracellular matrix comprised of collagens, noncollagen glycoproteins, glycosaminoglycans, growth factors, proteoglycans, and modulators of the cell-matrix interaction.[24] Variations in the concentrations of these individual components of the extracellular matrix play a major role in the

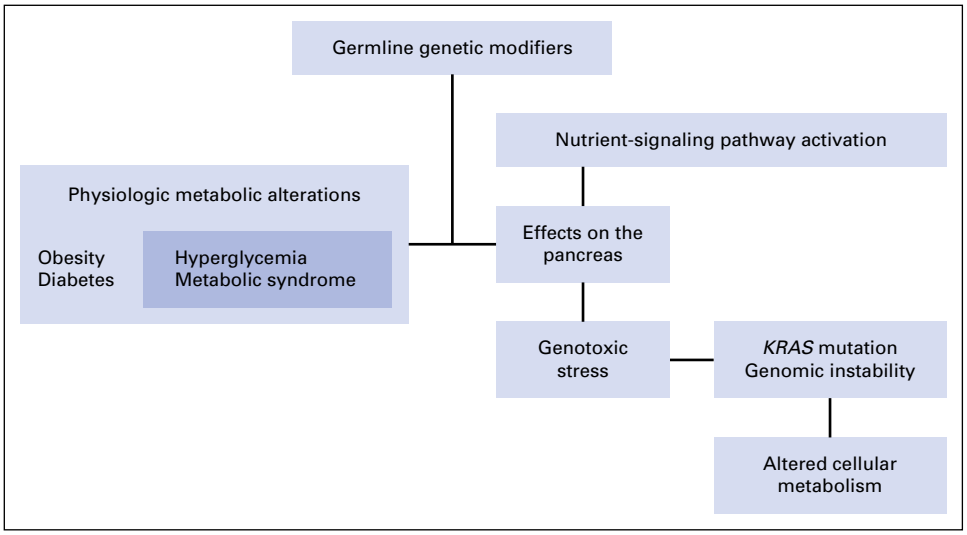

FIG 2. Aberrant metabolism is both a cause and a result of pancreatic carcinogenesis.

migration of pancreatic cancer cells.[25,26] Furthermore, variations in the structural organization of the extracellular matrix proteins also contribute to increased invasiveness by altering the mobility of pancreatic cancer cells.[27]

It has been suggested that various stromal factors enhance pancreatic cancer proliferation and invasiveness; thus, the paradigm of the tumor stroma as a supporter and promoter of cancer cell growth and proliferation has been proposed.[28] The desmoplastic reaction seen in pancreatic cancer has impeded drug delivery because of high interstitial fluid pressures, which induce vascular collapse and present a barrier to perfusion, diffusion, and convection of standard chemotherapeutic agents. Enzymatic ablation of an extracellular matrix component, hyaluronic acid, can normalize the interstitial fluid pressure, re-expand the microvasculature, and double overall survival when used in combination with gemcitabine.[29] Such studies highlight the potential promise of developing antistromal approaches to treat pancreatic cancer.

Pancreatic cancer is also marked by leukocyte infiltration into the tumor stroma, a feature that is recapitulated in the well-validated, clinically relevant KPC murine model of the disease. In these mice, myeloid-derived suppressor cells prominently accumulated in the tumor and the spleen, comprised 20% to 30% of all leukocytes in these tissues, and suppressed antigen-specific T cells.[30] Granulocyte macrophage colony-stimulating factor (GM-CSF) secreted by pancreatic cancer cells is necessary and sufficient to drive the development of myeloid-derived suppressor cells, and antibody-mediated neutralization and genetic knockdown of GM-CSF limited tumor growth and recruitment of myeloid-derived suppressor cells in vivo. These data demonstrate the potential role of GM-CSF as an important regulator of inflammation and immune suppression within the tumor microenvironment. GM-CSF can also function as a key immunologic activator, rather than suppressor, when tumor cells are transduced to express GM-CSF. GVAX, a vaccine composed of two irradiated allogeneic pancreatic cancer cell lines that have been transduced to express GM-CSF, induces T-cell activation against pancreatic cancer antigens. The determinants of GM-CSF that lead to immune suppression in the tumor microenvironment and to immune activation via GVAX may be due to differences in GM-CSF dose and location, and such therapeutic strategies may require combinatorial strategies with other anti-immunosuppressant drugs.

In addition to recruitment of myeloid-derived suppressor cells, pancreatic cancer cells promote mast cell migration and stimulate mast cell activation, which in turn stimulates pancreatic cancer cell growth in vitro and promotes proliferation of stromal fibroblasts through the secretion of IL-13 and tryptase.[31,32] Furthermore, blockade of mast cell migration to the tumor microenvironment and blockade of mast cell degranulation with cromolyn suppresses pancreatic cancer growth and promotes increased survival in vivo.[31] Mast cell infiltration is statistically significantly associated with survival in patients who have pancreatic cancer.[32] These data highlight the role of mast cells and other inflammatory cells in pancreatic cancer cell growth and prognosis.

Despite the infiltration of inflammatory cells in pancreatic cancer, immunotherapies, including checkpoint inhibitors like anti–cytotoxic T lymphocyte–associated protein 4 (anti–CTLA-4) and anti–programmed death ligand 1 (anti–PD-L1), are largely ineffective in pancreatic cancer.[33,34] Carcinoma-associated fibroblasts that express fibroblast activation protein secrete the chemokine ligand 12 (CXCL12). A CXCL12 inhibitor has induced rapid T-cell accumulation and fostered synergy with an anti–PD-L1 agent, which resulted in decreased tumor growth, and the residual tumor was composed only of premalignant epithelial cells and inflammatory cells.[35] Therefore, CXCL12 from fibroblast activation protein-expressing carcinoma-associated fibroblasts may be directly responsible for the ability of pancreatic cancer to evade the immune system, which suggests that a possible combinatorial strategy approach of antistromal-directed therapies with checkpoint inhibitors may enhance the therapeutic efficacy of these immunotherapies that have robust activity in other malignancies.

Another molecule inherent to the stromal-associated immune cells that may be targetable in combination with checkpoint inhibitors is Bruton's tyrosine kinase (BTK). BTK is a member of the Tec family of nonreceptor kinases, and it is expressed in hematopoietic cells, including B cells, myeloid cells, mast cells, and platelets, in which it regulates a number of different processes, including proliferation, differentiation, apoptosis, and migration.[36] BTK is activated in immune cells found in the stroma and has been shown to sustain the complex microenvironment needed in tumors of lymphoid and solid organ origin. The BTK inhibitor ibrutinib has antitumoral activity in hematologic malignancies, including chronic lymphocytic leukemia, Waldenström's macrogloubulinemia, and mantle cell lymphoma.[37-40] Preclinical work has demonstrated that mouse models of pancreatic cancer treated with ibrutinib have reduced tumor stroma and improved survival; thus, trials to inhibit BTK are now underway in both the first- and second-line setting

in metastatic pancreatic cancer with first- and second-generation BTK inhibitors (NCT02403271, NCT02362048).[41]

In addition to the recruitment of inflammatory cells to the tumor stroma, pancreatic cancer cells promote proliferation of fibroblasts, particularly the pancreatic stellate cells, star-shaped cells located in the periacinar and periductal regions of the exocrine pancreas.[24] Pancreatic stellate cells can be activated by cytokines and growth factors, such as transforming growth factor–β1, activin A, IL-1, IL-6, platelet-derived growth factor, and vascular endothelial growth factor (VEGF), which may be produced in the context of inflammation. Furthermore, reactive oxygen species are also known to activate pancreatic stellate cells, which serves as a link between nutrient excess and effects on the stroma. The complexity of the relationship between pancreatic stroma and pancreatic cancer cells is suggested by studies in which transgenic mice with deletion of myofibroblasts had more invasive, undifferentiated tumors and increased hypoxia, epithelial-to-mesenchymal transition, cancer stem cells, and $CD4^+Foxp3^+$ regulatory T cells.[42] These myofibroblast-depleted mouse tumors were associated with reduced survival, and decreased myofibroblasts correlated with poor survival in patients. Furthermore, myofibroblast-depleted tumors in mice resulted in a lack of response to gemcitabine; however, anti–CTLA-4 immunotherapy slowed disease progression and prolonged survival in these mice.

Despite the data to suggest that myofibroblast depletion leads to more aggressive tumors, worse survival, and a lack of response to chemotherapy, activated pancreatic stellate cells have also been shown to affect intracellular signaling in pancreatic cancer cells and can promote the proliferation of pancreatic cancer through Notch signaling pathway activation, expression of galectin-3, and reduction of apoptosis after oxidative stress.[43-46] Activated pancreatic stellate cells secrete a number of extracellular matrix proteins, matrix metalloproteinases, and tissue inhibitors of metalloproteinases that are known to directly promote migration and invasiveness. Activated pancreatic stellate cells may directly affect tumor vasculature by contributing to hypoxia through the secretion of profibrogenic factors and through the secretion of proangiogenic factors, such as periostin, fibroblast growth factor, and VEGF.[44,47,48] Pancreatic stellate cells also might play a role in the regulation of the immune response to the tumor, because they have been shown to promote the differentiation of monocytes into myeloid-derived suppressor cells through the activation of STAT3 signaling via IL-6 expression.[49] They also induce apoptosis of both $CD4^+$ and $CD8^+$ T cells and may sequester $CD8^+$ T cells via CXCL12/CXCR4, which blocks their contact with tumor cells.[50] Given the suggestion that fibroblast deletion may be deleterious in pancreatic cancer, translational approaches that hone in on the specific roles that activated pancreatic stellate cells play may be necessary. These roles and the potential therapies that may target them are modulation of the immune system (anti–CTLA-4 antibodies, anti–PD-1 antibodies, inhibitors of the chemokine receptor CCR2, macrophage colony-stimulating factor 1 receptor [CSF1R] inhibitor), angiogenesis (bevacizumab, CXCR2 inhibitor), extracellular matrix formation (nab-paclitaxel, hyaluronidase, anti–β1-integrin antibody), and fibrogenesis (all-*trans*-retinoic acid, Sonic hedgehog [Shh] inhibitor, focal adhesion kinase [FAK] inhibitor).[24]

The Shh pathway also plays a role in stromal development. Shh is a soluble ligand overexpressed by pancreatic ductal adenocarcinoma cells, and it drives the formation of a fibroblast-rich desmoplastic stroma.[51] Yet, tumors with deletion of Shh were surprisingly more aggressive and exhibited undifferentiated histology, increased vascularity, and greater proliferation. Furthermore, treatment with a Smoothened inhibitor mimicked these findings, which supports the complex role that the Shh pathway plays in the pathobiology of pancreatic cancer. It seems that the Shh-driven stroma suppresses tumor growth in part by impairing tumor angiogenesis, because administration of an anti-VEGF receptor antibody selectively improves survival of Shh-deficient tumors.[51] Tumors in a mouse model of pancreatic cancer that was refractory to the standard chemotherapeutic agent gemcitabine were poorly perfused and poorly vascularized.[52] However, coadministration of IPI-926, a drug that depletes tumor-associated stromal tissue by inhibition of the Shh pathway, resulted in a transient increase in intratumoral vascular density and intratumoral concentration of gemcitabine, which led to transient stabilization of the disease. Deletion of Shh in a well-defined mouse model of pancreatic cancer resulted in reduced stromal content, which additionally supports the role of Shh in maintenance of the stroma.[51] Despite the suggestion that inhibition of Shh contributes to more aggressive phenotype, Shh deletion may also enhance drug delivery and, thus, offers another possible target for combination therapy of pancreatic cancer.

In conclusion, the most common currently used chemotherapeutic regimens for the treatment of pancreatic cancer result in dismal survival: approximately 6 months with gemcitabine, 8.5 months with gemcitabine and nab-paclitaxel, and

12 months with fluorouracil, oxaliplatin, and irinotecan.[53-55] The only currently used targeted therapy, erlotinib, adds scarcely 10 days to the median survival compared with that of gemcitabine alone.[56] Therefore, new and thoughtful therapeutic approaches to prevent and treat pancreatic cancer are desperately needed to improve upon these outcomes. Primary prevention of nutrient excess through obesity prevention and glycemic control is an important strategy to prevent development of the disease. Given that the majority of patients with pancreatic cancer are diagnosed with unresectable or metastatic disease, methods for earlier detection are needed. To this end, circulating tumor DNA assays and blood-based biomarker research, we hope, will enable earlier detection. Emerging evidence suggests that a specific form of pancreatogenic (paraneoplastic) diabetes leads to glucose intolerance due to β-cell dysfunction induced by factors elaborated by pancreatic adenocarcinoma cells. Understanding the pathobiology of this observation may facilitate identification of a patient population with early pancreatic cancer and may lead to early diagnosis and intervention. Careful study of the biology of the disease, including mechanisms of oncogenesis, genomic alterations, environmental influences, alterations in cell signaling pathways, and contributions of the stroma, will provide insights that will aid in the development of novel therapies to treat this devastating disease. JOP

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AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Clinical Insights Into the Biology and Treatment of Pancreatic Cancer

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