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The Interface of Pancreatic Cancer With Diabetes, Obesity, and Inflammation: Research Gaps and Opportunities:

Summary of a National Institute of Diabetes and Digestive and Kidney Diseases Workshop

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Abstract

A workshop on “The Interface of Pancreatic Cancer with Diabetes, Obesity, and Inflammation: Research Gaps and Opportunities” was held by the National Institute of Diabetes and Digestive and Kidney Diseases on October 12, 2017. The purpose of the workshop was to explore the relationship and possible mechanisms of the increased risk of pancreatic ductal adenocarcinoma (PDAC) related to diabetes, the role of altered intracellular energy metabolism in PDAC, the mechanisms and biomarkers of diabetes caused by PDAC, the mechanisms of the increased risk of PDAC associated with obesity, and the role of inflammatory events and mediators as contributing causes of the development of PDAC. Workshop faculty reviewed the state of the current knowledge in these areas and made recommendations for future research efforts. Further knowledge is needed to elucidate the basic mechanisms contributing to the role of hyperinsulinemia, hyperglycemia, adipokines, and acute and chronic inflammatory events on the development of PDAC.

Keywords

diabetes; inflammation; obesity; pancreatic cancer; research gaps

Pancreatic ductal adenocarcinoma (PDAC) is projected to be the second leading cause of adult cancer mortality by 2030.[1] Pancreatic ductal adenocarcinoma has a complex association with diabetes mellitus (DM). The increased incidence of pancreatic cancer in diabetic populations has been observed repeatedly in epidemiologic studies with a relative risk that ranges from 1.5 to 2.0.[2] Importantly, among a subset of patients with new-onset DM, the diagnosis of DM occurred 24 to 36 months prior to the diagnosis of PDAC in close to 1% of such patients.[3] These facts illustrate that DM and PDAC demonstrate “dual causality” in that DM is a risk factor for the development of PDAC, and conversely, PDAC is a presumed cause of DM in a subset of cases. The mechanisms of these causal relationships are unclear, as are the diagnostic criteria for differentiating type 2 DM (T2DM) from DM that occurs in the setting of PDAC or other forms of diabetes related to pancreatic exocrine disease, sometimes referred to as T3cDM or pancreatogenic DM. In this article, we use the following nomenclature: (1) pancreatic cancer–related diabetes that has its onset in the months just prior to or after the diagnosis of PDAC; (2) T2DM to refer to hyperglycemia

usually associated with obesity, insulin resistance, and treated with oral medications and sometimes insulin; (3) postpancreatitis-related diabetes to refer to diabetes occurring in the setting of acute or chronic pancreatitis. This article does not discuss diabetes associated with other types of pancreatic disease or type 1 DM, which is not a risk factor for PDAC.[4,5] These are important considerations clinically given that PDAC has an overall 5-year survival rate of 7% to 8%[6] and recognition that pancreatic cancer–related diabetes may provide the means to diagnose PDAC at a potentially curable point in its natural history. Risk factors associated with PDAC include T2DM and obesity, disorders that are associated with chronic caloric excess.

The relationship between PDAC and total body energy excess and altered cellular energy production within pancreatic cancer cells and its local microenvironment is complex, but suggests the importance of energy balance in the development and maintenance of PDAC.

Given the challenges inherent in treating advanced PDAC, understanding the pathophysiology governing these key modifiable risk factors for pancreatic cancer is important for reducing the incidence of this lethal disease. Toward this end, the National Institute of Diabetes and Digestive and Kidney Diseases developed a workshop focused on exploring what is currently known about these relationships in order to outline areas where significant gaps in knowledge can be considered for future research and targeted funding opportunities. The symposium was organized around 4 sessions designed to examine these complex relationships: (1) The Role of Altered Energy Metabolism in PDAC, (2) PDAC as a Cause of Diabetes, (3) Obesity as a Cause/Risk Factor for PDAC, and (4) Inflammation and the Immune System as a Cause/Mediator of PDAC.

THE ROLE OF ALTERED ENERGY METABOLISM IN PDAC

Mechanisms of Increased Risk for PDAC in T2DM

The statistics regarding the prevalence of T2DM in the United States are sobering. The Centers for Disease Control and Prevention estimates that 30.3 million individuals were living with diabetes in 2017. The underlying causes are complex, but T2DM is clearly linked to increased obesity rates due to excess calorie consumption and reduced energy expenditure and has been associated with insulin resistance, production of proinflammatory and diabetogenic adipokines by adipose tissues and adipose-associated macrophages, excessive hepatic glucose release, and beta cell failure to meet the increased insulin secretion demands.

To better understand the approximately 2-fold increased risk of PDAC in T2DM, it is important to delineate how T2DM may contribute to the development of PDAC. It is recognized that T2DM is associated with insulin resistance and islet dysfunction, including disordered insulin and glucagon secretion. Insulin resistance is partly due to the production of proinflammatory and diabetogenic adipokines by adipose tissues and resident macrophages and excessive reactive oxygen species generation.[7] In addition, there is a propensity by the liver to excessively release glucose. To prevent hyperglycemia under the above circumstances, there is increased secretion of insulin by the beta cells. The increase in insulin levels raises insulinlike growth factor 1 (IGF-1) levels.[7] Both insulin and IGF-1

activate phosphoinositide 3-kinase that enhances mitogenic and prosurvival signaling and activate the RAC-α serine/threonine-protein kinase (AKT) that in turn activates mammalian target of rapamycin (mTOR), leading to enhanced protein synthesis.[7]

Fat-derived adipokines also activate AMP-activated protein kinase that further enhances protein synthesis and modulates cell polarity and division.[7] In addition, adipocytes release free fatty acids, leptin, plasminogen activator inhibitor 1 and lipocalin 2, which combine to enhance proinflammatory signals and promote insulin resistance.[8] Lipocalin 2, which is also produced by cancer cells and macrophages, induces a proinflammatory tumor microenvironment (TME) in PDAC.[8] Moreover, adipose tissue macrophages produce tumor necrosis factor α, galectin 3, interleukin 6 (IL-6), and IL-1β, exacerbating inflammatory signaling, whereas lipolysis releases acetyl-CoA that enhances hepatic insulin resistance and promotes mitogenesis and autophagy.[9] Galectin 3 is an important component of inflammation-driven insulin resistance.[10] It is overexpressed in chronic pancreatitis and can enhance Kras activity and may therefore contribute to malignant transformation in chronic pancreatitis and to PDAC initiation and progression.[11] Biochemical studies also point to attenuated positive feedback regulation of insulin receptor (IR) substrate 1 by mTOR complex 1 (mTORC1) leading to decreased levels of IRs, FOXO1, and GLUT4 in T2DM, thereby inducing insulin resistance in adipose tissue.[12]

The persistent and excessive demand for insulin in the context of a systemic proinflammatory state results in prolonged beta cell stress that is exacerbated by activated intraislet macrophages, endoplasmic reticulum stress pathway activation, and oxidative stress, all modulated by genetic susceptibility factors.[13,14] There is also impaired processing of proinsulin to insulin, intraislet vascular perturbations, and loss of highly metabolic beta cells that normally function as pacemakers to properly propagate insulin oscillatory secretory dynamics.[15–17] As a consequence of all these alterations, there is progressive deterioration in beta cell function with eventual beta cell failure and clinically evident T2DM.

An underappreciated aspect of the dispersal of endocrine islets throughout the exocrine pancreas is that a portion of the blood draining from the islets is distributed into an intrapancreatic portal circulation that likely exposes the adjoining acinar and ductal cells to very high levels of insulin that exert trophic effects on these cells.[18,19] Moreover, high insulin levels readily activate the IR and IGF-1 receptor (IGF-1R), as well as their hybrid forms (IR–IGF-1R), which may lead to excessive activation of mitogenic signaling cascades in precursor lesions arising in these regions of the pancreas.[20] Thus, a prolonged insulin-resistant state in combination with many years of hyperinsulinemia, a tendency toward hyperglycemia and slow but progressive deterioration in beta cell function, may combine with a proinflammatory state to increase the risk of developing PDAC.[13,21]

Chronic hyperglycemia is associated with increased levels of advanced glycation end products (AGE) that activate the receptor for AGE (RAGE) that sustains chronic inflammation pathways and activates Kras.[22,23] Receptor for AGE, a member of the immunoglobulin super family, also binds members of the S100 family of proteins that have been implicated in inflammation and cancer, including PDAC.[24] Thus, excessive RAGE

activation may contribute to the higher incidence of PDAC in T2DM and may lead to accelerated PDAC growth in new-onset diabetes because such patients often exhibit deterioration in glycemic control.

There is also strong evidence that obesity is associated with an increased risk of pancreatic cancer.[25] In fact, the anticipated increase in pancreatic cancer incidence and deaths may be at least partially attributed to the obesity endemic. There are many possible mechanisms by which obesity leads to (pancreatic) cancer, including insulin resistance with resulting hyperinsulinemia and inflammation.[26] Nonsteroidal anti-inflammatory drugs can attenuate pancreatic cancer development in a genetically engineered mouse model possibly suggesting an important role for tissue inflammation in this disease.[27,28] Obesity-associated tissue inflammation is thought to create a fertile microenvironment conducive to tumor initiation and/or promotion. Recent evidence indicates that in addition to measures of general obesity, for example, body mass index (BMI), visceral adiposity carries a strong association to metabolic diseases and gastrointestinal cancers, including pancreatic cancer.[29]

Modulating Risk: The Effects of Metformin and Other Therapies for Diabetes on Pancreatic Cancer Risk

Given the risk of PDAC in patients with T2DM, it is important to identify interventions that can mitigate this risk. Li and colleagues[30] demonstrated in a hospital-based case-control study that individuals with diabetes treated with metformin had a 60% reduction in incidence of pancreatic cancer compared with never users. Thus, while the effect of metformin on survival of individuals with diabetes with established pancreatic cancer appears to be negligible, a decreased risk of developing pancreatic cancer in diabetic patients was found in a subsequent meta-analysis.[31] The mechanisms of metformin's effects on pancreatic cancer risk are not fully understood but appear to be diverse, including direct effects on cancer cells inhibiting mitochondrial respiratory complex I and activation of AMP-activated protein kinase/mTOR pathway that reduces cell proliferation and induces apoptosis. Indirect effects also include its ability to lower insulin levels by increasing hepatic sensitivity to insulin and as yet poorly understood effects on the TME of PDAC.[32] Attempts to uncover other relationships between the use of medications to control blood sugar in patients with T2DM and an enhanced risk of PDAC have yielded only provocative correlations. For example, the use of sulfonylureas and thiazolidinediones in patients withT2DM has shown slight and statistically insignificant increases in PDAC risk of 1.2- and 1.6- fold, respectively, whereas the tenuous association between incretin use and increased PDAC incidence is likely due to the presence of undiagnosed PDAC that has become evident shortly after initiation of incretin therapy.[33,34] Similarly, the association with insulin use in new-onset diabetes is likely due to the deterioration of glycemic control caused by the underlying PDAC.[33,35]

The Role of Altered Intracellular Metabolism in PDAC

In addition to the deregulated systemic physiology conferred by disruption of energy homeostasis discussed previously, metabolic processes within the cells that constitute a pancreatic tumor are also rewired.[36] In the malignant cells of a pancreatic tumor, these alterations are mediated both by oncogene-driven programs and the unique physiology of the

tumor. Pancreatic tumors are typified by a dense, fibrotic stroma that inhibits vascular function and thus nutrient and oxygen delivery.[37] To survive and proliferate under these circumstances, mutant Kras expression rewires metabolic networks that facilitate redox balance, bioenergetics, and anabolic metabolism.[38–40] These pathways are fueled by nutrients recycled through autophagy[41,42] and those scavenged by nonspecific bulk extracellular space engulfment (via the process macropinocytosis)[43] and overexpressed nutrient importers.[38,44] Collectively, the rewiring of metabolism in pancreatic cancer cells, enforced by the constraints of the TME and conferred by oncogene-driven pathways, engages nutrient scavenging mechanisms and drives efficient nutrient utilization to fulfill the shortcomings of insufficient vascularization. The recent detailing of these processes has revealed metabolic vulnerabilities in preclinical models, several of which are now being explored in clinical trials.[36]

Beyond the cell autonomous alterations within the malignant cells, more recent studies have revealed how metabolic crosstalk networks among cells in a pancreatic tumor are also deregulated. Malignant cells can constitute as little as 10% of the total cellular content of a pancreatic tumor.[37] Accordingly, the nonmalignant cells play an important role in shaping the metabolic nature of the TME and facilitating tumor growth.[45] These interactions can be classified generally into 2 categories. First are the cooperative interactions between malignant and nonmalignant cells that support metabolism in the cancer cells. The second type of interaction is competitive and occurs between tumor cells and the antitumor immune response.

A notable cooperative interaction is the nutrient exchange pathway between pancreatic cancer cells and activated pancreatic stellate cells (PSCs).[46] In this example, pancreatic cancer cells induce autophagy in the PSCs. This leads to protein breakdown through autophagy and the release of nonessential amino acids. Among these, the pancreatic cancer cells avidly capture alanine and utilize this to support mitochondrial metabolism and the biosynthesis of cellular building blocks. Importantly, alanine can be utilized in metabolism in place of glucose and glutamine, 2 biosynthetic substrates that are rate limiting in the pancreatic TME. Moreover, blocking this metabolic crosstalk pathway by inhibiting autophagy specifically in the PSCs leads to a dramatic decrease in tumor growth.

Pancreatic tumors are profoundly immune suppressive and have proven highly resistant to immunotherapies.[47] Indeed, there is a growing appreciation that local nutrient depletion and waste accumulation play active roles in facilitating tumor immune suppression.[45] Cytotoxic T-cells, which are intrinsically less fit than oncogene-driven cells at obtaining nutrients, are forced to compete for the limited carbohydrates and amino acids in a tumor to mount an effective antitumor immune response. For example, the limited antitumor T-cell response observed in melanoma and sarcoma models has been directly linked to glucose deprivation, [48,49] and high levels of lactate drive the polarization of anti-inflammatory macrophages.[50] Given that mutant Kras-expressing pancreatic cancer cells avidly consume glucose and release lactate (so-called, Warburg metabolism),[38] these mechanisms are likely to play an immune-suppressive function in pancreatic cancer. Furthermore, alternatively polarized, anti-inflammatory macrophages and cancer cells can deplete tumors of the amino acids arginine and tryptophan.[51] This limits the antitumor T-cell response and favors the

differentiation of T-cells into anti-inflammatory T-regulatory cells. The importance of many of these competitive metabolic interactions remains to be determined in pancreatic cancer. However, these represent exciting new potential opportunities to leverage immunotherapy in pancreatic cancer patients.

Integrating Information From Rodent Models to Human Disease

The human pancreas is particularly challenging to study. Accordingly, the sequence of molecular events leading to PDAC is derived from study of animal models and examination of advanced human PDAC samples. Serial biopsies or sampling of pancreatic tissue in living humans is rarely done because of safety concerns. A further challenge is that the pancreas rapidly undergoes auto-digestion after death, so detailed molecular analyses of the human pancreatic exocrine and ductal tissue (eg, RNA analysis) are quite limited. In contrast, human islets for research have become more readily available for research over the past decade as the result of human islet isolation programs related to allograft islet transplantation.[52] This availability has allowed for a range of in vitro studies and in vivo studies following the transplantation into immunodeficient mice, similar to the patient-derived xenograft approach often used to study human tumors. This has led to a large number of investigators pursuing the molecular characterization and functional analysis of human islets. During islet isolation, enzymatic digestion to “free” islets (representing 1%–2% of pancreatic mass) results in damage or destruction of pancreatic acinar and ductal tissue. Thus, the recent availability of human islets that has led to an increase in knowledge about human islet biology has not been accompanied by greater availability of human pancreatic exocrine or ductal tissue for research. This challenge has led to development of a variety of rodent models of PDAC that utilize genetic or chemical manipulations.[53,54]

Important for this discussion is the realization that human islet biology and rodent islet biology have both similarities and differences. For example, pancreatic islet and exocrine cells share common embryologic lineage, but the sequence of events and molecular markers in humans and rodents have several notable differences. It has also become clear that there are considerable differences in islet cell composition and cell arrangement, proliferative capacity, function, and gene expression in human islet cells compared with the response to insulin resistance.[55–57] Furthermore, rodent models of several forms of monogenic diabetes may not recapitulate the features of the human disease. Rodent models of type 1 DM and T2DM, although having some features of the human disease, do not completely mirror human physiology or pathophysiology involving insulin secretion, insulin resistance, and adipocyte biology. Likewise, the fidelity of rodent models of PDAC or its early lesions is uncertain, and new model systems involving primary human pancreatic epithelial cells, inducible pleuripotent stem cells, or tumor cell organoids are under developments as new types of preclinical models.[58]

Research Gaps and Opportunities

- Conduct further studies on pathogenesis and mediators of PDAC, especially insulin resistance, obesity, and inflammation.
- Improve understanding of how current model systems can be used to understand the early events in human PDAC.

- Develop new animal and cellular models of human PDAC, its early lesions, and tumor-associated microenvironment.
- Develop new approaches to define and characterize normal human pancreatic exocrine and ductal biology.
- Develop methods to study cellular metabolism in vivo.
- Characterize the cellular compartments that make up the pancreatic TME.
- Refine understanding of the mechanisms contributing to the immunosuppressive microenvironment of PDAC.

PANCREATIC CANCER AS A CAUSE OF DIABETES

Pathophysiology of Pancreatic Cancer–Related Diabetes

There is growing evidence that PDAC frequently causes DM.[59] Nearly 85% of PDAC patients have DM or hyperglycemia, often manifesting in the 2 to 3 years preceding their cancer diagnosis.[59] In addition, patients with new-onset diabetes have a 5- to 8-fold increased risk of being diagnosed with PDAC within 1 to 3 years of developing diabetes.[59] Paradoxically, this form of DM occurs in the face of ongoing, often profound, weight loss and frequently resolves with cancer resection.[59,60]

Of the many hypotheses for why PDAC causes DM is a paraneoplastic phenomenon caused by 1 or more tumor-secreted products that cause both insulin resistance and an inadequate beta cell response to stimuli, leading to beta cell failure.[59,60] Apart from the clinical and epidemiological evidence, this notion is supported by laboratory data that the supernatant from cultured PDAC cell lines inhibits insulin secretion. Similarly, PDAC exosomes inhibit insulin secretion. In a set of studies, these effects were attributed to adrenomedullin,[61,62] and it has been suggested that PDAC-DM is an exosomopathy,[62,63] a disease caused by exosomes, a novel hypothesis that needs further study. Another candidate mediator is neuromedin U, a peptide overexpressed in pancreatic cancer and chronic pancreatitis (pancreatogenic diabetic states) that may be an important mediator of insulin resistance and diabetes in the setting of PDAC.[58] Such a finding, if confirmed, could potentially be used as a biomarker for early detection of patients with PDAC in patients presenting with new-onset diabetes. One of the impediments to progress in this area has been the difficulty in developing animal model(s) of PDAC-DM. Because hyperglycemia is one of the earliest, albeit nonspecific, harbingers of PDAC, understanding the molecular mechanisms of PDAC-induced DM is likely to lead to discovery of a biomarker that may lead to early detection of PDAC.[64] Differentiating T2DM from pancreatic cancer–related diabetes would allow for early detection of PDAC in subjects with new-onset hyperglycemia and DM. In addition to the effects of inflammatory or other products released by the tumor itself, insulin secretory deficits may be due to the inhibitory effects of activated PSCs, an impairment of incretin secretion, or the inhibitory effects of cytokines released by macrophages recruited by the tumor to the pancreas.

Beta cell loss of function and apoptosis have been shown in a model of PSC/beta cell coculture,[65] and the cytokine interferon γ has been shown to reversibly inhibit the nuclear

translocation of the transcription factor pancreatic duodenal homeobox 1 in models of pancreatitis-induced pancreatogenic diabetes.[66]

The suppression of hepatic glucose production is an important component of insulin's regulation of glucose homeostasis, and the availability of hepatic IRs has been shown to be regulated by the islet peptide pancreatic polypeptide (PP).[67] A deficiency in PP has been shown to be a reversible cause of hepatic insulin resistance,[68] and a deficiency in PP has now been shown to be associated with PDAC.[69,70] Insulin sensitivity may be impaired by inflammatory cytokines such as inhibitor of nuclear factor κB kinase subunit β,[71] or the loss of peptide mediators of hepatic IR availability such as PP.[72] Incretins such as glucose-dependent insulinotropic polypeptide (GIP) stimulate the release of insulin as well as PP.[73] Reduced GIP levels have been observed in PDAC, possibly due to an increase in dipeptidyl peptidase IV levels induced by the tumor,[74] and this process is reversible by resection of the tumor.[70] Therefore, deficient PP and GIP levels may be both a cause of PDAC-DM and a biomarker of the condition.

Early Detection of PDAC-Induced Diabetes

The screening of all patients with new-onset diabetes is not currently feasible because approximately only 1% of these individuals older than 50 years will develop PDAC within 2 to 3 years. Therefore, various approaches have been undertaken to identify PDAC-DM specifically or to differentiate the 8% to 10% of patients with new-onset diabetes who harbor pancreatogenic, or T3cDM, and the more common T2DM. Using isobaric tags for relative and absolute quantification (iTRAQ) coupled with liquid chromatography–tandem mass spectrometry and immunoassays (Luminex, Rules Based Medicine, enzyme-linked immunosorbent assays, and Western blotting), the Pancreas Research Group at the University of Liverpool, United Kingdom, has conducted studies on cohorts of subjects with PDAC. Using these methods, in collaboration with the University College London, the group has found that CA 19–9 is increased up to 24 months prior to the diagnosis of PDAC[75] and that thrombospondin 1 is decreased in PDAC.[76] By combining these analytes with other markers, the Liverpool group has identified a panel of proteins that are highly discriminatory for T3cDM. Validation studies are currently being carried out in collaboration with the PANDIA study, the United Kingdom's first biobank of samples from subjects with newonset diabetes for PDAC detection.

The concept of assessing a panel of circulating immunoregulatory markers, rather than only a single protein, has been explored extensively in cancer diagnostics, by the group at Lund University in Sweden.[77] This has been applied to the study of markers of PDAC, where a panel of approximately 25 serum biomarkers has been identified.[78,79] These markers displayed a characteristic set of profiles on PDAC patients compared with control subjects, those with chronic pancreatitis and autoimmune pancreatitis, or with other inflammatory conditions or malignancies.[80] Work by Borrebaeck et al suggests that by targeting some of the key immunoregulatory molecules that are abnormally expressed in PDAC the multiplexed approach overcomes the limitations of a single protein marker and has shown high sensitivity and specificity in subsequent validation studies.[81] Further investigations are

underway to determine the feasibility of this detection method in those with new-onset diabetes and other patients at high risk of PDAC.

Research Gaps and Opportunities

- Conduct further studies on pathogenesis and mediators of pancreatic cancer–related diabetes.
- Develop animal models of pancreatic cancer–related diabetes.
- Validate cytokine markers associated with impaired beta cell function and apoptosis in PDAC.
- Understand the role of microvesicles and exosomes in pancreatic cancer and T3cDM.
- Conduct preclinical trials of anti-inflammatory agents on pancreatic cancer–related diabetes.
- Validate circulating biomarkers of pancreatic cancer–related diabetes.
- Confirm diagnostic criteria to differentiate pancreatic cancer– related diabetes and T3cDM from T2DM.
- Develop clinical algorithms that can predict pancreatic cancer– related diabetes among subjects with new-onset diabetes.

OBESITY AS A CAUSE/RISK FACTOR FOR PDAC

The Risk of Obesity and the Role of Bariatric Surgery

Although the overall rate of new cancer diagnoses has decreased since the 1990s, a dramatic increase has been observed for obesity-associated cancers.[82] Premorbid obesity adversely influences PDAC-related mortality in a dose-dependent manner.[83,84] In addition, a high BMI has been associated with an increased risk of PDAC, age at onset, and overall survival.[83,84]

The pathogenesis of obesity-related diseases begins with positive energy balance and triglyceride deposition in the adipose tissue. When excess triglyceride cannot be fully deposited in the adipose tissue, ectopic fat deposition occurs in organs such as the liver and pancreas. In the liver, triglyceride deposition leads to oxidative stress and inflammation, which leads to steatohepatitis, cirrhosis, and hepatocellular carcinoma. Increasing evidence indicates that a similar pathway may occur in the pancreas. Both free fatty acids and inflammatory mediators occur in high amounts in the pancreas of obese mice,[85] and tumor growth is accelerated in obese animals.[86] Hepatic and pancreatic fats are also increased in obese individuals.

Following weight loss after bariatric surgery, there is rapid resolution of both hepatic and pancreatic fats.[87] Insulin resistance and circulating levels of some inflammatory mediators rapidly normalize following weight loss.[88] Weight loss induced by bariatric surgery in humans reduces all-cause cancer mortality by 40% to 60%.[89,90] A recent matched retrospective study showed that the risk of PDAC was significantly lower among those

patients who had undergone bariatric surgery compared with control patients.[91] However, bariatric surgery in these trials has been limited to individuals with severe obesity (mean BMI >40 kg/m^2) in whom substantial weight loss (mean >30% total body weight) has been achieved. Whether a similar reduction in the incidence and/or mortality of pancreatic and other cancers could be achieved in patients with less severe obesity or with lesser amounts of weight loss is not known. This study suggests that intentional weight loss may reduce the risk of cancer specifically in obese patients. Further studies into the role of intentional weight loss via bariatric surgery and/or other interventions such as lifestyle interventions, pharmacotherapy, or less invasive surgical/endoscopic procedures are needed to understand their role and possible mechanisms in cancer prevention.

Mechanisms of Obesity Risk and Inflammation

While there have been many epidemiological studies indicating the dangers of obesity in promoting and increasing the risk of PDAC development, many fundamental questions regarding the molecular mechanisms underlying the detrimental effects of obesity remain unanswered. Plausible mediators include insulin, estrogens, and inflammatory molecules such as adipokines.[84]

Using genetically engineered mouse models of PDAC and diet-induced obesity mouse models that mimic the obesity phenotype, it has been shown that diet-induced obesity acts as an inflammatory stimulus to trigger increased $KRas^{G12D}$ signaling and that cyclooxygenase 2 is critical in the inflammatory loop that leads to inflammation, increased fibrosis, $KRas^{G12D}$ signaling, pancreatic intraepithelial neoplasia lesion progression, and accelerated tumor growth.[28] Moreover, the novel adipokine, lipocalin 2, which is secreted by adipose tissue in obese subjects, has been linked to promoting the development of obesity-associated PDAC and stimulating a receptor-mediated proinflammatory response in the TME.[8]

Another factor that suggests a possible link between, obesity, diabetes, and PDAC may involve the RAGE. This factor is present in PDAC and capable of influencing the critical mechanisms involved in the Ras-induced inflammation feed-forward loop that is observed as a result of obesity-associated PDAC.[28] A recent review summarizes signals from the adipose tissue microenvironment that are associated with obesity and cancer in humans,[92] but there are currently no studies in PDAC, highlighting an important knowledge gap. Further insights into these relationships will allow the development of novel preventative approaches for obese patients at increased risk of developing PDAC.

Role of Visceral and Peripancreatic Fat on Carcinogenesis

Although the BMI is widely used as a marker for general adiposity, several studies have identified that visceral obesity has a stronger correlation to the metabolic syndrome, insulin resistance, and certain gastrointestinal malignancies, including PDAC.[93] The close proximity to visceral organs and drainage via the portal system may explain the strong correlation of inflamed visceral adipose tissue (VAT) in obese subjects with metabolic dysfunction and gastrointestinal cancer.

The importance of VAT on PDAC development was suggested by studies using genetically engineered mouse models. Conditional $KRas^{G12D}$ (KC) mice fed a diet high in fats and

calories gained significantly more weight compared with lean mice fed a control diet; developed metabolic dysfunction, including hyperinsulinemia and hyperleptinemia; and were characterized by VAT expansion and inflammation.[94–96] Obese KC mice developed a stronger fibroinflammatory reaction in the pancreas and more PDAC than their lean littermates.[94] Interestingly, the increased incidence of PDAC in obese KC mice was largely seen in male mice, suggesting a role for sex hormones in this process.[94] This correlated with an expansion of VAT in obese male KC mice, whereas female obese KC mice gained adipose tissue preferentially subcutaneously.[96] Overall, there is strong evidence emphasizing an important role of VAT and VAT inflammation in PDAC. Further studies are clearly needed to explore the underlying mechanisms, to investigate sex- and adipose depot-specific differences, and to develop strategies aimed at reducing VAT inflammation.[97]

PDAC and the Microbiome

Recent data suggest that the human microbiome could shed light on how to better tackle prevention, early detection, and treatment of PDAC.[98–100] Many diseases are now associated with changes in the microbiome composition, and there is increasing evidence of bacterial microbiota playing a key role in carcinogenesis. Preclinical and clinical evidence suggests that bacteria are likely to influence the interface of PDAC with diabetes, obesity, and inflammation.[101] Pancreatic ductal adenocarcinoma has been recognized as an inflammation-driven cancer. Bacteria can induce chronic inflammation via molecular pattern recognition receptors. Pattern recognition receptors and associated signaling molecules have been implicated in the pathogenesis of inflammation-driven cancers. The gut microbiome may influence the efficiency of intestinal calorie absorption and contribute to obesity. The mechanisms may involve an association of obesity with diabetes, chronic low-level inflammation, increased hormones, and adipokines. Diabetes, obesity, and chronic pancreatitis can lead to chronic inflammation, which may promote pancreatic carcinogenesis.[102] Changes in the oral microbiome have also been associated with an increased risk of PDAC, and presence of distinct oral microbial community profile for PDAC may be useful as a biomarker of the disease. Differential abundance in oral bacteria and the microbiome of the pancreatic secretions or stool may be associated with risk of PDAC. Research on the microbiome and PDAC could lead to innovative strategies for prevention, early detection, and targets for intervention.

Research Gaps and Opportunities

- Investigate the impact of bariatric surgery and weight loss on PDAC and explore the underlying mechanisms, including GIPs, inflammation, and gut microbiome.
- Conduct mechanistic studies in preclinical models to understand the link between VAT and pancreatic fibroinflammatory diseases, including pancreatitis and PDAC.
- Develop strategies which target the obesogenic signaling network and feedback loops in VAT and pancreas, including the effect of US Food and Drug Administration–approved drugs (eg, metformin, statins).

- Study how factors secreted from adipose tissue and the adipose cellular microenvironment affect the pancreatic tissue microenvironment of pancreatic diseases.
- Develop and characterize the best preclinical models that mimic human obesity-associated PDAC.
- Validate preclinical findings of obesity-associated PDAC using human-derived samples, particularly adipose tissue.
- Assess the impact of intentional weight loss programs, for example, exercise interventions, to understand their role and possible mechanisms in cancer prevention.
- Develop markers of obesity-associated development of PDAC to facilitate identification of individuals with obesity who are at particular risk of PDAC and other cancers in efforts to recommend weight loss interventions.
- Explore the obesity-associated changes in the gut microbiome and their impact on fibroinflammatory diseases of the pancreas.
- Identify the metabolites and their molecular pathways linking changes in gut microflora to pancreatic diseases.

INFLAMMATION AND THE IMMUNE SYSTEM AS A CAUSE/MEDIATOR OF PDAC

Chronic inflammation of the pancreas or chronic pancreatitis is a major risk factor for developing PDAC. Activated PSCs play a central role in chronic pancreatitis progression by regulating the synthesis and degradation of extracellular matrix proteins. Activation of PSCs is increased by cytokines from injured acinar cells and immune cells. The mechanisms by which macrophages trigger and sustain the fibrotic processes by interacting with PSCs were recently elucidated by Habtezion and colleagues, and interfering with these immune signals resulted in inhibition of the inflammation and fibrosis in experimental models of chronic pancreatitis.[103] Environmental factors such as alcohol and smoking are also well-known risk factors for chronic pancreatitis and pancreatic adenocarcinoma. The role of inflammation and cross talk between immune cells and PSCs mediated via IL-22 signaling were described in smoking-induced progression of experimental chronic pancreatitis.[104] Similarly, smoking-related effects in promoting experimental pancreatic cancer involving pathways such as IL-6 and histone deacetylases in immune and cancer cell interactions were delineated recently.[105] Thus, immune-related signals are important in promoting pancreatitis and pancreatic cancer progression, and understanding complex multicellular interactions that lead to the development and progression of PDAC will be of great significance.

Pancreatic ductal adenocarcinoma remains with a poor prognosis despite advances in elucidation of underlying molecular mechanisms, genomic/epigenetic/transcriptome analyses, early detection strategies, risk stratification, and targeted therapies. Moreover, most cases of PDAC are resistant to treatment with immunotherapies such as immune checkpoint antibodies. Accumulating evidence indicates that inflammatory processes play a pivotal role

in promoting the malignant transformation, growth, and metastasis of pancreatic cancer. Kras mutations induce aberrant cytokine and chemokine expression in tumor epithelial cells and subsequently remodel the TME by recruiting immune cells such as macrophages, dendritic cells (DCs), and myeloid-derived suppressive cells, which promote tumor growth. As a result, reprograming these and other cells in the PDAC TME in an effort to create an immunostimulatory environment is an attractive approach that may hold the key to enabling efficacious immunotherapy.

Because PDAC is often followed by distant metastatic relapse after complete surgical resection and, as mentioned previously, generally fails to respond to immunotherapy, a better understanding of the factors affecting metastasis is also critical for the development of more effective treatments. Utilizing an orthotopic mouse model of PDAC that resembles the human disease in its genetics, histopathology, and clinical manifestations and also predictably metastasizes to the liver has permitted a systematic investigation of the metastasis-associated immune response.[106] Recent studies of these mice by Engleman and colleagues revealed that early metastases are associated with dense networks of $CD11b^{+}CD11c^{+}MHC\text{-}II^{+}CD24^{+}CD64^{low}F4/80^{low}$ cells, which develop from monocytes and promote metastasis by inducing the expansion of regulatory T-cells and inhibiting the development of cytotoxic T-cells.[107] Phenotypically similar DCs accumulate at primary and secondary sites in other PDAC models and in human PDAC.[107] Given the importance of these DCs in tumor metastasis, groups have been working on immunotherapeutic strategies designed to reprogram them into immunostimulatory antigen-presenting cells. One such strategy is based on the discovery that tumor-binding immunoglobulin G antibodies in combination with certain DC-stimulating molecules enable tumor-associated DCs to take up, process, and present a wide range of tumor antigens to T-cells, which then proliferate and attack tumors throughout the host. This approach can overcome tumor-mediated immunosuppression and lead to eradication of metastases, as well as primary tumors in a wide range of cancers in mice, including PDAC.[108]

Despite this promising research, metastatic PDAC remains a challenging disease, as tumor cells tend to disseminate into the circulation and colonize distant organs and compartments.[109] Metastatic PDAC has been postulated to involve several different mechanisms, including the selection of mutant clones in the primary tumor that are fated to metastasize, epigenetic modifications in the primary tumor, circulating cells that travel in clusters, and the establishment of a premetastatic niche in distant organs involving proinflammatory and immune cells and the interplay with exosomes.[110] Work by Rustgi et al (manuscript submitted) now supports the notion that epithelial plasticity in the spectrum of epithelial-mesenchymal transition and mesenchymal-epithelial transition influences not only the metastatic potential of PDAC but also the specification of which organ will be the recipient of metastatic PDAC cells for colonization, referred to as metastatic organotropism. This opens up new approaches to therapy that may involve different agents for primary PDAC versus PDAC in the liver versus lung.

Research Gaps and Opportunities

- Understand how the immune/inflammatory environment promotes PDAC or its progression.
- Define the role of activated PSCs, immune cells, and antigen-presenting cells in PDAC progression and whether targeted interventions of these cells may be beneficial.
- Identify markers and regulators of the metastatic potential of PDAC.
- Define local and metastatic immune cell networks and determine how to reprogram them in order to generate system-wide antitumor immunity.
- Define metastatic organotropism pathways with goals of developing specific targets to target the different metastatic PDAC sites.
- Validate experimental findings using human samples from patients undergoing therapeutic trials.

SUMMARY

Pancreatic cancer is a challenging malignancy with an increasing incidence and high lethality. The disease has complex relationships with diabetes and obesity that are only partially understood. Diabetes can be both a risk factor and early manifestation of pancreatic cancer. Obesity is strongly linked to increased risk of pancreatic cancer, but the specific mechanisms that contribute to pancreatic carcinogenesis are not clear. This symposium reviewed the current understanding of the role that altered energy metabolism plays in pancreatic cancer risk, data supporting the epidemiologic evidence that pancreatic cancer can be a cause of diabetes, observations linking obesity to pancreatic cancer, and inflammation and immune system dysfunction as critical processes contributing to pancreatic cancer development, metastases, and therapeutic resistance. Specific research gaps and scientific opportunities have been outlined as a guide to funding agencies and investigators working in this field.

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REFERENCES

1. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74: 2913–2921. [PubMed: 24840647]

2. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995;273:1605–1609. [PubMed: 7745774]
3. Pannala R, Leirness JB, Bamlet WR, et al. Prevalence and clinical profile of pancreatic cancer–associated diabetes mellitus. Gastroenterology 2008;134:981–987. [PubMed: 18395079]
4. Woodmansey C, McGovern AP, McCullough KA, et al. Incidence, demographics, and clinical characteristics of diabetes of the exocrine pancreas (type 3c): a retrospective cohort study. Diabetes Care 2017;40: 1486–1493. [PubMed: 28860126]
5. Petrov MS. Diabetes of the exocrine pancreas: American Diabetes Association–compliant lexicon. Pancreatology 2017;17:523–526. [PubMed: 28655595]
6. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2017. CA Cancer J Clin 2017;67:7–30. [PubMed: 28055103]
7. Li D, Abbruzzese JL. New strategies in pancreatic cancer: emerging epidemiologic and therapeutic concepts. Clin Cancer Res 2010;16: 4313–4318. [PubMed: 20647474]
8. Gomez-Chou SB, Swidnicka-Siergiejko AK, Badi N, et al. Lipocalin-2 promotes pancreatic ductal adenocarcinoma by regulating inflammation in the tumor microenvironment. Cancer Res 2017;77: 2647–2660. [PubMed: 28249896]
9. Perry RJ, Camporez JP, Kursawe R, et al. Hepatic acetyl CoA links adipose tissue inflammation to hepatic insulin resistance and type 2 diabetes. Cell 2015;160:745–758. [PubMed: 25662011]
10. Li P, Liu S, Lu M, et al. Hematopoietic-derived galectin-3 causes cellular and systemic insulin resistance. Cell 2016;167: 973–984.e12. [PubMed: 27814523]
11. Seguin L, Camargo MF, Wettersten HI, et al. Galectin-3, a druggable vulnerability for KRAS-addicted cancers. Cancer Discov 2017;7: 1464–1479. [PubMed: 28893801]
12. Rajan MR, Nyman E, Kjølhede P, et al. Systems-wide experimental and modeling analysis of insulin signaling through forkhead box protein O1 (FOXO1) in human adipocytes, normally and in type 2 diabetes. J Biol Chem 2016;291:15806–15819. [PubMed: 27226562]
13. Kahn SE. The relative contributions of insulin resistance and beta-cell dysfunction to the pathophysiology of type 2 diabetes. Diabetologia 2003;46:3–19. [PubMed: 12637977]
14. Dooley J, Tian L, Schonefeldt S, et al. Genetic predisposition for beta cell fragility underlies type 1 and type 2 diabetes. Nat Genet 2016;48: 519–527. [PubMed: 26998692]
15. Nolan CJ, Delghingaro-Augusto V. Reversibility of defects in proinsulin processing and islet β-cell failure in obesity-related type 2 diabetes. Diabetes 2016;65:352–354. [PubMed: 26798122]
16. Nyman LR, Wells KS, Head WS, et al. Real-time, multidimensional in vivo imaging used to investigate blood flow in mouse pancreatic islets. J Clin Invest 2008;118:3790–3797. [PubMed: 18846254]
17. Kolic J, Johnson JD. Specialized hub beta cells trade maximal insulin production for perfect timing. Cell Metab 2016;24:371–373. [PubMed: 27626196]
18. Henderson JR, Daniel PM. A comparative study of the portal vessels connecting the endocrine and exocrine pancreas, with a discussion of some functional implications. Q J Exp Physiol Cogn Med Sci 1979;64: 267–275. [PubMed: 118478]
19. Bertelli E, Bendayan M. Association between endocrine pancreas and ductal system. More than an epiphenomenon of endocrine differentiation and development? J Histochem Cytochem 2005;53: 1071–1086. [PubMed: 15956021]
20. Belfiore A, Frasca F, Pandini G, et al. Insulin receptor isoforms and insulin receptor/insulin-like growth factor receptor hybrids in physiology and disease. Endocr Rev 2009;30:586–623. [PubMed: 19752219]
21. Wolpin BM, Bao Y, Qian ZR, et al. Hyperglycemia, insulin resistance, impaired pancreatic β-cell function, and risk of pancreatic cancer. J Natl Cancer Inst 2013;105:1027–1035. [PubMed: 23847240]
22. Leclerc E, Vetter SW. The role of S100 proteins and their receptor RAGE in pancreatic cancer. Biochim Biophys Acta 2015;1852: 2706–2711. [PubMed: 26435083]
23. Kang R, Hou W, Zhang Q, et al. RAGE is essential for oncogenic KRAS-mediated hypoxic signaling in pancreatic cancer. Cell Death Dis 2014;5:e1480. [PubMed: 25341034]

24. Song F, Hurtado del Pozo C, Rosario R, et al. RAGE regulates the metabolic and inflammatory response to high-fat feeding in mice. Diabetes 2014;63:1948–1965. [PubMed: 24520121]
25. Renehan AG, Zwahlen M, Egger M. Adiposity and cancer risk: new mechanistic insights from epidemiology. Nat Rev Cancer 2015;15: 484–498. [PubMed: 26205341]
26. Park J, Morley TS, Kim M, et al. Obesity and cancer—mechanisms underlying tumour progression and recurrence. Nat Rev Endocrinol 2014;10:455–465. [PubMed: 24935119]
27. Funahashi H, Satake M, Dawson D, et al. Delayed progression of pancreatic intraepithelial neoplasia in a conditional Kras(G12D) mouse model by a selective cyclooxygenase-2 inhibitor. Cancer Res 2007;67: 7068–7071. [PubMed: 17652141]
28. Philip B, Roland CL, Daniluk J, et al. A high-fat diet activates oncogenic Kras and COX2 to induce development of pancreatic ductal adenocarcinoma in mice. Gastroenterology 2013;145:1449–1458. [PubMed: 23958541]
29. Vongsuvanh R, George J, Qiao L, et al. Visceral adiposity in gastrointestinal and hepatic carcinogenesis. Cancer Lett 2013;330: 1–10. [PubMed: 23201597]
30. Li D, Yeung SC, Hassan MM, et al. Antidiabetic therapies affect risk of pancreatic cancer. Gastroenterology 2009;137:482–488. [PubMed: 19375425]
31. Wang Z, Lai ST, Xie L, et al. Metformin is associated with reduced risk of pancreatic cancer in patients with type 2 diabetes mellitus: a systematic review and meta-analysis. Diabetes Res Clin Pract 2014; 106:19–26. [PubMed: 24837144]
32. Ben Sahra I, Le Marchand-Brustel Y, Tanti JF, et al. Metformin in cancer therapy: a new perspective for an old antidiabetic drug? Mol Cancer Ther 2010;9:1092–1099. [PubMed: 20442309]
33. Andersen DK, Andren-Sandberg A, Duell EJ, et al. Pancreatitis-diabetes-pancreatic cancer: summary of an NIDDK-NCI workshop. Pancreas 2013;42:1227–1237. [PubMed: 24152948]
34. Boniol M, Franchi M, Bota M, et al. Incretin-based therapies and the short-term risk of pancreatic cancer: results from two retrospective cohort studies. Diabetes Care 2018;41:286–292. [PubMed: 29146599]
35. Hart PA, Bellin MD, Andersen DK, et al. Type 3c (pancreatogenic) diabetes mellitus secondary to chronic pancreatitis and pancreatic cancer. Lancet Gastroenterol Hepatol 2016;1:226–237. [PubMed: 28404095]
36. Halbrook CJ, Lyssiotis CA. Employing metabolism to improve the diagnosis and treatment of pancreatic cancer. Cancer Cell 2017;31:5–19. [PubMed: 28073003]
37. Ying H, Dey P, Yao W, et al. Genetics and biology of pancreatic ductal adenocarcinoma. Genes Dev 2016;30:355–385. [PubMed: 26883357]
38. Ying H, Kimmelman AC, Lyssiotis CA, et al. Oncogenic Kras maintains pancreatic tumors through regulation of anabolic glucose metabolism. Cell 2012;149:656–670. [PubMed: 22541435]
39. Son J, Lyssiotis CA, Ying H, et al. Glutamine supports pancreatic cancer growth through a KRAS-regulated metabolic pathway. Nature 2013;496:101–105. [PubMed: 23535601]
40. DeNicola GM, Karreth FA, Humpton TJ, et al. Oncogene-induced Nrf2 transcription promotes ROS detoxification and tumorigenesis. Nature 2011;475:106–109. [PubMed: 21734707]
41. Yang S, Wang X, Contino G, et al. Pancreatic cancers require autophagy for tumor growth. Genes Dev 2011;25:717–729. [PubMed: 21406549]
42. Perera RM, Stoykova S, Nicolay BN, et al. Transcriptional control of autophagy-lysosome function drives pancreatic cancer metabolism. Nature 2015;524:361–365. [PubMed: 26168401]
43. Commisso C, Davidson SM, Soydaner-Azeloglu RG, et al. Macropinocytosis of protein is an amino acid supply route in Ras-transformed cells. Nature 2013;497:633–637. [PubMed: 23665962]
44. Kamphorst JJ, Nofal M, Commisso C, et al. Human pancreatic cancer tumors are nutrient poor and tumor cells actively scavenge extracellular protein. Cancer Res 2015;75:544–553. [PubMed: 25644265]
45. Lyssiotis CA, Kimmelman AC. Metabolic interactions in the tumor microenvironment. Trends Cell Biol 2017;27:863–875. [PubMed: 28734735]

46. Sousa CM, Biancur DE, Wang X, et al. Pancreatic stellate cells support tumour metabolism through autophagic alanine secretion. Nature 2016; 536:479–483. [PubMed: 27509858]
47. Zhang Y, Velez-Delgado A, Mathew E, et al. Myeloid cells are required for PD-1/PD-L1 checkpoint activation and the establishment of an immunosuppressive environment in pancreatic cancer. Gut 2017;66: 124–136. [PubMed: 27402485]
48. Chang CH, Qiu J, O'Sullivan D, et al. Metabolic competition in the tumor microenvironment is a driver of cancer progression. Cell 2015;162: 1229–1241. [PubMed: 26321679]
49. Ho PC, Bihuniak JD, Macintyre AN, et al. Phosphoenolpyruvate is a metabolic checkpoint of anti-tumor T cell responses. Cell 2015;162: 1217–1228. [PubMed: 26321681]
50. Colegio OR, Chu NQ, Szabo AL, et al. Functional polarization of tumour-associated macrophages by tumour-derived lactic acid. Nature 2014;513:559–563. [PubMed: 25043024]
51. Murray PJ. Amino acid auxotrophy as a system of immunological control nodes. Nat Immunol 2016;17:132–139. [PubMed: 26784254]
52. Kaddis JS, Olack BJ, Sowinski J, et al. Human pancreatic islets and diabetes research. JAMA 2009;301:1580–1587. [PubMed: 19366778]
53. Storz P Acinar cell plasticity and development of pancreatic ductal adenocarcinoma. Nat Rev Gastroenterol Hepatol 2017;14:296–304. [PubMed: 28270694]
54. Hwang CI, Boj SF, Clevers H, et al. Preclinical models of pancreatic ductal adenocarcinoma. J Pathol 2016;238:197–204. [PubMed: 26419819]
55. Stewart AF, Hussain MA, Garcia-Ocana A, et al. Human β-cell proliferation and intracellular signaling: part 3. Diabetes 2015;64: 1872–1885. [PubMed: 25999530]
56. Brissova M, Fowler MJ, Nicholson WE, et al. Assessment of human pancreatic islet architecture and composition by laser scanning confocal microscopy. J Histochem Cytochem 2005;53:1087–1097. [PubMed: 15923354]
57. Dai C, Kayton NS, Shostak A, et al. Stress-impaired transcription factor expression and insulin secretion in transplanted human islets. J Clin Invest 2016;126:1857–1870. [PubMed: 27064285]
58. Lee J, Snyder ER, Liu Y, et al. Reconstituting development of pancreatic intraepithelial neoplasia from primary human pancreas duct cells. Nat Commun 2017;8:14686. [PubMed: 28272465]
59. Sah RP, Nagpal SJ, Mukhopadhyay D, et al. New insights into pancreatic cancer–induced paraneoplastic diabetes. Nat Rev Gastroenterol Hepatol 2013;10:423–433. [PubMed: 23528347]
60. Permert J, Adrian TE, Jacobsson P, et al. Is profound peripheral insulin resistance in patients with pancreatic cancer caused by a tumor-associated factor? Am J Surg 1993;165:61–66; discussion 66–67. [PubMed: 8380314]
61. Aggarwal G, Ramachandran V, Javeed N, et al. Adrenomedullin is up-regulated in patients with pancreatic cancer and causes insulin resistance in β cells and mice. Gastroenterology 2012;143:1510–1517. [PubMed: 22960655]
62. Javeed N, Sagar G, Dutta SK, et al. Pancreatic cancer–derived exosomes cause paraneoplastic β-cell dysfunction. Clin Cancer Res 2015;21: 1722–1733. [PubMed: 25355928]
63. Korc M Pancreatic cancer–associated diabetes is an "exosomopathy". Clin Cancer Res 2015;21:1508–1510. [PubMed: 25645860]
64. Pannala R, Basu A, Petersen GM, et al. New-onset diabetes: a potential clue to the early diagnosis of pancreatic cancer. Lancet Oncol 2009;10: 88–95. [PubMed: 19111249]
65. Kikuta K, Masamune A, Hamada S, et al. Pancreatic stellate cells reduce insulin expression and induce apoptosis in pancreatic β-cells. Biochem Biophys Res Commun 2013;433:292–297. [PubMed: 23500461]
66. Pondugala PK, Sasikala M, Guduru VR, et al. Interferon-γ decreases nuclear localization of Pdx-1 and triggers β-cell dysfunction in chronic pancreatitis. J Interferon Cytokine Res 2015;35:523–529. [PubMed: 25839229]
67. Seymour NE, Volpert AR, Lee EL, et al. Alterations in hepatocyte insulin binding in chronic pancreatitis: effects of pancreatic polypeptide. Am J Surg 1995;169:105–109; discussion 110. [PubMed: 7817978]

68. Seymour NE, Brunicardi FC, Chaiken RL, et al. Reversal of abnormal glucose production after pancreatic resection by pancreatic polypeptide administration in man. Surgery 1988;104:119–129. [PubMed: 3041640]
69. Hart PA, Baichoo E, Bi Y, et al. Pancreatic polypeptide response to a mixed meal is blunted in pancreatic head cancer associated with diabetes mellitus. Pancreatology 2015;15:162–166. [PubMed: 25766398]
70. Skrha J, Busek P, Uhrova J, et al. Lower plasma levels of glucose-dependent insulinotropic peptide (GIP) and pancreatic polypeptide (PP) in patients with ductal adenocarcinoma of the pancreas and their relation to the presence of impaired glucoregulation and weight loss. Pancreatology 2017;17:89–94. [PubMed: 28027898]
71. Zhou X, You S. Rosiglitazone inhibits hepatic insulin resistance induced by chronic pancreatitis and IKK-β/NF-κB expression in liver. Pancreas 2014;43:1291–1298. [PubMed: 25036911]
72. Sun YS, Brunicardi FC, Druck P, et al. Reversal of abnormal glucose metabolism in chronic pancreatitis by administration of pancreatic polypeptide. Am J Surg 1986;151:130–140. [PubMed: 3946744]
73. Chia CW, Odetunde JO, Kim W, et al. GIP contributes to islet trihormonal abnormalities in type 2 diabetes. J Clin Endocrinol Metab 2014;99: 2477–2485. [PubMed: 24712564]
74. Busek P, Vanickova Z, Hrabal P, et al. Increased tissue and circulating levels of dipeptidyl peptidase-IV enzymatic activity in patients with pancreatic ductal adenocarcinoma. Pancreatology 2016;16: 829–838. [PubMed: 27320722]
75. O'Brien DP, Sandanayake NS, Jenkinson C, et al. Serum CA19–9 is significantly upregulated up to 2 years before diagnosis with pancreatic cancer: implications for early disease detection. Clin Cancer Res 2015; 21:622–631. [PubMed: 24938522]
76. Jenkinson C, Elliott VL, Evans A, et al. Decreased serum thrombospondin-1 levels in pancreatic cancer patients up to 24 months prior to clinical diagnosis: association with diabetes mellitus. Clin Cancer Res 2016;22:1734–1743. [PubMed: 26573598]
77. Borrebaeck CA. Precision diagnostics: moving towards protein biomarker signatures of clinical utility in cancer. Nat Rev Cancer 2017; 17:199–204. [PubMed: 28154374]
78. Gerdtsson AS, Wingren C, Persson H, et al. Plasma protein profiling in a stage defined pancreatic cancer cohort—implications for early diagnosis. Mol Oncol 2016;10:1305–1316. [PubMed: 27522951]
79. Gerdtsson AS, Malats N, Sall A, et al. A multicenter trial defining a serum protein signature associated with pancreatic ductal adenocarcinoma. Int J Proteomics 2015;2015:587250. [PubMed: 26587286]
80. Wingren C, Sandström A, Segersvärd R, et al. Identification of serum biomarker signatures associated with pancreatic cancer. Cancer Res 2012;72:2481–2490. [PubMed: 22589272]
81. Mellby LD, Holmér A, Wingren C, et al. Early-stage diagnosis of pancreatic cancer offers opportunity to improve overall patient survival. Ann Oncol 2016;27(suppl 6):129Pabstract.
82. Steele CB, Thomas CC, Henley SJ, et al. Vital signs: trends in incidence of cancers associated with overweight and obesity—United States, 2005–2014. MMWR Morb Mortal Wkly Rep 2017;66:1052–1058. [PubMed: 28981482]
83. Calle EE, Rodriguez C, Walker-Thurmond K, et al. Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 2003;348:1625–1638. [PubMed: 12711737]
84. Eibl G, Cruz-Monserrate Z, Korc M, et al. Diabetes mellitus and obesity as risk factors for pancreatic cancer [9 11, 2017]. J Acad Nutr Diet 2017.
85. Mathur A, Zyromski NJ, Pitt HA, et al. Pancreatic steatosis promotes dissemination and lethality of pancreatic cancer. J Am Coll Surg 2009; 208:989–994; discussion 994–986. [PubMed: 19476877]
86. Zyromski NJ, Mathur A, Pitt HA, et al. Obesity potentiates the growth and dissemination of pancreatic cancer. Surgery 2009;146:258–263. [PubMed: 19628082]
87. Gaborit B, Abdesselam I, Kober F, et al. Ectopic fat storage in the pancreas using 1H-MRS: importance of diabetic status and modulation with bariatric surgery-induced weight loss. Int J Obes (Lond) 2015;39: 480–487. [PubMed: 25042860]

88. Purnell JQ, Selzer F, Wahed AS, et al. Type 2 diabetes remission rates after laparoscopic gastric bypass and gastric banding: results of the longitudinal assessment of bariatric surgery study. Diabetes Care 2016;39: 1101–1107. [PubMed: 27289123]

89. Adams TD, Gress RE, Smith SC, et al. Long-term mortality after gastric bypass surgery. N Engl J Med 2007;357:753–761. [PubMed: 17715409]

90. Sjöström L, Gummesson A, Sjöström CD, et al. Effects of bariatric surgery on cancer incidence in obese patients in Sweden (Swedish Obese Subjects Study): a prospective, controlled intervention trial. Lancet Oncol 2009;10:653–662. [PubMed: 19556163]

91. Schauer DP, Feigelson HS, Koebnick C, et al. Bariatric surgery and the risk of cancer in a large multisite cohort [published online ahead of print September 21, 2017]. Ann Surg 2017.

92. Himbert C, Delphan M, Scherer D, et al. Signals from the adipose microenvironment and the obesity-cancer link—a systematic review. Cancer Prev Res 2017;10:494–506.

93. Aune D, Greenwood DC, Chan DS, et al. Body mass index, abdominal fatness and pancreatic cancer risk: a systematic review and non-linear dose-response meta-analysis of prospective studies. Ann Oncol 2012; 23:843–852. [PubMed: 21890910]

94. Chang HH, Moro A, Takakura K, et al. Incidence of pancreatic cancer is dramatically increased by a high fat, high calorie diet in $Kras^{G12D}$ mice. PLoS One 2017;12:e0184455. [PubMed: 28886117]

95. Dawson DW, Hertzer K, Moro A, et al. High-fat, high-calorie diet promotes early pancreatic neoplasia in the conditional $Kras^{G12D}$ mouse model. Cancer Prev Res 2013;6:1064–1073.

96. Hertzer KM, Xu M, Moro A, et al. Robust early inflammation of the peripancreatic visceral adipose tissue during diet-induced obesity in the $Kras^{G12D}$ model of pancreatic cancer. Pancreas 2016;45:458–465. [PubMed: 26495779]

97. Eibl G, Rozengurt E. KRAS, YAP, and obesity in pancreatic cancer: a signaling network with multiple loops [published online ahead of print October 24, 2017]. Semin Cancer Biol 2017.

98. Memba R, Duggan SN, Ni Chonchubhair HM, et al. The potential role of gut microbiota in pancreatic disease: a systematic review. Pancreatology 2017;17:867–874. [PubMed: 28935288]

99. Signoretti M, Roggiolani R, Stornello C, et al. Gut microbiota and pancreatic diseases. Minerva Gastroenterol Dietol 2017;63:399–410. [PubMed: 28240004]

100. Ertz-Archambault N, Keim P, Von Hoff D. Microbiome and pancreatic cancer: a comprehensive topic review of literature. World J Gastroenterol 2017;23:1899–1908. [PubMed: 28348497]

101. Boulange CL, Neves AL, Chilloux J, et al. Impact of the gut microbiota on inflammation, obesity, and metabolic disease. Genome Med 2016;8:42. [PubMed: 27098727]

102. Jandhyala SM, Madhulika A, Deepika G, et al. Altered intestinal microbiota in patients with chronic pancreatitis: implications in diabetes and metabolic abnormalities. Sci Rep 2017;7:43640. [PubMed: 28255158]

103. Xue J, Sharma V, Hsieh MH, et al. Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. Nat Commun 2015;6:7158. [PubMed: 25981357]

104. Xue J, Zhao Q, Sharma V, et al. Aryl hydrocarbon receptor ligands in cigarette smoke induce production of interleukin-22 to promote pancreatic fibrosis in models of chronic pancreatitis. Gastroenterology 2016;151:1206–1217. [PubMed: 27769811]

105. Edderkaoui M, Xu S, Chheda C, et al. HDAC3 mediates smoking-induced pancreatic cancer. Oncotarget 2016;7:7747–7760. [PubMed: 26745602]

106. Tseng WW, Winer D, Kenkel JA, et al. Development of an orthotopic model of invasive pancreatic cancer in an immunocompetent murine host. Clin Cancer Res 2010;16:3684–3695. [PubMed: 20534740]

107. Kenkel JA, Tseng WW, Davidson MG, et al. An immunosuppressive dendritic cell subset accumulates at secondary sites and promotes metastasis in pancreatic cancer. Cancer Res 2017;77: 4158–4170. [PubMed: 28611041]

108. Carmi Y, Spitzer MH, Linde IL, et al. Allogeneic IgG combined with dendritic cell stimuli induce antitumour T-cell immunity. Nature 2015; 521:99–104. [PubMed: 25924063]

109. Makohon-Moore A, Iacobuzio-Donahue CA. Pancreatic cancer biology and genetics from an evolutionary perspective. Nat Rev Cancer 2016;16: 553–565. [PubMed: 27444064]

110. Giovannetti E, van der Borden CL, Frampton AE, et al. Never let it go: stopping key mechanisms underlying metastasis to fight pancreatic cancer. Semin Cancer Biol 2017;44:43–59. [PubMed: 28438662]