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Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases: Workshop Proceedings

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The Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases workshop was a 1.5-day scientific conference at the National Institutes of Health (Bethesda, MD) that engaged clinical and basic science investigators interested in diseases of the pancreas. This report provides a summary of the proceedings from the workshop. The goals of the workshop were to forge connections and identify gaps in knowledge that could guide future research directions. Presentations were segregated into six major theme areas, including *1*) pancreas anatomy and physiology, *2*) diabetes in the setting of exocrine disease, *3*) metabolic influences on the exocrine pancreas, *4*) genetic drivers of pancreatic diseases, *5*) tools for integrated pancreatic analysis, and *6*) implications of exocrine–endocrine cross talk. For each theme, multiple presentations were followed by panel discussions on specific topics relevant to each area of research; these are summarized here. Significantly, the discussions resulted in the identification of research gaps and opportunities for the field to address. In general, it was concluded that as a pancreas research community, we must more thoughtfully integrate our current knowledge of normal physiology as well as the disease mechanisms that underlie endocrine and exocrine disorders so that there is a better understanding of the interplay between these compartments.

The pancreas is an organ composed of two functional compartments, the endocrine and exocrine pancreas, which are highly coordinated to facilitate their role in metabolism

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and digestion, respectively (1). Specifically, the functions of the endocrine and exocrine pancreas are integrated through both neural and hormonal mechanisms in the brain, brainstem, nutrient absorption, and gut hormone responses. Despite this physiologic interdependence, disorders of the endocrine and exocrine pancreas are managed by different pediatric and medical subspecialties (endocrinology and gastroenterology, respectively) that may not approach pancreatic diseases in a multidisciplinary manner. Similarly, the basic science and the translational research related to the study of these two compartments are very minimally integrated. As a result, silos exist and present significant challenges to our greater understanding of pancreatic structure, function, and dysfunction.

Interestingly, there are many disease states where the initial dysfunction or defect in one compartment eventually results in dysfunction or defect in the other. For example, exocrine pancreatic insufficiency (EPI) is highly correlated with diabetes in patients with chronic pancreatitis (CP) and cystic fibrosis (CF) (2,3). Moreover, the effects of the inflammatory milieu of pancreatitis may lead to diabetes through enhancing β-cell dysfunction or causing some islet destruction (4,5). Upon recognition of these strong connections in both the normal and diseased states, a workshop was organized to explore the integration and cross talk between the exocrine and endocrine pancreas as well as to develop an expanded view of pancreatic development, structure, innervation, blood flow, and function. The workshop took place on 29 and 30 June 2022 at the National Institutes of Health (NIH) Natcher Conference Center (Bethesda, MD) and was hosted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) (Table 1). The discussions initiated by this workshop may improve multidisciplinary research approaches such that we more thoughtfully integrate our current knowledge of both the normal physiology and disease mechanisms that underlie endocrine and exocrine disorders, leading to a better understanding of the interplay between these compartments (Fig. 1).

INSIGHTS INTO PANCREAS ANATOMY AND PHYSIOLOGY

Overview

To understand the integrated function of the pancreas, it is important to define the key components that establish its structure and function. These components include the specialized cells of the pancreas, such as acinar cells, duct cells, and islet cells, as well as the vascular structures that feed these cells, the local immune system, the nervous systems that regulate specialized cell activity, and the supporting cells that play critical roles in health and disease. This session focused on our current understanding of pancreas development and maturation as well as the interconnection of the vasculature, neurons, and stellate cells.

Development and Maturation of the Human Pancreas

The pancreas develops as two buds emerging from the foregut endoderm that rotate and merge to form the organ (6). Both acinar (exocrine) and islet (endocrine) cells differentiate from the progenitor cells within the ductal epithelium. Along with this continued differentiation, there is progressive growth and organization of each compartment as well as interconnection with the ductal, vascular, and neuronal systems. In humans, the pancreas is underdeveloped at birth such that continued growth and maturation is required postnatally. Evidence from human islets in the first decade of life suggests that there are dynamic changes in endocrine cell arrangement, composition, proliferation, formation of neuronal connections, and macrophage infiltration during this stage (https://pancreatlas.org/datasets/531/overview). These major morphogenic processes continue in the human islet several years after birth, plateauing during childhood (~6 years). This continued growth and development is also important as variations in this process may predispose to autoimmune-mediated type 1 diabetes (T1D). It is within the first decade of life that β-cell mass is established (7,8), and for individuals at higher risk of T1D, the variability in β-cell mass may play a role in T1D onset. β-Cell-directed autoimmunity also emerges within the juvenile pancreas maturation period (9). The number of autoantibodies accrued during the juvenile period strongly correlates with the future risk of developing T1D. The mechanisms leading to autoimmunity in the maturation stage are unknown. Understanding the structural and mechanistic interactions between different cell types within the pancreatic islet ecosystem in the first decade of life will require combining *1*) functional recordings of endocrine, vascular, and immune cells in living human pancreas tissue slices with *2*) anatomical studies of islet cytoarchitecture and vasculature, *3*) measurements of hormone secretion from

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Table 1—Topics presented by invited speakers at the NIDDK Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases workshop

Theme	Speaker	Presentation topic
Pancreas anatomy and physiology	David C. Whitcomb	Overview: anatomy, physiology, function
	Alejandro Caicedo	Development/maturation of the human pancreas
	Manami Hara	Vascular flow and regulation
	Abdelfattah El Ouaamari	Innervation
	Minoti Apte	Stellate cells
Diabetes in the setting of exocrine disease	Dhiraj Yadav	Diabetes after acute pancreatitis
	Mark O. Goodarzi	Diabetes after chronic pancreatitis
	Rebecca L. Hull-Meichle	CFRD
Metabolic influences on the exocrine pancreas	Mandar D. Muzumdar	β-Cell drivers of pancreatic cancer (PDAC)
	Zobeida Cruz-Monserrate	Obesity and PDAC
	Martha Campbell-Thompson	Exocrine mass in T1D
	Janel L. Kopp	Effects of hyperinsulinism on exocrine cells
	Steven Artandi	Acinar cell heterogeneity
Genetic drivers of pancreatic diseases	Andrea Geisz	Genetic drivers of exocrine disease
	Kyle J. Gaulton	Genetic drivers of diabetes
	Alison P. Klein	Genetic drivers of PDAC
Tools for integrated pancreatic analysis	Temel Tirkes	Pancreatic histology and imaging
	Alex Kleger	Organoid and pancreas on chip
	Alexandra Alvarsson	Imaging and innervation in T2D
	Edward A. Phelps	Pancreas slices to study immune cell–islet interactions
Implications of exocrine–endocrine cross talk	Anjaparavanda P. Naren	Exocrine ductal system and CF/diabetes
	Jing Yong	β-Cell/ER stress in the exocrine
	Rohit N. Kulkarni	Exocrine influences on islet function and diabetes
	Teresa L. Mastracci	Translational regulation of exocrine–endocrine cross talk

pancreas slices and isolated juvenile islets, and *4*) transcriptomic studies such as single-cell RNA-sequencing analyses to define molecular signatures of all islet cell types at different stages of postnatal life.

Vascular Flow and Regulation

The pancreas is an organ with a complex vascular network. The conventional model of unidirectional blood flow from the islets to exocrine cells has recently been questioned. The combination of confocal laser scanning microscopy, tissue-clearing techniques, and image analysis software have enabled the study of vascular networks in situ in thick pancreas tissues (600–800 μm) in 3D (10–12). Large-scale image capture has been used to examine the spatial relationship among islets, blood vessels, and arterioles (labeled with α-smooth muscle actin) in various species, including human, monkey, pig, rabbit, ferret, and mouse. Some arterioles situated by islets have brief peripheral contact with them, whereas others pass through. Capillaries in the pancreas directly branch out from the arterioles, which is a phenomenon not observed in kidney, spleen, or liver. Overall, islets were found to be in proximity to arterioles but not necessarily in direct contact. The arterioles emerge to feed the endocrine pancreas regionally, not targeting individual islets. Vascularizing the pancreas in this way may allow an entire downstream region of islets within a lobe of the pancreas to be simultaneously exposed to changes in blood glucose levels, hormones, and other factors circulating in the blood. Furthermore, islets that directly contact the vasculature are significantly larger in size and fewer in number than those without contact (12). The identification of mechanisms that guide islet–vasculature connections as well as the physical routes of cross talk by vasculature between the exocrine and endocrine pancreas represent significant gaps in knowledge in the field.

Neuronal Control of Pancreatic Cells

The nervous system plays key roles in stimulating and inhibiting the endocrine and exocrine pancreas. In the endocrine pancreas, the autonomic and sensory neurons play critical roles in fine-tuning the activity of insulin-producing pancreatic β-cells (13,14). Studies have shown that male and female mice have different responses following denervation of the pancreas-projecting sensory neurons that regulate β-cell function and glucose homeostasis. In particular, the positive effects of sensory denervation on glucose tolerance and β-cell function were observed in male but not female mice, indicative of a sex difference in sensory modulation of β-cell activity (15). The number of pancreatic axonal endings originating from the dorsal root and nodose ganglia was greater in male than in female mice, and these effects were blunted when mice were gonadectomized prior to the removal of sensory fibers. In female mice, chemical denervation of sensory fibers did not affect glucose-induced insulin secretion or glucose excursion, and ovariectomy did not modify these

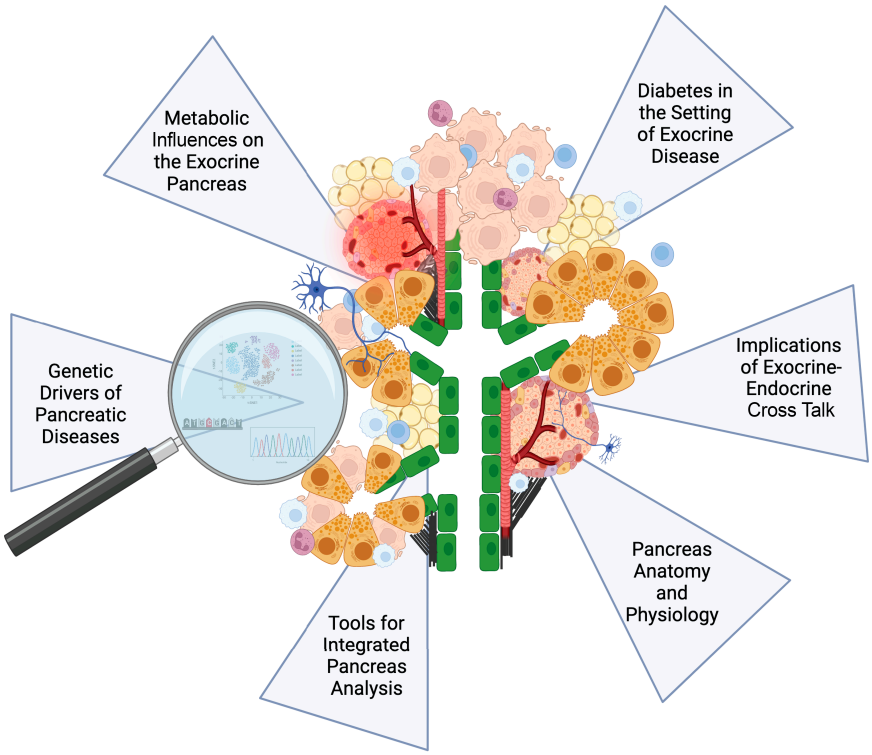

Figure 1—Understanding exocrine–endocrine cross talk. The NIDDK-sponsored workshop, Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases, showcased talks in six areas of research related to how the exocrine and endocrine compartments interact in the healthy and diseased pancreas. Panel discussions between experts in these fields and conference participants resulted in the identification of gaps in knowledge and opportunities for future research. As a pancreas research community, we must more thoughtfully integrate our current knowledge of the normal physiology and the disease mechanisms that underlie endocrine and exocrine disorders so that there is a better understanding of the interplay between these compartments.

(16). A possible translational implication is that the larger density of sensory fibers in the male pancreas may have functional consequences in insular and acinar tissues, which may account for greater prevalence of diabetes and pancreatic cancer in men compared with women (17–20).

Stellate Cells

Over the past several decades, it has become increasingly recognized that the vitamin A-containing myofibroblast-like cells, known as pancreatic stellate cells (PCSs), play a critical role in organ structure, response to injury, immunity, and, under pathologic conditions, such as CP and pancreatic cancer, excessive fibrosis (21). PSCs are resident cells of the pancreas, found around basolateral aspects of acinar cells and also around and within islets. PSCs play important roles in health, including *1*) regulating extracellular matrix (ECM) turnover, *2*) an innate immune function via the expression of toll-like receptors and phagocytic capability, *3*) potential function as intermediary cells for cholecystokinin (CCK)-induced acinar enzyme secretion, and *4*) progenitor function. During pancreatic disease, PSCs are activated by a host of activating factors, and this process is mediated by a range of signaling pathways. More recently, signaling molecules that drive reversion of activated PSCs to quiescence have been identified, such as the peroxisome proliferator–activated receptor-γ ligand troglitazone, all-*trans*-retinoic acid (a metabolite of retinol), and the vitamin D receptor ligand calcipotriol.

The excessive ECM deposition in CP results from persistent PSC activation via the secretion of cytokines by the cells themselves and also an interaction with infiltrating macrophages via the secretion of interleukin-4 (IL-4) and IL-13 (22). These interleukins drive macrophages to an M2 phenotype; M2 macrophages secrete growth factors such as transforming growth factor-β and platelet-derived growth factor that in turn activate PSCs, thus setting up a feed-forward loop. Interestingly, PSCs are present in pancreatic intraepithelial neoplasms and pancreatic ductal adenocarcinoma (PDAC). PSCs promote cancer progression via bidirectional interactions with cancer cells and stromal elements such as immune, endothelial, and neuronal cells and the ECM itself (23). Targeting cancer cells alone with chemotherapy is inadequate; rather, inhibiting specific stromal tumor interactive pathways may be required for improved patient outcomes. One of the major challenges in this area is the increasingly recognized heterogeneity of PSCs within the cancer stroma. An elegant study by Helms et al. (24) used lineage-tracing strategies to demonstrate that PSCs were a numerically

minor component of cancer-associated fibroblasts in cancer stroma; however, PSCs play major nonredundant roles in cancer progression. Consequently, rather than blanket ablation of cancer-associated fibroblasts, strategic interventions to block specific pathways mediating PSC–cancer interactions is the way forward.

Activated PSCs also reduce insulin secretion from β-cells, an effect that is aggravated by hyperglycemia but abrogated by glucagon-like peptide-1 agonists, suggesting a role for PSCs in diabetes associated with CP (25). The cross talk between PSCs and pancreatic intraepithelial neoplasms may lead to the secretion of exosomes that affect islet PSCs and cause islet cell dysfunction and diabetes in PDAC as well as peripheral insulin signaling in hepatocytes, adipocytes, and myocytes, causing insulin resistance. Further investigation is needed to fully understand these PSC interactions.

Research Gaps and Opportunities

- The importance of the structural and functional relationships between the endocrine and exocrine pancreas will require multidisciplinary teams collaborating to provide new insights into mechanisms of physiology and disease.
- The use of new approaches and new tools is needed to investigate interaction between endocrine and exocrine systems and how the interconnections between these systems develop from embryonic through postnatal stages.
- Heterogeneity of PSCs in PDAC and CP needs to be investigated in depth to enable the development of targeted and specific therapies.
- Study approaches will require managing and analyzing large data sets to overcome the limitations of the reductionist focus, as these miss integrative insights needed to help in the understanding of complex human disorders.
- The role of the vascular and neural systems must be considered.
- Approaches to understand the mechanisms underlying the heterogeneity in disease risk, initiation, severity, and progression of disease need to be developed.

DIABETES IN THE SETTING OF EXOCRINE DISEASE

Overview

Diseases that primarily affect the exocrine pancreas are recognized as important risk factors for diabetes. These pancreatogenic forms of diabetes include diabetes resulting from acute pancreatitis (AP), CP, and CF. PDAC can also present as diabetes and is discussed elsewhere (26). Recognizing the knowledge gaps concerning pancreatitis-related diabetes, the NIDDK has established two multicenter clinical research consortiums: the Chronic Pancreatitis, Diabetes, and Pancreatic Cancer Consortium (CPDPC) in 2015 and the Type 1 Diabetes in Acute Pancreatitis Consortium (T1DAPC) in 2020. These groups are currently undertaking clinical studies directed at defining risk for and mechanisms of diabetes in AP and CP populations. These include longitudinal cohorts that are followed for risks of diabetes in CP and AP as well as cross-sectional studies aimed at determining underlying physiology. This session discussed the impact of AP, CP, CF, and EPI on the development and/or progression of diabetes.

CP and Diabetes

Overall, 30% of patients with CP have diabetes at the time of diagnosis, with rates increasing to 50–80% after 20–25 years of follow-up. CP-related diabetes (CP-D) is often misdiagnosed as type 2 diabetes (T2D) (27), but its recognition has important implications for treatment and monitoring. Patients with CP-D need insulin earlier after diagnosis than is typical for T2D, have a fivefold higher risk of severe hypoglycemia compared with that for patients with T2D (27,28), and have an increased risk of pancreatic cancer and all-cause mortality (28,29). Therefore, there is a great need to develop biomarkers and diagnostic models (based on clinical, hormonal, or genetic factors) to distinguish CP-D from T2D.

Clinical features associated with CP-D include traditional risk factors for T2D (e.g., age, male sex, obesity, and family history of diabetes) and pancreatitis-related features (e.g., duration of CP, EPI, pancreatic surgery, and pancreatic calcifications) (30). Genetic variants robustly associated with T2D in genome-wide association studies (GWAS) are also associated with CP-D (5). While insulin deficiency is clearly a main driver of CP-D, other contributing factors to CP-D may include hepatic insulin resistance linked to deficiency of pancreatic polypeptide and possible incretin hormone dysregulation (31).

AP and Diabetes

Until a few years ago, diabetes in the context of AP was thought to occur only in patients with severe AP. A systematic review of 24 studies published in 2014 noted the risk of diabetes after AP to be much greater than previously recognized and not simply attributable to severe AP (32). In a recent prospective study of 152 patients with AP followed every 6 months with fasting blood glucose and hemoglobin A_{1c} levels, the risk of diabetes and prediabetes at 2 years was observed to be 11% and 45%, respectively (4). Population-based studies estimate the risk of AP-related diabetes (AP-D) to be about twofold greater than that for age- and sex-matched individuals, with similar estimates when data are restricted to patients with mild AP (33). Because AP is 6- to 10-fold more common than CP, the burden of diabetes from AP far exceeds that from CP (27). Compared with patients with T2D, patients with AP-D require insulin more frequently and have suboptimal management of blood glucose levels (27,34).

The mechanisms leading to AP-D, especially in the context of mild AP, have not been fully identified. β-Cell loss and reduced insulin secretion may account for diabetes in patients with severe AP (35). However, reduced insulin

sensitivity has been demonstrated in patients with mild AP, suggesting that in a subset of patients the pathophysiology of AP-D resembles that of T2D (36). Emerging data suggest that a subset of patients with recurrent AP and CP with diabetes have one or more β-cell autoantibodies, suggesting that autoimmunity plays a role in the development of AP-D (37).

CF and Diabetes

Significant advances in the treatment and management of CF (especially lung disease) have greatly increased life expectancy from ∼20 years in the 1980s to ∼45 years today. With this improved survival, age-related components of CF are becoming more of a focus; cystic fibrosis–related diabetes (CFRD) is one of the most common complications of CF, affecting 20% of adolescents and 40% of adults and contributing to disease morbidity and disease burden (38). Importantly, CF patients suffering from CFRD have a less than <25% likelihood of surviving to 30 years of age compared with 60% of CF patients who have normal glucose tolerance. Despite the severe clinical implications, large gaps in knowledge remain regarding the pathophysiology of CF pancreas disease and especially CFRD (39).

Exocrine pancreatic pathology is one of the earliest manifestations of CF, present in 85% of people with CF (40). Loss of CFTR function in pancreatic ductal epithelium leads to duct obstruction, inflammation, and premature activation of pancreatic enzymes, resulting ultimately in destruction of exocrine tissue. Impaired insulin release is also present in most individuals with CF, especially those with EPI (41–43). Surprisingly, islets largely survive the widespread inflammation and exocrine tissue destruction that characterizes CF, with most studies reporting only a modest decrease in β-cell area in patients with CF or CFRD (44,45). This suggests that mechanisms other than β-cell loss are important.

Several groups have reported early and widespread inflammation in CF islets, increased immunoreactivity for the proinflammatory cytokine IL-1β (46), and/or increased T-cell infiltration (45,47), which could mediate impaired insulin release. In addition to inflammatory damage, changes in the microenvironment of the islets, including vasculature and resident macrophages, may impact normal islet function and survival (48–51). Our understanding of how these supportive cell types are affected by CF is still limited, but emerging data suggest profound abnormalities exist. Preliminary data suggest a substantial decrease in islet (and exocrine) vascularity in CF (52). These abnormalities are likely detrimental to islet function and probably contribute to the insulin deficiency that characterizes CF. While it is clear that the prevalence of islet autoantibody positivity in CF is far below that seen in T1D, there are discrepant reports of whether rates of islet autoantibody positivity in CF differs from that of the general population (53–56). It has been suggested that screening for autoimmunity is warranted in a specific subset of at-risk CFRD patients (57).

EPI and Diabetes

While EPI has been classically associated with CP or CF, EPI appears to also be present in 39% and 28% of patients with T1D and T2D, respectively, based on the imperfect measure of low fecal elastase (58). Potential mechanisms for EPI in diabetes include immune cell infiltration, ectopic fat deposition, fibrosis, and loss of the trophic effect of insulin on exocrine tissue (59). The clinical relevance of EPI in T1D and T2D is unclear, and specific treatment recommendations for EPI in this setting are lacking.

Research Gaps and Opportunities

- Investigations are needed to determine to what extent CP-D is a unique disease versus a subtype of T2D.
- Better biomarkers for CP-D diagnosis should be developed for use in research and clinical care.
- Underlying mechanisms of CP-D should be defined in order to identify treatment targets to inform much-needed treatment trials for CP-D.
- Whether pancreatic enzyme replacement therapy in CP-D can improve dysglycemia should be studied.
- Factors associated with short- and long-term risk of AP-D, including morphological features on cross-sectional imaging, should be defined, and models should be developed to predict risk of AP-D (clinical, biomarker, and imaging).
- Metabolic alterations in AP, and how they impact and can predict the risk of AP-D and the potential role of islet autoimmunity in pathogenesis of AP-D, should be determined.
- Preventative and therapeutic interventions to reduce the risk of AP-D need to be developed.
- Factors other than loss of β-cell mass that contribute to CFRD, including inflammatory and immunologic contributors, should be defined.
- The role of loss of islet vascularity in CFRD risk should be determined.
- Understanding of the impact of EPI on endocrine function and islet mass is needed.

METABOLIC INFLUENCES ON THE EXOCRINE PANCREAS

Overview

Secretory components, including peptide hormones from the islets of Langerhans, are major regulators of the exocrine pancreas. These hormones exert key effects on the acinar cells by diffusion, which manifests as peri-insular halos of acinar cells and by the islet–acinar portal system. The portal system contributes to how acinar cells are exposed to high levels of islet hormones and other regulatory molecules. Insulin is the most abundant secretory hormone from islets and serves as a trophic factor for the exocrine pancreas by promoting digestive enzyme synthesis and

regulation of acinar mass. The regulation of insulin levels by nutrients and insulin-resistant states, such as obesity and diabetes, provides a direct link between diet, weight, and hyperinsulinemia and the regulation of pancreatic mass and acinar function. These mechanisms are also emerging as potential drivers of the progression of PDAC, the predominant exocrine tumor of the pancreas. PDAC is the third leading cause of cancer death in the U.S., with a 5-year survival rate of ~11% (60). Rapidly rising in worldwide prevalence (61,62), obesity increases the risk of both developing and dying from PDAC (63–65), yet the mechanistic basis for these relationships is not well understood. Therefore, this session discussed the mechanisms linking the cross talk among different pancreatic compartments and how obesity increases PDAC risk, in particular the role of hyperinsulinemia and other islet secretory products.

Obesity and PDAC

Cancer preventive studies in humans can take a long time and PDAC (despite being deadly) is a rare disease, therefore researchers rely on preclinical models that recapitulate the genetic and histologic features of the human disease to study the role of obesity in promoting PDAC pathogenesis. One of the most common models used to study the mechanistic links between cancer and obesity is the high-fat diet–induced obesity model (66). This diet increases tumor initiation, accelerates tumor progression, and decreases survival of mice that have acinar cells genetically altered to express mutant *Kras* (*Kras*^{G12D}), a driver oncogene in >90% of human PDAC (66). Studies showed increased levels of the adipokine lipocalin 2 (LCN2) in the circulation of obese mice with *Kras* mutations, while LCN2 deletion delayed weight gain and adiposity and decreased the formation of early PDAC lesions, inflammation, and fibrosis in the model (67). Importantly, it is clear that there are significant gaps in our knowledge with respect to how the adipose tissue microenvironment and/or products contribute to the risk and the progression of PDAC and what adipocyte factors are involved in augmented PDAC risk and the regulation of the tumor microenvironment. Characterization of the PDAC phenotype between lean and obese models could also uncover obesity-specific factors that drive PDAC pathogenesis. Finally, validation of preclinical models that mimic human obesity–associated PDAC is also necessary to further investigate the mechanisms linking obesity to PDAC. These discoveries will allow us to develop strategies to prevent PDAC in individuals with obesity.

β-Cell Drivers of Pancreatic Cancer

The role of the β-cell in experimental models of obesity-driven PDAC has been demonstrated using a genetic mouse model of obesity (*Lep*$^{ob/ob}$) combined with mutant *Kras*^{G12D} expression, as described above. These studies showed that obesity accelerated oncogenic Kras-driven pancreatic tumorigenesis, while weight loss inhibited PDAC tumor development (68). By analyzing human and murine biospecimens, researchers found that obesity-driven PDAC was associated with islet cell reprogramming. Specifically, obesity reduced insulin expression and increased expression of putative protumorigenic hormones, including the peptide hormone CCK (68,69). Transgenic CCK overexpression in β-cells was sufficient to promote acinar cell proliferation and ductal transformation and oncogene-driven tumorigenesis in nonobese mutant Kras-expressing mice (68). Conversely, β-cell ablation impaired PDAC progression even in nonobese mice, demonstrating that the endocrine pancreas plays a critical role in tumor promotion. Using single-cell RNA-sequencing analyses of β-cells from obese mice, a role for obesity-induced islet stress and β-cell dysfunction in aberrant protumorigenic hormone expression was demonstrated (68). Strikingly, lowering blood glucose levels using inhibitors of sodium–glucose cotransporter 2 (SGLT2) improved β-cell function and insulin production and secretion while reducing CCK expression and tumor development. This argues that islet hormonal adaptations beyond changes in insulin drive tumorigenesis in obesity (68). These findings suggest that obesity-driven PDAC progression may be promoted by endocrine–exocrine signaling beyond insulin itself.

Hyperinsulinism and the Exocrine Pancreas

Obesity and T2D are risk factors for PDAC, and hyperinsulinemia is a common denominator in these diseases (70,71). In the pathogenesis of T2D, hyperinsulinemia precedes and promotes obesity-driven insulin resistance (72,73). Genetic models of insulin reduction in combination with the expression of Kras^{G12D} in acinar cells showed a causal contribution of hyperinsulinemia in promoting tumor initiation from an acinar cell of origin (74–76). Inducing loss of insulin receptor in mouse acinar cells specifically demonstrated that hyperinsulinemia directly acts on acinar cells to promote Kras^{G12D}-expressing acinar cells to initiate tumor development (77). Insulin signaling in acinar cells promotes acinar cell transformation by increasing digestive enzyme production (77) and thus increasing the potential for trypsinogen to convert into trypsin and induce inflammation. Importantly, insulin synergistically cooperates with transforming growth factor-α, an activator of Ras–mitogen-activated protein kinase signaling, to promote conversion of acinar cells into duct-like rings (acinar-to-ductal metaplasia) in vitro, and this synergism is blocked by trypsin inhibitors (77). These findings provide evidence for a potential mechanism underlying obesity/insulin-driven tumorigenesis with major implications for cancer risk and suggest that this pathway can be used to design strategies for primary and secondary prevention.

Decreased Exocrine Mass in T1D

Studies of islet inflammation (insulitis) in patients with T1D show heterogeneity between pancreatic lobules in terms of loss of islet β-cells and islet number and types

of infiltrating immune cells (78). Importantly, patients with T1D exhibit reduced pancreas size (79,80). First-degree relatives of patients with T1D also have small pancreas volumes, determined by MRI radiology (81,82). Theories of exocrine pancreas loss in T1D include an exocrine deficiency secondary to β-cell deficiency, combined endocrine and exocrine dysfunctions, and/or an exocrine deficiency that leads to β-cell dysfunction (83). These data suggest the possibility that the exocrine compartment influences β-cell function, including β-cell susceptibility to autoimmunity in T1D and β-cell failure in T2D. In addition to changes in acinar mass, alterations in the islet vasculature have been reported in T1D; however, vessels in the peri-islet region were not different between control and T1D patients (84–86). In addition, neuroplasticity of sympathetic innervation was observed in inflammatory conditions of the exocrine pancreas (86–88). The development of diabetes following recurrent AP or CP indicates another condition in which inflammation of the exocrine pancreas decreases β-cell insulin secretion. Finally, subjects with diabetes associated with an exocrine pancreatopathy have decreased pancreas weight or volume, with histological findings of increased interacinar fibrosis and acinar atrophy (89). Together, these findings document an interplay between the exocrine and endocrine pancreas functions for which many unanswered questions remain.

Research Gaps and Opportunities

- The mechanisms by which obesity and/or fatty pancreas promote pancreatic cancer should be investigated in animal models with validation in humans.
- The roles of pancreatic islets and their β-cells in the promotion of pancreatic cancer should be determined.
- The potential roles of islets and β-cells in inflammatory and immune responses in the exocrine pancreas should be determined.
- An understand of how insulin causes trypsin activation leading to pancreatic inflammation, which is known to promote tumor initiation in mutant Kras-expressing exocrine pancreas, is needed.
- The roles of the pancreatic vasculature and neural systems in the interplay of exocrine and endocrine functions and disease should be investigated.

GENETIC DRIVERS OF PANCREATIC DISEASE

Overview

Studies of inherited predisposition to PDAC, pancreatitis, diabetes, and pancreatic endocrine cancers have progressed at different paces, driven in part by differences in their incidence. As these studies progress and sample sizes increase, an overlap in risk variants and genes between exocrine and endocrine diseases is becoming clear for both rare large-effect variants and more common small-effect variants. As these studies have almost exclusively been performed in individuals of European ancestry, there is an unmet clinical need for greater diversity in genetic studies of pancreatic diseases. This session discussed our current understanding of the genetic drivers of pancreatic diseases, including pancreatitis, PDAC, and diabetes.

Genetic Drivers of Pancreatitis

Three forms of pancreatitis, AP, recurrent AP, and CP, form a disease continuum where progression is often driven by genetic risk factors (90). Human genetic studies and functional analyses established a mechanism-based classification of CP-associated risk variants, which includes the trypsin-dependent, protein misfolding, and ductal pathways (91). Most CP patients carry risk variants that control intrapancreatic trypsin activity (90,91). Intrapancreatic trypsin levels may increase due to enhanced trypsinogen activation triggered by mutations in serine protease 1 (PRSS1) or by the failure of antitrypsin mechanisms such as the serine protease inhibitor Kazal type 1 (SPINK1) or the trypsinogen-degrading protease chymotrypsin C (CTRC).

The origin of intrapancreatic trypsin activity has been controversial, as trypsinogen may be activated by cathepsin B (CTSB) (92,93), but it can also undergo autoactivation when trypsin activates trypsinogen. The concept that trypsinogen autoactivation is pathogenic was supported by genetic, biochemical, and, more recently, mouse studies (91,94–96). The most compelling published evidence comes from the T7D23A mouse model that carries the D23A mutation in mouse cationic trypsinogen, which is analogous to the human D22G mutation. These T7D23A mice exhibit robust intrapancreatic trypsinogen autoactivation, resulting in spontaneous AP with rapid progression to CP (94). Whereas *T7D23A* mice and related models clearly demonstrate that increased trypsinogen autoactivation governs disease onset, progression, and severity, similarly convincing evidence for the role of CTSB has been lacking. Thus, therapeutic efforts for pancreatitis should focus on controlling trypsinogen autoactivation.

Genetic Drivers of PDAC

Family history of PDAC, as well as a family history of other cancers, has been associated with an increased pancreatic cancer risk (97,98). Rare pathogenic variants in several genes have been associated with a high risk of PDAC (e.g., *BRCA2, ATM, BRCA1, PALB2, CDKN2A, MLH1, MSH2, MSH5, PMS2, STK11*, and *PRSS1*); while pathogenic variants in these genes are more prevalent in those with a family history, they have also been reported in 5–20% of patients unselected for family history (97–102). In addition to rare variants, common genetic variants, identified via GWAS, also play an important role. GWAS of PDAC are in their infancy compared with those for other cancers; the latest meta-analysis in European populations (including 9,040 PDAC and 12,496 control subjects) identified a total of 20 common risk loci (103). Smaller GWAS performed in Asian populations have replicated some risk loci reported

in Europeans and identified others that may be population specific (104,105).

PDAC heritability is estimated to be 21.2–36% (106,107). However, the identified genetic changes explain only 20–25% of the GWAS heritability, indicating that more remains to be discovered. As in other complex diseases, rare highly penetrant and common low-penetrance variants for PDAC tend to have different functional mechanisms. The former most often affect protein-coding sequences, whereas the latter mostly alter noncoding gene regulatory elements, leading to changes in gene expression of nearby or distant genes. However, this could be limited by our ability to interpret rare genetic variation. Further investigation of inherited variants that influence risk of PDAC and its mechanistic underpinnings would help the understanding of PDAC etiology and the development of early detection strategies.

Genetic Drivers of Diabetes

The genetics of T1D is highly heritable, with over 90 known loci contributing to disease (108,109). Most T1D loci map to noncoding sequences and likely affect the epigenome and gene regulation in disease-relevant cells, but the mechanisms of most loci are unknown. A recent study by Chiou et al. (109) reported the largest-to-date GWAS of T1D in combination with cell type–specific *cis*-regulatory elements (cCREs) defined using single-nucleus assay for transposase-accessible chromatin with high-throughput sequencing of pancreas and blood. The study identified enrichment of T1D variants for cCREs active in T cells and β-cells as well as acinar and ductal cells. Variants at numerous T1D loci that mapped to exocrine cCREs were linked to genes with exocrine-specific expression. For example, at the *CFTR* locus, T1D variants affected cCRE activity and regulated *CFTR* expression in ductal cells. Variants in exocrine cCREs were also broadly associated with pancreatitis and PDAC. Beyond T1D, studies have also shown enrichment of variants associated with T2D and glycemic traits for exocrine cCREs (110,111). At the *CTRB1/2* locus, T1D variants are also associated with glucose levels 2 h after oral glucose tolerance test and T2D, where the T1D risk alleles are protective for T2D (112,113). Together, these results that integrate human genetics with large omics data sets argue that genetic regulation of exocrine cell function may play a causal role in T1D and T2D. However, the underlying mechanisms that lead to altered diabetes risk and/or glycemia are currently unknown.

Research Gaps and Opportunities

- Larger genetic association studies are needed for pancreatitis and PDAC to identify more disease-associated genetic loci and pinpoint causal variants.
- GWAS need to consider non-European populations to resolve causal variants shared across populations, identify population-specific risk loci and variants, and inform on population differences in disease risk and prevalence.
- Collaborative efforts are needed to understand the relationship between genetic risk of diabetes and exocrine pancreatic diseases, both broadly as well as at individual loci.
- Detailed assessment of personalized risk scores for pancreatic diseases is needed, including in the context of high-penetrance familial mutations.
- Genomic and epigenomic studies are needed in large samples from diverse populations to map the effects of risk variants on gene regulation and expression in disease-relevant cell types.
- Advanced, genetically tractable systems in human cells, such as stem cell–derived organoids and coculture models that include both exocrine and endocrine cells, are needed to better understand risk variant function in the context of the entire pancreas.

TOOLS FOR INTEGRATED PANCREATIC ANALYSIS

Overview

A major challenge in the study of the physiology and pathophysiology of the pancreas is the inherent heterogeneity of the organ, which is further exacerbated in disease. Recent technological advancements have improved our ability to detect disease earlier, study pathophysiology in in vitro models, and gain insight into the heterogeneity of the pancreas. Leveraging these resources will continue to push the field in new directions and improve our understanding of complex exocrine and endocrine interactions. However, it must be noted that each technology has strengths and limitations. Therefore, it is important to clearly identify the study question at the outset to ensure that the technology is capable of addressing the question. This session discussed current technology that assists our understanding of pancreatic development and function in the healthy and diseased settings as well as how these tools might be used to study exocrine–endocrine cross talk.

MRI Technology

Recent advances are improving the clinical use of MRI with magnetic resonance cholangiopancreatography (MRCP) for the detection and monitoring of CP. MRCP is the most common cross-sectional imaging tool used to evaluate CP. The Cambridge classification (114) is designed to interpret endoscopic retrograde cholangiopancreatography (ERCP) and is still the imaging criterion used in clinical practice. The Cambridge classification used for MRCP primarily captures periductal fibrosis. However, as the pancreatic ductal system comprises only a small fraction (4%) of the normal pancreas (115,116) and imaging does not directly detect the fibrosis in the parenchyma or loss of acinar cells, the diagnosis of noncalcific CP can be elusive or delayed when using ductal imaging alone (117,118). Furthermore, unsatisfactory interobserver agreement is present when using the Cambridge

classification, even among abdominal imagers with significant experience (119,120). Several studies have reported that MRI investigation of changes in the pancreatic parenchyma might more accurately reflect the histopathologic changes related to CP and could be incorporated into a new classification system (117,121–124). MRI parenchymal signal changes may provide a more comprehensive evaluation of CP (125–127) and potentially earlier detection of the pathophysiology, considering that acinar cells comprise greater than 90% of the normal pancreas (128). In fact, multiple studies reported a significant correlation of MRI parenchymal findings with the degree of fibrosis observed histologically (125–127). Therefore, we can assume that certain parenchymal features have the potential to become a biomarker for the severity of fibrosis and may assist physicians in clinical practice and clinical trials. There are long-term studies looking into the benefit of MRI in evaluation of CP under the Chronic Pancreatitis, Diabetes, and Pancreatic Cancer Consortium (129). Most recently, the T1 signal intensity ratio (T1 score) has been proposed as an imaging biomarker for the staging of the CP (130). Quantitative MRI biomarkers of the pancreas, including T1 relaxation time, extracellular volume fraction, apparent diffusion coefficient, and fat signal fraction, have also been found to be helpful in diagnosis of CP (131). Multi-institutional longitudinal results are needed to verify these parameters as potential imaging biomarkers of pancreatic fibrosis and generate a new scoring system for CP. This more comprehensive imaging approach may lead to early diagnosis and treatment for people living with CP.

Organoid and Chip-Based Technology

Traditional cell culture methods provide a means for studying cell–cell interactions and signaling; however, in cells maintained in typical 2D, monolayer cultures often fail to mimic physiological phenotypes. A recent technical advancement combines 3D culturing techniques with human pluripotent stem cells to create highly functional organoids. Briefly, a multistage differentiation protocol combined with state-of-the-art transcriptomic and proteomic analysis revealed that induction of pluripotent stem cells into pancreatic-duct-like organoids (PDLOs) was associated with the maintenance of morphological and functional features of the human pancreatic duct epithelium (132–134). These PDLOs could therefore be an experimental tool to study pancreatic cell plasticity. Moreover, the addition of a microwell chip facilitated the uniform aggregation and chemical induction of human induced pluripotent stem cell-derived pancreatic progenitors into ductal intermediates and eventually mature duct-like and nonductal cells (135). This technology permitted the delineation of the emergent cell types at each stage of differentiation on the basis of their gene expression profiles and organoid structures. Further studies using this resource included PDLO cocultures with pancreatic stellate cells to understand epithelial-to-mesenchymal signaling as well as ductal disease modeling (136). Altogether, this resource represents a new method for modeling human carcinogenesis and hereditary syndromes at early stages of plasticity and dysplasia. Methods developed in this approach can be broadly translated to numerous other queries, from developmental biology to diabetes pathophysiology.

3D Imaging Technology

Understanding the detailed anatomy of the endocrine pancreas, its innervation, and the remodeling that occurs in diabetes can provide new insights into metabolic diseases. In particular, a tissue-clearing protocol based on iDisco+ has been developed to facilitate imaging endocrine cells and innervation in intact pancreata from mouse models of T1D as well as human donor pancreatic tissue from individuals with T2D (137). The use of tissue clearing combined with light-sheet microscopy and 3D analysis provided detailed quantification of the abundance of α-cells, β-cells, and pancreatic nerve fibers as well as their distribution and heterogeneity within both control and diabetic pancreatic tissue. In the mouse, innervation was highly enriched in the endocrine pancreas, with regional differences. Moreover, an increase in islet nerve density in nonobese diabetic mice, mice treated with streptozotocin, and pancreata of human donors with T2D was documented (137). Unexpectedly, nerve contacts with β-cells were preserved in diabetic mice and in people with diabetes. In summary, the development of this technique has revealed dynamic changes in pancreatic innervation in the setting of diabetes.

Pancreatic Slice Culture

Whole isolated islets retrieved from the enzymatically digested pancreas have been widely studied and have provided a useful model for understanding fundamental β-cell properties (138). However, isolated islets cannot answer all questions of relevance to the in vivo islet niche. The use of live pancreas tissue slices permits the study of islet physiology and other pancreatic structures within the context of the native tissue microenvironment (139). The ability to study complex interactions between islets and the surrounding acellular components of the environment as well as the nonendocrine cells that contribute to the islet niche has begun to provide a better understanding of islet physiology and pathophysiology (140). Because living tissue slices retain islets in the native 3D tissue, other cell types and signals contributing to islet physiology can also be studied, including nerves (86), vasculature (141), pancreatic ductal cells (142), exocrine cells (143), ECM (144), and immune cells (145–147). Furthermore, slices make it possible to monitor islet and immune cell behavior in the pancreas parenchyma under pathophysiological states, such as T1D, which result in compromised islet morphology and thus make isolation of whole islets challenging (145,148). Slice cultures enable researchers to explore questions of the integrated physiology of the endocrine and exocrine compartments of the pancreas, incorporating chemical

and fluorescence reporters as well as electrophysiology approaches (149–151). Whereas continued technology development is required and there are caveats with respect to nerve and vasculature connections, slice cultures provide a complementary approach to assist our understanding of the interactions and cellular communications that occur in the pancreatic environment.

Research Gaps and Opportunities

- The involvement of cellular and molecular pathways in human pancreatic tissue by applying multiomic techniques, including advanced microscopic techniques, should be established to provide pathophysiologic information needed as a foundation for hypothesis testing.
- Experimental approaches and advanced techniques in whole-body imaging should be developed to identify and measure contributors to disease in patients with diabetes and exocrine pancreatic disease.
- The use of in vitro systems to culture human donor pancreatic tissue needs to be expanded, and researches should answer pointed questions about structural organization of the pancreas as well as cellular interactions.
- Current human pluripotent stem cell pancreas models should be improved to develop an in vivo-mimicking cell model of the human pancreas amenable to gene editing for hypothesis testing.
- Observations from in vitro cultures and in vivo animal models should be integrated to determine the similarities and differences between human disease states and observations in animal models.

IMPLICATIONS OF EXOCRINE–ENDOCRINE CROSS TALK

Overview

Traditionally, the exocrine and endocrine cellular compartments of the pancreas have been considered distinct functional systems. However, there is growing evidence for exocrine–endocrine cross talk in development, physiology, and dysfunction of the pancreas, which is forcing us to rethink our understanding of structure/function as well as current disease classifications and treatment approaches. Detailed clinical studies show that disease in one compartment of the pancreas results in failure or dysfunction of the other compartment. Therefore, this session discussed the need to understand how exocrine–endocrine cross talk influences development, function, and disease of the pancreas.

Lessons Learned from CF

Mutations in the CF transmembrane conductance regulator (CFTR) gene are one of the strongest risk factors for the development for CP and EPI. However, as treatments for CF have significantly increased life expectancy, over 50% of CF patients living into adulthood now suffer from CFRD (https://www.cff.org). As described in the section *Diabetes in the Setting of Exocrine Disease*, above, the pathophysiology of CFRD is poorly understood, preventing the development of therapeutic interventions that halt or slow the progression of pancreatic endocrine insufficiency. Possible mechanisms for CFRD include inherent β-cell dysfunction as well as islet destruction and/or dysfunction
as a bystander to exocrine pancreatic damage from CFTR-mediated duct obstruction (39). Recent work has also suggested a role for inflammatory stress emanating from the ductal epithelial cells themselves (134,152), inflamed vasculature/endocrine cells, and/or lymphocytes (39,45–47). An in vitro system has been developed that will be invaluable in modeling these processes, wherein patient-derived pancreatic ductal epithelial cells (PDECs) and islet cells are cocultured in a novel microfluidic device (pancreas-on-a-chip). As a result, it has been observed that attenuating CFTR function in PDECs reduces insulin secretion in islet cells by 54%. This pancreas-on-a-chip is an innovative approach to study and develop personalized medicine approaches (based on the specific CFTR mutation) to treat the defective pancreatic exocrine–endocrine cross talk in CF (153).

Exocrine Influences on Endocrine Function

Several observations implicate the exocrine pancreas in diabetes pathology. Recent data generated from genetics and single-cell epigenomics implicate ductal and acinar cells in the pathogenesis of T1D (110). Moreover, analyses of clinical samples from patients with T1D show an overall decrease in pancreas volume (81–83). Several studies have also highlighted the importance of exocrine-derived proteins in pancreas pathology. For example, individuals with T1D show altered levels of serum trypsinogen (154) and, in the setting of maturity-onset diabetes of the young 8, mutant carboxy ester lipase (CEL) protein was shown to be internalized, leading to β-cell secretory dysfunction (155). Intervening in this exocrine–endocrine cross talk may be of possible therapeutic relevance, as was observed with the serine protease inhibitor SerpinB1, identified as an inhibitor of pancreatic elastase with consequences on endocrine function (156). Recombinant SerpinB1 or small-molecule compounds that mimic its protease inhibitor effects were shown to enhance β-cell proliferation, thus illustrating the potential opportunity to exploit communication between the pancreatic compartments to resolve aspects of disease.

Exocrine–endocrine cross talk has also been implicated in PDAC. Large epidemiologic and cohort studies identified obesity and T2D as significant risk factors for PDAC development, progression, and metastasis (65,157). In diet-induced obese mouse models, depletion of the endoplasmic reticulum (ER) stress transcription factor CHOP/DDIT3 selectively in β-cells normalized insulin secretion and consequently improved glycemic control (158). Moreover, CHOP depletion specifically in β-cells prevented tumor growth and metastasis in mouse models of PDAC by impacting insulin signaling in hepatocytes and PDAC

cancer cells (75). These studies highlight a causal relationship between ER stress in the endocrine pancreas compartment and tumorigenesis in the exocrine pancreas.

Cellular Mechanisms Driving Cross Talk

The mechanisms that facilitate how the exocrine compartment or components therein influence endocrine growth and function are not well understood. One suggested mechanism is that of mRNA translational control, which has recently been linked to organ development with possible relevance for cross talk. In particular, the mRNA translation factor eukaryotic initiation factor 5A (eIF5A), when in its active "hypusinated" form, was shown to play a role in exocrine pancreas development (159). The hypusination of eIF5A requires the rate-limiting enzyme deoxyhypusine synthase (DHPS) to posttranslationally modify a critical lysine residue, which in turn produces the active form of eIF5A that functions in mRNA translation (160). Mice with a genetic deletion in the embryonic pancreas of either the DHPS enzyme or the translation factor eIF5A demonstrate altered mRNA translation and reduced synthesis of proteins critical for acinar cell differentiation and growth (159). Interestingly, the resultant postnatal phenotype was dramatic exocrine insufficiency but apparently normal endocrine growth and function. Therefore, the question becomes whether it is possible to suffer damage to one compartment in the pancreas without negatively impacting the other over the long term. Perhaps the cellular mechanism that is critical to maintain one compartment also simultaneously can cause damage to the other. These studies suggest that patients initially presenting with exocrine or endocrine disease should have their entire pancreas assessed and followed knowing that there exists risk for pan-pancreatic injury. Moreover, these findings have implications for how we prevent and treat diseases of the pancreas, including diabetes, pancreatitis, and PDAC. For example, given the apparent trophic support that pancreatic acinar cells provide to β-cells, should acinar cells or signals be included as part of β-cell replacement therapy?

Research Gaps and Opportunities

- How exocrine and endocrine cells communicate should be determined. Is the communication due to a physical connection or perhaps mediated by vascular connections? Could insulin reduction mitigate exocrine pancreas disease in general?
- Whether factors secreted from exocrine cells (e.g., pancreatic elastase, extracellular vesicles, or exosomes) act locally (paracrine) or enter the systemic circulation (endocrine) to regulate pancreatic endocrine biology should be identified.
- Whether there exist factors secreted by peri-islet acinar cells that assist in the maintenance of healthy islet cells should be determined.
- The impact of pancreatic fibrosis on endocrine cell viability/function as well as how exocrine-derived digestive enzymes may influence islet cell growth and function should be measured.
- The therapeutic potential of extracellular matrix remodeling in restoring normal exocrine and endocrine homeostasis should be evaluated.
- Infrastructure should be developed to overcome the difficulty in obtaining pancreas tissues from humans in both physiological and pathophysiological states.
- New animal models and tools to address these questions of cross talk should be developed.

CONCLUSION

We are only beginning to understand the complex communication between the exocrine and endocrine compartments of the pancreas. This workshop identified many knowledge gaps and research opportunities that will extend and initiate the studies needed to examine cross talk more critically between various cell types that make up the pancreatic niche. Pursuing these opportunities will advance the understanding of how cross talk impacts normal physiology as well as its role in many disease states.

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