UC San Diego
UC San Diego Previously Published Works

Title

Integrated Physiology of the Exocrine and Endocrine Compartments in Pancreatic Diseases

Permalink

Journal

ISSN

Authors

Mastracci, Teresa L
Apte, Minoti
Amundadottir, Laufey T
et al.

Publication Date

DOI

Peer reviewed

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

Teresa L. Mastracci, PhD[1],[*], **Minoti Apte, PhD**[2], **Laufey T. Amundadottir, PhD**[3], **Alexandra Alvarsson, PhD**[4], **Steven Artandi, MD, PhD**[5], **Melena D. Bellin, MD**[6], **Ernesto Bernal-Mizrachi, PhD**[7], **Alejandro Caicedo, PhD**[8], **Martha Campbell-Thompson, DVM, PhD**[9], **Zobeida Cruz-Monserrate, PhD**[10], **Abdelfattah El Ouaamari, PhD**[11], **Kyle J. Gaulton, PhD**[12], **Andrea Geisz, PhD**[13], **Mark O. Goodarzi, MD, PhD**[14], **Manami Hara, PhD**[15], **Rebecca L. Hull-Meichle, PhD**[16], **Alexander Kleger, MD**[17], **Alison P. Klein, PhD**[18], **Janel L. Kopp, PhD**[19], **Rohit N. Kulkarni, MD, PhD**[20], **Mandar D. Muzumdar, MD**[21], **Anjaparavanda P. Naren, PhD**[22], **Scott A. Oakes, MD**[23], **Søren S. Olesen, MD**[24], **Edward A. Phelps, PhD**[25], **Alvin C. Powers, MD**[26], **Cherie L. Stabler, PhD**[25], **Temel Tirkes, MD**[27], **David C. Whitcomb, MD, PhD**[28], **Dhiraj Yadav, MD**[28], **Jing Yong, PhD**[29], **Norann A. Zaghloul, PhD**[30], **Maike Sander, MD**[31], **Stephen J. Pandol, MD**[32]

[1]Department of Biology, Indiana University–Purdue University Indianapolis, Indianapolis, IN

[2]Faculty of Medicine and Health, University of New South Wales, Sydney, Australia

[3]National Cancer Institute, National Institutes of Health, Rockville, MD

[4]Diabetes, Obesity and Metabolism Institute, Mount Sinai Hospital, New York, NY

[5]Department of Internal Medicine, Stanford University, Stanford, CA

[6]Departments of Pediatrics and Surgery, University of Minnesota Medical School, Minneapolis, MN

[7]Department of Medicine, University of Miami Miller School of Medicine and Miami VA Health Care System, Miami, FL

[8]Department of Medicine, University of Miami, Miami, FL

[9]Department of Pathology, Immunology & Laboratory Medicine, University of Florida, Gainesville, FL

[10]Department of Internal Medicine, The Ohio State University Wexner Medical Center, Columbus, OH

[11]Department of Medicine, Rutgers The State University of New Jersey, New Brunswick, NJ

[12]Department of Pediatrics, University of California San Diego, La Jolla CA

[13]Department of Molecular and Cell Biology, Boston University Henry M. Goldman School of Dental Medicine, Boston, MA

[14]Division of Endocrinology, Diabetes and Metabolism, Cedars-Sinai Medical Center

[*]**Corresponding Author**: Teresa L. Mastracci, Ph.D., Department of Biology, Indiana University–Purdue University Indianapolis, 723 W. Michigan St., SL306, Indianapolis, IN 46202 tmastrac@iu.edu.

[15]Department of Medicine, The University of Chicago, Chicago, IL

[16]Department of Medicine, VA Puget Sound Health Care System and University of Washington, Seattle, WA

[17]Institute of Molecular Oncology and Stem Cell Biology, Ulm University, Ulm, Germany

[18]Department of Pathology and Medicine, Johns Hopkins School of Medicine, Baltimore MD

[19]Department of Cellular & Physiological Sciences, University of British Columbia, Vancouver, Canada

[20]Department of Medicine, Harvard Medical School, Boston MA

[21]Departments of Genetics and Internal Medicine (Oncology), Yale University School of Medicine, New Haven, CT

[22]Department of Medicine, Cedars-Sinai Medical Center, Los Angeles, CA

[23]Department of Pathology, University of Chicago, Chicago, IL

[24]Department of Gastroenterology and Hepatology, Aalborg University Hospital, Aalborg, Denmark

[25]J. Crayton Pruitt Family Department of Biomedical Engineering, University of Florida, Gainesville, FL

[26]Division of Diabetes, Endocrinology, and Metabolism, Vanderbilt University Medical Center and VA Tennessee Valley Healthcare System, Nashville

[27]Department of Radiology and Imaging Sciences, Indiana University School of Medicine, Indianapolis, IN

[28]Department of Medicine, University of Pittsburgh, Pittsburgh, PA

[29]Degenerative Diseases Program, SBP Medical Discovery Institute, La Jolla, CA

[30]National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda MD

[31]Department of Pediatrics and Department of Cellular & Molecular Medicine, University of California San Diego, La Jolla CA

[32]Department of Gastroenterology, Cedars-Sinai Medical Center, Los Angeles, CA

Abstract

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 summarizes the workshop proceedings. The goal of the workshop was to forge connections and identify gaps in knowledge that could guide future research directions. Presentations were segregated into six major themes, including: (a) Pancreas Anatomy and Physiology; (b) Diabetes in the Setting of Exocrine Disease; (c) Metabolic Influences on the Exocrine Pancreas; (d) Genetic Drivers of Pancreatic Diseases; (e) Tools for Integrated Pancreatic Analysis; and (f) Implications

of Exocrine-Endocrine Crosstalk. For each theme, there were multiple presentations followed by panel discussions on specific topics relevant to each area of research; these are summarized herein. 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 the 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.

Keywords

Exocrine pancreas; endocrine pancreas; exocrine-endocrine crosstalk; integrated physiology; interpancreatic communication

Introduction

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 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 inter-dependence, disorders of the endocrine and exocrine pancreas are managed by different pediatric and medical subspecialties (endocrinology and gastroenterology, respectively), which 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 beta cell dysfunction or causing some islet destruction.[4,5] Recognizing these strong connections in both the normal and diseased states, a workshop was organized to explore the integration and crosstalk between the exocrine and endocrine pancreas as well as develop an expanded view of pancreatic development, structure, innervation, blood flow and function. The workshop took place on June 29 and 30, 2022, at the National Institutes of Health (NIH) Natcher Conference Center (Bethesda, MD) hosted by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). 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.

A. New 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. Anecdotal 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. 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 beta cell mass is established[7,8], and for individuals at higher risk of T1D, the variability in beta cell mass may play a role in T1D onset. Beta 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 is 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 (a) functional recordings of endocrine, vascular and immune cells in living human pancreas tissue slices with (b) anatomical studies of islet cytoarchitecture and vasculature, (c) measurements of hormone secretion from pancreas slices and isolated juvenile islets, and (d) transcriptomic studies such as single cell RNA-sequencing (scRNA-seq) 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 exocrine pancreas regionally, not targeting individual islets. Vascularizing the pancreas in this way may allow an entire downstream region of islets and acinar cells to be simultaneously exposed to changes in blood glucose levels, hormones and other circulating factors (e.g. digestive enzymes). 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-vascular connections as well as the physical routes of crosstalk 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 beta cells.[13,14] Studies have shown that male and female mice have difference responses following denervation of the pancreas-projecting sensory neurons that regulate beta cell function and glucose homeostasis. In particular, the positive effects of sensory denervation on glucose tolerance and beta cell function were observed in male but not female mice, indicative of a sex difference in sensory modulation of beta cell activity.[15] The number of pancreatic axonal endings originating from the dorsal root and nodose ganglia were 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.[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 (PCS), play a critical role in organ structure, response to injury, immunity and, under pathologic conditions such as CP and pancreatic cancer, excessive fibrosis.[21] The PSCs are resident cells of the pancreas, found around basolateral aspects of acinar cells and also around and within islets. The PSCs play important roles in health, including (a) regulating extracellular matrix (ECM) turnover; (b) an innate immune function via the expression of toll-like receptors and phagocytic capability; (c) potential function as intermediary cells for cholecystokinin (CCK)-induced acinar enzyme secretion; and (d) 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 PPARγ ligand troglitazone, all trans retinoic acid (ATRA, 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 interleukins 4 and 13.[22] These interleukins drive macrophages to an

M2 phenotype; M2 macrophages secrete growth factors such as TGFβ and PDGF that in turn activate PSCs, thus setting up a feed forward loop. Interestingly, PSCs are present in pancreatic intraepithelial neoplasms (PanIN) and pancreatic ductal adenocarcinoma (PDAC). The 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-tumour 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 (CAF) in cancer stroma; however, PSCs play major non-redundant roles in cancer progression. Consequently, rather than blanket ablation of CAFs, strategic interventions to block specific pathways mediating PSC-cancer interactions is the way forward.

Activated PSCs also reduce insulin secretion from beta cells, an effect that is aggravated by hyperglycemia, but abrogated by glucagon-like peptide-1 (GLP1) agonists, suggesting a role for PSCs in the diabetes associated with CP.[25] The crosstalk between PSCs and PanINs 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 intimate 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 are needed to investigate interaction between endocrine and exocrine systems and how the interconnections between these systems develops from embryonic through postnatal stages.

- Heterogeneity of PSCs in PDAC and CP needs to be investigated in depth to enable targeted and specific therapies to be developed.

- Study approaches will require managing and analyzing large datasets 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 great heterogeneity in disease risk, initiation, severity and progression of disease need to be developed.

B. 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. Pancreatic ductal adenocarcinoma

(PDAC) can also present as diabetes and is discussed elsewhere.[26] Recognizing the knowledge gaps in 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.

Chronic Pancreatitis 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. Whereas CP-related diabetes (CP-D) is often mis-diagnosed as type 2 diabetes (T2D)[27], its recognition has important implications for treatment and monitoring. Patients with CP-D need insulin earlier after diagnosis than typical for T2D, have a five-fold higher risk of severe hypoglycemia compared 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, family history of diabetes) and pancreatitis-related features (e.g. duration of CP, EPI, pancreatic surgery, 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 (PP) and possible incretin hormone dysregulation.[31]

Acute Pancreatitis 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 A1c 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 two-fold greater than age and sex matched individuals, with similar estimates when data are restricted to patients with mild AP.[33] Because AP is six- to ten-fold more common than CP, the burden of diabetes from AP far exceeds that from CP.[27] When compared with T2D, patients with AP-D require insulin more frequently and have suboptimal control of blood sugar levels.[27,34]

The mechanisms leading to AP-D, especially in the context of mild AP, have not been fully identified. Beta 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 may resemble T2D.[36] Emerging data suggest that a subset of patients with recurrent AP and CP

with diabetes have one or more beta cell autoantibodies, suggesting that autoimmunity may play a role in the development of AP-D.[37]

Cystic Fibrosis 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; CF-related diabetes (CFRD) is one 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 less than a 25% likelihood of surviving to 30 years of age compared with 60% of CF patients that 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 beta cell area in patients with CF/CFRD.[44,45] This suggests that mechanisms other than beta cell loss are likely important.

Compared with non-CF, several groups have reported early and widespread inflammation in CF islets, increased immunoreactivity for the proinflammatory cytokine IL-1β[46] and/or increased T-lymphocyte 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 the general population.[53–56] It has been suggested that screening for autoimmunity may be warranted in a specific subset of at-risk CFRD patients.[57]

Exocrine Pancreatic Insufficiency 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

- Investigate to what extent CP-D is a unique disease, versus a subtype of T2D.

- Develop better biomarkers for CP-D diagnosis for use in research and clinical care.

- Define underlying mechanisms of CP-D in order to identify treatment targets to inform much-needed treatment trials for CP-D.

- Study whether pancreatic enzyme replacement therapy in CP-D can improve dysglycemia.

- Define factors associated with short- and long-term risk of AP-D, including morphological features on cross-sectional imaging. Develop models to predict risk of AP-D (clinical, biomarker, imaging).

- Determine 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.

- Develop preventative and therapeutic interventions to reduce the risk of AP-D.

- Define factors other than loss of beta-cell mass that contribute to CFRD, including inflammatory and immunologic contributors.

- Determine the role of loss of islet vascularity in CFRD risk.

- Understand the impact of EPI on endocrine function and islet mass.

C. 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 tumour of the pancreas. The third leading cause of cancer death in the United States is PDAC, 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 Pancreatic Ductal Adenocarcinoma—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 (DIO) model.[66] This diet increases tumour initiation, accelerates tumour 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 obese individuals.

Beta Cell Drivers of Pancreatic Cancer—The role of the beta 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 pro-tumorigenic hormones, including the peptide hormone CCK.[68,69] Transgenic CCK overexpression in beta cells was sufficient to promote acinar cell proliferation and ductal transformation and oncogene-driven tumorigenesis in non-obese mutant Kras-expressing mice.[68] Conversely, beta cell ablation impaired PDAC progression even in non-obese mice, demonstrating that the endocrine pancreas plays a critical role in tumour promotion. Using scRNA-seq analyses of beta cells from obese mice, a role for obesity-induced islet stress and beta cell dysfunction in aberrant pro-tumorigenic hormone expression was demonstrated.[68] Strikingly, lowering blood glucose levels using inhibitors of sodium-glucose co-transporter 2 (SGLT2) improved beta 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.

Effects of Hyperinsulinism on the Exocrine—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 TGF-alpha, an activator of RAS-MAPK 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 could be used to design strategies for primary and secondary prevention.

Decreased Exocrine Mass in Type 1 Diabetes—Studies of islet inflammation (insulitis) in patients with T1D show heterogeneity between pancreatic lobules in terms of loss of islet beta cells and islet number, and types of infiltrating immune cells.[78] Importantly, patients with T1D exhibit reduced pancreas size.[79,80] First-degree relatives (FDR) of patients with T1D also have small pancreas volumes determined by magnetic resonance imaging (MRI) radiology.[81,82] Theories of exocrine pancreas loss in T1D include an exocrine deficiency secondary to beta cell deficiency, combined endocrine and exocrine dysfunctions, and/or an exocrine deficiency that leads to beta cell dysfunction.[83] These data suggest the possibility that the exocrine compartment influences beta cell function, including beta cell susceptibility to autoimmunity in T1D and beta 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 controls 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 beta cell insulin secretion. Finally, subjects with diabetes associated with an exocrine pancreatopathy have decreased pancreas weight or volume with histological findings of increased inter-acinar 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

- Investigate the mechanisms by which obesity and/or fatty pancreas promotes pancreatic cancer in animal models with validation in humans.

- Determine the roles of pancreatic islets and their beta cells on the promotion of pancreatic cancer.

- Determine the potential role of islets and beta cells on inflammatory and immune responses in the exocrine pancreas.

- Understand how insulin causes trypsin activation leading to pancreatic inflammation, which is known to promote tumour initiation in mutant Kras-expressing exocrine pancreas.

- Investigate the roles of the pancreatic vasculature and neural systems in the interplay of exocrine and endocrine functions and disease.

D. 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 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 anti-trypsin 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 come 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 Pancreatic Ductal Adenocarcinoma—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. The GWAS studies of PDAC are in their infancy

compared with other cancers; the latest meta-analysis in European populations (including 9,040 PDAC and 12,496 controls) 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]

Heritability of PDAC 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 penetrant 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 non-coding 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 Gaulton and colleagues reported the largest to-date GWAS of T1D in combination with cell type-specific *cis*-regulatory elements (cCREs) defined using snATAC-seq in pancreas and blood.[109] The study identified enrichment of T1D variants for cCREs active in T cells and beta 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 two hour post-oral glucose tolerance test (OGTT) and T2D, where the T1D risk alleles are protective for T2D.[112,113] Together these results integrating human genetics with large 'omics datasets 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.

- Any 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.

- Need for detailed assessment of personalized risk scores for pancreatic diseases 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 co-culture models that include both exocrine and endocrine cells are needed to better understand risk variant function in the context of the entire pancreas.

E. 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 also 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 assisting our understanding of pancreatic development and function in the healthy and diseased setting, as well as how these tools might be utilized to study of exocrine-endocrine crosstalk.

Magnetic Resonance Imaging Technology—Recent advances are improving the clinical use of MRI with Magnetic Resonance Cholangiopancreatography (MRCP) for the detection and monitoring of CP. The most common cross-sectional imaging tool used to evaluate CP is MRCP. The Cambridge classification[114] is designed to interpret endoscopic retrograde cholangiopancreatography (ERCP) and is still the imaging criterium 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 non-calcific CP can be elusive or delayed when using ductal imaging alone.[117,118] Furthermore, unsatisfactory inter-observer 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] Parenchymal signal changes observed by MRI 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 Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer (CPDPC).[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, 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 (hPSC) to create highly functional organoids. Briefly, a multi-stage differentiation protocol combined with state-of-the-art transcriptomic and proteomic analysis revealed that induction of pluripotent stem cells into pancreatic-duct-like organoids (PDLO) 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 cells (hiPSC)-derived pancreatic progenitors into ductal intermediates and eventually mature duct-like and non-ductal 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. Future studies using this resource include PDLO co-cultures with pancreatic stellate cells to understand epithelial-to-mesenchymal signaling as well as ductal disease modelling.[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 alpha cells, beta 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 beta cells were preserved in diabetic

mice and humans. 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 beta 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 non-endocrine 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

- Establish the involvement of cellular and molecular pathways in human pancreatic tissue by applying multi-omic techniques including advanced microscopic techniques to provide pathophysiologic information needed as a foundation for hypothesis testing.

- Experimental approaches and advanced techniques in whole body imaging are needed to identify and measure contributors to disease in patients with diabetes and exocrine pancreatic disease.

- Expand the use of *in vitro* systems to culture human donor pancreatic tissue and answer pointed questions about structural organization of the pancreas as well as cellular interactions.

- Further improve current hPSC pancreas models to develop an *in vivo*-mimicking cell model of the human pancreas amenable to gene editing for hypothesis testing.

- Integrate observations from *in vitro* cultures and *in vivo* animal models to determine the similarities and differences between human disease states and observations in animal models.

F. Implications of Exocrine-Endocrine Crosstalk

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 crosstalk 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 crosstalk influences development, function, and disease of the pancreas.

Lessons Learned from Cystic Fibrosis—Mutations in the cystic fibrosis 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 section B, 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 beta 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, which will be invaluable in modeling these processes, wherein patient-derived pancreatic ductal epithelial cells (PDECs) and islet cells are co-cultured in a novel microfluidic devise (pancreas-on-a chip). Resultantly, 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 crosstalk 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 (MODY8), mutant Carboxy Ester Lipase (CEL) protein was shown to be internalized leading to beta cell secretory dysfunction.[155] Intervening in this exocrine-endocrine crosstalk 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 beta cell proliferation, thus illustrating the potential opportunity to exploit communication between the pancreatic compartments to resolve aspects of disease.

Exocrine-endocrine crosstalk 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 beta cells normalized insulin secretion and consequently improved glycemic control.[158] Moreover, CHOP depletion specifically in beta 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 Crosstalk—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 crosstalk. 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 post-translationally 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 is it 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 would 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 beta cells, should acinar cells or signals be included as part of beta cell replacement therapy?

Research Gaps and Opportunities

- Determine how exocrine and endocrine cells communicate. Is the communication due to a physical connection or perhaps mediated by vascular connections? Could insulin reduction mitigate exocrine pancreas disease in general?

- Identify 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.

- Determine whether there exist factors secreted by peri-islet acinar cells that assist in the maintenance of healthy islets cells.

- Measure 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.

- Evaluate the therapeutic potential of extracellular matrix remodeling in restoring normal exocrine and endocrine homeostasis.

- Develop infrastructure to overcome the difficulty in obtaining pancreas tissues from humans in both physiological and pathophysiological states.

- Develop new animal models and tools to address these questions of crosstalk.

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 crosstalk more critically between various cell types that make up the pancreatic niche. Pursuing these opportunities will advance the understanding for how crosstalk impacts normal physiology as well as its role in many disease states.

Funding

Conflict of Interest

MDB has received research funding from Viacyte, Dexcom and serves on Advisory boards/DSMB membership for Insulet, Vertex, Ariel Precision Medicine. MOG has served on an advisory board for Nestle Health Science. KJG is a consultant for Genentech and stockholder of Neurocrine Biosciences. SAO is a cofounder and consultant at OptiKira., L.L.C. (Cleveland, OH). All other authors declare no conflict of interest.

List of Abbreviations

AP   acute pancreatitis

AP-D   acute pancreatitis-related diabetes

CAF	cancer associated fibroblast
CCK	cholecystokinin
cCRE	*cis*-regulatory element
CEL	Carboxy Ester Lipase
CF	cystic fibrosis
CFRD	cystic fibrosis-related diabetes
CFTR	cystic fibrosis transmembrane conductance regulator
CP	chronic pancreatitis
CP-D	chronic pancreatitis-related diabetes
CPDPC	Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer
CTRC	chymotrypsin C
CTSB	cathepsin B
DHPS	deoxyhypusine synthase
ECM	extracellular matrix
eIF5A	eukaryotic initiation factor 5A
EPI	exocrine pancreatic insufficiency
ER	endoplasmic reticulum
ERCP	endoscopic retrograde cholangiopancreatography
FDR	first-degree relatives
GWAS	genome-wide association studies
hiPSC	human induced pluripotent stem cell
hPSC	human pluripotent stem cells
LCN2	lipocalin 2
MODY	Maturity Onset Diabetes of the Young
MRI	magnetic resonance imaging
MRCP	Magnetic Resonance Cholangiopancreatography
NIDDK	National Institute of Diabetes and Digestive and Kidney Diseases
NIH	National Institutes of Health

OGTT	oral glucose tolerance test
PanIN	pancreatic intraepithelial neoplasm
PCS	pancreatic stellate cells
PDAC	pancreatic ductal adenocarcinoma
PDEC	pancreatic ductal epithelial cell
PDLO	pancreatic-duct-like organoids
PRSS1	trypsinogen
scRNA-seq	single cell RNA-sequencing
SGLT2	sodium-glucose co-transporter 2
SPINK1	serine protease inhibitor Kazal type 1
T1D	type 1 diabetes
T2D	type 2 diabetes

References

1. Overton DL & Mastracci TL Exocrine-Endocrine Crosstalk: The Influence of Pancreatic Cellular Communications on Organ Growth, Function and Disease. Front Endocrinol 13, 904004 (2022).

2. Bellin MD et al. Patient and Disease Characteristics Associated With the Presence of Diabetes Mellitus in Adults With Chronic Pancreatitis in the United States. Am J Gastroenterol 112, 1457–1465 (2017). [PubMed: 28741615]

3. Zhan W et al. Low serum trypsinogen levels in chronic pancreatitis: Correlation with parenchymal loss, exocrine pancreatic insufficiency, and diabetes but not CT-based cambridge severity scores for fibrosis. Pancreatology 20, 1368–1378 (2020). [PubMed: 32967795]

4. Bharmal SH et al. Trajectories of glycaemia following acute pancreatitis: a prospective longitudinal cohort study with 24 months follow-up. J Gastroenterol 55, 775–788 (2020). [PubMed: 32494905]

5. Goodarzi MO et al. Genetic Risk Score in Diabetes Associated With Chronic Pancreatitis Versus Type 2 Diabetes Mellitus. Clin Transl Gastroenterol 10, e00057 (2019). [PubMed: 31232720]

6. Pan FC & Wright C Pancreas organogenesis: from bud to plexus to gland. Dev Dyn 240, 530–65 (2011). [PubMed: 21337462]

7. Meier JJ et al. β-cell development and turnover during prenatal life in humans. European Journal of Endocrinology 162, 559–568 (2010). [PubMed: 20022941]

8. Chen C, Cohrs CM, Stertmann J, Bozsak R & Speier S Human beta cell mass and function in diabetes: Recent advances in knowledge and technologies to understand disease pathogenesis. Molecular Metabolism 6, 943–957 (2017). [PubMed: 28951820]

9. Ziegler AG et al. Seroconversion to multiple islet autoantibodies and risk of progression to diabetes in children. JAMA 309, 2473–2479 (2013). [PubMed: 23780460]

10. Fowler JL et al. Three-Dimensional Analysis of the Human Pancreas. Endocrinology 159, 1393–1400 (2018). [PubMed: 29390052]

11. Dybala MP et al. Integrated Pancreatic Blood Flow: Bidirectional Microcirculation Between Endocrine and Exocrine Pancreas. Diabetes 69, 1439–1450 (2020). [PubMed: 32198213]

12. Dybala MP & Hara M In Vivo and In Situ Approach to Study Islet Microcirculation: A Mini-Review. Front Endocrinol (Lausanne) 12, 602620 (2021). [PubMed: 34040578]

13. Ahrén B Autonomic regulation of islet hormone secretion--implications for health and disease. Diabetologia 43, 393–410 (2000). [PubMed: 10819232]

14. Ahrén B & Holst JJ The cephalic insulin response to meal ingestion in humans is dependent on both cholinergic and noncholinergic mechanisms and is important for postprandial glycemia. Diabetes 50, 1030–1038 (2001). [PubMed: 11334405]

15. Bou Karam J et al. TRPV1 neurons regulate β-cell function in a sex-dependent manner. Mol Metab 18, 60–67 (2018). [PubMed: 30473098]

16. McEwan S et al. Deconstructing the origins of sexual dimorphism in sensory modulation of pancreatic β cells. Mol Metab 53, 101260 (2021). [PubMed: 34023484]

17. Arslan AA et al. Anthropometric measures, body mass index, and pancreatic cancer: a pooled analysis from the Pancreatic Cancer Cohort Consortium (PanScan). Arch Intern Med 170, 791–802 (2010). [PubMed: 20458087]

18. Mauvais-Jarvis F Sex differences in metabolic homeostasis, diabetes, and obesity. Biol Sex Differ 6, 14 (2015). [PubMed: 26339468]

19. Mauvais-Jarvis F Gender differences in glucose homeostasis and diabetes. Physiol Behav 187, 20–23 (2018). [PubMed: 28843891]

20. Petersen GM et al. Pancreatic cancer genetic epidemiology consortium. Cancer Epidemiol Biomarkers Prev 15, 704–710 (2006). [PubMed: 16614112]

21. Pang TCY, Wilson JS & Apte MV Pancreatic stellate cells: what's new? Curr Opin Gastroenterol 33, 366–373 (2017). [PubMed: 28590306]

22. Xue J et al. Alternatively activated macrophages promote pancreatic fibrosis in chronic pancreatitis. Nat Commun 6, 7158 (2015). [PubMed: 25981357]

23. Pothula SP, Pirola RC, Wilson JS & Apte MV Pancreatic stellate cells: Aiding and abetting pancreatic cancer progression. Pancreatology 20, 409–418 (2020). [PubMed: 31928917]

24. Helms EJ et al. Mesenchymal Lineage Heterogeneity Underlies Nonredundant Functions of Pancreatic Cancer-Associated Fibroblasts. Cancer Discov 12, 484–501 (2022). [PubMed: 34548310]

25. Yang Y, Kim J-W, Park H-S, Lee E-Y & Yoon K-H Pancreatic stellate cells in the islets as a novel target to preserve the pancreatic β-cell mass and function. J Diabetes Investig 11, 268–280 (2020).

26. Chari ST et al. Early detection of sporadic pancreatic cancer: summative review. Pancreas 44, 693–712 (2015). [PubMed: 25931254]

27. Woodmansey C et al. Incidence, Demographics, and Clinical Characteristics of Diabetes of the Exocrine Pancreas (Type 3c): A Retrospective Cohort Study. Diabetes Care 40, 1486–1493 (2017). [PubMed: 28860126]

28. Olesen SS, Viggers R, Drewes AM, Vestergaard P & Jensen MH Risk of Major Adverse Cardiovascular Events, Severe Hypoglycemia, and All-Cause Mortality in Postpancreatitis Diabetes Mellitus Versus Type 2 Diabetes: A Nationwide Population-Based Cohort Study. Diabetes Care 45, 1326–1334 (2022). [PubMed: 35312752]

29. Cho J, Scragg R & Petrov MS Risk of Mortality and Hospitalization After Post-Pancreatitis Diabetes Mellitus vs Type 2 Diabetes Mellitus: A Population-Based Matched Cohort Study. Am J Gastroenterol 114, 804–812 (2019). [PubMed: 31021833]

30. Goodarzi MO, Petrov MS, Andersen DK & Hart PA Diabetes in chronic pancreatitis: risk factors and natural history. Curr Opin Gastroenterol 37, 526–531 (2021). [PubMed: 34074860]

31. Hart PA et al. Evaluation of a Mixed Meal Test for Diagnosis and Characterization of PancrEaTogEniC DiabeTes Secondary to Pancreatic Cancer and Chronic Pancreatitis: Rationale and Methodology for the DETECT Study From the Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Pancreas 47, 1239–1243 (2018). [PubMed: 30325863]

32. Das SLM et al. Newly diagnosed diabetes mellitus after acute pancreatitis: a systematic review and meta-analysis. Gut 63, 818–831 (2014). [PubMed: 23929695]

33. Shen H-N, Yang C-C, Chang Y-H, Lu C-L & Li C-Y Risk of Diabetes Mellitus after First-Attack Acute Pancreatitis: A National Population-Based Study. Am J Gastroenterol 110, 1698–1706 (2015). [PubMed: 26526084]

34. Viggers R et al. Glucose-Lowering Therapy in Patients With Postpancreatitis Diabetes Mellitus: A Nationwide Population-Based Cohort Study. Diabetes Care 44, 2045–2052 (2021). [PubMed: 34362812]

35. Malecka-Panas E, Gasiorowska A, Kropiwnicka A, Zlobinska A & Drzewoski J Endocrine pancreatic function in patients after acute pancreatitis. Hepatogastroenterology 49, 1707–1712 (2002). [PubMed: 12397772]

36. Pendharkar SA, Singh RG, Bharmal SH, Drury M & Petrov MS Pancreatic Hormone Responses to Mixed Meal Test in New-onset Prediabetes/Diabetes After Non-necrotizing Acute Pancreatitis. J Clin Gastroenterol 54, e11–e20 (2020). [PubMed: 30480566]

37. Yadav D et al. Autoimmunity May Explain Diabetes in a Subset of Patients With Recurrent Acute and Chronic Pancreatitis: A Pilot Study. Clin Gastroenterol Hepatol S1542–3565(21)01223–4 (2021) doi:10.1016/j.cgh.2021.11.011.

38. Moran A et al. Cystic fibrosis-related diabetes: current trends in prevalence, incidence, and mortality. Diabetes Care 32, 1626–1631 (2009). [PubMed: 19542209]

39. Norris AW et al. Survival in a bad neighborhood: pancreatic islets in cystic fibrosis. J Endocrinol JOE-18–0468.R1 (2019) doi:10.1530/JOE-18-0468.

40. Imrie JR, Fagan DG & Sturgess JM Quantitative evaluation of the development of the exocrine pancreas in cystic fibrosis and control infants. Am J Pathol 95, 697–708 (1979). [PubMed: 453330]

41. Merjaneh L, He Q, Long Q, Phillips LS & Stecenko AA Disposition index identifies defective beta-cell function in cystic fibrosis subjects with normal glucose tolerance. J Cyst Fibros 14, 135–141 (2015). [PubMed: 24998161]

42. Yi Y et al. Abnormal Glucose Tolerance in Infants and Young Children with Cystic Fibrosis. Am J Respir Crit Care Med 194, 974–980 (2016). [PubMed: 27447840]

43. Sheikh S et al. Reduced β-Cell Secretory Capacity in Pancreatic-Insufficient, but Not Pancreatic-Sufficient, Cystic Fibrosis Despite Normal Glucose Tolerance. Diabetes 66, 134–144 (2017). [PubMed: 27495225]

44. Gibson-Corley KN, Meyerholz DK & Engelhardt JF Pancreatic pathophysiology in cystic fibrosis. J Pathol 238, 311–320 (2016). [PubMed: 26365583]

45. Hart NJ et al. Cystic fibrosis-related diabetes is caused by islet loss and inflammation. JCI Insight 3, 98240 (2018). [PubMed: 29669939]

46. Hull RL et al. Islet Interleukin-1β Immunoreactivity Is an Early Feature of Cystic Fibrosis That May Contribute to β-Cell Failure. Diabetes Care 41, 823–830 (2018). [PubMed: 29437698]

47. Bogdani M et al. Structural abnormalities in islets from very young children with cystic fibrosis may contribute to cystic fibrosis-related diabetes. Sci Rep 7, 17231 (2017). [PubMed: 29222447]

48. Peiris H, Bonder CS, Coates PTH, Keating DJ & Jessup CF The β-cell/EC axis: how do islet cells talk to each other? Diabetes 63, 3–11 (2014). [PubMed: 24357688]

49. Hogan MF & Hull RL The islet endothelial cell: a novel contributor to beta cell secretory dysfunction in diabetes. Diabetologia 60, 952–959 (2017). [PubMed: 28396983]

50. Hogan MF et al. Markers of Islet Endothelial Dysfunction Occur in Male B6.BKS(D)-Leprdb/J Mice and May Contribute to Reduced Insulin Release. Endocrinology 158, 293–303 (2017). [PubMed: 27870582]

51. Nackiewicz D et al. Islet Macrophages Shift to a Reparative State following Pancreatic Beta-Cell Death and Are a Major Source of Islet Insulin-like Growth Factor-1. iScience 23, 100775 (2020). [PubMed: 31962237]

52. 13-OR: Cystic Fibrosis Donors Exhibit Striking Decrease in Pancreatic Islet and Exocrine Capillaries. https://en.x-mol.com/paper/article/1543666895735066624.

53. Minicucci L et al. Beta-cell autoantibodies and diabetes mellitus family history in cystic fibrosis. J Pediatr Endocrinol Metab 18, 755–760 (2005). [PubMed: 16200841]

54. Bizzarri C et al. ZnT8 antibodies in patients with cystic fibrosis: an expression of secondary beta-cell damage? J Cyst Fibros 12, 803–805 (2013). [PubMed: 23535193]

55. Gottlieb PA et al. No relation between cystic fibrosis-related diabetes and type 1 diabetes autoimmunity. Diabetes Care 35, e57 (2012). [PubMed: 22826450]

56. Konrad K et al. Does β-Cell Autoimmunity Play a Role in Cystic Fibrosis-Related Diabetes? Analysis Based on the German/Austrian Diabetes Patienten Verlaufsdokumentation Registry. Diabetes Care 39, 1338–1344 (2016). [PubMed: 27271187]

57. Kim GJ & Merjaneh L Pediatric Case Series of Cystic Fibrosis, Diabetes, and Islet Cell Autoimmunity. Clin Diabetes 36, 331–333 (2018). [PubMed: 30364027]

58. Hardt PD et al. High prevalence of steatorrhea in 101 diabetic patients likely to suffer from exocrine pancreatic insufficiency according to low fecal elastase 1 concentrations: a prospective multicenter study. Dig Dis Sci 48, 1688–1692 (2003). [PubMed: 14560984]

59. Radlinger B, Ramoser G & Kaser S Exocrine Pancreatic Insufficiency in Type 1 and Type 2 Diabetes. Curr Diab Rep 20, 18 (2020). [PubMed: 32239341]

60. Siegel RL, Miller KD, Fuchs HE & Jemal A Cancer statistics, 2022. CA Cancer J Clin 72, 7–33 (2022). [PubMed: 35020204]

61. Ogden CL et al. Trends in Obesity Prevalence by Race and Hispanic Origin-1999–2000 to 2017–2018. JAMA 324, 1208–1210 (2020). [PubMed: 32857101]

62. Blüher M Obesity: global epidemiology and pathogenesis. Nat Rev Endocrinol 15, 288–298 (2019). [PubMed: 30814686]

63. Yuan C et al. Prediagnostic body mass index and pancreatic cancer survival. J Clin Oncol 31, 4229–4234 (2013). [PubMed: 24145341]

64. Larsson SC, Orsini N & Wolk A Body mass index and pancreatic cancer risk: A meta-analysis of prospective studies. Int J Cancer 120, 1993–1998 (2007). [PubMed: 17266034]

65. Klein AP Pancreatic cancer epidemiology: understanding the role of lifestyle and inherited risk factors. Nat Rev Gastroenterol Hepatol 18, 493–502 (2021). [PubMed: 34002083]

66. Dawson DW et al. High-fat, high-calorie diet promotes early pancreatic neoplasia in the conditional KrasG12D mouse model. Cancer Prev Res (Phila) 6, 1064–1073 (2013). [PubMed: 23943783]

67. Badi N & Cruz-Monserrate Z Murine Model of Obesity-Induced Cancer. Methods Mol Biol 2435, 195–201 (2022). [PubMed: 34993948]

68. Chung KM et al. Endocrine-Exocrine Signaling Drives Obesity-Associated Pancreatic Ductal Adenocarcinoma. Cell 181, 832–847.e18 (2020). [PubMed: 32304665]

69. Egozi A, Bahar Halpern K, Farack L, Rotem H & Itzkovitz S Zonation of Pancreatic Acinar Cells in Diabetic Mice. Cell Rep 32, 108043 (2020). [PubMed: 32814046]

70. Calle EE, Rodriguez C, Walker-Thurmond K & Thun MJ Overweight, obesity, and mortality from cancer in a prospectively studied cohort of U.S. adults. N Engl J Med 348, 1625–1638 (2003). [PubMed: 12711737]

71. Zhang AMY, Wellberg EA, Kopp JL & Johnson JD Hyperinsulinemia in Obesity, Inflammation, and Cancer. Diabetes Metab J 45, 285–311 (2021). [PubMed: 33775061]

72. Mehran AE et al. Hyperinsulinemia drives diet-induced obesity independently of brain insulin production. Cell Metab 16, 723–737 (2012). [PubMed: 23217255]

73. Templeman NM et al. Reduced Circulating Insulin Enhances Insulin Sensitivity in Old Mice and Extends Lifespan. Cell Rep 20, 451–463 (2017). [PubMed: 28700945]

74. Zhang AMY et al. Endogenous Hyperinsulinemia Contributes to Pancreatic Cancer Development. Cell Metab 30, 403–404 (2019). [PubMed: 31378465]

75. Zhang AMY et al. Effects of hyperinsulinemia on pancreatic cancer development and the immune microenvironment revealed through single-cell transcriptomics. Cancer Metab 10, 5 (2022). [PubMed: 35189981]

76. Zhang AMY et al. Insulin receptors in pancreatic acinar cells contribute to KrasG12D-driven cancer initiation in the context of diet-induced obesity. 2022.05.06.490845 Preprint at 10.1101/2022.05.06.490845 (2022).

77. Zhang AMY et al. Hyperinsulinemia acts through acinar cell insulin receptors to drive obesity-associated pancreatic cancer initiation by promoting digestive enzyme production and inflammation. 2022.05.06.490845 Preprint at 10.1101/2022.05.06.490845 (2022).

78. Campbell-Thompson M et al. Insulitis and β-Cell Mass in the Natural History of Type 1 Diabetes. Diabetes 65, 719–731 (2016). [PubMed: 26581594]

79. Campbell-Thompson ML et al. The influence of type 1 diabetes on pancreatic weight. Diabetologia 59, 217–221 (2016). [PubMed: 26358584]

80. Campbell-Thompson M, Wasserfall C, Montgomery EL, Atkinson MA & Kaddis JS Pancreas organ weight in individuals with disease-associated autoantibodies at risk for type 1 diabetes. JAMA 308, 2337–2339 (2012).

81. Campbell-Thompson ML et al. Relative Pancreas Volume Is Reduced in First-Degree Relatives of Patients With Type 1 Diabetes. Diabetes Care 42, 281–287 (2019). [PubMed: 30552130]

82. Virostko J et al. Pancreas Volume Declines During the First Year After Diagnosis of Type 1 Diabetes and Exhibits Altered Diffusion at Disease Onset. Diabetes Care 42, 248–257 (2019). [PubMed: 30552135]

83. Wright JJ et al. Decreased pancreatic acinar cell number in type 1 diabetes. Diabetologia 63, 1418–1423 (2020). [PubMed: 32388592]

84. Canzano JS et al. Islet Microvasculature Alterations With Loss of Beta-cells in Patients With Type 1 Diabetes. J Histochem Cytochem 67, 41–52 (2019). [PubMed: 29771178]

85. Tang S-C, Jessup CF & Campbell-Thompson M The Role of Accessory Cells in Islet Homeostasis. Curr Diab Rep 18, 117 (2018). [PubMed: 30267158]

86. Campbell-Thompson M et al. Islet sympathetic innervation and islet neuropathology in patients with type 1 diabetes. Sci Rep 11, 6562 (2021). [PubMed: 33753784]

87. Rodriguez-Calvo T, Ekwall O, Amirian N, Zapardiel-Gonzalo J & von Herrath MG Increased immune cell infiltration of the exocrine pancreas: a possible contribution to the pathogenesis of type 1 diabetes. Diabetes 63, 3880–3890 (2014). [PubMed: 24947367]

88. Vecchio F, Messina G, Giovenzana A & Petrelli A New Evidence of Exocrine Pancreatopathy in Pre-symptomatic and Symptomatic Type 1 Diabetes. Curr Diab Rep 19, 92 (2019). [PubMed: 31471779]

89. Mohapatra S et al. Diabetes Mellitus Is Associated With an Exocrine Pancreatopathy: Conclusions From a Review of Literature. Pancreas 45, 1104–1110 (2016). [PubMed: 26918874]

90. Hegyi E & Sahin-Tóth M Genetic Risk in Chronic Pancreatitis: The Trypsin-Dependent Pathway. Dig Dis Sci 62, 1692–1701 (2017). [PubMed: 28536777]

91. Mayerle J et al. Genetics, Cell Biology, and Pathophysiology of Pancreatitis. Gastroenterology 156, 1951–1968.e1 (2019). [PubMed: 30660731]

92. van Acker GJD, Perides G & Steer ML Co-localization hypothesis: a mechanism for the intrapancreatic activation of digestive enzymes during the early phases of acute pancreatitis. World J Gastroenterol 12, 1985–1990 (2006). [PubMed: 16610045]

93. Halangk W et al. Role of cathepsin B in intracellular trypsinogen activation and the onset of acute pancreatitis. J Clin Invest 106, 773–781 (2000). [PubMed: 10995788]

94. Geisz A & Sahin-Tóth M A preclinical model of chronic pancreatitis driven by trypsinogen autoactivation. Nat Commun 9, 5033 (2018). [PubMed: 30487519]

95. Jancsó Z & Sahin-Tóth M Mutation That Promotes Activation of Trypsinogen Increases Severity of Secretagogue-Induced Pancreatitis in Mice. Gastroenterology 158, 1083–1094 (2020). [PubMed: 31751559]

96. Demcsák A & Sahin-Tóth M Rate of Autoactivation Determines Pancreatitis Phenotype in Trypsinogen Mutant Mice. Gastroenterology 163, 761–763 (2022). [PubMed: 35667407]

97. Klein AP et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 64, 2634–2638 (2004). [PubMed: 15059921]

98. McWilliams RR, Rabe KG, Olswold C, De Andrade M & Petersen GM Risk of malignancy in first-degree relatives of patients with pancreatic carcinoma. Cancer 104, 388–394 (2005). [PubMed: 15912495]

99. Roberts NJ et al. Whole Genome Sequencing Defines the Genetic Heterogeneity of Familial Pancreatic Cancer. Cancer Discov 6, 166–175 (2016). [PubMed: 26658419]

100. Amundadottir LT Pancreatic Cancer Genetics. Int J Biol Sci 12, 314–325 (2016). [PubMed: 26929738]

101. Lowery MA et al. Prospective Evaluation of Germline Alterations in Patients With Exocrine Pancreatic Neoplasms. J Natl Cancer Inst 110, 1067–1074 (2018). [PubMed: 29506128]

102. Hu C et al. Association Between Inherited Germline Mutations in Cancer Predisposition Genes and Risk of Pancreatic Cancer. JAMA 319, 2401–2409 (2018). [PubMed: 29922827]

103. Klein AP et al. Genome-wide meta-analysis identifies five new susceptibility loci for pancreatic cancer. Nat Commun 9, 556 (2018). [PubMed: 29422604]

104. Lin Y et al. Genome-wide association meta-analysis identifies GP2 gene risk variants for pancreatic cancer. Nat Commun 11, 3175 (2020). [PubMed: 32581250]

105. Wu C et al. Genome-wide association study identifies five loci associated with susceptibility to pancreatic cancer in Chinese populations. Nat Genet 44, 62–66 (2011). [PubMed: 22158540]

106. Chen F et al. Analysis of Heritability and Genetic Architecture of Pancreatic Cancer: A PanC4 Study. Cancer Epidemiol Biomarkers Prev 28, 1238–1245 (2019). [PubMed: 31015203]

107. Lichtenstein P et al. Environmental and heritable factors in the causation of cancer--analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 343, 78–85 (2000). [PubMed: 10891514]

108. Robertson CC et al. Fine-mapping, trans-ancestral and genomic analyses identify causal variants, cells, genes and drug targets for type 1 diabetes. Nat Genet 53, 962–971 (2021). [PubMed: 34127860]

109. Chiou J et al. Interpreting type 1 diabetes risk with genetics and single-cell epigenomics. Nature 594, 398–402 (2021). [PubMed: 34012112]

110. Chiou J et al. Single-cell chromatin accessibility identifies pancreatic islet cell type- and state-specific regulatory programs of diabetes risk. Nat Genet 53, 455–466 (2021). [PubMed: 33795864]

111. Ng NHJ et al. Tissue-Specific Alteration of Metabolic Pathways Influences Glycemic Regulation. 790618 Preprint at 10.1101/790618 (2019).

112. Mahajan A et al. Fine-mapping type 2 diabetes loci to single-variant resolution using high-density imputation and islet-specific epigenome maps. Nat Genet 50, 1505–1513 (2018). [PubMed: 30297969]

113. Chen J et al. The trans-ancestral genomic architecture of glycemic traits. Nat Genet 53, 840–860 (2021). [PubMed: 34059833]

114. Axon AT et al. Pancreatography in chronic pancreatitis: international definitions. Gut 25, 1107–1112 (1984). [PubMed: 6479687]

115. Tang X et al. Image-Based Machine Learning Algorithms for Disease Characterization in the Human Type 1 Diabetes Pancreas. Am J Pathol 191, 454–462 (2021). [PubMed: 33307036]

116. Barreto SG, Carati CJ, Toouli J & Saccone GTP The islet-acinar axis of the pancreas: more than just insulin. Am J Physiol Gastrointest Liver Physiol 299, G10–22 (2010). [PubMed: 20395539]

117. Tirkes T et al. Detection of exocrine dysfunction by MRI in patients with early chronic pancreatitis. Abdom Radiol (NY) 42, 544–551 (2017). [PubMed: 27660281]

118. Balci NC, Alkaade S, Magas L, Momtahen AJ & Burton FR Suspected chronic pancreatitis with normal MRCP: findings on MRI in correlation with secretin MRCP. J Magn Reson Imaging 27, 125–131 (2008). [PubMed: 18058927]

119. Swensson J et al. Is Cambridge scoring in chronic pancreatitis the same using ERCP and MRCP?: A need for revision of standards. Abdom Radiol (NY) 46, 647–654 (2021). [PubMed: 32740862]

120. Tirkes T et al. Inter-observer variability of radiologists for Cambridge classification of chronic pancreatitis using CT and MRCP: results from a large multi-center study. Abdom Radiol (NY) 45, 1481–1487 (2020). [PubMed: 32285180]

121. Tirkes T et al. T1 mapping for diagnosis of mild chronic pancreatitis. J Magn Reson Imaging 45, 1171–1176 (2017). [PubMed: 27519287]

122. Tirkes T et al. Quantitative MR Evaluation of Chronic Pancreatitis: Extracellular Volume Fraction and MR Relaxometry. AJR Am J Roentgenol 210, 533–542 (2018). [PubMed: 29336598]

123. Winston CB, Mitchell DG, Outwater EK & Ehrlich SM Pancreatic signal intensity on T1-weighted fat saturation MR images: clinical correlation. J Magn Reson Imaging 5, 267–271 (1995). [PubMed: 7633102]

124. Balci NC et al. MRI and S-MRCP findings in patients with suspected chronic pancreatitis: correlation with endoscopic pancreatic function testing (ePFT). J Magn Reson Imaging 31, 601–606 (2010). [PubMed: 20187202]

125. Frøkjær JB et al. Guidelines for the Diagnostic Cross Sectional Imaging and Severity Scoring of Chronic Pancreatitis. Pancreatology 18, 764–773 (2018). [PubMed: 30177434]

126. Tirkes T et al. Reporting Standards for Chronic Pancreatitis by Using CT, MRI, and MR Cholangiopancreatography: The Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer. Radiology 290, 207–215 (2019). [PubMed: 30325281]

127. Steinkohl E et al. Progression of parenchymal and ductal findings in patients with chronic pancreatitis: A 4-year follow-up MRI study. Eur J Radiol 125, 108868 (2020). [PubMed: 32070871]

128. Atkinson MA, Campbell-Thompson M, Kusmartseva I & Kaestner KH Organisation of the human pancreas in health and in diabetes. Diabetologia 63, 1966–1973 (2020). [PubMed: 32894306]

129. Serrano J et al. Consortium for the Study of Chronic Pancreatitis, Diabetes, and Pancreatic Cancer: From Concept to Reality. Pancreas 47, 1208–1212 (2018). [PubMed: 30325859]

130. Tirkes T et al. T1 signal intensity ratio of the pancreas as an imaging biomarker for the staging of chronic pancreatitis. Abdom Radiol (NY) 47, 3507–3519 (2022). [PubMed: 35857066]

131. Tirkes T et al. Quantitative MRI of chronic pancreatitis: results from a multi-institutional prospective study, magnetic resonance imaging as a non-invasive method for assessment of pancreatic fibrosis (MINIMAP). Abdom Radiol (NY) 47, 3792–3805 (2022). [PubMed: 36038644]

132. Breunig M et al. Modeling plasticity and dysplasia of pancreatic ductal organoids derived from human pluripotent stem cells. Cell Stem Cell 28, 1105–1124.e19 (2021). [PubMed: 33915078]

133. Breunig M et al. Differentiation of human pluripotent stem cells into pancreatic duct-like organoids. STAR Protoc 2, 100913 (2021). [PubMed: 34917972]

134. Hohwieler M et al. Human pluripotent stem cell-derived acinar/ductal organoids generate human pancreas upon orthotopic transplantation and allow disease modelling. Gut 66, 473–486 (2017). [PubMed: 27633923]

135. Wiedenmann S et al. Single-cell-resolved differentiation of human induced pluripotent stem cells into pancreatic duct-like organoids on a microwell chip. Nat Biomed Eng 5, 897–913 (2021). [PubMed: 34239116]

136. Merkle J et al. CDKN2A-Mutated Pancreatic Ductal Organoids from Induced Pluripotent Stem Cells to Model a Cancer Predisposition Syndrome. Cancers (Basel) 13, 5139 (2021). [PubMed: 34680288]

137. Alvarsson A et al. Optical Clearing and 3D Analysis Optimized for Mouse and Human Pancreata. Bio Protoc 11, e4103 (2021).

138. Gloyn AL et al. Every islet matters: improving the impact of human islet research. Nat Metab 4, 970–977 (2022). [PubMed: 35953581]

139. Rupnik M The physiology of rodent beta-cells in pancreas slices. Acta Physiol (Oxf) 195, 123–138 (2009). [PubMed: 18983446]

140. Almaça J, Caicedo A & Landsman L Beta cell dysfunction in diabetes: the islet microenvironment as an unusual suspect. Diabetologia 63, 2076–2085 (2020). [PubMed: 32894318]

141. Almaça J, Weitz J, Rodriguez-Diaz R, Pereira E & Caicedo A The Pericyte of the Pancreatic Islet Regulates Capillary Diameter and Local Blood Flow. Cell Metab 27, 630–644.e4 (2018). [PubMed: 29514070]

142. Gál E et al. A Novel in situ Approach to Studying Pancreatic Ducts in Mice. Front Physiol 10, 938 (2019). [PubMed: 31396104]

143. Liang T et al. Ex vivo human pancreatic slice preparations offer a valuable model for studying pancreatic exocrine biology. J Biol Chem 292, 5957–5969 (2017). [PubMed: 28242761]

144. Cottle L et al. Structural and functional polarisation of human pancreatic beta cells in islets from organ donors with and without type 2 diabetes. Diabetologia 64, 618–629 (2021). [PubMed: 33399909]

145. Huber MK et al. Observing Islet Function and Islet-Immune Cell Interactions in Live Pancreatic Tissue Slices. J Vis Exp (2021) doi:10.3791/62207.

146. Weitz JR et al. Secretory Functions of Macrophages in the Human Pancreatic Islet Are Regulated by Endogenous Purinergic Signaling. Diabetes 69, 1206–1218 (2020). [PubMed: 32245801]

147. Weitz JR et al. Mouse pancreatic islet macrophages use locally released ATP to monitor beta cell activity. Diabetologia 61, 182–192 (2018). [PubMed: 28884198]

148. Panzer JK et al. Pancreas tissue slices from organ donors enable in situ analysis of type 1 diabetes pathogenesis. JCI Insight 5, 134525 (2020). [PubMed: 32324170]

149. Dolenšek J et al. Membrane Potential and Calcium Dynamics in Beta Cells from Mouse Pancreas Tissue Slices: Theory, Experimentation, and Analysis. Sensors (Basel) 15, 27393–27419 (2015). [PubMed: 26516866]

150. Dolenšek J, Stožer A, Skelin Klemen M, Miller EW & Slak Rupnik M The relationship between membrane potential and calcium dynamics in glucose-stimulated beta cell syncytium in acute mouse pancreas tissue slices. PLoS One 8, e82374 (2013). [PubMed: 24324777]

151. A S, J D & Ms R Glucose-stimulated calcium dynamics in islets of Langerhans in acute mouse pancreas tissue slices. PloS one 8, (2013).

152. Rotti PG et al. Lack of CFTR alters the ferret pancreatic ductal epithelial secretome and cellular proteome: Implications for exocrine/endocrine signaling. J Cyst Fibros 21, 172–180 (2022). [PubMed: 34016558]

153. Shik Mun K et al. Patient-derived pancreas-on-a-chip to model cystic fibrosis-related disorders. Nat Commun 10, 3124 (2019). [PubMed: 31311920]

154. Campbell-Thompson M, Rodriguez-Calvo T & Battaglia M Abnormalities of the Exocrine Pancreas in Type 1 Diabetes. Curr. Diab. Rep 15, 79 (2015). [PubMed: 26318606]

155. Kahraman S et al. Abnormal exocrine-endocrine cell cross-talk promotes β-cell dysfunction and loss in MODY8. Nat Metab 4, 76–89 (2022). [PubMed: 35058633]

156. El Ouaamari A et al. SerpinB1 Promotes Pancreatic β Cell Proliferation. Cell Metab. 23, 194–205 (2016). [PubMed: 26701651]

157. Truong E, Pandol S & Jeon C Uniting epidemiology and experimental models: pancreatic steatosis and pancreatic cancer. EBioMedicine 79, 103996 (2022). [PubMed: 35405390]

158. Yong J et al. Chop/Ddit3 depletion in β cells alleviates ER stress and corrects hepatic steatosis in mice. Sci Transl Med 13, eaba9796 (2021). [PubMed: 34321322]

159. Padgett LR et al. Deoxyhypusine synthase, an essential enzyme for hypusine biosynthesis, is required for proper exocrine pancreas development. FASEB J 35, e21473 (2021). [PubMed: 33811703]

160. Park MH The post-translational synthesis of a polyamine-derived amino acid, hypusine, in the eukaryotic translation initiation factor 5A (eIF5A). J Biochem 139, 161–9 (2006). [PubMed: 16452303]