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The Pancreas: Biology, Diseases, and Therapy

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Every May, GASTROENTEROLOGY publishes a supplementary issue, the "13th Issue", that is devoted to a specific theme. In 2011, the theme was inflammatory bowel disease and last year's was viral hepatitis. This year the board of editors unanimously decided that it was necessary to devote the 13th Issue to the exocrine pancreas and its disorders. Because of the rapid pace of developing new information on mechanisms of the diseases of the exocrine pancreas in the recent past, and the fact that we are approaching a crossroads of converting this mechanistic understanding into new treatments for patients with these diseases, it was an ideal choice. For these reasons, we had the privilege to recruit leading authorities in both the basic and clinical sciences to update our readers in topics of importance in both domains. Also, we will outline the challenges that lie ahead, as well as the approaches that may be utilized to advance the care of patients with pancreatic disease. We anticipate that this juxtaposition of topics will spur innovations and lead to critical new treatments. We have divided the issue into 2 sections. The first section includes topics of basic investigation related to biology and disease mechanisms; the second is focused on clinical manifestations and management of pancreatic disorders.

Dr John Williams (pages 1166–1169) sets the stage for the first section by delivering a historical perspective on the critical role that the exocrine pancreas has played in the biologic sciences.[1] He uses the work of several scientists, who received Nobel Prize awards, as benchmarks, pointing out that much of our general understanding of the regulation of organ function and mechanisms of protein synthesis, transport, and secretion originated with studies in the pancreas. The next article in this section, by developmental biology experts Drs Ben Stanger and Matthias Hebrok (pages 1170–1179), emphasizes that the cells in the pancreas are in flux, even in the adult pancreas.[2] They point out that both the endocrine and exocrine cells of the pancreas are not static but can change their differentiation state in response to injury or stress. They review key biologic processes in differentiation of cell types in the pancreas and point out how understanding the plasticity of pancreatic cells can be used to influence formation of certain cell types (eg, insulin producing β cells) or decrease others (eg, neoplastic cells).

For understanding the molecular mechanisms of pancreatitis, we turn to a review by Drs Markus M. Lerch and Fred S. Gorelick (pages 1180–1193) and a commentary by Drs Ashok K. Saluja and Vikas Dudeja (pages 1194–1198) on animal models to study both pancreatitis and pancreatic cancer.[3,4] Drs Lerch and Gorelick detail the animal models available for pancreatitis research along with the key findings that have emerged from studies using these

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models over the past few decades. Their paper, along with the commentary by Drs Saluja and Dudeja, shows that there has been a lag in fully converting knowledge gained from the models of pancreatitis to new therapies, although several molecular targets for therapy have emerged. In addition, their commentary addresses the types of animal models used in pancreatic cancer research, pointing out that genetically engineered mouse models have been developed with similar characteristics to human pancreatic cancer and that they are providing important insights into the initiation and progression of this cancer. For both pancreatitis and pancreatic cancer, all agree that preclinical work should be done with several models to increase the probability of efficacy in human trials.

The reviews and commentaries on animal models set the stage for 5 reviews discussing molecular mechanisms that underlie disease initiation and progression for both pancreatitis and pancreatic cancer. The review by Drs Ilya Gukovsky, Ning Li, Jelena Todoric, Anna Gukovskaya, and Michael Karin (pages 1199–1209) discusses the mechanisms of acute inflammation, as well as how unresolved chronic inflammation leads to chronic pancreatitis.[5] They further discuss how inflammation underlies the pathogenic effects of (defective) autophagy and obesity in pancreatitis and pancreatic cancer. Drs Minoti V. Apte, Jeremy S. Wilson, Aurelia Lugea, and Stephen J. Pandol (pages 1210–1219) describe the tumor microenvironment in pancreatic cancer and propose that failures to develop effective therapies for this cancer have occured, at least in part, because the complex tumor stroma and pancreatic stellate cell have not been adequately addressed in therapeutic development.[6] Then, Drs Marina Pasca di Magliano and Craig D. Logsdon (pages 1220–1229) provide us with a robust analysis of the key pancreatic cancer oncogene *Kras*, with a focus on recent studies that provide new insight into the contribution of K-ras to tumor initiation and maintenance.[7] They go on to describe the role and mechanisms of action of other key tumor suppressor genes in this cancer. In the subsequent article, Drs Lei Zheng, Jing Xue, Elizabeth M. Jaffee, and Aida Habtezion (pages 1230–1240) point out that the stroma of pancreatic cancer and chronic pancreatitis have inflammatory cell infiltrates that are very similar, and that in cancer there are immunosuppressive signals that allow the tumor to evade immune surveillance.[8] Investigating differences and similarities between these 2 diseases may provide important information for the development of immunebased therapies. In the last review of the first section, Drs Ethan V. Abel and Diane M. Simeone (pages 1241–1248) describe the central role of cancer stem cells in the promotion and dissemination of the disease.[9] They describe markers for the stem cells, how they are regulated, and the interplay between cancer stem cells and the stromal elements of the cancer. Advances in therapeutic targeting of pancreatic cancer stem cells are also addressed.

The second section is devoted to clinical issues in pancreatology. Dr Anil K. Rustgi (pages 1249–1251) introduces the section by providing a historical perspective from the first descriptions of pancreatitis by Fitz in 1889 to the identification of genetic mutations in trypsin as the cause of hereditary pancreatitis by Whitcomb and colleagues in 1996.[10] Dr Rustgi also points out that our understanding of pancreatic diseases has been impacted by the recent identification of an autoimmune disorder (autoimmune pancreatitis) underlying a subset of patients with pancreatitis; the finding of a strong association between chronic pancreatitis and the development of pancreatic cancer; the characterization of pancreatic cysts; and the introduction of genetic models of pancreatic cancer for research. Then Drs

Dhiraj Yadav and Albert B. Lowenfels (pages 1252–1261), reviewing the epidemiology and risk factors of pancreatic disorders, remind the readers that acute pancreatitis is one of the most frequent gastrointestinal causes for inpatient hospital admission and that pancreatic cancer is the among the top 5 causes of cancer death.[11] Drs Gregory A. Coté, Jeffrey Smith, Stuart Sherman, and Kimberly Kelly (pages 1262–1271) provide a historical perspective on advancements in pancreatic imaging from the early abdominal roentogram to the development of endoscopic retrograde pancreatography, multi-detector computed tomography, magnetic resonance cholangiopancreatography, endoscopic ultrasound, and pancreatoscopy.[12] They highlight the fact that these advances still have not allowed us to detect early pancreatic cancer or chronic pancreatitis and present the possibility that molecular-based imaging techniques, under development, may improve our abilities to diagnose and treat these disorders.

The reviews of acute pancreatitis by Drs Bechien U. Wu and Peter A. Banks (pages 1272–1281) and chronic pancreatitis by Dr Chris E. Forsmark (pages 1282–1291), convey the state-of-the-art in diagnosing and managing patients, with reference to current guidelines.[13,14] The reviews also underline opportunities for improved care in patients with these disorders, including development of specific therapies for the inflammation and fibrosis that accompany both acute and chronic pancreatitis. Dr David C. Whitcomb (pages 1292–1302) reviews the role of genetic information as a factor in managing patients with acute and chronic pancreatitis, including a description of new associations between genetic and environmental factors. [15] He proposes that as our understanding of genetic factors increases, clinical algorithms specific to mutations and environmental factors will emerge.

The final two reviews of the issue discuss management of pancreatic cystic neoplasms and pancreatic cancer. Drs James J. Farrell and Carlos Fernández-del Castillo (pages 1303–1315) review the controversial topic of work-up and management of pancreatic cystic neoplasms that are being increasingly recognized as CT and MRI machines improve in their resolution and these studies are increasingly ordered as a routine part of patient care.[16] They discuss the role of endoscopic ultrasound and fine needle aspiration in the diagnosis and management of these lesions and unresolved issues in their management. Drs Andrew Scott Paulson, Hop Tran Cao, Margaret A. Tempero, and Andrew M. Lowy (pages 1316–1326) review the state of current treatment for pancreatic cancer.[17] They report that despite our improved understanding of pancreatic cancer biology and ability to perform more complex pancreatic cancer surgeries, major progress toward increasing survival times has been painstakingly slow. However, they point out that there is an undercurrent of advances in pancreatic imaging to better define extent of disease and operability; changes in surgical approach moving to minimally invasive pancreatectomy; the ability to more safely give combinations of cytotoxic chemotherapy agents; and the promise of personalized approaches based on individual patient biomarkers and their tumor genome—all of these advances should lead us to better outcomes.

In summary, we believe that this 13th Issue gives our readers important and state-of-the-art information about pancreatic biology and disease. We hope that the reviews will inspire our readers not only by knowledge transfer but also in ways that will lead to new discoveries and therapies to improve the lives of patients afflicted with pancreatic disorders. We wish to

extend our special thanks and appreciation to the authors for their outstanding contributions, the reviewers who helped improve the various pieces of this special issue, as well as the editorial staff for their hard work in putting the final product together. We hope you enjoy the issue!

Biographies

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