

Foreword

Molecular Basis of Inherited Pancreatic Disorders



Derek LeRoith, MD, PhD
Consulting Editor

In this issue of the *Endocrinology and Metabolism Clinics of North America*, Drs. Lerch, Griesbacher, and Whitcomb have compiled several articles on the molecular basis of inherited pancreatic disorders by experts in this field of research.

In a comprehensive approach to developmental and metabolic disorders of the pancreas, Lerch, Zenker, Turi, and Mayerle describe some rare abnormalities that may result in pancreatitis. In some cases, pancreatitis is the major feature of the disorder, whereas in others it is associated with other quite serious abnormalities in other organs. Although the various disorders may be unusual, they present important challenges to pediatricians, internists, and specialists and are important conditions to be aware of.

The gene for Johansen-Blizzard syndrome has been identified as the UBR1 gene product by Zenker, Mayerle, Reis, and Lerch, who summarize the positional cloning that they used to identify the gene and the clinical findings of the syndrome. Interestingly, in addition to numerous developmental defects, there is exocrine pancreatic insufficiency, hypothyroidism, and short stature. UBR1 is a ubiquitin ligase, and it is therefore postulated that mutations in UBR1 in this syndrome may cause a prolongation of the half-life of certain proteins. The result, as far as the pancreas is concerned, is an embryonic variety of pancreatitis.

The article by Whitcomb covers the issues of complex polygenic disorders and reviews both the usefulness of meta-analyses as well as its limitations.

Although the article is largely theoretical, it is extremely useful to the reader with regard to diseases of the pancreas, as well as to other disorders not discussed in this issue, and as such is a welcome addition.

Vitone, Greenhalf, Howes, Raraty, and Neoptolemos describe mutations in the trypsinogen gene that are related to pancreatitis. The phenotypic presentation of this heritable form of pancreatitis is extremely variable, with some individuals presenting with severe acute pancreatitis followed by chronic disease, alternatively with milder later onset of the disorder and a small but significant number not suffering from the clinical disorder. Although the hereditary form constitutes approximately 1% of all cases of pancreatitis (acquired cases being induced by alcohol or gallbladder disease), it represents a fascinating entity worthy of further study. The biochemistry and mechanistic models that explain the connection between these mutations and the clinical presentation of hereditary pancreatitis are discussed in a separate chapter by Sahin-Toth.

Germline mutations and gene polymorphisms that are associated with human pancreatitis are outlined in the article by Weiss, Simon, Mayerle, Kraft, and Lerch and then discussed in more detail in the articles by Liddle (SPINK-1) and Vitone et al (trypsinogen).

An important article that introduces the topic of pancreatitis to the less knowledgeable reader is the one contributed by Ruthenberger, Mayerle, and Lerch, who describe the cell biology of pancreatic proteases. They discuss the cellular events following ductal obstruction, pancreatitis, and auto-digestion. In addition, they describe sites of protease activation and the role of various enzymes such as trypsin and cathepsin B in digestive protease activation.

Liddle describes a newly identified association between SPINK mutations and pancreatitis. SPINK-1 protects the pancreas by inhibiting trypsin, and mutations in the SPINK-1 molecule may be associated with acute and chronic pancreatitis. However, the mutation is also found in the general population without pancreatitis. This suggests that SPINK-1 mutations are not sufficient to cause pancreatitis and that other genetic or environmental factors are necessary, making it a fascinating molecule for further study. The biochemistry and biology of SPINK-PST1 is presented by Graf and Bimmler in a separate article.

Type 2 diabetes is associated with two major pathologic features: the dysfunction of beta cells and insulin resistance. There are numerous genes and proteins that may be affected in each of these pathways, leading to this common disorder. Trajkovski, Miziaut, Schwarz, and Solimena cover the most commonly known genetic disorders of beta cells that are associated with type 2 diabetes. These susceptibility genes involve beta cell glucose metabolism, insulin gene expression, and insulin secretion.

Vaxillaire and Froguel address the genetic basis of maturity-onset diabetes of the young (MODY). Six subtypes have been identified with autosomal dominant mutations in single genes. These include glucokinase; hepatocyte

nuclear factors 4 α , 1 α , and 1 β ; insulin promoter factor 1; and NeuroD1. Many of the MODY patients are from large family cohorts and this has helped with the identification of the gene mutation. Presentation before the age of 25 years is usually associated with beta cell dysfunction and clinically resembles type 2 diabetes. These forms of diabetes represent less than 5% of Caucasians with type 2 diabetes.

Maassen, Tafrechi, Janssen, Raap, Lemkes, and 't Hart discuss new aspects of the molecular biology of maternally inherited diabetes and deafness syndrome, a genetic disorder with a mutation in the mitochondrial DNA-encoded tRNA. The 3243A > G mutation is associated with a propensity of beta cells of the pancreatic islets to prematurely age, which results in beta cell dysfunction leading to a 100% penetrance and the development of diabetes. In addition to the beta cell aging, there is a reduction in insulin biosynthesis and insulin secretion.

As described in the article by Lewis, the notch and hedgehog signaling pathways are important for pancreatic development, and these pathways are reactivated in pancreatic tumors. In the common form, pancreatic ductal adenocarcinoma, activating mutations in KRAS, AKT oncogenes and inactivating mutations in p16, p53, and Smad4 have been found. In this article, Lewis presents work from his laboratory on an interesting mouse model of pancreatic cancer, supporting the role of these signaling pathways as pathogenic in this disease.

Brand and Lynch's article deals with the problems of genotype/phenotype aspects of rare disorders such as familial pancreatic cancer and suggests that any model requires the inclusion of environmental factors such as smoking on a polygenic model.

Familial pancreatic cancer is a rare (~2%) component of pancreatic cancers and is discussed in the article by Habbe, Langer, Sina-Frey, and Bartsch. The occurrence of familial pancreatic cancer is seen in situations of genetic mutations resulting in conditions such as Peutz-Jeghers syndrome, familial multiple mole melanomas, hereditary breast and ovarian (BRCA 1 and 2) cancers, and ataxia telangiectasia, among others. Screening of family members in these high-risk families offers the best answer to early detection and perhaps reasonable management.

Simon, Spilcke-Liss, and Wallaschofski summarize our current understanding of endocrine tumors of the pancreas—both those secreting hormones as well as nonfunctioning tumors. They describe the clinical presentation, criteria, and tools for making an accurate diagnosis, as well as our knowledge regarding molecular aspects of the pathogenesis. Most significantly, they address the therapeutic approaches for those tumors that are not cured by surgery.

Although the syndromes and disorders discussed in this issue are not common, they represent examples of disease entities that have enabled investigators to gain insight into critical processes, both genetic and environmental, that are causative in the development of these diseases and will

certainly pertain to more common diseases. For these and other reasons, including the clarity of the articles, this issue of the *Endocrinology and Metabolism Clinics of North America* should stand as an example to editors attempting to bring this type of information to our readers.

Derek LeRoith, MD, PhD
Division of Endocrinology and Diabetes
Department of Medicine
Mount Sinai School of Medicine
One Gustave L. Levy Place, Box 1055
Annenberg Building, Room 23-66B
New York, NY 10029-6574, USA
E-mail address: derek.leroith@mssm.edu