Lessons from Hereditary Pancreatitis

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For decades there has been slow progress in understanding pancreatic diseases, particularly acute and chronic pancreatitis. As a result, there were no significant advances in the management of these patients. Treatment was mostly directed towards symptomatic relief and management of complications. A simple clinical observation that multiple members of a large family are affected by acute and chronic pancreatitis, some at very young age and in the absence of any alcohol use, led physician-scientists of the Midwest Multicenter Pancreatic Study Group (investigators from the University of Cincinnati, University of Kentucky, and University of Pittsburgh) to investigate the genetic basis of hereditary pancreatitis. Using information from the human genome project, the hereditary pancreatitis gene was identified as the cationic trypsinogen gene (protease serine 1, PRSS1). This discovery has led to the identification of a number of other genes and their products playing role in the pathogenesis of acute and chronic pancreatitis. In the emerging picture of pathogenesis of acute and chronic pancreatitis, trypsin appears to play a central role. This newly acquired knowledge is setting the stage for new preventive and management strategies for hereditary and sporadic acute and chronic pancreatitis.

Key words: base sequence; cystic fibrosis transmembrane conductance regulator; hereditary diseases; membrane proteins; pancreatitis; trypsin inhibitors; trypsinogen

Management of acute and chronic pancreatitis remains a challenge for patients, physicians, and surgeons. Our understanding of the disease process has been limited by lack of reliable animal models and destruction of the gland during the course of the acute and chronic pancreatitis disease process (1-4). For years, medical and surgical interventions have been limited to symptomatic relief, attempts to replace lost organ function, and management of complications. The relative status quo changed with the discovery of the gene defect responsible for hereditary pancreatitis. This ignited a renewed interest in the etiopathogenesis of acute and chronic pancreatitis and resulted in further important discoveries. This breakthrough was facilitated by the human genome project initiated on October 1, 1990, as a 15-year project with the goal to map and sequence the complete set of human chromosomes comprised of 3,200,000,000 nucleotides and over 30,000 genes (5). The development of detailed maps of the human chromosome (6) allowed us to perform genetic linkage studies and pinpoint the one mutation out of 3.2 billion possibilities, which causes hereditary pancreatitis.

Hereditary Pancreatitis

Hereditary pancreatitis is an autosomal dominant genetic disorder manifested by recurrent attacks of acute pancreatitis in approximately 80% of individuals with the susceptibility gene (7,8). Progression to chronic pancreatitis is seen in half of the patients with acute pancreatitis and the risk of pancreatic cancer is significantly increased (9,10). The clinical and pathologic appearance of both acute and chronic pancreatitis in these patients is indistinguishable from sporadic forms of acute and chronic pancreatitis (10), suggesting that the understanding the pathogenesis of hereditary pancreatitis may provide clues to sporadic disease. Specifically, the normal product of the gene mutated in hereditary pancreatitis is likely to play a role in the protective mechanism preventing acute and chronic pancreatitis (11).

From the Patient to the Gene...

In the spring of 1995, the proband of a large family was identified by a member of the Midwest Multicenter Pancreatic Study Group through the gastroenterology clinic at the University of Kentucky. Review of the family tree revealed that numerous members had unexplained pancreatitis characteristic of hereditary pancreatitis. Genetic linkage studies identified the locus for the hereditary pancreatitis gene on chromosome 7q35 (Fig. 1) (11). At the same time, a French group also located the gene to chromosome 7 (12). These findings were confirmed by a Vir...
ginia (USA) group (13). With candidate gene approach and information from the human genome project, the disease gene was determined to be cationic trypsinogen (protease serine 1, PRSS1) (14). Using a nested polymerase chain reaction (PCR) strategy, a point mutation within exon 3 of the cationic trypsinogen gene was identified in every individual tested within 5 families with autosomal dominant form of hereditary pancreatitis (Fig. 2) (14). This suggested that cationic trypsinogen plays a central role in the pathogenesis of both acute and chronic pancreatitis.

Figure 1. Discovery of the hereditary pancreatitis gene through a genetic linkage study. First, a family with hereditary pancreatitis was identified and blood was collected from all available family members. Second, the segment of DNA that is always inherited with the disease was identified as a part of chromosome 7. Third, the portion of DNA identified in step 2 was sequenced and compared with the data available from the human genome project. This revealed that the cause of hereditary pancreatitis is a point mutation in the cationic trypsinogen gene.

...And from the Gene to the Disease

The importance of trypsin (Fig. 2) is explained by its central role in digestion (15). The pancreas has three important functions in digestion: 1) secretion of sodium bicarbonate to neutralize hydrochloric acid from the stomach, 2) secretion of digestive enzymes, and 3) secretion of hormones to regulate intermediate metabolism after a meal. Except for amylase and lipase, all pancreatic enzymes are synthesized and secreted in an inactive form to protect the pancreas from autodigestion. All inactive enzymes are then activated by trypsin within the intestinal lumen. Trypsin itself is generated from trypsinogen by the action of enterokinase and previously activated trypsin. Activated trypsin can then activate other trypsinogen molecules and other proenzymes.

Obviously, premature activation of trypsin within the pancreas would initiate the activation cascade and lead to pancreatic autodigestion. Fortunately, several protective mechanisms are in place to prevent premature activation of trypsinogen and the other proenzymes (15). Pancreatic secretory trypsin inhibitor (PSTI), or serine protease inhibitor, Kazal type 1 (SPINK1) is a trypsin inhibitor with a capacity of neutralizing approximately 20% of pancreatic trypsin activity (15). Prematurely activated trypsin is normally inhibited within the pancreas by PSTI/SPINK1 before it can activate other enzymes and cause pancreatitis. Other important protective mechanisms are low intracellular calcium concentrations (15-18), isolation of digestive enzymes into zymogen granules, and disposal of pancreatic enzymes into the intestinal lumen by the high flow rate of bicarbonate rich fluids in the ductal system. In addition, trypsin is also capable of feedback inhibition because trypsin can digest itself.

The mutation responsible for hereditary pancreatitis in the originally described kindred results in a change from arginine to histidine at codon 122 (R122H) (amino acid No. 117, according to the chymotrypsinogen numbering system) (9). The arginine at codon 122 is the recognition site for trypsin hydrolysis by other trypsin molecules. If trypsinogen activation exceeds the inhibitory capacity of PSTI/SPINK1, cleavage at the R122 can serve as an additional protective mechanism (Fig. 3A). Change to the histidine as the result of the hereditary pancreatitis mutation makes trypsin resistant to hydrolysis by a second trypsin molecule (Fig. 2) (14). Therefore, in hereditary pancreatitis, there is no fail-safe autolysis site for additional protection from pancreatitis. If the inhibitory capacity of PSTI/SPINK1 is exceeded for any reason, active trypsin can no longer be stopped by this mechanism, and this sets the stage for acute pancreatitis by activating other proenzymes without inhibition (Fig. 3B).

Additional Mutations Implicated in Hereditary and Sporadic Pancreatitis

Other mutations responsible for hereditary pancreatitis include an N29I substitution in the trypsin...
molecule (chymotrypsinogen system No. N21I) (19), as well as mutations in the trypsinogen activation peptide region A16V (20), D22G (21), and K23R (22). These mutations are believed to increase susceptibility to pancreatitis by facilitating early activation. Furthermore, mutations in the trypsinogen inhibitor PSTI/SPINK1 were also found to be associated with idiopathic chronic pancreatitis in children and familial pancreatitis (23-25). These findings also point to the central role of excessive intrapancreatic trypsin in the pathogenesis of pancreatitis. Interestingly, both homozygous and heterozygous PSTI/SPINK1 produces acute and chronic pancreatitis but only in a minority of carriers (23-25). PSTI/SPINK1 genes appear to be modifier genes that increase the risk of pancreatitis but themselves might not be sufficient to cause the disease since up to 2% of the population may carry these mutations (25). Acute and chronic pancreatitis are also associated with atypical cystic fibrosis suggesting that cystic fibrosis transmembrane conductance regulator (CFTR) gene mutations may also play a pathogenic role not only in classic forms of cystic fibrosis but also in some patients with presumed idiopathic pancreatitis. Indeed, several groups have demonstrated association between mutations in the CFTR gene and recurrent acute and chronic pancreatitis (26,27). Other mutations, yet to be identified, may explain increased susceptibility of some individuals to alcohol-induced acute and chronic pancreatitis.

Pathogenesis of Pancreatitis

These discoveries allowed us to better understand the pathogenesis of acute pancreatitis. Current evidence suggests that increased amounts of active trypsin within the pancreas, as a result of specific mutations, such as the R122H, A16V, D22G, or K23R mutations and possibly N29I, plays a central role in hereditary forms of acute and possibly chronic pancreatitis. Mutations resulting in diminished inhibitory capacity of PSTI/SPINK1 appear to play a modulatory role (24,25). This model explains how different mutations result in a similar clinical picture. Furthermore, one can extrapolate these findings and assume that some form of early trypsin activation is also likely to play a central role in non-hereditary forms of acute and chronic pancreatitis.

Future Directions

Although the genetics of hereditary pancreatitis has answered a number of important questions, the picture is not complete yet. Undiscovered genes and mutations are likely to be present in families which have been thoroughly investigated and all known mutations excluded (9). For unclear reasons, 20% of carriers of the most severe mutations of trypsinogen gene do not develop pancreatitis. Studies on identical twins did not bring any clear answers in that regard (28). Interplay of other genetic, epigenetic, and environmental factors is likely to play a role. Obviously, these issues will be difficult to address without a representative animal model of pancreatitis.

Practical Implications

How can we use this information today? There is not a full answer to this question yet. Genetic testing should be limited to high-risk individuals and only done if accompanied by genetic counseling (1). A positive finding would prevent the patient from undergoing extensive and often invasive workup in a search for the etiology of acute recurrent pancreatitis (29). On the other hand, the psychosocial consequences of a positive result cannot be ignored (30). Because of the complexity of these issues, patients with suspected or established hereditary pancreatitis are best managed at expert, multidisciplinary pancreatic disease centers.

Conclusion

Acute and chronic pancreatitis cannot be treated after being fully developed because they represent the destruction of the pancreatic gland. However, the new genetic insights have given us clues as to what causes pancreatitis and through further studies we may know who is at risk. Use of this information may help us limit and prevent diseases of the pancreas that we cannot reverse. Application of these strategies will prevent years of suffering for many people who would otherwise suffer the effects of acute and chronic pancreatitis.

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References


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