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Molecular Genetic and Pathophysiological Features of Pancreatitis

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Abstract The first discovery of trypsinogen mutations in populations with hereditary pancreatitis led to rapid developments in the field of pancreatic molecular genetics. The identification of mutations in genes involved in the digestive enzyme pathway provided further evidence that pancreatitis is a disease associated with self-digestion. Clinical and retrospective analyses have provided compelling evidence that premature intrapancreatic activation of digestive enzymes plays a crucial role in the development of chronic pancreatitis. The course and severity of the disease are also largely determined by inflammatory cells that cause local and systemic immune inflammation. All of the above determines the relevance of this problem.

Keywords Pancreatitis, Molecular genetic features, Pathophysiological features

1. Introduction

Pancreatitis is the leading cause for GI-disease related hospital admissions and it is associated with considerable morbidity, mortality and socioeconomic burden. Recent years shed light on the pathophysiology of pancreatitis opening up new avenues for causal treatment. In this review article, we dissect the complexity of premature protease activation and its effect on local and systemic inflammation in pancreatitis [1].

Acute pancreatitis (AP), recurrent acute pancreatitis (RAP) and chronic pancreatitis (CP) form a disease continuum. The progression of a sentinel attack of AP to RAP and eventually to CP is often driven by chronic alcohol consumption or genetic risk factors. Genetic risk for RAP and CP overlaps, while genetic studies in AP are difficult to interpret in the absence of adequate follow-up that can exclude RAP and CP cases.

The majority of the pancreatitis risk genes codes for digestive proteases, a trypsin inhibitor or other proteins highly expressed in the pancreas. Functional studies classified the various mutations and other genetic alterations into pathological pathways driving pancreatitis onset and progression. Here we discuss the trypsin-dependent, misfolding-dependent and ductal pathways of pancreatitis risk [2].

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Pancreatic acinar cells secrete digestive proteases in inactive precursor forms that are flushed from the ductal system in a sodium bicarbonate-rich fluid. Trypsinogen, the precursor to trypsin, becomes activated by the serine protease enteropeptidase in the duodenum. Trypsin activates chymotrypsinogens, proelastases and procarboxypeptidase B1 (CPB1) while activation of procarboxypeptidases A1 (CPA1) and A2 (CPA2) requires the concerted action of trypsin and chymotrypsin C (CTRC). Trypsinogen can be also activated by trypsin, and this process is called autoactivation. Premature, intra-pancreatic activation of trypsinogen may occur via autoactivation or may be catalyzed by the lysosomal cysteine protease cathepsin B. Protective mechanisms that prevent trypsinogen activation in the pancreas include trypsin inhibition by the serine protease inhibitor Kazal type 1 (SPINK1) and trypsinogen degradation by CTRC and cathepsin L. Although the principal action of CTRC is to promote trypsinogen degradation, it also enhances trypsinogen activation by processing the trypsinogen activation peptide to a shorter form, which is more sensitive to trypsin-mediated activation. As discussed below, certain trypsinogen mutations can hijack this mechanism and thereby stimulate trypsinogen activation to a pathological extent. Human genetic studies strongly support trypsinogen autoactivation and CTRC-dependent trypsinogen degradation as key mechanisms determining intrapancreatic trypsin activity whereas similarly compelling genetic evidence for the role of cathepsins B and L has been lacking [6].

Mutations in human cationic trypsinogen cause autosomal dominant hereditary pancreatitis with incomplete penetrance or act as risk factors in sporadic CP. Around 90% of *PRSS1*-mutation positive HP families carry the p.N29I, p.R122C, or p.R122H mutation in the heterozygous state. Mechanistically, the p.R122C and p.R122H mutations prevent CTRC-mediated trypsinogen degradation. The p.N29I mutation has multiple distinct effects on trypsinogen biochemistry, the combination of which markedly increases trypsinogen autoactivation. These effects include an increase in N-terminal processing, decreased CTRC-dependent degradation and a slightly increased propensity for autoactivation. The p.A16V variant, sensitizes the activation peptide of trypsinogen to CTRC-mediated processing, which, in turn, enhances autoactivation. Pathological trypsin levels generated by mutation p.A16V are lower than those seen with the p.R122H variant, which explains the reduced penetrance of the p.A16V variant. More recently, mutation p.P17T was found to exhibit characteristics that were similar to those of p.A16V. Rare mutations affecting the activation peptide of cationic trypsinogen (p.D19A, p.D21A, p.D22G, p.K23R and p.K23_I24insIDK) robustly stimulate autoactivation independently of CTRC. Cell culture experiments indicate that these activation peptide mutants are secreted poorly due to intracellular activation and degradation, which can lead to cellular stress and consequent acinar cell death. Taken together, *PRSS1* mutations stimulate activation of cationic trypsinogen by reducing CTRC-dependent trypsinogen degradation, increasing CTRC-mediated processing of the activation peptide or directly stimulating autoactivation. GWAS studies identified a commonly occurring haplotype in the *PRSS1-PRSS2* locus that slightly decreases CP risk (OR 1.5) with a more pronounced effect in alcoholic CP. A variant (c.−204C>A) that lies in the promoter region of *PRSS1* and reduces trypsinogen expression appears to be responsible for this small protective effect [3].

The association between the most common p.N34S *SPINK1* variant and CP was first described by a candidate gene study in 2000. A meta-analysis reported a carrier frequency of 9.7% in CP patients and 1% in controls with an average odds ratio (OR) of 11, making the p.N34S the clinically most significant risk factor for CP. When considering European populations only, p.N34S increases CP risk by about 10-fold. Although several studies attempted to identify the functional effect of p.N34S and its associated haplotype, the molecular mechanism underlying CP risk remains unclear. Neither p.N34S nor any of the four linked intronic variants affect trypsin inhibitory function or cellular expression of SPINK1. Interestingly, in pancreatic cancer cell lines carrying the heterozygous p.N34S variant reduced expression of the mutant allele was observed in comparison to the wild-type allele. The authors suggested that the c.−4141G>T variant or a hitherto unknown variant located in the 5' region of the gene may be responsible for the reduced expression of the p.N34S allele. The second most frequently reported *SPINK1* haplotype in CP contains the c.−215G>A promoter variant and the c.194+2T>C variant in intron 3. This haplotype was observed more frequently in East Asia than in Europe. Functional studies revealed that the c.194+2T>C variant causes skipping of exon 3, which results in diminished *SPINK1* expression. However, the c.−215G>A variant increases promoter activity, which might mitigate the effect of the c.194+2T>C mutation and allow for some residual SPINK1 expression even in homozygous carriers. Finally, a large number of rare or private alterations in *SPINK1* have been found in CP, which cause loss of SPINK1 function by various mechanisms [4].

Although PRSS1 and PRSS2 share 90% identity at the amino acid level and PRSS2 rapidly autoactivates, no pathogenic *PRSS2* variants were identified in HP or sporadic CP. The absence of *PRSS2* mutations in CP may be due to the more effective CTRC-mediated degradation of anionic trypsinogen, which would prevent intra-pancreatic activation of the enzyme even if it were mutated. However, a protective variant p.G191R with a ~3–6-fold effect and circa 5% population frequency was discovered. The mutation introduces a new trypsin cleavage site into anionic trypsinogen, which increases autocatalytic proteolysis and inactivation [5].

Direct DNA sequencing of the *CTRC* gene in patients with nonalcoholic CP revealed heterozygous mutations in 4% of patients that increased CP risk by 5-fold on average. The mutations cause loss of CTRC function by various mechanisms, which include defective secretion due to misfolding, resistance to trypsin-mediated activation, catalytic deficiency or increased degradation by trypsin. Considering the clinically significant variants, p.A73T exhibits a severe secretion defect, p.K247_R254del is inactive and prone to degradation, p.R254W is degraded by trypsin and p.V235I has partially reduced activity. Subsequent studies reported a frequent p.G60= variant found in about 30% of CP patients. The heterozygous p.G60= increases the risk of CP by 2.5-fold, while the homozygous state by 10-fold. The variant is associated with reduced *CTRC* mRNA expression (GTEx Portal), possibly due to altered pre-mRNA splicing [7].

A recent European GWAS study identified a large inversion at the *CTRB1/CTRB2* locus that modestly (OR 1.35) modifies the risk for alcoholic and nonalcoholic CP. The inversion changes the expression ratio of the CTRB1 and CTRB2 chymotrypsin isoforms in such a manner that protective trypsinogen degradation is increased and CP risk is reduced. In China the reported population frequency of the inverted (major) allele is 99.6%, thus the allele is virtually fixed and does not contribute to CP risk. A mouse model with genetic deletion of the major mouse chymotrypsin CTRB1 exhibited increased intra-acinar trypsin activation and more severe pancreatitis induced by the secretagogue caerulein. These observations provided the first *in vivo* proof for the protective role of chymotrypsin-mediated trypsinogen degradation against pancreatitis [8].

More recently, an alternative pathomechanism seemingly unrelated to premature intra-pancreatic trypsinogen activation has been identified, in which mutation-induced misfolding and consequent endoplasmic reticulum (ER) stress lead to acinar cell damage and pancreatitis. In 2009 it was

demonstrated that a subset of *PRSS1* variants cause reduced secretion, intracellular retention and elevated ER stress markers, as judged by *in vitro* cell culture experiments. These *PRSS1* mutations occur rarely and are mostly associated with sporadic disease (e.g., p.C139F, p.C139S, p.G208A), but were also found in HP families with incomplete penetrance (p.L104P, p.R116C). Variant p.G208A is prevalent in East Asia (4% of CP cases) and was detected in Europe only in a single case so far [9].

A candidate gene study in 2013 revealed that mutations in the *CPA1* gene are associated with CP (OR ~25), especially with early-onset disease (OR~80). The vast majority of pathogenic *CPA1* variants occur with low frequency and are mostly found in sporadic CP. The p.S282P variant was described in two HP families [20]. Pathogenic *CPA1* variants cause proenzyme misfolding resulting in a secretion defect, intracellular retention and ER stress. In contrast to CPA1, variants of CPB1 and CPA2 are not associated with CP. Interestingly, ER stress-inducing *CPA1* and *CPB1* variants were overrepresented in pancreatic cancer patients without a clinical history of RAP or CP. Most of these variants caused premature truncation and did not overlap with those found in CP. A mouse model for the misfolding-dependent pathway was described recently. This study demonstrates that *CPA1 N256K* knock-in mice harboring the most frequent p.N256K human *CPA1* mutation develop spontaneous and progressive CP and exhibit signs of ER stress in their pancreas [10].

Single-nucleotide deletions in the last exon of the *CEL* gene encoding carboxyl ester lipase cause maturity-onset diabetes of the young type 8 (MODY8). The deletions alter the reading frame of the C-terminal variable number tandem repeat (VNTR) sequence resulting in CEL proteins with unnatural extensions that are prone to aggregation. The exocrine dysfunction in MODY8 is in all likelihood caused by misfolding-induced ER stress and consequent acinar cell loss [19]. A hybrid *CEL* allele (*CEL-HYB1*) formed between *CEL* and its neighboring pseudogene *CELP* was found about 5-fold overrepresented in idiopathic CP versus the average population frequency of 0.5–1%. In cell culture experiments, the hybrid protein was secreted poorly due to intracellular retention, suggesting that the *CEL-HYB1* variant may increase CP risk via the misfolding-dependent pathway. A second hybrid *CEL* allele (*CEL-HYB2*) that does not associate with CP was described in Asian populations. Interestingly, the CEL protein carries blood group antigens and a GWAS study in 2015 indicated that fucosyltransferase 2 (FUT2) non-secretor status and blood group B are risk factors for CP. Although other studies in ethnically mixed cohorts failed to replicate this association with the exception of azathioprine-induced pancreatitis in IBD patients it is still interesting to speculate that the observed effects may have been due to changes in CEL folding or trafficking [11].

The cystic fibrosis transmembrane conductance regulator (CFTR) is a cyclic AMP-regulated chloride/bicarbonate channel localized to the apical plasma membrane of epithelial cells. *CFTR* mutations disrupt channel activity or affect membrane levels and are associated with various phenotypes, ranging from asymptomatic state to multi-organ symptoms leading to the diagnosis of cystic fibrosis (CF) in homozygous carriers of severe mutations. Observations that heterozygous and compound heterozygous *CFTR* mutations are associated with CP were reported by two papers in 1998. In the first analysis of the entire *CFTR* coding region, the frequency of abnormal *CFTR* alleles in CP patients was 18.6% in comparison to 9.2% in controls. More recent, large cohort analyses corroborate the pathogenic role of *CFTR* variants in CP although the effect and frequency of *CFTR* variants was less pronounced than reported previously. Heterozygous carrier status of the severe p.F508del mutation confers a small risk for CP with an OR of 2.5, whereas the mild p.R117H mutation increases risk by about 4-fold. Compound heterozygous state for one severe and one mild *CFTR* allele represents strong risk for CP and may be considered causative [18].

The role of common polymorphic *CFTR* alleles (e.g. T5, TG12) and the non-CF-causing, so-called bicarbonate-defective *CFTR* variants in CP remains controversial as the preponderance of data does not support their association with CP. Unlike *CFTR*, variants in the solute-linked carrier 26 member 6 anion transporter (*SLC26A6*) do not alter the genetic risk in CP [12].

GWAS studies of CP identified several SNPs in the *CLDN2-MORC4* locus to be associated with CP risk. The OR was about 2 and the effect was more pronounced in alcoholic CP. Within this locus, *CLDN2* seems to be the clinically relevant risk gene, as it is expressed in pancreatic ducts at low levels as a tight junction protein. It was proposed that *CLDN2-MORC4* variants might cause CLDN2 mislocalization. Additional work is required to clarify the mechanism of action of this risk locus and to confirm whether assignment to the ductal pathway is appropriate [13].

The calcium-sensing receptor (CASR) regulates calcium homeostasis through parathyroid hormone secretion and renal tubular calcium reabsorption. Functional CASR is also expressed in the pancreas, including ductal cells where CASR may respond to high calcium concentrations in the juice by increasing ductal fluid secretion, thereby preventing stone formation and pancreatitis. A US population based study failed to demonstrate the previously anticipated association between *CASR* variants and the *SPINK1* p.N34S haplotype, but reported the p.R990G variant to increase CP risk, especially in subjects with moderate or heavy alcohol consumption. More recently, a French study found overrepresentation of rare *CASR* coding variants in idiopathic CP and significant association of the p.A986S variant, but only in the homozygous state, with CP. However, the previously reported association with the p.R990G variant was not observed in this cohort. Taken together, current evidence does not support a clear role for *CASR* variants in CP pathogenesis [14].

In summary, human genetic data indicate that premature activation or mifolding of pancreatic proteases play a central role in the onset of pancreatitis and progression to chronic pancreatitis [15].

While genetic evidence for the involvement of the protease/antiprotease balance in the pathogenesis of pancreatitis dates back only two decades and mainly focusses on chronic pancreatitis, pathophysiological and biochemical investigations have implicated this system for over a century. Due to lack of adequate animal models and the inability to keep isolated pancreatic acinar cells in culture for long periods of time, experimental studies has focussed primarily on acute pancreatitis. The relative importance of the pathways discussed below might change with respect to etiology. It is our general understanding that these mechanisms are also relevant to chronic pancreatitis, although experimental evidence is mostly lacking [16].

The pathophysiological concept of autodigestion was first developed by the Austrian pathologist Hans Chiari in Prague more than 120 years ago. He claimed that pancreatitis was caused and driven by the glands own digestive properties. Ever since the pathomechanism of premature activation of pancreatic enzymes and its contribution to disease severity and progression has captured the attention of many pancreatologists. Bialek and colleagues first showed, that protease activation during pancreatitis begins in the exocrine pancreas and Saluja et al. reported that it begins in a membrane-confined vesicular compartment and parallels acinar cell damage. Although the fact that activation of digestive proteases is an early event during acute pancreatitis is widely accepted, the question where and through what mechanism this process is initiated and whether it plays a role in chronicity remains under debate [17].

2. Conclusions

In conclusion, early protease activation as well as NFκB activation are essential characteristics of pancreatitis, both events occur in parallel during disease manifestation and strongly influence each other. Recent prove that not only the activation of proteases and NFκB play a critical role, but also the type of cell, in which their activation takes place is of importance. Pancreatitis is not a disease of acinar cells alone.

REFERENCES

[1] Etemad B, Whitcomb DC: Chronic pancreatitis: diagnosis, classification, and new genetic developments. Gastroenterology, 2001; 120: 682–707.

[2] Witt H: Chronic pancreatitis and cystic fibrosis. Gut, 2003; 52(Suppl.2): ii31–41.

[3] Comfort M, Steinberg A: Pedigree of a family with hereditary chronic relapsing pancreatitis. Gastroenterology, 1952; 21: 54–63.

[4] Keim V, Bauer N, Teich N et al: Clinical characteristics of patients with hereditary pancreatitis and mutations in cationic trypsinogen. Am J Med, 2001; 111: 622–26.

[5] Moir CR, Konzen KM, Perrault J: Surgical therapy and long-term follow-up of childhood hereditary pancreatitis. J Pediatr Surg, 1992; 27: 282–86.

[6] Miller AR, Nagorney DM, Sarr MG: The surgical spectrum of hereditary pancreatitis in adults. Ann Surg, 1992; 215: 39–43.

[7] Lowenfels AB, Maisonneuve P, DiMagno EP et al: Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst, 1997; 89: 442–46.

[8] Ulrich CD: Pancreatic Cancer in Hereditary Pancreatitis: Consensus Guidelines for Prevention, Screening and Treatment. Pancreatology, 2001; 1: 416–22.

[9] Whitcomb DC, Gorry MC, Preston RA et al: Hereditary pancreatitis is caused by a mutation in the cationic trypsinogen gene. Nat Genet, 1996; 14: 141–45.

[10] Gorry MC, Gabbaizedeh D, Furey W et al: Mutations in the cationic trypsinogen gene are associated with recurrent acute and chronic pancreatitis. Gastroenterology, 1997; 113: 1063–68.

[11] Witt H, Luck W, Becker M: A signal peptide cleavage site mutation in the cationic trypsinogen gene is strongly associated with chronic pancreatitis. Gastroenterology, 1999; 117: 7–10.

[12] Teich N, Bauer N, Mössner J, Keim V: Mutational screening of patients with nonalcoholic chronic pancreatitis: Identification of further trypsinogen variants. Am J Gastroenterol, 2002; 97: 341–46.

[13] Kukor Z, Mayerle J, Kruger B et al: Presence of cathepsin B in the human pancreatic secretory pathway and its role in trypsinogen activation during hereditary pancreatitis. Biol Chem, 2000; 277: 21389–96.

[14] Kukor Z, Toth M, Pal G, Sahin-Toth M: Human cationic trypsinogen. Arg (117) is the reactive site of an inhibitory surface loop that controls spontaneous zymogen activation. J Biol Chem, 2002; 277: 6111–17.

[15] Sahin-Toth M: Human cationic trypsinogen. Role of Asn-21 in zymogen activation and implications in hereditary pancreatitis. J Biol Chem, 2000; 275: 22750–55.

[16] Sahin-Toth M. The pathobiochemistry of hereditary pancreatitis: studies on recombinant human cationic trypsinogen. Pancreatology, 2001; 1: 461–65.

[17] Sahin-Toth M, Toth M: Gain-of-function mutations associated with hereditary pancreatitis enhance autoactivation of human cationic trypsinogen. Biochem Biophys Res Commun, 2000; 278: 286–89.

[18] Simon P, Weiss FU, Sahin-Toth M et al: Hereditary pancreatitis caused by a novel PRSS1 mutation (Arg-122->Cys) that alters autoactivation and autodegradation of cationic trypsinogen. J Biol Chem, 2002; 277: 5404–10.

[19] Szilagyi L, Kenesi E, Katona G et al: Comparative in vitro studies on native and recombinant human cationic trypsins. Cathepsin B is a possible pathological activator of trypsinogen in pancreatitis. J Biol Chem, 2001; 276: 24574–80.

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