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Pancreatitis and pancreatic cystosis in Cystic Fibrosis

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Abstract

The pathologic effects of an altered cystic fibrosis transmembrane receptor (CFTR) protein on the exocrine pancreas is ubiquitous and of varying severity. In this section, pancreatitis and pancreatic cystosis are covered.

Keywords: Pancreatitis; Pancreatic cystosis, cystic fibrosis; CFTR

1. Background

The pathologic effects of an altered cystic fibrosis transmembrane receptor (CFTR) protein on the exocrine pancreas is ubiquitous and of varying severity. In this section, pancreatitis and pancreatic cystosis are covered.

1.1. Pathophysiology

1.1.1. Pancreatitis in CF

The development of symptomatic pancreatitis in patients with CF is uncommon. Although cases of pancreatitis in pancreatic insufficient (PI) patients exist [1–3], pancreatitis in CF is generally believed to occur exclusively within pancreatic sufficient (PS) patients, with ~20% of PS patients developing pancreatitis [4,5]. In the majority, damage to the pancreas begins in utero and often continues into infancy and early childhood, eventually resulting in PI from loss of acinar tissue (see Fig. 1) [6,7]. Only 1–2% of residual pancreatic reserve is required to maintain PS [8]. This process of pancreatic damage is detectable by the release of pancreatic protein trypsinogen into the blood stream, which forms the basis of newborn screening for CF. Symptomatic pancreatitis results from an intricate balance between the degree of pancreatic acinar reserve and severity of ductal obstruction, both of which are related to the severity of CFTR dysfunction but in opposing directions (Fig. 2). A "critical mass" of acinar tissue in the presence of ductal obstruction is required to elicit an episode of symptomatic pancreatitis, explaining why only a small proportion of CF patients develop clinical pancreatitis [9,10].

Impaired HCO_3^- secretion also appears important in the development of pancreatitis. In non-CF mouse models, acinar exocytosis of zymogens is associated with acidification of the lumen secondary to impaired neutralization resulting from HCO_3^- deficiency. Impaired control of luminal pH is believed to contribute to tissue damage and pancreatitis [11]. Furthermore, separate animal and human models have shown that CFTR Cl^- channel and anion exchangers are inhibited by trypsin resulting in decreased luminal pH that could promote premature zymogen activation resulting in acute and/or chronic pancreatitis [12].

1.1.2. CFTR impact on disease severity

Mouse models utilizing both CFTR knockout ($CFTR^{-/-}$) and p.F508del mice have shown overexpression of pro-inflammatory cytokines genes within the pancreas resulting in a more severe acute pancreatitis after cerulean hyper-stimulation as compared to

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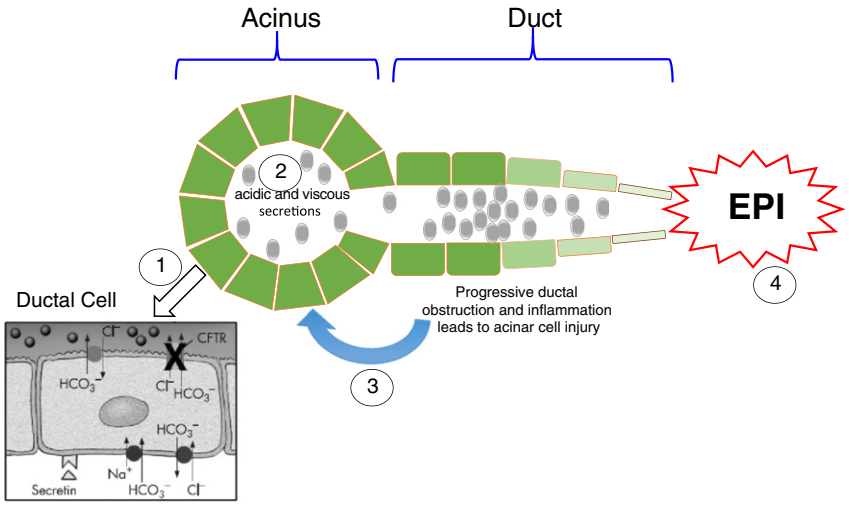

Fig. 1. Theorized mechanism for the progression of pancreatic damage resulting in pancreatic insufficiency in utero. Mutation in CFTR (1) impairs HCO_3^- secretion which leads to acidic and viscous pancreatic secretions (2). This results in progressive ductal obstruction and inflammation (3) that causes acinar cell injury and ultimately, exocrine pancreatic insufficiency (4) (adapted from Wilschanski and Durie [10]).

wild type (WT) littermates [13,14]. Subsequent mouse models examining the role of Na+/H+ exchange regulatory factor-1 (NHERF-1) in acute pancreatitis showed that NHERF-1$^{-/-}$ mice expressed decreased levels of CFTR at the apical membrane of the pancreatic duct resulting in reduced fluid and HCO_3^- secretion and a more severe acute pancreatitis. In total, these models suggest that CFTR is associated with the development of pancreatitis and influences severity through altered secretion of pancreatic fluid and HCO_3^-, rather than direct acinar cell or ductal injury.

1.1.3. Modifiers of CFTR

Interactions between CFTR and modifying intrinsic (e.g. genetics, bile) and extrinsic (e.g. smoking, alcohol) factors may influence the development of pancreatitis. A summary of these pancreatitis-influencing factors on CFTR is shown in Table 1.

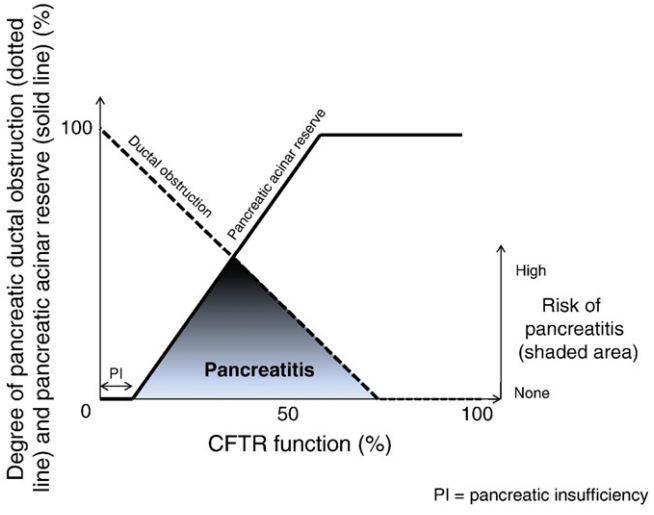

Fig. 2. Conceptual model demonstrating CFTR-related factors that contribute to pancreatitis. Development of pancreatitis is associated with the opposing factors of severity of ductal obstruction and degree of pancreatic acinar reserve. Adapted from Ooi et al. [5].

1.1.4. Genetics

Several reports have shown an increase incidence of CFTR mutations among patients with chronic pancreatitis (CP) and acute recurrent pancreatitis (ARP). In a study of 42 adolescents and adults with idiopathic ARP and CP, extensive CFTR genotyping identified 50% of patients with either 1 or 2 variants [15]. Among adult patients with CP or ARP, between 16 and 39% of patients have at least one CFTR mutation for an odds ration of ~3.0 compared to controls [16–18]. When those patients diagnosed with alcohol-induced pancreatitis were eliminated, the frequency has been reported as high as 60% [19]. Although genetic causes of pancreatitis are more common among children, the frequency of CFTR mutations is similar ranging from 19% to 48% among the relatively larger pediatric studies including the International Study Group of Pediatric Pancreatitis: In Search for a Cure (INSPPIRE) consortium database [20–22]. However, in only three of these studies were full CFTR sequencing performed for all patients [15,16,21]. This represents a major limitation as the highest risk mutations are associated with more mild CF disease that are often not picked up through standard screening panels and likely underrepresents the true incidence of CFTR mutations in these cohorts. This has resulted in the reporting of a relatively small number of CFTR mutations being reported; with non-CF causing mutations or mutations whose association to disease severity is unknown, likely being under recognized. The predominantly reported mutations include heterozygotes known to be associated with CF (e.g. p.F508del) or compound heterozygozity with a non-CFTR mutation associated with pancreatitis such as cationic trypsinogen (PRSS1), serine protease inhibitor Kazal 1 (SPINK1) and/or chymotrypsinogen C (CTRC) [16,17,19–21].

The risk of developing pancreatitis can be predicted using the pancreatic insufficiency prevalence (PIP) score [5,23]. The PIP score was developed and validated to categorize CFTR mutations according to predicted severity of mild vs.