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Review article

The role of pancreatic ducts in the pathogenesis of acute pancreatitis

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ABSTRACT

Pancreatic ducts secrete 2.5 l of alkaline, HCO_3^--rich fluid daily which greatly contributes to the homeostasis of the pancreas. Ducts are also important in the pathophysiology of the pancreas; alteration of ductal function can lead to severe diseases such as cystic fibrosis and chronic pancreatitis. The role of pancreatic ducts in the development of acute pancreatitis has only been uncovered recently. Pancreatitis inducing agents like bile acids and ethanol dose-dependently affect pancreatic ductal secretion; low concentrations stimulate, whereas high concentrations inhibit secretion. The majority of the review will focus on the central role of cystic fibrosis transmembrane conductance regulator (CFTR), a critical protein in the regulation of ductal secretion, in the pathogenesis of acute pancreatitis which is highlighted by numerous investigations. Downregulation of CFTR expression results in increased severity of acute pancreatitis in mice. Furthermore, human genetic studies have demonstrated statistically significant association of *CFTR* mutations with acute recurrent pancreatitis. Overall, the data support the involvement of pancreatic ducts in the pathogenesis of acute pancreatitis.

Acute pancreatitis: an enigmatic inflammatory disease

It is without question that acute pancreatitis remains a challenging inflammatory disease. The incidence of acute pancreatitis is increasing and has recently become the most common reason of hospitalisation amongst gastrointestinal diseases in the United States [1]. The severity of acute pancreatitis can range from mild to severe [2]. However, unfortunately there is really no reliable way to tell in advance what disease course the patient will follow [3] This would be of utmost importance, since while the management of the mild form of disease is straightforward, treatment of the severe form (in cases of local and systemic complications) is rather difficult as there is no specific therapy. In fact, the severe disease form accounts for the unacceptably high mortality rate. Unfortunately, the narrow therapeutic window does not help us in finding reliable treatment. Taking these facts into consideration, it is not surprising that acute pancreatitis is also a huge financial burden; the annual aggregate inpatient costs in the United States add up to about $2.6 billion [1].

Although there are numerous causes of acute pancreatitis, about 80% of the cases are related to heavy alcohol consumption and biliary disease [3]. Fortunately, only a small proportion of alcoholics and patients with biliary disease ever get acute pancreatitis, so other factors also contribute to the development of the disease. Despite intensive research, the pathomechanism of acute pancreatitis remains unclear. However, premature activation of trypsinogen, activation of the proinflammatory transcription factor nuclear factor-κB and/or mitochondrial injury are thought to be essential in the development of this inflammatory disorder [4]. The consequential upregulation and release of proinflammatory mediators (e.g. chemokines and cytokines) and the activation of leukocytes not only escalate the inflammatory process, but also contribute to local and systemic injury [5,6]. Mortality in acute pancreatitis is related to these latter complications: the first peak (within a week) is caused by the development of systemic inflammatory response syndrome and multiorgan failure (including lung, kidney, liver and heart), whereas the second peak occurs from the second week onwards, and is related to infected pancreatic necrosis and sepsis [5]. The number of extrapancreatic organs affected (one or more) and the duration of organ failure (more or less than 48 h) are critical in determining patient survival [2,5].

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Pancreatic ducts: more than just a framework for the pancreas

The exocrine pancreas mainly consists of acinar and duct cells. Besides providing structural framework for the pancreas, ducts convey digestive enzymes secreted by acinar cells and most importantly they also secrete 2.5 l of alkaline, HCO_3^--rich fluid daily which greatly contributes to the homeostasis of the organ [7]. Pancreatic ductal secretion is regulated by neuronal (vagal) and hormonal factors such as secretin (the action of which is mediated by cAMP). The regulation of pancreatic luminal pH is essential and duct cells have an important part in this process [8]. Protons released during acinar exocytosis cause significant extracellular acidosis [9], whereas, HCO_3^- secreted by duct cells alkalize the lumen. Therefore, duct cells neutralize acidic content secreted by acinar cells.

Although the mechanism of pancreatic ductal HCO_3^- and fluid secretion is itself an interesting topic, the detailed discussion of these processes are outside the scope of this review and the reader is referred to other recent publications like the ones by Lee et al. [7], Ishiguro et al. [10] and Argent et al. [11]. Just briefly, a large proportion of the secreted HCO_3^- is taken up from the extracellular space by the basolateral Na^+/HCO_3^- cotransporter. The rest of the HCO_3^- comes from the conversion of CO_2 to HCO_3^- and H^+ (catalyzed by carbonic anhydrases) and backward transport of H^+ by Na^+/H^+ exchangers and an H^+-ATPase (leaving HCO_3^- in the cell). HCO_3^- is then transported into the ductal lumen by SLC26 anion transporters (two strong candidates are SLC26A3 and SLC26A6) and the cystic fibrosis transmembrane conductance regulator (CFTR) located on the apical membrane of duct cells. To this day it remains a question exactly how HCO_3^- concentration can reach 140 mM in humans, however, CFTR has critical roles in mediating the secretory process. This unique protein that belongs to the ATP Binding Cassette transporter family is more than just a cAMP-protein kinase A-regulated Cl^- channel: it can also conduct HCO_3^-, and it directly and indirectly interacts with other transporters involved in secretion (like SLC26 anion exchangers).

Evidence for the role of pancreatic ducts in acute pancreatitis

It is clear that pancreatic ducts have an essential part in debilitating diseases like cystic fibrosis and chronic pancreatitis. Although the role of pancreatic ducts in acute pancreatitis has been implicated a long time ago, this field was only thoroughly investigated recently (mostly by our group in Szeged). One of the first papers highlighting the possible role of pancreatic ducts in the pathogenesis of acute pancreatitis was published by Niederau et al. in 1985 [12]. The authors could detect a small, but significant protective effect of secretin administration (s.c.) in caerulein-induced acute necrotizing pancreatitis in mice. More stronger evidence came from an elegant study performed by Lerch et al. [13] who showed that ligation of the pancreatic duct triggered acute necrotizing hemorrhagic pancreatitis in American opossum. Furthermore, these results also suggest that bile reflux into the pancreatic duct may not be necessary for induction of acute pancreatitis.

The effects of pancreatitis-inducing agents on ductal secretion

Pancreatitis-inducing agents have a dose-dependent effect on pancreatic ductal secretion. Here we will discuss the two most common etiological factors: bile acids and ethanol. Interestingly, it seems that they have similar effects on duct cells (Fig. 1).

Bile acids

Although it is debated whether bile can enter the pancreatic duct in biliary pancreatitis [14], we have demonstrated that low concentrations of bile acids stimulate, whereas high concentrations of bile acids inhibit secretion in both guinea pig [15–17] and human duct cells [18]. Luminal administration of low doses of chenodeoxycholate most likely stimulates the SLC26A6 anion exchanger via phospholipase C- and inositol triphosphate-mediated Ca^{2+} signaling pathways in guinea pig pancreatic duct cells [16]. CFTR expression, but not Cl^- transport, is necessary for the stimulatory effect of chenodeoxycholate on apical Cl^-/HCO_3^- exchange activity [18]. Bile acid-induced Ca^{2+} signaling also activates large-conductance Ca^{2+}-activated potassium (BK) channel which also seems to be essential in ductal hypersecretion [17]. The inhibition of pancreatic HCO_3^- secretion by high concentrations of chenodeoxycholate may be related to mitochondrial damage followed by intracellular ATP depletion which will affect apical and basolateral HCO_3^- transport mechanisms [15]. Notably, a small pilot study has shown that intraluminal pancreatic ductal pH is lower in patients with biliary pancreatitis vs control patients [19]. The decrease in ductal pH was greater in patients with biliary pancreatitis who had symptoms for longer time-periods before endoscopic retrograde cholangio-pancreatography. Taken together, these results indicate that HCO_3^- secretion is likely impaired in patients with biliary pancreatitis. Does one have to be concerned about this? The detrimental effects of low extracellular pH have been confirmed by a number of investigations. Decreased extracellular pH enhances both trypsinogen autoactivation [20] in the ductal lumen and secretagogue-induced zymogen activation and injury in acinar cells [21]. Trypsin will then activate protease-activated receptor 2 (PAR-2) found on the luminal membrane of duct cells, which further reduces pancreatic ductal HCO_3^- secretion in a vicious circle via inhibition of apical anion exchangers and CFTR [20]. Importantly, the effects of trypsin were markedly diminished in PAR-2 knock-out mice. Behrendorff et al. [9] also found harmful effects of low extracellular pH in an *in vitro* acute pancreatitis model. Supramaximal concentrations (100 nM) of cerulein induced large increases in acinar secretory activity which were associated with marked, prolonged acidification of the luminal space [9]. These pathological changes in luminal pH led to disruption of intercellular junctional coupling, measured by movement of occludin and E-cadherin [9]. Weakening of cell junctions may then lead to leak of zymogens into the interstitial space. The importance of extracellular pH in acute pancreatitis is highlighted by the paper of Noble et al. [22]. Injection of radio-opaque contrast solution with a pH of 6.0 or 6.9 into the rat pancreatic duct (to model post-ERCP pancreatitis) caused a significant increase in pancreatic edema, serum amylase, neutrophil infiltration, and histological damage, whereas solutions of pH 7.3 injected at equal pressure caused only small damage [22].

Ethanol

Similarly to bile acids, both Yamamoto et al. [23] and we [24,25], have found dose-dependent effects of ethanol on pancreatic ductal function. In guinea pig ducts, the administration of 1 mM ethanol transiently inhibited fluid secretion which then recovered to steady levels [23]. The addition of 1 mM mannitol induced similar effects in secretion, so they seem to be causing non-specific response. In fact, the initial transient inhibition of ductal secretion appears to be due to osmotic effects. The effects of ethanol on secretin-stimulated fluid secretion were markedly different [23]. 0.3–30 mM ethanol significantly augmented secretin-stimulated fluid secretion which is mediated via intracellular Ca^{2+}- and cAMP-dependent pathways [23]. Furthermore, 100 mM ethanol significantly decreased ductal secretion stimulated by physiological concentrations (1 pM) of

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