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The Acinar Cell and Early Pancreatitis Responses

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Abstract

Pathologic responses arising from the pancreatic acinar cell appear to have a central role in initiating acute pancreatitis. Environmental factors that sensitize the acinar cell to harmful stimuli likely have a critical role in many forms of pancreatitis, including that induced by alcohol abuse. Activation of zymogens within the acinar cell and an inhibition of secretion are critical, but poorly understood, early pancreatitis events. While there is firm evidence relating trypsinogen activation to pancreatitis, the importance of other zymogens has been less studied. Preliminary studies suggest that trypsin may be activated by mechanisms that are distinct from other zymogens. Further, unlike the small intestine, it may not catalyze the activation of other zymogens. These features could affect strategies aimed at inhibiting proteases to treat pancreatitis. Specific intracellular signals are required to activate pancreatitis pathways in the acinar cell. The most important is calcium. Recent studies have suggested that calcium release through specific calcium channels in the endoplasmic reticulum is the means by which pathological elevations in cytosolic calcium occur. Although the targets of abnormal calcium signaling are unknown, calcineurin, a calcium-dependent phosphatase, may serve such a role. Finally, recent work suggests that an acute acid load might sensitize the acinar cell to pancreatitis responses. Therapies aimed at preventing or reversing the effects of an acid load on the pancreas may be important for treatment.

The pathogenesis of acute pancreatitis is poorly understood. However, information from cellular and in vivo studies, as well as genetic studies in humans, suggests that pathologic events that begin in the pancreatic acinar cell often initiate this disease. This cell is designed to synthesize, store, and secrete the enzymes required for nutrient digestion. Under physiologic conditions, most of these enzymes, particularly proteases, become active only when they reach the small intestine. Conditions that cause pancreatitis result in distinct changes in acinar cell signaling. These changes initiate a spectrum of pathologic changes within the acinar cell that include the activation of digestive enzymes, generation and release of inflammatory and vascular mediators, inhibition of acinar cell secretion, changes in paracellular permeability, and stimulation of cell death pathways. The molecular details of these responses have been the focus of many recent studies and have linked the genetics of pancreatitis with molecular and cellular studies.

Sensitization

One feature of acute pancreatitis is that the pathologic acinar cell responses that have been linked to disease often represent modifications of physiologic stimuli and cellular responses. As shown in Table 1, both neural and humoral pathways stimulate the acinar cell's

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Conflict of interest

The authors disclose no conflicts.

physiologic response to a meal. Much like the nervous system's "excitatory neurotoxicity" response to supraphysiologic concentrations of endogenous ligands, supraphysiologic concentrations of cholecystokinin (CCK) cause pancreatitis responses in the acinar cell and can initiate pancreatitis in vitro and in vivo. The potential relevance of this response has been underscored by the recent observation that functional CCK-1 receptors are present on the human pancreatic acinar cell.¹ However, the levels of cholecystokinin necessary to cause pancreatitis are probably at least 10-fold greater than those observed in response to a meal; there is no evidence that such levels are reached, even in pathologic settings. This and other observations has led to the concept that multiple factors may be required, acting in concert, to initiate acute pancreatitis. Thus, agents that sensitize the pancreas to physiologic stimulation by CCK or acetylcholine, could represent a key disease mechanism. In this context, a number of studies have suggested that ethanol alone does not cause pancreatitis, but that it sensitizes the pancreas to physiologic stimulation by CCK and acetylcholine.²⁻⁴

Zymogen Activation

A series of molecular and cellular mechanisms have developed to protect the pancreas from enzymes that are activated in the cell, especially proteases. First, many of the digestive enzymes, and all of the proteases, are synthesized and stored as inactive proproteins known as zymogens. Second, the storage of zymogens in zymogen granules limits their access to other acinar cell compartments should they become active. Under physiologic conditions, zymogens are converted to active enzymes only after they reach the small intestine. During the initial phases of acute pancreatitis, these zymogens are activated within the pancreatic acinar cell. Several mechanisms protect the acinar cell from activated proteases. The best known is that for trypsin and shown in Figure 1. Thus, trypsin activity that might be generated in the acinar cell is reduced by 2 mechanisms; a trypsin inhibitor and trypsin-degrading proteases. Mutations of proteins involved in these pathways affect the risk of developing pancreatitis. Such mutations can either lead to generation of more trypsin, reduce the activity of the trypsin inhibitor, SPINK1, or reduce trypsin degradation.⁵⁻⁷

There are a number of issues that are unresolved with respect to zymogen activation within the acinar cell. First, the identity of the activation compartments remains unclear. We and others have provided evidence that trypsinogen activation occurs within a compartment that contains markers of lysosomes and recycling endosomes. Whether this represents the compartment in which activation takes place or that has fused with another compartment remains unclear. Using differential centrifugation of homogenates from caerulein pancreatitis, we have detected active enzymes in both a heavy and very light compartment.⁸ Thus, it is possible that multiple acinar cell compartments might support protease activation. Moreover, distinct acinar cell compartments might support activation in a time-dependent manner or vary according to insult. In this context, external factors may modulate pathologic responses of the acinar cell, including zymogen activation. For example, 1 study has shown that inflammatory cells mediate a major late component of acinar cell trypsinogen activation through a reduced nicotinamide adenine dinucleotide phosphate-oxidase dependent mechanism.⁹ Though the mechanism of this response is unclear, it does suggest the role of inflammation may be broader than predicted.

Although the features of trypsinogen processing in the acinar cell have been widely studied, there is little information relating to the activation of other zymogens in the acinar cell. It is believed that in the small intestine, the major mechanism for zymogen activation begins with processing of trypsinogen by enterokinase, followed by trypsin-dependent activation of other proteases. Whether such a cascade exists in the pancreatic acinar cell is unknown. Indeed, we have found that chymotrypsinogen and procarboxypeptidases can be activated in a trypsin-independent manner.⁸ Further, preliminary studies from our laboratory suggest that

trypsinogen and chymotrypsinogen processing can take place in distinct acinar cell compartments (C. Shugrue, unpublished observations). These findings suggest that the activation of trypsinogen might not mediate the activation of other proteases in the acinar cell. Although identity of the other activator remains unknown, the observation does have clinical implications. First, the contribution of trypsin versus other proteases to cell injury and pancreatitis remains unclear. Even though disordered trypsinogen processing causes hereditary pancreatitis and predisposes to other forms of pancreatitis, its overall importance in acute pancreatitis is uncertain. In this context, in a transgenic model in which trypsinogen is spontaneously activated in the acinar cell, no pancreatitis is observed.¹⁰ Others have observed that reducing trypsinogen activation in mice by either genetically deleting cathepsin B or overexpressing a trypsin inhibitor did not prevent acute pancreatitis. One implication of these findings is that strategies aimed at inhibiting trypsin to prevent or reduce acute pancreatitis might fail if other harmful proteases are being activated.

Stimulation of acinar cell autophagy has been a recognized feature of acute pancreatitis for years, although its role is poorly understood. Recent studies in mice with genetic deletion of a key autophagy protein (Atg5) found a requirement for autophagy in trypsinogen activation in the acinar cell.¹¹ Thus, mice with defective autophagic function were protected from acute pancreatitis. A more recent study has suggested that autophagy is defective in a model of pancreatitis that uses lipopolysaccharide with chronic ethanol feeding.¹² One potential explanation for the discrepancy between these two studies could be that autophagy might have multiple roles in acute pancreatitis. For example, in the context of Figure 1, it is conceivable that distinct autophagic events could modulate zymogen activation versus the degradation of active enzymes.

Cell Signaling

Two pathologic intracellular signals in the acinar cell have been linked to the initiation of acute pancreatitis. First, acute changes in cytosolic Ca^{2+} signaling have been firmly associated with several forms of acute pancreatitis. Features of this abnormal signal include a loss of Ca^{2+} oscillations and the appearance of sustained elevated peak levels of cytosolic Ca^{2+} . Although there are likely several mechanisms for developing this pathologic signal, it appears that a Ca^{2+} release channel in the endoplasmic reticulum, the ryanodine receptor, makes a prominent early contribution.¹³ Subsequent studies suggest that an important target of Ca^{2+} may be protein phosphatase 2B, calcineurin.¹⁴ Because both the ryanodine receptor and calcineurin can be targeted by specific drugs, they may represent important therapeutic targets.

A second pathologic signal that appears to be linked to acute pancreatitis responses is the activation of specific protein kinase C isoforms.¹⁵ This includes stimulation of $\text{NF}\kappa\beta$ and zymogen activation.^{16,17} After physiologic stimulation, activation of protein kinase C (PKC)- δ is observed. However, under conditions that generate acute pancreatitis, activation of both PKC- δ and PKC- ϵ is observed. The sensitizing effects of ethanol may be linked to PKC activation. Thus, when combined with physiologic CCK activation of PKC- δ , ethanol causes activation of PKC- ϵ .¹⁶ This pattern recapitulates that elicited by supraphysiologic concentrations of CCK. Protein kinase D (PKD), which is downstream from PKC- δ and PKC- ϵ , appears to mediate some of these responses (Thrower et al, unpublished observations). Although these studies provide compelling evidence that specific PKC isoforms might mediate early acute pancreatitis responses, the molecular targets of these enzymes are unknown.

Inhibition of Secretion

A recognized feature of acute pancreatitis is decreased secretion into the small intestine. A number of factors probably contribute to this response.¹⁸ These include reduced apical secretion from the acinar cell, enhanced basolateral secretion, and disruption of the paracellular barrier (Figure 2). These responses occur soon after the onset of disease.¹⁹ For example, reduced secretion from the acinar cell and disruption of the paracellular barrier can be observed within 15 minutes of disease onset.²⁰ Although the decreased apical secretion has been attributed to disruption of the actin cytoskeleton, the precise mechanism of this response is not fully understood.²¹ However, recent studies have elucidated mechanisms that regulate non-apical secretion from the basolateral domains of the acinar cell. In the basal state, 2 factors restrict the interaction of zymogen granules with the basolateral membrane. First, their distribution is restricted to the apical domain of the acinar cell. This appears to occur by tethering of zymogen granules to the apical actin cytoskeleton. When this structure is disrupted in acute pancreatitis, the zymogen granules disperse throughout the cytoplasm.²² Other studies have demonstrated that under basal conditions, specific cellular machinery blocks zymogen granule exocytosis at the basolateral membrane. At this membrane, the munc18 protein (mammalian homologue of the unc-18 gene; also called nSec1 or rbSec1) binds syntaxin 4, a protein required for zymogen granule exocytosis.⁴ At the onset of pancreatitis, the phosphorylation of munc18 by PKC eliminates its inhibition of syntaxin 4, allowing the protein to participate in basolateral exocytosis of zymogen granules. It is very likely that the combined disruption of the apical junctional barrier and basolateral exocytosis allow pancreatic enzymes to enter the interstitium and contribute to the increase in serum levels of pancreatic enzymes observed very early in the course of acute pancreatitis. It is the retention of most of the activated enzymes, however, within the pancreatic acinar cell which is likely to be most important to the pathogenesis of the disease.

Low pH Effects

One of the features of zymogen activation in the pancreatic acinar cell is that it appears to require a low pH compartment. Early studies used purified enzyme preparations to demonstrate that the processing of trypsinogen to trypsin, through autoactivation or by cathepsin B, required an acidic pH.²³ Subsequent studies used chloroquine and monensin, drugs that nonselectively raise intracellular pH, to demonstrate that a low-pH compartment is required for activation of pro-carboxypeptidases, trypsinogen, and chymotrypsinogen by the acinar cell.^{24,25} Recent studies suggest that activation of a particular proton transporter, the vacuolar adenosine triphosphatase (vATPase), is critical for zymogen activation in the pancreatic acinar cell. Inhibitors of the vATPase, such as bafilomycin and concanamycin completely inhibit zymogen activation in the acinar cell. Multiple isoforms of the vATPase mediate proton transport across different organelles, as well as the plasma membrane, and thus mediate many critical cell functions. Unfortunately, because bafilomycin and concanamycin inhibit *all* vATPase isoforms and often cause cell toxicity, they cannot be used for therapeutic applications.

Clinical conditions that predispose to acute pancreatitis can provide important clues related to disease mechanisms. A good example may be conditions that expose the pancreas to an acute acid load. Subjects with mitochondrial energy defects and propionic acidemia develop severe lactic acidosis and acute pancreatitis.²⁶ Similarly, exposure to mitochondrial toxins has been associated with fatal pancreatitis.²⁷ In patients with diabetic ketoacidosis, the extent of the acidosis is the major risk factor for those who will develop acute pancreatitis.²⁸ A final example may be that of post endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis. The contrast dye used to opacify the pancreatic duct during ERCP is mildly acidic. In a rat model of post ERCP pancreatitis, this dye caused pancreatitis that was

largely alleviated by buffering the contrast to a more neutral pH.²⁹ This pancreatitis response appears to result, in part, from stimulation of pH-sensitive channels that reside on pancreatic nerves.

The pancreas may be particularly susceptible to either systemic or regional acidosis. Even in its basal state, the pancreatic parenchyma is mildly acidic; its pH drops further in humans and in animal models of acute pancreatitis.³⁰ Further, acute ethanol administration dramatically decreases pancreatic pH.³¹ This effect is likely due to decreased pancreatic blood flow and can reach values of less than pH 7.0. In the early phases of acute pancreatitis, arterial vasospasm is observed and would be anticipated to further decrease gland pH.³² Recent experimental studies from our laboratory support the concept that an acute acid load can sensitize the pancreas to the development of acute pancreatitis.³³

Two disease models have now been used to examine the role of an acid load in pancreatitis: a cellular model of acute pancreatitis that uses isolated groups of acinar cells known as acini and an in vivo disease model.³³ In acini, reducing extracellular pH to mimic an acid load was found to dramatically sensitize acini to the effects of a CCK analogue (caerulein) on zymogen (trypsinogen and chymotrypsinogen) activation and cell injury. An acid load alone had no effect on these pancreatitis responses. In addition, the effects of acid were mediated by the vATPase. When similar studies were performed in vivo, an acid load sensitized rats to pancreatitis responses induced by either physiologic or supraphysiologic concentrations of caerulein. These studies suggest that an acute acid load can both reduce the threshold for development of pancreatitis and worsen disease.

Although these studies have emphasized the potential effects of an acid load on the pancreatic acinar cell, the effects of such metabolic changes may be much broader.³⁴ This includes effects of pH on nerves, inflammatory responses, and epithelial function.³⁵ Thus, nerves have pH sensitive channels, many of which are linked to pain responses and the release of inflammatory mediators such as substance P.³⁶ An acid load can also affect the activation of inflammatory cells and the elaboration of inflammatory mediators such as TNF, NO, and IL-6.³⁴ Finally, in addition to our observations relating to the pancreatic acinar cell, an acid load can also affect paracellular permeability in epithelial cells.³⁷ These studies suggest that the effects of an acid load can affect many regulatory events that influence the severity of acute pancreatitis (Figure 3).

These studies of acid loads are likely to be directly relevant to the treatment of acute pancreatitis. Aggressive volume expansion is a cornerstone for acute pancreatitis treatment. In addition to reducing tissue hypoxia and free radical generation, volume expansion is likely to have another benefit: raising pancreatic pH. However, the optimal solution for volume expansion has not been established. In this context, the pH of normal saline is usually below 6.0 and provides a significant acid load. Further, the effects of various buffers on neural and inflammatory responses vary considerably. Prospective studies comparing these buffer systems in acute pancreatitis and other inflammatory diseases are needed.

Summary

Pathologic responses arising from the pancreatic acinar cell have a central role in initiating acute pancreatitis. Trypsinogen activation is a critical component of the disease. Although genetic studies unequivocally link trypsinogen mutations directly to pancreatitis and as a risk factor for developing disease, the impact of trypsin versus other proteases in disease pathogenesis remains unclear. There is growing evidence that the mechanisms for activating trypsinogen may differ from those that activate other zymogens. Further, unlike the intestine, when trypsin is generated in the acinar cell, it may not activate other zymogens.

Strategies to reduce protease activities in the acinar cell as a treatment for acute pancreatitis might need to target both trypsin and other proteases to be maximally effective. Distinct intracellular signals, such as pathologic changes in cytosolic calcium signaling and activation of PKC isoforms, are likely required to initiate disease. In experimental models, some of the mechanisms of this calcium signaling, such as the ryanodine receptor, and candidate target molecules, such as calcineurin, have been identified. However, the cellular targets of calcium and calcineurin remain unclear. Nonetheless, these findings might have clinical implications because drugs are available that affect these signaling and effector mechanisms. Finally, factors that appear to increase the risk of acute pancreatitis or its severity, such as ethanol, do not cause pancreatitis alone, but often appear to act by sensitizing the acinar to other injurious factors. This may also be true of an acute acid load. Therapies aimed at reducing the impact of these sensitizers may be useful for preventing or treating acute pancreatitis.

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Abbreviations used in this paper

CCK	cholecystokinin
ERCP	endoscopic retrograde cholangiopancreatography
PKC	protein kinase C
PKD	protein kinase D
vATPase	vacuolar adenosine triphosphatase

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Figure 1.

Trypsinogen activation, trypsin inhibition, and degradation in the acinar cell. The acinar cell has evolved specific mechanisms that regulate the processing of trypsinogen and trypsin within the acinar cell that are distinct from its metabolism in the intestine. Thus, cathepsin B has a central role in regulating trypsinogen activation (A). Two mechanisms have evolved to reduce trypsin activity when generated in the acinar cell. SPINK1 is an endogenous trypsin inhibitor that is present in the secretory pathway; the basal levels of SPINK1 would inhibit very small amounts of trypsin (B). Some proteases (anionic trypsin, chymotrypsin C) within the secretory pathway, and perhaps some lysosomal proteases, can degrade trypsin (C). Notably, mutations in proteins in these pathways have been found to either cause (cationic trypsinogen) or predispose to (eg, SPINK1, chymotrypsin C) the development of pancreatitis (model suggested by Szmola R).

Figure 2.

Pancreatic secretion is inhibited by multiple mechanisms in acute pancreatitis. In physiologic conditions, zymogen granules are concentrated at the apical pole of the acinar cell where secretion occurs. Secretion from the basolateral region is inhibited. Tight paracellular barriers prevent the flux of secretory products from the lumen to the interstitium. In acute pancreatitis, apical secretion is inhibited, zymogen granules redistribute away from the apical pole, and exocytosis at the basolateral membrane is no longer inhibited. Disruption of the tight junctions allows flux of luminal contents into the interstitium.

Figure 3.
An acute acid load can affect many pancreatitis responses.

Table 1

Acinar Cell Responses

Physiologic	Pancreatitis
Stimuli	Stimuli
<ul style="list-style-type: none"> • Hormones (cholecystokinin) • Neurotransmitters (acetylcholine) 	<ul style="list-style-type: none"> • Hyperstimulation • Sensitizers • Ethanol • Acid load
Responses	Responses
<ul style="list-style-type: none"> • Ca^{2+} oscillations • PKC-δ activation • Increased secretion • Cell growth 	<ul style="list-style-type: none"> • Sustained elevated Ca^{2+} signal • PKC-δ and PKC-ϵ activation • Reduced secretion • Zymogen activation • Inflammatory mediators • Cell death