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Molecular basis for pancreatitis

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Abstract

Purpose of review—This timely review will focus on clinical and basic science studies that have greatly advanced our knowledge of the molecular mechanisms of both acute pancreatitis and chronic pancreatitis over the last year.

Recent findings—Animal models of both severe acute pancreatitis and chronic pancreatitis have recently been developed. Several unexpected protective mechanisms, mediated by the protease activated receptor 2 and heat shock protein 70, have been described. A genetic study suggested that polymorphisms in toll-like receptor-4 might affect the risk of developing infections in acute pancreatitis. Studies of chronic pancreatitis have shown that specific neural receptors, transient receptor potential vanilloid subtype 1, mediate pain responses in a model of chronic pancreatitis. The pancreatic zymogen, chymotrypsin C, can degrade pathologically activated trypsin in the acinar cell. Inactivating mutations in chymotrypsin C have been reported to predispose to the development of chronic pancreatitis, especially in those who are prone to alcohol abuse.

Summary—The implications of the last year's findings are widespread. Improved animal models of acute pancreatitis and chronic pancreatitis will be critical for performing pilot studies of therapy. A greater understanding of genetic factors and pain responses could lead to potential treatments. This review will first discuss issues related to acute pancreatitis, and then conclude with studies most relevant to chronic disease.

Keywords

calcium; chymotrypsin C; lipopolysaccharide; toll-like receptor

Introduction

Recent clinical and basic science studies have furthered our understanding of pancreatitis. An important advance for studies of both acute and chronic disease has been the development of animal models that may more closely recapitulate human disease. These should be useful for understanding disease mechanisms and testing therapeutic interventions. In this review we focus on the molecular basis underlying the mechanism of the disease at both the acute and chronic level.

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Acute pancreatitis

There are many potential causes of acute pancreatitis, the two major ones being gallstones and alcohol. The majority of recent studies, detailed in the following section, have employed experimental models of acute pancreatitis to explore the molecular basis of subsequent cellular responses.

Causes of pancreatitis

Recent studies have identified potential mechanisms for several of the common causes of acute pancreatitis.

Bile acids—Exposure of pancreatic acinar cells to bile during biliary acute pancreatitis may contribute to the disease. Many past studies have shown that pathologic increases in acinar cell cytosolic calcium ($[Ca^{2+}]_i$) are linked to the early events in acute pancreatitis. Fischer *et al.* [1] found that bile acids induced pathologic increases in acinar cell $[Ca^{2+}]_i$ through a phosphatidylinositol-3 kinase (PI3K)-dependent mechanism by preventing re-uptake of Ca^{2+} into the endoplasmic reticulum. It was also shown by Barrow *et al.* [2] that bile-mediated Ca^{2+} responses are enhanced by cellular ATP depletion, suggesting that elevations in bile acids and ischemia may synergize to cause pancreatic injury.

Alcohol—Disordered secretion, including inhibition of apical secretion and enhanced basolateral exocytosis, are early features of acute pancreatitis and may be central to disease pathogenesis. Gaisano's group confirmed that caerulein hyperstimulation, a condition that causes acute pancreatitis, results in increased basolateral exocytosis, then linked this response to disinhibition by Munc 18c of a sensitive factor attachment protein receptor (SNARE) complex that includes syntaxin 4 and synaptosomal associated protein (SNAP)-23. Lam *et al*. [3••] and Cosen-Binker *et al*. [4,5] have now shown that acute ethanol exposure sensitizes the acinar cell to the effects of physiologic concentrations of cholecystokinin (CCK) by causing both inhibition of apical inhibition and basolateral exocytosis through the same mechanism.

Hypertriglyceridemia—The mechanism of hypertriglyceridemic pancreatitis may involve the release of free fatty acids (FFA) through the hydrolysis of triglycerides by pancreatic lipase. Pancreatitis-associated ascitic fluid plays a critical role in acute pancreatitis. Gutierrez *et al*. [6] have now shown ascites to contain high concentrations of oxidized FFA, which interferes with the endogenous regulation of inflammation and may promote macrophage activation in acute pancreatitis.

Hemolysis—Clinical evidence suggests that acute pancreatitis can arise as a complication of massive hemolysis; a recent study by Saruc *et al*. [7] supports this hypothesis using an experimental model. Hemolysis induced in rats by intra-peritoneal (i.p.) injection of acetylphenylhydrazine (APH) caused increased pancreatic cytokine levels and histological signs of acute pancreatitis. Furthermore, free vascular heme seems to act as the signaling molecule for triggering inflammation, though the mechanism remains undetermined.

Experimental models of pancreatitis—A limiting feature of the commonly used caerulein-hyperstimulation model of acute pancreatitis is that it causes only mild disease. Several new in-vivo mouse models now generate severe acute pancreatitis. This includes mouse models of acute pancreatitis that use retrograde pancreatic duct infusion of the bile salt, sodium taurocholate by Laukkarinen *et al*. [8], and i.p. injection of L-arginine by Dawra *et al*. [9•]. These models may prove useful for studying therapeutic interventions and examining disease mechanisms in transgenic mice.

Cellular responses

A series of acinar cell and inflammatory cell responses underlie the pathogenesis of acute pancreatitis. Some of these have been explored in publications during the last year.

Membrane permeability—One of the earliest events in acute pancreatitis may be the disruption of the acinar cell plasma membrane. Muller *et al*. [10] used both caerulein and taurocholate-induced models of acute pancreatitis in rats to demonstrate that endogenous albumin and immunoglobulin G (IgG) entered acinar cell cytosol. Such defects could contribute to pathologic increases in $[Ca^{2+}]_i$ and allow cytoplasmic proteins to leak from the cell. It will be of interest to determine how these defects occur, whether they might be related to the plasma-membrane blebbing that has been observed in acute pancreatitis or to defects in the complex process of membrane resealing, and if such defects are found in human acute pancreatitis.

Zymogen activation—Premature intracellular activation of trypsinogen by the lysosomal hydrolase cathepsin B has generally been considered a pivotal event in the initiation of acute pancreatitis. However, using a cathepsin B inhibitor, CA074Me, Van Acker *et al*. [11] showed that enzyme colocalization and other acute pancreatitis events, such as actin redistribution and inflammation, were cathepsin B independent. Other mechanisms, such as those mediated by $[Ca^{2+}]_i$ and its protein targets, might mediate these responses. The Ca^{2+}-dependent protein phosphatase calcineurin (PP2B) might serve this role. Husain *et al*. [12] showed that the calcineurin inhibitor FK506 or a cell-permeable calcineurin inhibitory peptide reduced zymogen activation without affecting initial elevations in $[Ca^{2+}]_i$ or enzyme secretion. Thus, PP2B may be down-stream to the pathologic $[Ca^{2+}]_i$ that typifies acute pancreatitis. The effects of elevating cAMP on acute pancreatitis are complex, but the most important response might be to enhance the secretion of active enzymes. Chaudhuri *et al*. [13] found that cyclic adenosine mono-phosphate (cAMP)-dependent protein kinase A (PKA) and the cAMP-binding protein Epac (exchange protein directly activated by cAMP) could mediate acinar cell secretion. These findings might explain the positive effects of secretin, a cAMP agonist, in reducing endoscopic retrograde cholangiopancreatography (ERCP)-associated acute pancreatitis reported by some studies.

Inflammation—Two recent studies have focused on the neuropeptide, substance P and its role in pancreatic inflammation. Ramnath *et al*. [14] reported that expression of the substance P gene (preprotachykinin-A, PPT-A) and neurokinin-1 receptor (NK-1R), the primary receptor for substance P, were increased in caerulein-treated mouse pancreatic acinar cells. Furthermore, the messenger hydrogen sulphide was shown to provoke inflammation through a substance P, NK-1R related pathway by Tamizhselvi *et al*. [15••]. Ramnath *et al*. [14] also showed that substance P stimulated early protein kinase C (PKC)-δ activation, followed by increases in mitogen-activated protein kinase kinase (MAPKK), mitogen extracellular response kinase kinase (MEKK1), MAP kinases, extracellular signal-regulated kinase (ERK) and c-Jun N-terminal kinase (JNK) activities as well as activating nuclear factor kappa B (NFKB) and activator protein (AP)-1. This led to production of the inflammatory chemokines monocyte chemotactic protein-1 (MCP-1), macrophage inflammatory protein (MIP)-19 and MIP-2. These two studies collectively highlight the importance of the substance P pathway in pancreatic inflammation.

The proto-oncogene *Tpl2* (tumor progression locus-2) can modulate some inflammatory processes. Van Acker *et al*. [16] showed that *Tpl2* ablation markedly reduced pancreatic and lung inflammation in secretagogue-induced or bile salt-induced pancreatitis but did not alter pancreatic injury/necrosis in either model.

Tumor necrosis factor (TNF)-α, a key regulator of pro-inflammatory genes, may be a target for the treatment of acute pancreatitis. In caerulein-induced acute pancreatitis, the TNF-α inhibitor thalidomide was found to reduce disease by Malleo *et al.* [17]. Study by Nishida *et al*. [18] found that in addition to TNF-α, interleukin (IL)-1β and interferon (IFN)-γ increase during experimental acute pancreatitis, leading to greater levels of the pro-inflammatory cytokine IL-32 in human pancreatic periacinar fibroblasts. The latter study underscores the fact that there are changes in multiple inflammatory cytokines/chemokines during acute pancreatitis and these have distinct mechanisms for causing injury. One implication of such findings is that clinical therapies may need to target multiple inflammatory mediators.

Endoplasmic reticulum stress—Endoplasmic reticulum stress can lead to accumulation of unfolded proteins, initiation of the unfolded protein response (UPR), inflammation and cell death. Kubisch and Logsdon [19•] reported that stimulation of rat pancreatic acini with three secretagogues, CCK8, CCK-JMV-180 or bombesin, resulted in distinct UPR responses that included increased chaperone BiP levels, PKR-like endoplasmic reticulum kinase (PERK) phosphorylation, X box-binding protein 1 (XBP1) splicing and CCAAT/enhancer binding protein homologous protein (CHOP) expression. Submaximal concentrations of CCK-8 or treatments with JMV-180 and bombesin only activated certain components of the UPR that are involved in protein 'quality control'. Supramaximal CCK-8, however, stimulated all components of the UPR including CHOP, a pro-apoptotic factor. The role of CHOP in accelerating pancreatitis has been further defined by Suyama *et al*. [20] in elegant studies using CHOP deficient ($CHOP^{-/-}$) mice. Treatment with caerulein and lipopolysaccharide (LPS), a more severe model of acute pancreatitis, resulted in less expression of inflammation-associated caspases (caspase-11 and caspase-1) in $CHOP^{-/-}$ mice. These studies indicate a pivotal role for the endoplasmic reticulum stress-CHOP pathway in accelerating pancreatitis through induction of inflammation-linked caspases.

Apoptosis—The severity of pancreatitis may depend on the mechanism of cell death; greater levels of apoptosis over necrosis favor milder disease. To examine the mechanisms of apoptosis, Baumgartner *et al*. [21] used the oxidative stressor menadione and identified two independent apoptotic pathways in pancreatic acinar cells. The first is the classical caspase-9-mediated pathway that is Ca^{2+}-dependent, mediated by mitochondria and is rapidly initiated. The second is much slower, mediated by caspase-8, depends on the lysosomal activities of cathepsins and is used when the caspase-9 pathway is disabled. This information might be used to develop strategies for shifting cell death pathways to favor apoptosis during acute pancreatitis.

Protective mechanisms—A number of protective and restorative mechanisms in acute pancreatitis have been characterized over the past year. Singh *et al*. [22] used protease-activated receptor-2 (PAR-2) deficient mice in a caerulein acute pancreatitis model to demonstrate that PAR-2 stimulation caused exocrine secretion, thus protecting acinar cells from the damaging effects of activated enzymes. Study by Bhagat *et al*. [23•] explored the protective role played by heat shock proteins (HSPs), particularly HSP 70, using both caerulein and L-arginine models of acute pancreatitis. Sodium arsenite pretreatment was used to upregulate HSP 70 expression and significantly reduced the severity of pancreatitis in both models. The pancreas is a rich source of the polyamine spermidine, and a study by Hyvonen *et al*. [24] showed that depletion of these polyamines led to acute necrotizing pancreatitis. Replacement of depleted polyamines using methylated polyamine analogues prior to induction of acute pancreatitis prevented development of the disease, strongly supporting an endogenous protective role for these compounds.

Recently, the pancreatitis-induced vacuole-membrane protein-1 (VMP-1) has been shown by Ropolo *et al*. [25•] to trigger autophagy in mammalian cells. Autophagy causes the

degradation of cytoplasmic cellular constituents characterized by the sequestration of bulk cytoplasm and organelles into double membrane-bound vesicles. Although autophagy is an early feature of acute pancreatitis, its role in the disease remains unclear.

The pancreas exhibits a remarkable ability to restore its function after severe acute pancreatitis, but the recovery mechanisms are poorly understood. Siveke *et al*. [26] used both chemical and genetic approaches to block Notch signaling in caerulein-induced pancreatitis in mice and found that cellular regeneration was impaired in Notch-compromized animals.

Genetic factors—Two studies from the last year have highlighted the importance of genetic factors in predisposing patients to acute pancreatitis [27,28•]. Gao *et al*. [28•] investigated why some patients are more prone to pancreatic infection during acute pancreatitis. LPS or endotoxin may cross leaky paracellular barriers in the colon or be released into the blood stream by circulating Gram-negative bacteria during acute pancreatitis. LPS can then bind to toll-like receptors (TLRs) on the surface of the acinar cell, producing a host defense response. However, in some patients, a polymorphism in TLR-4 led to impaired signaling and lack of a defensive response, rendering them more prone to infection. In another genetic study, Chang *et al*. [27] found that mutations on the cystic fibrosis transmembrane conductance regulator (CFTR) predisposed patients with elevated lipids to developing hypertrigly-ceridemic pancreatitis. Further studies that use newer genome-wide analysis will likely reveal additional genetic factors that affect the risk of developing acute pancreatitis or its severity.

Miscellaneous mechanisms—Ghrelin is a ligand of the growth hormone secretagogue receptor (GHSR) and has been shown to affect exocrine pancreatic secretion. Previous studies have suggested that ghrelin may modulate the severity of acute pancreatitis and that serum ghrelin levels predict severity in acute pancreatitis. Lai *et al*. [29] reported that both ghrelin and its receptor are present in pancreatic acinar cells and that the receptor was downregulated in acute pancreatitis. The data indicate that a ghrelin-dependent system is present in the exocrine pancreas. However, its function in normal pancreatic physiology and pancreatitis requires further study.

Chronic pancreatitis

Chronic pancreatitis is characterized by chronic inflammation, progressive fibrosis, pain and loss of exocrine and endocrine function. The molecular basis of these responses is addressed by many of the studies detailed in the following section.

Inflammation and fibrosis

Pancreatic stellate cells (PSCs) play a key role in pancreatic fibrosis. Masamune *et al*. [30] reported that the nicotinamide adenine dinucleotide phosphate (NADPH) oxidase in PSCs generated reactive oxygen species that modulate their activation and the subsequent deposition of extracellular matrix (ECM), leading to pancreatic fibrosis. Coculture experiments with PSCs and peripheral blood mononuclear cells (PBMCs) reported by Michalski *et al*. [31••] demonstrated increased fibronectin secretion from the PBMCs as well as increased levels of IL-6, MCP-1, transforming growth factor (TGF)-β, and ECM from the PSCs. Thus, an increased infiltration of mononuclear cells, as seen in chronic pancreatitis, might be a trigger for PSCs to initiate fibrosis and inflammation.

Inflammation and pain

Michalski *et al*. [32] also implicated PBMCs in the neuroimmune regulation of chronic pancreatitis pain. They reported that pain levels in patients with chronic pancreatitis correlated with neuropeptide pituitary adenylate cyclase-activating polypeptide (PACAP) levels. PBMCs from patients with chronic pancreatitis were more responsive to the effects of PACAP. Xu *et al*. [33••] reported that pancreatic hyperalgesia is mediated by upregulation of the transient receptor potential vanilloid 1 (TRPV1) in a model of chronic pancreatitis. As pharmacologic TRPV1 inhibition reduced visceral pain responses in this model, this might be a target for pain treatment in chronic pancreatitis.

Alcohol use and chronic pancreatitis

Fortunato *et al*. [34•] reported that chronic alcohol exposure in rats increased the pancreatic activity of an anti-inflammatory nuclear receptor, peroxisome proliferator-activated receptor gamma (PPARγ). Although PPARγ activity was associated with reduced immune cell and inflammatory responses, damage to acinar cell mitochondria and lysosomes and pericellular fibrosis and protease activation occurred. These results could explain how chronic alcohol use might predispose the pancreas to chronic pancreatitis without causing intense inflammation.

As only a small percentage of alcohol abusers develop pancreatitis, additional genetic, host or environmental factors are thought to be important. Jerrells *et al*. [35•] examined the effects of coxsackievirus B3 viral infection on the development of alcoholic pancreatitis in rats. Although the virus caused pancreatitis in the absence of alcohol, the ethanol-fed animals developed much worse disease. The study raises the possibility that acute or chronic viral infections might predispose to alcoholic pancreatitis.

Animal models of chronic pancreatitis

Two experimental models having features of alcoholic chronic pancreatitis were developed. Gukovsky *et al*. [36•] combined ethanol feeding with cyclosporine and caerulein at specific times to induce loss of parenchyma, prolonged inflammation and fibrosis. A second model reported by Vonlaufen *et al*. [37••] was induced by giving bacterial endotoxin LPS to rats fed with alcohol for 10 weeks. Pancreatic injury, PSC activation and pancreatic fibrosis were all noted. Whether either of these models will cause the enduring disease of chronic pancreatitis as seen in humans is unclear.

Genetic factors

Patients with chronic pancreatitis have an increased risk of developing pancreatic cancer, though the etiologic mechanisms are unclear. Guerra *et al*. [38•] reported that somatic activation of the pro-oncogene K-Ras in a transgenic mouse during the embryonic period in cells of acinar/centroacinar origin resulted in pancreatic intra-epithelial neoplasia (PanINs) and invasive pancreatic ductal adenocarcinoma. However, K-Ras activation in adult mice led to cancer progression only when mice were challenged with a mild form of chronic pancreatitis. The findings suggest that tissue damage from chronic pancreatitis in addition to genetic factors could lead to pancreatic cancer development.

New genetic etiologies for chronic pancreatitis have been reported this year. Le Marechal *et al*. [39] and Masson *et al*. [40] reported that both duplication and triplication copy number variants of the cationic trypsinogen gene may result in a gain of function in trypsin by a gene dosing effect. Mutations in the signal peptide region of SPINK were reported to cause chronic pancreatitis in the absence of other genetic defects by Kiraly *et al*. [41]. It is likely that this represents a special situation for SPINK and does not change the paradigm that most SPINK mutations do not alone cause chronic pancreatitis. Degradation of trypsin by

chymotrypsin C (CTRC) may provide protection against the development of chronic pancreatitis was reported by Szmola *et al.* [42••]. Rosendahl *et al.* [43••] and Masson *et al.* [44•] reported that mutations in CTRC that either impair its activity or reduce its secretion or both could block its degradation of trypsin,. Thus both gain of function mutations in cationic trypsinogen as seen in hereditary pancreatitis as well as loss of function in its degrading enzyme CTRC are linked to chronic pancreatitis.

Conclusion

The last year's publications have advanced our understanding of the mechanisms responsible for acute pancreatitis and chronic pancreatitis. Particularly noteworthy have been the development of rodent models of severe acute pancreatitis and potential models of chronic pancreatitis. Those involving LPS hold particular promise for recapitulating the events observed clinically in chronic pancreatitis. Additional studies have focused on the activation of proteases within the acinar cell as a contributing factor to both acute and chronic disease. Of particular interests are studies showing that chymotrypsin C can degrade trypsin in the acinar cell and that inactivating mutations in this enzyme may be linked to chronic pancreatitis.

References and recommended reading

Papers of particular interest, published within the annual period of review, have been highlighted as:

• of special interest

•• of outstanding interest

Additional references related to this topic can also be found in the Current World Literature section in this issue (p. 644).

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