Intricacies of Host Response in Acute Pancreatitis

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Pancreatitis is, in some instances, a life-threatening disease that arises from multiple causes, through mechanisms that to date remain elusive. But all etiologies have a common outcome, which is inflammation of the pancreas, with variable degrees of systemic inflammatory response. Such a confluence suggests the existence of one or various common pathways, most likely not particular to pancreatitis per se but, rather, dedicated to inflammation in general.

Ongoing research has proved that inflammation is by no means a simple or one-track phenomenon. On the contrary, inflammation has inherent specificity, which at its most basic, is evident when one contemplates the lack of inflammatory response toward undamaged "self." In addition, inflammation may be seen as an entity with different "shades," brought on by stimuli different in nature and intensity, potentially resulting in drastically different end points, with ad integrum restitution and death as extremes in a varied spectrum.

Although inflammation is commonly presented to one degree or another as an autonomous process inherent to the innate immune response, it is undoubtedly linked to, and modulated by, the adaptive immune response. Application of this concept as it pertains to pancreatitis has seldom been encountered in the revised literature.

The goal of this article is to describe the key cellular aspects of host response to acute pancreatic injury, attempting at the same time to identify critical nodes at which divergences in response occur. In addition, some closing remarks about the application of chaos theory to this field will be offered.

Mechanisms of injury

In the majority of patients, acute pancreatitis causes mild to moderate symptoms that correlate with mild parenchymal edema and interlobular infiltration by inflammatory cells. There is no marked compromise of acinar cells or circulatory elements. In contrast, severe pancreatitis is associated with hemorrhagic destruction of the gland.[1,2]

The chief physiopathologic event in acute pancreatitis is abnormal activation of zymogens within the acinar cell. Such intraacinar enzyme activation, with subsequent membrane damage and spillage of cellular contents into the general circulation, causes increases in the circulating levels of amylase and lipase. Of note, such increases do not necessarily correlate with the severity of the disease. Instead, markers for the systemic impact of the subjacent physiopathologic processes have better correlation.[1,3]

There is quite a long list of inciting events that can lead to pancreatitis. In the clinical setting, the two most relevant ones are passage of gallstones and alcohol abuse.[1,4,5] The former is thought to cause pancreatitis through a reflux of bile into the pancreatic ductal system, an increase in the intraluminal pressure in the pancreas, or both.[5,6]

Mechanisms for alcohol-induced pancreatitis are less well understood. It has been demonstrated in the Australian possum that alcohol increases pressure in the common bile duct and reduces flow through the sphincter of Oddi.[7] Alcohol acts by increasing the exocrine activity of the pancreas, through direct stimulation or through an increase in the sensitivity to cholecystokinin (CCK). Intragastric ethanol has also been shown to decrease pancreatic perfusion in the Australian possum, suggesting a possible ischemic component.[8] Based on these findings, one could speculate that gallstone pancreatitis and ethanol-induced pancreatitis share increases in pressure in the pancreatic ducts as a common injury mechanism.

There is, literally, another side to the decrease of transsphincteric flow in acute pancreatitis. Biliopancreatic juice exclusion in rats leads to a neurohormonal duodenal response characterized by an increased production of CCK and elevated vagal stimulation of the pancreas through muscarinic receptors. Replacement of bile and pancreatic juices produces a marked attenuation of this

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Abbreviations and Acronyms

ACAMP = apoptotic cell-associated molecular pattern
CCK = cholecystokinin
HSP = heat shock protein
ICAM = intercellular adhesion molecule
IL = interleukin
NF-κB = nuclear factor κB
PAMP = pathogen-associated molecular pattern
RIP = receptor interacting protein
TGF-β = transforming growth factor-β
TLR = Toll-like receptor
TNF = tumor necrosis factor

response. It correlates with a decrease in the severity of pancreatitis induced by ligation of the pancreatobiliary duct in rats.[9]

Pancreatic acinar cell hyperstimulation by CCK has several effects. It induces activation of janus kinase and p38 mitogen-activated protein kinase, both proliferative mediators. CCK enhances the expression of type 3 muscarinic receptors and CCK receptors, priming the cell for further hyperstimulation.[9] CCK is also a direct promoter of acinar cell apoptosis through caspase activation, mitochondrial depolarization, and release of cytochrome c. At the same time, caspase-mediated apoptosis inhibits the development of necrosis and hinders trypsinogen activation.[10]

Even though the mechanisms described refer to alcoholic and gallstone pancreatitis, it is likely that they are also active in other less frequent scenarios. Regardless of the diverse etiologies, the immune system appears to behave homogeneously in acute pancreatitis, showing mostly quantitative variations. The nature of this behavior is the local and systemic overproduction of inflammatory mediators, whose cumulative effect leads to vascular leakage, hypovolemia, acute respiratory distress syndrome, shock, and organ dysfunction.

Acinar cell response to injury: apoptosis versus necrosis

Once injured in a lethal manner, the pancreatic acinar cell can take one of two pathways: necrosis or apoptosis. Traditionally, acute pancreatitis was associated with necrosis, and atrophy was associated with apoptosis. But it has been demonstrated that both forms of cell death occur in diverse models of acute pancreatitis.[11] In addition, a predominance of apoptosis over necrosis has been associated with mild forms of pancreatitis; the opposite holds true for severe forms.[12-14]

The mechanisms through which a pancreatic cell falls into either pathway have become a topic of intense research, and excellent reviews have been published.[14-17] Generally speaking, apoptosis can be initiated through intrinsic and extrinsic pathways, with abundant crosstalk between the two.[15] It can occur under physiologic or pathologic conditions.[16] Morphologically, this process is defined by cytoplasmic and nuclear condensation, chromatin margination, and fragmentation, affecting scattered cells within a given tissue. Ultimately, cellular breakdown into multiple apoptotic bodies that retain selective membrane permeability occurs.[15] Such bodies are promptly phagocytized by neighboring cells or resident macrophages without inflammation.[15] Once committed to apoptosis, a pancreatic acinar cell is less likely to undergo necrosis and intraacinar cell activation of trypsinogen.[12,14]

Classically, necrosis was thought to be triggered by extrinsic factors that overwhelmed the cell's homeostatic capabilities, occurring only in pathologic settings. More recently, it has been described as a nonaccidental process, closely intertwined with apoptosis.[16] It is characterized by enlargement of mitochondria and loss of the plasma membrane integrity, with uncontrolled release of cellular constituents. There is also DNA degradation, which is less extensive and organized than that occurring in apoptosis.[16] Necrosis tends to affect adjacent cells exposed to the same noxious stimulus, and it triggers recruitment of inflammatory cells.

It has been proposed that one factor determining whether a cell remains in the apoptotic pathway or is detoured into necrosis is the level of ATP within the injured cell. Apoptosis is a thermodynamically uphill process, and, as such, the participating enzymes require ATP; necrosis does not seem to require an energy investment. Depletion of this substrate would lead to failure of activation of caspases and other apoptogenic factors, allowing necrosis to ensue by default.[18-20]

Nuclear factor κB (NF-κB) has been proposed as an inhibitor of apoptosis, and, as such, it is an indirect promoter of necrosis. Its activity has been demonstrated in early acute pancreatitis in relation to the onset of inflammation.[21] NF-κB inhibition by curcumin produces an increase in caspase activity in pancreatic acinar cells, leading to enhanced apoptosis.[22] Heat shock proteins (HSP) are endogenous blockers of NF-κB. Caerulein-induced pancreatitis is ameliorated in mice submersed in warm water. These findings are credited to