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EDITORIAL

Location, Location, Location . . . It Is Important in Pancreatitis, Too

The phrase "location, location, location" has been used in the real estate business for more than 90 years to convey the overriding importance of location in determining value, function, and opportunity. It now may be important in how we approach pancreatitis.

Pancreatitis is a painful and often debilitating disease for which there are no specific or effective treatments. Although patient mortality has decreased over the past 40 years, this is attributed to improvements in supportive care. The reason why pancreatitis is so difficult to treat likely is owing to 2 interrelated problems. First, the pancreas is unique in its biology. It is the only organ that produces vast amounts of digestive enzymes that, if activated in the wrong location (ie, within the gland itself instead of the duodenum), can induce a catastrophic process known as *autodigestion*. Once pancreatitis has been initiated, global inhibition of numerous enzymes including proteases, elastase, lipases, and so forth is a difficult task. However, if that was the only problem, perhaps a solution could be found. The second problem complicating pancreatitis treatment is that injury to the pancreas initiates an inflammatory cascade characterized by release of cytokines and chemokines that induce a systemic inflammatory response. When severe, this cytokine storm rains down significant mortality. Cytokine production within pancreatic acinar cells follows activation of key inflammatory pathways that immediately follow pancreatic injury. Together, pancreatic enzyme activation and its associated autodigestion compounded by a complicated inflammatory reaction pose a daunting therapeutic hurdle.

Daunting, yes, but perhaps not insurmountable. Aside from preventing pancreatic injury in the first place, the most logical approach to treating pancreatitis is to abrogate the injury at the most proximal step, before enzyme and cytokine activation. But where is that step?

Alterations in intracellular calcium handling consistently accompany pancreatic injury, leading to pancreatitis. This indicates that precise regulation of the cellular Ca^{2+} concentration is critical for pancreatic health. Calcineurin is a serine/threonine-specific protein phosphatase that is activated by Ca^{2+} and calmodulin. Calcineurin is best known for its dephosphorylation and activation of the transcription factor nuclear factor of activated T cell, cytoplasmic (NFATc).

Upon activation in T cells, NFATc is translocated to the nucleus and up-regulates cytokine expression. However, calcineurin also is found in pancreatic acinar cells where it mediates pancreatic protein synthesis[1] and trypsin activation,[2] a key enzyme in the generation of other proteolytic enzymes. Thus, calcineurin by virtue of its effects on NFATc may be a node in the pathway for both enzyme and cytokine activation in the pancreas.

To this end, Orabi et al,[3] in this issue of *Cellular and Molecular Gastroenterology and Hepatology*, evaluated the role of calcineurin in an animal model of endoscopic retrograde cholangiopancreatography (ERCP)-induced pancreatitis. This group previously reported that pancreatitis produced by injection of either bile acids or radiocontrast into the pancreatic duct activated calcineurin and nuclear factor-κB and was ameliorated by pharmacologic calcineurin inhibition or global deletion of the calcineurin gene in mice.[4]

Although this earlier work showed a critical role for calcineurin in the generation of pancreatitis, it did not clarify the location of the calcineurin that was involved. Was calcineurin in T cells or acinar cells important for pancreatitis? To address this question, Orabi et al[3] deleted the calcineurin gene specifically in acinar cells in conditional knockout mice or with an acinar cell–specific viral targeting vector. Their results showed that calcineurin in the pancreas mediated acute pancreatitis. This led to their concluding experiment showing that injection of the calcineurin inhibitors FK506 or cyclosporine into the pancreatic duct along with radiocontrast in an ERCP-like fashion prevented pancreatitis.

Previous evaluations of calcineurin inhibitors raised serious concerns about their potential use in pancreatitis. In 2 different mouse models of acute pancreatitis[5] and 1 model of chronic pancreatitis,[6] systemically administered pharmacologic calcineurin inhibitors exacerbated pancreatitis. Not to be dissuaded by these negative results, other investigators focusing on the role of calcineurin in T cells recently showed that pancreatitis severity was reduced by cyclosporine in a T-cell–mediated mouse model of autoimmune pancreatitis.[7]

These conflicting findings most likely reflect effects on different cell types, but at this juncture it is difficult to judge whether calcineurin inhibitors could offer a possible treatment for pancreatitis.

However, we must not forget about location. The real value of the study by Orabi et al[3] was proving that it is calcineurin in acinar cells that mediates ERCP pancreatitis. The therapeutic implication is that systemic administration of calcineurin inhibitors is unnecessary. Instead, it may be possible to inject a calcineurin inhibitor where it is needed—directly into the pancreatic duct to prevent ERCP pancreatitis.

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