

ROUND TABLE

Antiproteases and the Pancreas: Basic and Clinical Update. Introduction

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It is generally accepted that the main pathogenic mechanism in the development of the tissue lesions which characterize acute pancreatitis is the autodigestion of the gland by the intra-parenchymal activation of pancreatic enzymes. Trypsin, which under normal conditions, is rapidly inactivated by specific inhibitors present in both the pancreatic tissue and its secretions, has been identified in a free and active state in the course of acute pancreatitis. Therefore, the idea that inhibitors of pancreatic enzymes may reduce the severity of acute pancreatitis and its complications has received much attention over the past 40 years. However, in the treatment of acute pancreatitis, the clinical use of protease inhibitors has not been shown to be of significant value in several studies and is not available for the treatment of acute pancreatitis in the United States. Several guidelines on the treatment of acute pancreatitis do not recommend them and mention the debate about the use of protease inhibitors. Although the effect of protease inhibitors is controversial, Japanese experts on treating pancreatitis recommend the administration of protease inhibitors as soon as the diagnosis of acute pancreatitis is confirmed. Furthermore, the use of protease inhibitors for pharmacologic prophylaxis against severe pancreatitis after ERCP was reported to be useful while the prolonged infusion of protease inhibitors may be expensive.

Protease inhibitors have been used mainly in Japan and Asian countries. Gabexate mesilate, nafamostat mesilate, ulinastatin and camostat mesilate are now available in Japan. Aprotinin is now unavailable for the treatment of acute pancreatitis in Japan, because it was re-evaluated as having no beneficial effects on acute pancreatitis and it frequently causes anaphylaxis as a serious side-effect. Nafamostat, as well as gabexate, is a synthetic serine protease inhibitor with a low molecular weight (539.6 Da) and a short half-life (1.1 min). Ulinastatin is an intrinsic trypsin inhibitor extracted and purified from human urine, which is a glycoprotein with a molecular weight of 24 kDa and a half-life of 35 min. Camostat is an orally active protease inhibitor with a molecular weight of 494.5 Da, which reaches a maximal blood concentration in 40 min and has a half-life of 73 min when administered orally.

Although the exact mechanisms which trigger the inflammatory and necrotizing process are not completely understood, it is generally accepted that activated leukocytes play an important role in the pathogenesis of acute pancreatitis. The serum levels of cytokines, including tumor necrosis factor alpha (TNF-alpha), interleukin-1 beta (IL-1beta), interleukin-6 (IL-6), and interleukin-8 (IL-8), have been reported to be significantly higher in severe acute pancreatitis as compared to mild pancreatitis. Furthermore, proinflammatory cytokines are associated with systemic

inflammatory response syndrome (SIRS) in acute pancreatitis. Gabexate mesilate, a synthetic serine protease inhibitor, was reported to reduce the serum levels of TNF-alpha and IL-6, increase serum IL-10 levels and improve pancreatic histopathology and survival in acute necrotizing pancreatitis in rats. It has been proposed that the beneficial effect of gabexate in acute pancreatitis may be, in part, due to the modulation of cytokine responses.

Recently, a trypsin receptor of the protease-activated receptor (PAR) family, PAR2, has been discovered to be present in abundance on the surface of pancreatic acinar and duct cells. The activation of PAR2 exerts a protective effect on these cells during acute inflammation of the pancreas. Conversely, PAR2 stimulation activated immune and endothelial cells, so that PAR2 activation during acute pancreatitis resulted in a reduction in blood pressure and its consequent hemodynamic effects which may aggravate the systemic complications of acute pancreatitis. These findings provide a new insight into understanding the pathogenesis of acute pancreatitis and offer new modalities in developing PAR2-based treatments for acute pancreatitis.

In recent years, research effort has also focused on the genetic abnormalities which may predispose to chronic pancreatitis. Genes regulating the activation of trypsinogen have received particular attention. Mutations in the cationic trypsinogen gene (PRSS1) were revealed to cause hereditary pancreatitis. It was thought that mutations in the anionic isoenzyme PRSS2 might predispose to pancreatitis. However, a recent study indicated that the PRSS2 mutation may be a protective factor against chronic pancreatitis. It has been hypothesized that mutations in a serine protease inhibitor gene (SPINK1) are associated with tropical pancreatitis. These mutations can lead to persistent trypsinogen activity, resulting in recurrent episodes of pancreatitis which can eventually progress to chronic pancreatitis.

Pancreatic stellate cells are myofibroblast-like cells in the pancreas. The sustained activation

of pancreatic stellate cells is reported to stimulate the fibrosis which is associated with chronic pancreatitis and pancreatic cancer. Targeting pancreatic stellate cells can offer therapeutic potentials for the treatment and prevention of chronic pancreatitis and pancreatic cancer. Among the potential treatments for pancreatic stellate cell disorders, camostat, an orally active protease inhibitor, is reported to attenuate pancreatic fibrosis.

Pancreatic cancer is characterized by local invasion, early metastasis and a strong desmoplastic reaction. Proteolytic degradation of extracellular matrix components is a process which is essential for tumor invasion and metastasis. Several classes of proteases may be involved in the proteolytic events which occur during pancreatic cancer cell invasion; these include serine proteases and matrix metalloproteases (MMPs), such as urokinase-type plasminogen activator (u-PA) and tumor associated trypsinogen (TAT), MMP-2, MMP-9, and membrane type (MT) MMPs.

Serine proteases and matrix metalloproteases are the focus of intense research, as they appear to be related to tumor progression. Gabexate is reported to inhibit the metastatic potential of cancer cell lines by two mechanisms: antagonizing the activities of TAT and u-PA or suppressing the production of TGF-beta1 and VEGF.

The aim of this virtual round table is to report the latest results on protease inhibitors for the treatment of pancreatic diseases coming from Japan and China where protease inhibitors are easily available. This "Round Table" will provide a comprehensive overview of proteases in order to elucidate their role in pancreatic inflammation and cancer, and describe the potential role of protease inhibitors which might be used to therapeutic advantage.

Keywords NF-kappa B; Pancreatic Neoplasms; Pancreatitis; Protease Inhibitors; Receptor, PAR-2

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