**The role of NF-kappa B activation in the pathogenesis of acute pancreatitis.**

Rakonczay Z, Hegyi P, Takacs T, McCarroll J, Saluja A.

University of Szeged. Szeged, Hungary

Acute pancreatitis is an inflammatory disease of the pancreas which, in its most severe form, is associated with multiorgan failure and death. Recently, signaling molecules and pathways which are responsible for the initiation and progression of this disease have been under intense scrutiny. One important signaling molecule, nuclear factor kappa B (NF-kappaB), has been shown to play an important role in the development of acute pancreatitis. NF-kappaB is a nuclear transcription factor which plays a critical role in regulating the transcription of a wide variety of genes involved in immunity and inflammation. Many of these genes have been implicated as central players in the development and progression of acute pancreatitis. This review discusses recent advances in the investigation of pancreatic and extrapancreatic (lungs, liver, monocytes and macrophages, and endothelial cells) NF-kappaB activation as it relates to acute pancreatitis.

---

**Effects of thalidomide in a mouse model of cerulein-induced acute pancreatitis.**


Department of Clinical and Experimental Medicine and Pharmacology, School of Medicine, University of Messina. Messina, Italy

Current knowledge shows that pathophysiology of acute pancreatitis is characterized by intra-acinar enzyme activation and subsequent dysregulation in immune response. Interactions between leukocytes, soluble mediators such as cytokines and vascular endothelium contribute to the systemic progression of the inflammatory response, whose entity may - in the end - determine disease severity and outcome. Recently, it has been shown that TNF-alpha may be a novel target for the treatment of acute pancreatitis; but the role of thalidomide, an immunomodulatory agent that inhibits TNF-alpha and angiogenesis, has not been investigated so far. The aim of the present study was to assess the effects of thalidomide in a murine model of necrotizing acute pancreatitis. Necrotizing acute pancreatitis was induced in mice by intraperitoneal injection of cerulein (hourly, x5, 50 µg/kg); in another group of animals, thalidomide was administered (200 mg/kg orally) at 1 h after first cerulein injection. After 24 h, biochemical, histological, and immunohistochemical evidences of acute pancreatitis developed in all cerulein-treated mice. On the contrary, pancreatitis histological features, amylase, lipase, TNF-alpha and IL-1beta levels, pancreas edema, and myeloperoxidase activity as well as immunohistochemical staining for inflammatory cytokines, leukocyte adhesion molecules, transforming growth factor beta, vascular endothelial growth factor, and apoptosis-related proteins were found reduced in thalidomide-treated mice. Therefore, thalidomide treatment attenuates the development of acute pancreatitis caused by cerulein in mice. The authors propose that this evidence may help to clarify the role of anti-TNF-alpha and immunomodulatory agents in patients with acute pancreatitis.
Mechanisms of disease: chronic inflammation and cancer in the pancreas - a potential role for pancreatic stellate cells?

Algul H, Treiber M, Lesina M, Schmid RM.

Department of Internal Medicine, Technical University of Munich, Munich, Germany.

Late diagnosis and ineffective therapeutic options mean that pancreatic ductal adenocarcinoma (PDA) is one of the most lethal forms of human cancer. The identification of genetic alterations facilitated the launch of the Pancreatic Intraepithelial Neoplasm nomenclature, a standardized classification system for pancreatic duct lesions, but the factors that contribute to the development of such lesions and their progression to high-grade neoplasia remain obscure. Age, smoking, obesity and diabetes confer increased risk of PDA, and the presence of chronic pancreatitis is a consistent risk factor for pancreatic cancer. It is hypothesized that chronic inflammation generates a microenvironment that contributes to malignant transformation in the pancreas, as is known to occur in other organs. Pancreatic stellate cells (PSCs) are the main mediator of fibrogenesis during chronic pancreatitis, but their contribution to the development of PDA has not been elucidated. Data now suggest that PSCs might assume a linking role in inflammation-associated carcinogenesis through their ability to communicate with inflammatory cells, acinar cells, and pancreatic cancer cells in a complicated network of interactions. In this review, the role of PSCs in the process of inflammation-associated carcinogenesis is discussed and new potential treatment options evaluated.

Mechanisms and natural history of pain in chronic pancreatitis: a surgical perspective.

Sakorafas GH, Tsiotou AG, Peros G.

Fourth Department of Surgery, Athens University Medical School, Attikon University Hospital, Athens, Greece.

Pain is a major clinical manifestation of chronic pancreatitis (CP) and a common indication for surgery in these patients. Pathogenesis of pain in CP is multifactorial and the mechanisms of pain may differ from patient to patient. This can explain why one therapeutic method of treatment of pain does not work in all patients and in different stages of the disease. Two main complimentary pathogenetic theories have been proposed to explain the mechanisms of pain in CP, the neurogenic theory and the theory of increased intraductal/intraparenchymal pressures. According to the neurogenic theory, in CP there are alterations of pancreatic/peripancreatic nerves, exposing them to noxious substances and/or activated immune cells, thereby generating pain ("neuroimmune interaction"). The other theory of intraductal/intraparenchymal hypertension suggests that pain in CP is generated as a result of increased pressures within the pancreatic ductal system and/or pancreatic parenchyma, like the pain in the classic compartment syndrome. The theory of intraductal/intraparenchymal hypertension is strongly supported by the good results of drainage procedures in the surgical management of CP. Pancreatic ischemia, oxygen-free radicals, centrally sensitized pain state, acute exacerbations of CP, development of complications from the pancreas (most commonly, pseudocysts) or adjacent organs (usually, duodenal and/or common bile duct stenosis), etc. are other possible contributing factors. Different patterns of pain have been described in idiopathic (early vs. late onset) and in alcoholic CP. Interestingly, pain is automatically relieved during the natural course of the disease in some patients (the "burn-out" phenomenon), after a relatively long time (from a few years to up to 3
decades). However, this is an unpredictable evolution for the individual patient. Therefore, surgery should be offered when pain is intense and after failure of conservative treatment. Surgical management should be individualized, depending on the particular findings of each patient. The knowledge of the pathophysiologic basis and of natural course of pain in CP is of paramount importance for the surgeon to select appropriate therapy for the individual patient with CP.

Pancreatic intraepithelial neoplasia in heterotopic pancreas: evidence for the progression model of pancreatic ductal adenocarcinoma.

Zhang L, Sanderson SO, Lloyd RV, Smyrk TC.
Department of Pathology, Mayo Clinic. Rochester, MN, USA.

Morphologic, clinical, and genetic evidence suggests that pancreatic intraepithelial neoplasia (PanIN) is a precursor to ductal adenocarcinoma. But understanding precursor lesions in a pancreas with existing tumor is hampered by the fact that chronic pancreatitis often accompanies carcinoma, and the possible interactions between tumor, chronic pancreatitis, and PanIN are complex. Furthermore, cancerization of ducts can mimic high-grade PanIN. Heterotopic pancreas has a genetic make-up, physiologic function, and local environmental exposure similar to that of the pancreas. It offers an opportunity to study putative precursor lesions in a setting with fewer confounding factors. The authors identified 6 pancreatic cancer patients who had heterotopic pancreas removed at the time of surgery. All 6 cases were immunostained for p53, cyclin D1, and p16. Molecular analysis of K-ras mutation was also done. All 6 cancer-associated heterotopias had PanIN-1A or 1B; 5 had PanIN-2 and 1 had PanIN-3. Three of 6 cases harbored the same K-ras codon 12 mutation as the PanINs in orthotopic pancreas, and a similar pattern of p53, cyclin D1, and p16 expression was observed between heterotopic and orthotopic pancreas in all 6 cases. There was no chronic pancreatitis in the cancer-associated heterotopias, but chronic pancreatitis was seen adjacent to carcinoma in 5 of 6 cases. The presence of PanIN in heterotopic pancreas from patients with ductal adenocarcinoma supports the progression model.

Strategies for screening for pancreatic adenocarcinoma in high-risk patients.

Canto MI.
Departments of Medicine (Gastroenterology) and Oncology, The Sol Goldman Pancreatic Cancer Research Center, The Johns Hopkins Medical Institutions. Baltimore, MD, USA.

Identification of high-risk individuals, genetic counseling, and informed consent are important components of a screening program for familial pancreatic cancer. Screening high-risk individuals with imaging tests, such as endoscopic ultrasound (EUS) and computed tomography (CT), can lead to the detection and treatment of predominantly asymptomatic early pancreatic neoplasms, as well as extrapancreatic tumors. These pancreatic neoplasms consist of resectable, mostly branch-type non-invasive intraductal papillary mucinous neoplasms (IPMNs). EUS can visualize these very early IPMNs as focal duct ectasias or cysts. EUS features of chronic pancreatitis are highly prevalent in high-risk individuals and these directly correlate with multifocal lobulocentric parenchymal atrophy due to multifocal pancreatic intraepithelial neoplasia (PanIN). No one molecular marker is ready for "prime time" screening of high-risk individuals. Translational studies are underway to discover novel biomarkers for IPMNs, PanIN-3 lesions, or microinvasive...
adenocarcinoma, which are likely to be cured by timely intervention. Long-term, multi-prospective studies are needed to determine if screening for early pancreatic neoplasia and timely intervention results in decreased pancreatic cancer incidence and mortality in high-risk individuals.


Magnetic resonance imaging in the detection of pancreatic neoplasms.

Zhong L.

Department of Radiology, Renji Hospital, Shanghai Jiaotong University School of Medicine, Shanghai, China.

Recently, with the rapid scanning time and improved image quality, outstanding advances in magnetic resonance (MR) methods have resulted in an increase in the use of MRI for patients with a variety of pancreatic neoplasms. MR multi-imaging protocol, which includes MR cross-sectional imaging, MR cholangiopancreatography and dynamic contrast-enhanced MR angiography, integrates the advantages of various special imaging techniques. The non-invasive all-in-one MR multi-imaging techniques may provide the comprehensive information needed for the preoperative diagnosis and evaluation of pancreatic neoplasms. Pancreatic neoplasms include primary tumors and pancreatic metastases. Primary tumors of the pancreas may be mainly classified as ductal adenocarcinomas, cystic tumors and islet cell tumors (ICT). Pancreatic adenocarcinomas can be diagnosed in a MRI study depending on direct evidence or both direct and indirect evidence. The combined MRI features of a focal pancreatic mass, pancreatic duct dilatation and parenchymal atrophy are highly suggestive of a ductal adenocarcinoma. Most cystic neoplasms of the pancreas are either microcystic adenomas or mucinous cystic neoplasms. Intraductal papillary mucinous tumors are the uncommon low-grade malignancy of the pancreatic duct. ICT are rare neoplasms arising from neuroendocrine cells in the pancreas or the periampullary region. ICT are classified as functioning and non-functioning. The most frequent tumors to metastasize to the pancreas are cancers of the breast, lung, kidney and melanoma. The majority of metastases present as large solitary masses with well-defined margins.


Hemoglobin A1c predicts diabetes but not cardiovascular disease in nondiabetic women.

Pradhan AD, Rifai N, Buring JE, Ridker PM.

Center for Cardiovascular Disease Prevention, Division of Cardiovascular Medicine, VA Boston Medical Center. Boston, MA, USA.

Hemoglobin A1c (HbA1c) is a marker of cumulative glycemic exposure over the preceding 2- to 3-month period. Whether mild elevations of this biomarker provide prognostic information for development of clinically evident type 2 diabetes and cardiovascular disease among individuals at usual risk for these disorders is uncertain. The authors examined baseline HbA1c levels as a predictor of incident clinical diabetes and cardiovascular disease (nonfatal myocardial infarction, coronary revascularization procedure, ischemic stroke, or death from cardiovascular causes) in a prospective cohort study beginning in 1992 of 26,563 US female health professionals aged 45 years or more without diagnosed diabetes or vascular disease (median follow-up 10.1 years). During follow-up, 1,238 cases of diabetes and 684 cardiovascular events occurred. In age-adjusted analyses using quintiles of HbA1c, a risk gradient was observed for both incident diabetes and cardiovascular disease. After multivariable adjustment, HbA1c remained a strong predictor of diabetes but was no longer significantly associated with incident
cardiovascular disease. In analyses of threshold effects, adjusted relative risks for incident diabetes in HbA1c categories of less than 5.0%, 5.0% to 5.4%, 5.5% to 5.9%, 6.0% to 6.4%, 6.5% to 6.9%, and 7.0% or more were 1.0, 2.9, 12.1, 29.3, 28.2, and 81.2, respectively. Risk associations persisted after additional adjustment for C-reactive protein and after excluding individuals developing diabetes within 2 and 5 years of follow-up.

These prospective findings suggest that HbA1c levels are elevated well in advance of the clinical development of type 2 diabetes, supporting recent recommendations for lowering of diagnostic thresholds for glucose metabolic disorders. In contrast, the association of HbA1c with incident cardiovascular events is modest and largely attributable to coexistent traditional risk factors.

Document URL: http://www.joplink.net/prev/200709/alerts.html