While the role of EUS in the evaluation of pancreaticobiliary disorders in adults is well established, its utility in children remains unproven. This prospective study evaluates the feasibility, the safety, and the impact of EUS in the evaluation of pancreaticobiliary disorders in children. All children (<18 years) referred for ERCP for evaluation of suspected pancreaticobiliary disorders who underwent EUS before scheduled ERCP. The main outcome measure was to evaluate the impact of EUS in the evaluation of pancreaticobiliary disorders in children. EUS was considered to have a significant impact if a new diagnosis was established or if the findings altered subsequent management. Fourteen patients (mean age 13 years; range 5-17 years) underwent 15 EUS procedures over a 3-year period. Main indications were the following: acute or recurrent pancreatitis (6 patients), suspected biliary obstruction (5), and abdominal pain suggestive of pancreaticobiliary origin (3). EUS diagnosed chronic pancreatitis (3 patients), idiopathic fibrosing pancreatitis (2), carcinoid tumor (1), pancreatic pseudocyst (1), pancreas divisum (1), choledocholithiasis (1), duodenal duplication cyst (1), and normal (4). Diagnosis of idiopathic fibrosing pancreatitis and carcinoid tumor was established by EUS-guided FNA. The procedure was successful in all patients, and no complications were encountered. EUS had an impact on patient management in 93% of cases: established new diagnosis (10), precluded need for ERCP (9), and provided additional information that facilitated focused endotherapy (4). A limitation was the small number of enrolled patients and absence of long-term clinical follow-up. The authors concluded that EUS and EUS-guided FNA are feasible, safe, and have significant impact that alters subsequent management in the majority of children with pancreaticobiliary disorders.
pancreatitis was determined by hyperamylasemia, neutrophil sequestration in the pancreas (pancreatic MPO activity), and pancreatic acinar cell injury/necrosis on histological examination of pancreas sections. The severity of acute pancreatitis-associated lung injury was assessed by neutrophil sequestration in the lungs (lung MPO activity) and by histological examination of lung sections. HCT1026 and flurbiprofen, given prophylactically as well as therapeutically, significantly reduced lung inflammation without having any significant effect on pancreatic injury. These results suggest the usefulness of flurbiprofen as well as HCT1026 as potential treatments for pancreatitis-associated lung injury.


Clinical implications of oxidative stress and antioxidant therapy.

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Oxidative stress occurs when there is an imbalance between generation of reactive oxygen species and inadequate antioxidant defense systems. Oxidative stress can cause cell damage either directly or through altering signaling pathways. Oxidative stress is a unifying mechanism of injury in many types of disease processes, including gastrointestinal diseases. For example, in alcoholic liver disease, reactive oxygen species have been detected through direct spin-trapping techniques and through indirect markers, such as products of lipid peroxidation. A host of antioxidants have protected against liver injury in animal models of alcoholic liver disease. Similarly, in inflammatory bowel disease, oxidative stress has been postulated to play a role in disease initiation and progression, and antioxidant therapy, such as green tea polyphenols and gene therapy with superoxide dismutase, has a markedly attenuated disease. Downregulation of specific detoxification genes may play a role in the pathogenesis of inflammatory bowel disease, especially in ulcerative colitis. Oxidative stress is postulated to play a sustaining role in acute and chronic pancreatitis. Antioxidant supplementation has been used with some success in the treatment of chronic pancreatitis.


Association of polymorphisms of IL and CD14 genes with acute severe pancreatitis and septic shock.

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The authors investigated IL-1beta+3 594 in the 5th intron, IL-10-1 082 and CD14-159 polymorphisms in patients with acute pancreatitis (AP) and septic shock. The study included 215 patients (109 with acute severe pancreatitis (SAP), 106 with acute mild pancreatitis (MAP)) and 116 healthy volunteers. Genomic DNA was prepared from peripheral blood leukocytes. Genotypes and allele frequencies were determined in patients and healthy controls using restriction fragment length polymorphism analysis of PCR products. The frequencies of IL-1beta+3 594T, IL-10-1082G and CD14-159T allele were similar in patients with mild or severe pancreatitis and in controls. Within SAP patients, no significant differences were found in the allele distribution examined when etiology was studied again. Patients with septic shock showed a significantly higher prevalence of IL-10-1082G allele than those without shock (squared-chi=5.921, P=0.015). IL-10-1082G plays an important role in the susceptibility of SAP patients to septic shock. The authors concluded that genetic factors are not important in determination of disease severity or susceptibility to AP.
Compartmentalization of the protease-antiprotease balance in early severe acute pancreatitis.

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The authors aimed to assess the balance between trypsin and protease inhibitors simultaneously in the systemic circulation and in the thoracic lymph and peritoneal exudate. Twenty patients with early severe acute pancreatitis were studied. Enzymatically active and immunoreactive trypsin in conjunction with its major inhibitors were measured in the 3 compartments at the onset of end-organ failure(s). The molecular forms of trypsin were determined in the lymph and ascites by gel filtration chromatography to separate trypsinogen and free-and inhibitor-bound trypsin. Both enzymatically active trypsin and immunoreactive trypsin levels were highest in ascites and lymph compared with the systemic circulation. Intra-compartmental alpha1 protease inhibitor gradient moved in the opposite direction, whereas alpha2 macroglobulin concentration was highest in ascites and lowest in the lymph. Although most of the enzymatically and immunoreactive material in ascites and lymph consisted of trypsin complexed with alpha2 macroglobulin and trypsinogen, respectively, free active trypsin was detected in more than 80% of the samples. The authors concluded that in patients with early severe acute pancreatitis, there is a significant trypsinogen activation resulting in protease-antiprotease imbalance and thereby free enzymatically active trypsin in the 2 body fluid compartments in close vicinity to the inflammatory process. This may be involved in the pathophysiology of local and distant tissue damage.

Genetic polymorphisms of GSTT1, GSTM1, GSTP1, MnSOD, and catalase in nonhereditary chronic pancreatitis: evidence of xenobiotic stress and impaired antioxidant capacity.


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Epidemiological studies have demonstrated a variety of potential environmental factors that may alter susceptibility to chronic pancreatitis through oxidative/xenobiotic stress; however, a direct causal and mechanistic role has not been established. The authors aimed to determine the prevalence of functional genetic polymorphisms in the antioxidant enzymes, glutathione S-transferase GSTM-1, GSTP-1, and GSTT-1, manganese superoxide dismutase, and catalase in chronic pancreatitis and to reveal evidence of oxidative stress in patients with chronic pancreatitis by measuring whole-blood glutathione redox status. In total, 122 patients with chronic pancreatitis (75 alcohol-induced, 33 idiopathic, and 13 hereditary) and 245 age- and sex-matched controls were recruited. The prevalence of the functional GSTT-1 genotype (GSTT-1*A) was significantly higher in chronic pancreatitis (88.5%) compared to healthy controls (76%; squared-chi=7.26, P=0.007). Stratification to disease etiology demonstrated that the GSTT-1*A genotype was also significantly more prevalent among patients with idiopathic chronic pancreatitis (94%; P=0.02; 95% CI: 0.04-9.16) but not in those with alcoholic chronic pancreatitis. In 22 patients with stable chronic pancreatitis, the whole-blood glutathione concentration (median [IQR]: 72 micromol/L [21-181 micromol/L]) and the glutathione redox ratio (GSH/GSSG) (median [IQR]: 9 [3-77]) were significantly reduced compared to those in 20 healthy volunteers.
Evidence of altered glutathione redox status suggests that this disease modification may be a consequence of oxidative stress or the bioactivation of xenobiotics.

(PMID: 16032492)

The treatment of patients with symptomatic common bile duct stenosis secondary to chronic pancreatitis using partially covered metal stents: a pilot study.

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Although surgery remains the gold standard for the treatment of symptomatic common bile duct stenosis associated with chronic pancreatitis, plastic and self-expandable open-mesh stents have been proposed as alternative treatments. These may dysfunction, however, mainly due to stent occlusion by clogging or by hyperplasia of inflammatory tissue. The aim of this study was to evaluate the safety and long-term results of using partially covered metal stents in this setting. A total of 14 patients (12 men, 2 women; mean age 50±3 years) underwent partially covered metal stent insertion for common bile duct stenosis secondary to chronic pancreatitis (12 alcohol-related, two idiopathic). They had all been treated previously with plastic prostheses. Either a 40-mm (n=13) or a 60-mm (n=1) partially covered metal stent was placed, depending on the length of the common bile duct stenosis and the level of the cystic duct bifurcation. Stent placement was successful, with resolution of cholangitis and improvement in cholestasis, in all patients. During the median follow-up period of 22 months (range 12-33 months) seven patients developed dysfunction of the stent and required re-treatment. At 12, 24, and 30 months, the stent patency rates were 100%, 40%, and 37.5% respectively. While partially covered metal stenting is safe and effective for the initial treatment of chronic pancreatitis-associated common bile duct stenosis and shows promising short-term results, long-term data show that dysfunction occurs in 50% of cases. In light of the continued interest in nonsurgical treatment of this condition, further research is warranted to investigate new stent designs with improved long-term patency.

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Differential and synergistic effects of platelet-derived growth factor-BB and transforming growth factor-beta1 on activated pancreatic stellate cells.

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The cytokines platelet-derived growth factor (PDGF) and transforming growth factor (TGF)-beta1 are major factors influencing the transformation from the quiescent to the activated phenotype of pancreatic stellate cells (PSC), a process involved in the pathogenesis of chronic pancreatitis. Albeit much effort has been made to study the effects of PDGF and TGF-beta1 on PSCs, their interaction is still unclear, because these cytokines show both differential and synergistic effects as outlined by this study. Culture-activated PSCs of rats were treated with PDGF-BB and TGF-beta1. Subsequent changes of cell proliferation and migration were determined by cell counting, (+)-bromo-2’-deoxyuridine enzyme-linked immuno-sorbent assay (ELISA), and migration assay.
Gene expression, synthesis of proteins, and activation of kinases were further studied by reverse transcription-polymerase chain reaction, real-time polymerase chain reaction, ELISA, and Western blot. PDGF-BB increased PSC proliferation and migration, accompanied by elevated expression of matrix metalloproteinases (MMP)-13 and MMP-3. The mRNA amount of procollagen alpha2(I), alpha-smooth muscle actin (alpha-SMA), tissue inhibitor of metalloproteinase (TIMP)-1, and TGF-beta1 was also increased by PDGF-BB. In contrast, PDGF-BB reduced collagen type I in culture medium and synthesis of alpha-SMA. Treatment of PSC with TGF-beta1 decreased proliferation, had no significant effect on migration and MMP expression, but increased expression and synthesis of procollagen alpha2(I) and alpha-SMA. Both cytokines induced phosphorylation of extracellular signal regulated kinase (ERK)-1/2 and p38, but only PDGF-BB activated the protein kinase B signaling pathway. PDGF-BB augments effects of TGF-beta1 on the mRNA level presumably because of up-regulation of TGF-beta1 synthesis and common signaling pathways of the 2 cytokines. However, at the protein level, PDGF-BB impairs typical TGF-beta1 effects such as increased synthesis of collagen (type I) and alpha-SMA. Moreover, PDGF-BB facilitates degradation of extracellular matrix proteins by enhancement of MMP synthesis, but MMP activity was probably limited because of elevated tissue inhibitor of metalloproteinase 1 expression.

Quantitative analysis of MUC1 and MUC5AC mRNA in pancreatic juice for preoperative diagnosis of pancreatic cancer.


Pancreatic juice is a promising type of diagnostic sample for pancreatic cancer, and members of the mucin (MUC) family are diagnostic candidates. To evaluate the utility of MUC family members as diagnostic markers, the authors measured MUC mRNA expression in pancreatic tissues and pancreatic juice obtained from patients with different pancreatic diseases as well as in pancreatic cancer cell lines by real-time PCR. Furthermore, to support the possibility of early diagnosis by quantification of MUC1 and MUC5AC, immunohistochemistry and microdissection-based quantitative analysis of mRNA were carried out. There was no significant correlation between MUC1 and MUC5AC expression in cell lines. When beta-actin was used as a reference gene, median MUC1 and MUC5AC mRNA expression levels were remarkably greater in tumoral tissues than in non-tumoral tissues, but median MUC4 and MUC6 mRNA expression levels were not. Receiver operating characteristic curve analysis showed that quantitative analysis of MUC1 and MUC5AC mRNA in pancreatic juice is better diagnostic modality than that of MUC4 and MUC6 mRNA. Immunohistochemistry showed that MUC1 and MUC5AC were highly expressed in invasive ductal carcinomas (IDC) and moderately expressed in high-grade pancreatic intraepithelial neoplasia (PanIN); no staining was observed in normal ducts. Analysis of cells isolated by microdissection showed stepwise upregulation of MUC1 and MUC5AC in the development of high-grade PanIN to IDC. These results suggest that MUC1 and MUC5AC are upregulated stepwise in pancreatic carcinogenesis and that quantitative assessment of MUC1 and MUC5AC mRNA in pancreatic juice has high potential for preoperative diagnosis of pancreatic cancer.
Fluvastatin synergistically enhances the antiproliferative effect of gemcitabine in human pancreatic cancer MIAPaCa-2 cells.


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The new combination between the nucleoside analogue gemcitabine and the cholesterol-lowering drug fluvastatin was investigated in vitro and in vivo on the human pancreatic tumour cell line MIAPaCa-2. The present study demonstrates that fluvastatin inhibits proliferation, induces apoptosis in pancreatic cancer cells harbouring a p21ras mutation at codon 12 and synergistically potentiates the cytotoxic effect of gemcitabine. The pharmacologic activities of fluvastatin are prevented by administration of mevalonic acid, suggesting that the shown inhibition of geranyl-geranylation and farnesylation of cellular proteins, including p21rhoA and p21ras, plays a major role in its anticancer effect. Fluvastatin treatment also indirectly inhibits the phosphorylation of p42ERK2/mitogen-activated protein kinase, the cellular effector of ras and other signal transduction peptides. Moreover, fluvastatin administration significantly increases the expression of the deoxycytidine kinase, the enzyme required for the activation of gemcitabine, and simultaneously reduces the 5’-nucleotidase, responsible for deactivation of gemcitabine, suggesting a possible additional role of these enzymes in the enhanced cytotoxic activity of gemcitabine. Finally, a significant in vivo antitumour effect on MIAPaCa-2 xenografts was observed with the simultaneous combination of fluvastatin and gemcitabine, resulting in an almost complete suppression and a marked delay in relapse of tumour growth. In conclusion, the combination of fluvastatin and gemcitabine is an effective cytotoxic, proapoptotic treatment in vitro and in vivo against MIAPaCa-2 cells by a mechanism of action mediated, at least in part, by the inhibition of p21ras and rhoA prenylation. The obtained experimental findings might constitute the basis for a novel translational research in humans.

Positron emission tomography/computed tomography influences on the management of resectable pancreatic cancer and its cost-effectiveness.


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The authors sought to determine the impact of positron emission tomography/computed tomography (PET/CT) on the management of presumed resectable pancreatic cancer and to assess the cost of this new staging procedure. PET using 18F-fluorodeoxyglucose (FDG) is increasingly used for the staging of pancreatic cancer, but anatomic information is limited. Integrated PET/CT enables optimal anatomic delineation of PET findings and identification of FDG-negative lesions on computed tomography (CT) images and might improve preoperative staging. Patients with suspected pancreatic cancer who had a PET/CT between June 2001 to April 2004 were entered into a prospective database. Routine staging included abdominal CT, chest x-ray, and CA 19-9 measurement. FDG-PET/CT was conducted according to a standardized protocol, and findings were confirmed by histology. Cost benefit analysis was performed based on charged cost of PET/CT and pancreatic resection and included the time frame of staging and surgery. Fifty-nine patients with a median age of 61 years (range, 40-80 years) were included in this analysis. Fifty-one patients had lesions in the head and 8 in the tail of the pancreas. The positive and
negative predictive values for pancreatic cancer were 91% and 64%, respectively. PET/CT detected additional distant metastases in 5 and synchronous rectal cancer in 2 patients. PET/CT findings changed the management in 16% of patients with pancreatic cancer deemed resectable after routine staging (P=0.031) and was cost-saving. The authors concluded that PET/CT represents an important staging procedure prior to pancreatic resection for cancer, since it significantly improves patient selection and is cost-effective.


Osteonectin influences growth and invasion of pancreatic cancer cells.


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The authors sought to examine the expression and functional role of osteonectin in primary and metastatic pancreatic ductal adenocarcinoma (PDAC). The glycoprotein osteonectin plays a vital role in cell-matrix interactions and is involved in various biologic processes. Overexpression of osteonectin is present in malignant tumors and correlates with disease progression and poor prognosis. Expression of osteonectin was analyzed by quantitative polymerase chain reaction and immunohistochemistry in pancreatic tissues and by enzyme-linked immunosorbent assay in the serum of patients and donors. Recombinant osteonectin and specific antisense oligonucleotides were used to examine the effects of osteonectin on induction of target genes, and on proliferation and invasiveness of pancreatic cancer cells. There was a 31-fold increase in osteonectin mRNA levels in PDAC and a 16-fold increase in chronic pancreatitis as compared with the normal pancreas (P<0.01). By immunohistochemistry, faint immunoreactivity was detected in the normal pancreas. In contrast, strong staining of the cancer cells was observed in addition to extensive osteonectin immunoreactivity in surrounding fibroblasts and in the extracellular matrix. In metastatic tissues, strong immunoreactivity was observed in fibroblasts and in extracellular matrix surrounding metastatic cancer cells, whereas the signal was absent in most tumor cells. In vitro studies showed that osteonectin was able to inhibit cancer cell growth while promoting invasiveness of pancreatic tumor cells. Osteonectin is markedly overexpressed in pancreatic cancer and has the potential to increase the invasiveness of pancreatic cancer cells.