PANCREAS ALERTS

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Identification of candidate genes involved in endogenous protection mechanisms against acute pancreatitis in mice.

Nakada S, Tsuneyama K, Kato I, Tabuchi Y, Takasaki I, Furusawa Y, et *al.*

Department of Japanese Oriental Medicine, University of Toyama Graduate School of Medicine and Pharmaceutical Sciences. Toyama, Japan.

The authors surveyed changes of the gene expression profile in caerulein-exposed pancreas using Affymetrix GeneChip system (39,000 genes). Up-regulation of genes coding for claudin 4, claudin 7, F11 receptor, cadherin 1, integrin beta 4, syndecan 1, heat shock proteins b1/90aa1, Serpinb6a, Serpinb6b, Serpinb9, Bax, Bak1, calpain 2, calpain 5, microtubule-associated protein 1 light chain 3 alpha, S100 calcium-binding proteins A4/A10 were found in mouse pancreas exposed to caerulein for 12 h. In contrast, the anti-apoptotic gene Bcl2 was down-regulated. The functions of these genes concern tight junction formation, cell-cell/cell-matrix adhesions, stress response, protease inhibition, apoptosis, autophagy, and regulation of cytoskeletal dynamics. Caerulein-exposed pancreatic acinar cells were immunohisto-chemically stained for claudin 4, cadherin 1, integrin beta 4, heat shock protein b1, and Serpinb6a. In conclusion, the authors have newly identified a set of genes that are likely to be involved in endogenous self-protection mechanisms against acute pancreatitis.

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Cutting-edge information for the management of acute pancreatitis.

Takada T, Hirata K, Mayumi T, Yoshida M, Sekimoto M, Hirota M, et *al.*

Department of Surgery, Teikyo University School of Medicine. Tokyo, Japan.

Considering that the Japanese (JPN) guidelines for the management of acute pancreatitis were published in Takada *et al*. (J HepatoBiliary Pancreat Surg 13:2-6, 2006), doubts will be cast as to the reason for publishing a revised edition of the Guidelines for the management of acute pancreatitis: the JPN guidelines 2010, at this time. The rationale for this is that new criteria for the severity assessment of acute pancreatitis were made public on the basis of a summary of activities and reports of shared studies that were conducted in 2008. The new severity classification is entirely different from that adopted in the 2006 guidelines. A drastic revision was made in the new criteria. For example, about half of the cases that have been assessed previously as being 'severe' are assessed as being 'mild' in the new criteria. The JPN guidelines 2010 are published so that consistency between the criteria for severity assessment in the first edition and the new criteria will be maintained. In the new criteria, severity assessment can be made only by calculating the 9 scored prognostic factors. Severity assessment according to the contrast-enhanced computed tomography (CT) grade was made by scoring the poorly visualized pancreatic area in addition to determining the degree of extrapancreatic progress of inflammation and its extent. Changes made in accordance with the new criteria are seen in various parts of the guidelines. In the present revised edition, post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis is treated as an independent item. Furthermore, clinical indicators (pancreatitis bundles) are presented to improve the quality of the management of acute pancreatitis and to increase adherence to new guidelines.

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Passive leg raising is predictive of fluid responsiveness in spontaneously breathing patients with severe sepsis or acute pancreatitis.

Préau S, Saulnier F, Dewavrin F, Durocher A, Chagnon JL.

Service de Réanimation polyvalente, Centre Hospitalier Jean Bernard. Valenciennes, France.

Rapid fluid loading is standard treatment for hypovolemia. Because volume expansion does not always improve hemodynamic status, predictive parameters of fluid responsiveness are needed. Passive leg raising is a reversible maneuver that mimics rapid volume expansion. Passive leg raising-induced changes in stroke volume and its surrogates are reliable predictive indices of volume expansion responsiveness for mechanically ventilated patients. The authors hypothesized that the hemodynamic response to passive leg raising indicates fluid responsiveness in nonintubated patients without mechanical ventilation. The authors investigated consecutive nonintubated patients, without mechanical ventilation, considered for volume expansion and they assessed hemodynamic

status at baseline, after passive leg raising, and after volume expansion (500 mL 6% hydroxyethyl starch infusion over 30 mins). The researchers measured stroke volume using transthoracic echocardiography, radial pulse pressure using an arterial catheter, and peak velocity of femoral artery flow using continuous Doppler. The authors calculated changes in stroke volume, pulse pressure, and velocity of femoral artery flow induced by passive leg raising (respectively, Deltastroke volume, Deltapulse pressure, and Deltavelocity of femoral artery flow). Among 34 patients included in this study, 14 had a stroke volume increase of 15% or more after volume expansion (responders). All patients included in the study had severe sepsis (n=28; 82%) or acute pancreatitis (n=6; 18%). The Deltastroke volume equal to, or greater than, 10% predicted fluid responsiveness with sensitivity of 86% and specificity of 90%. The Deltapulse pressure equal to, or greater than, 9% predicted fluid responsiveness with sensitivity of 79% and specificity of 85%. The Deltavelocity of femoral artery flow equal to, or greater than, 8% predicted fluid responsiveness with sensitivity of 86% and specificity of 80%. In conclusions, changes in stroke volume, radial pulse pressure, and peak velocity of femoral artery flow induced by passive leg raising are accurate and interchangeable indices for predicting fluid responsiveness in nonintubated patients with severe sepsis or acute pancreatitis.

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Increased markers of oxidative stress in plasma of patients with chronic pancreatitis.

Podborska M, Sevcikova A, Trna J, Dite P, Lojek A, Kubala L.

Institute of Biophysics, Academy of Sciences of the Czech Republic. Brno, Czech Republic.

Chronic pancreatitis (CP) is a heterogeneous disease defined as chronic inflammatory changes of the pancreatic tissue caused by variety of aetiologies. Oxidative stress accompanying the inflammatory processes has been suggested as an important factor contributing to CP development. The aim of this study was to determine levels of lipid peroxidation products malondialdehyde (MDA) and 4-hydroxynonenal (4-HNE), together with nitrites and the total antioxidant capacity in the plasma of patients with CP and control subjects. One hundred and five patients with chronic pancreatitis and twenty seven healthy controls were included into this study. Levels of MDA and 4-HNE were analyzed using high-performance liquid chromatography. The total antioxidant capacity of plasma against peroxyl radicals was evaluated using chemiluminescent determination. Nitrites were determined using Griess reaction. Biochemical and haematological parameters were measured by standard methods. The plasma levels of both MDA and 4-HNE, together with the plasma levels of nitrites, were significantly higher in CP patients, compared to healthy controls. The total antioxidant capacity did not differ significantly. Biochemical parameters were in the normal range. The MDA and 4-HNE levels correlated positively with the levels of high-density lipoprotein cholesterol. Nitrite levels correlated positively with C-reactive protein, total white blood cells, and triglycerides. The significantly increased plasma levels of MDA, 4-HNE, and nitrites indicate that oxidative stress is present in patients with CP and that it may play a role in initiation and maintenance of inflammation within the pancreatic tissue in CP patients.

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Pancreatic duct glands are distinct ductal compartments that react to chronic injury and mediate Shh-induced metaplasia.

Strobel O, Rosow DE, Rakhlin EY, Lauwers GY, Trainor AG, Alsina J, et *al.*

Department of Surgery, Massachusetts General Hospital and Harvard Medical School. Boston, MA, USA.

Pancreatic intraepithelial neoplasia (PanIN) are pancreatic cancer precursor lesions of unclear origin and significance. PanIN aberrantly express sonic hedgehog (Shh), an initiator of pancreatic cancer, and gastrointestinal mucins. The majority of PanIN are thought to arise from ducts. The authors identified a novel ductal compartment that is gathered in gland-like outpouches (pancreatic duct glands, PDG) of major ducts and characterized its role in injury and metaplasia. The ductal system was analyzed in normal pancreata and chronic pancreatitis in humans and mice. Anatomy was assessed by serial H&E sections and scanning electron microscopy of corrosion casts. Expression of mucins and developmental genes and proliferation were assessed by immunohistochemistry or RT-qPCR. Effects of Shh on ductal cells were investigated by exposure to Shh *in vitro* and transgenic misexpression *in vivo*. Three-dimensional analysis revealed blind-ending outpouches of ducts in murine and human pancreata. These PDG are morphologically and molecularly distinct from normal ducts; even in normal pancreata they display PanIN and metaplastic features such as expression of Shh and gastric mucins. They express other developmental genes, such as Pdx-1 and Hes-1. In injury, Shh is upregulated along with gastric mucins. Expansion of the PDG compartment results in a mucinous metaplasia. Shh promotes this transformation *in vitro* and *in vivo*. In conclusion, PDG are a distinct gland-like mucinous compartment with a distinct molecular signature. In response to injury PDG

undergo a Shh-mediated mucinous gastrointestinal metaplasia with PanIN-like features. PDG may provide a link between Shh, mucinous metaplasia and neoplasia.

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Laparoscopic distal pancreatectomy for solid and cystic pancreatic neoplasms: outpatient postoperative management.

Elola-Olaso AM, Allen A, Gagliardi RJ.

Department of Minimally Invasive Surgery, General Surgery, University of Kentucky Medical Center. Lexington, KY, USA.

Laparoscopic distal pancreatectomy is a challenging procedure that has been reported in the last decade. The aim of this study is to describe the experience of authors with laparoscopic distal pancreatectomy and an outpatient postoperative management after an early hospital discharge. The authors evaluated retrospectively 11 laparoscopic distal pancreatectomies carried out between November 2005 and June 2007 for cystic and solid pancreatic neoplasms. Mean age was 55.5 years and 10 patients were females. A splenopancreatectomy was carried out in 9 cases, and a spleen-preserving resection was carried out in 2 cases. Mean blood loss was 73.6 mL and mean operative time was 238.3 minutes. Patients were able to tolerate regular diet after a mean of 1.2 days and were discharged with a drain after a mean of 2.3 days. Two patients developed a mild pancreatic fistula that resolved with conservative management. One patient developed a pancreatic pseudocyst that was followed up with an MRI. Laparoscopic distal pancreatectomy is feasible with a fast postoperative recovery. The authors recommend close follow-up of the patient in the outpatient clinic and maintaining the intraabdominal drain until a pancreatic fistula can be ruled out based on biochemical analysis of the fluid.

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Solid-pseudopapillary neoplasm: a pancreatic enigma.

Chakhachiro ZI, Zaatari G.

Department of Pathology and Laboratory Medicine, American University of Beirut Medical Center. Beirut, Lebanon.

Solid-pseudopapillary neoplasm of the pancreas is a relatively uncommon tumor. It typically affects young women, has nonspecific clinical and radiologic manifestations, and can be readily diagnosed by ultrasound-guided fine-needle aspiration and histopathologic evaluation. Histologic features characteristically show loosely cohesive, relatively uniform polygonal cells surrounding delicate capillary-sized blood vessels. Other features include cytoplasmic vacuolization, finely stippled chromatin, nuclear grooving, eosinophilic hyaline globules, and degenerative changes. Almost all solid-pseudopapillary neoplasms harbor mutations in the beta-catenin gene. They stain with beta-catenin, CD10, and focally with neuroendocrine markers. Although previously considered benign, this tumor is currently considered a low-grade malignant epithelial neoplasm with low metastatic rate and high overall survival. Most patients are cured by complete surgical excision. Despite the characterization of the morphologic and molecular features of this enigmatic neoplasm, more work is needed to uncover its cell of origin and true histogenesis.

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Mucinous nonneoplastic cyst of the pancreas: apomucin phenotype distinguishes this entity from intraductal papillary mucinous neoplasm.

Cao W, Adley BP, Liao J, Lin X, Talamonti M, Bentrem DJ, et *al.*

Department of Pathology, Feinberg School of Medicine, Northwestern University. Chicago, IL, USA.

Mucinous nonneoplastic cyst of the pancreas is a newly described and rare cystic lesion with unknown histogenesis. It is defined as a cystic lesion lined with mucinous epithelium, supported by hypocellular stroma and not communicating with the pancreatic ducts. It is very challenging to differentiate this lesion from other cystic mucinous neoplasms of the pancreas such as branch-duct intraductal papillary mucinous neoplasm by morphology. In this study, a total of 436 pancreatic specimens resected between 2002 and 2007 were reviewed. Fifteen (3.4%, 15/436) mucinous nonneoplastic cysts were identified. They included 3 males and 12 females, with a median age of 60 years. Forty-six percent of cases (7/15) occurred in pancreatic head, 27% (4/15) in neck, 7% (1/15) in body, and 20% (3/15) in tail. The size of lesions ranged from 0.5 to 3.5 cm in greatest dimension. In most cases (12/15, 80%), mucinous nonneoplastic cyst was associated or adjacent to acinar-ductal mucinous metaplasia. These morphologic data indicate that mucinous nonneoplastic cyst is not really a rare disease and may originate from acinar-duct mucinous metaplasia histogenetically. Furthermore, apomucin immunostains of mucinous nonneoplastic cyst showed MUC1 expressed in 27% (4/15) cases, MUC5AC in 67% (10/15 cases), and MUC2 was were negative in all cases, whereas

intraductal papillary mucinous neoplasm (n=17; 5 main duct type, 12 branch-duct type) showed focal and weak MUC1 positivity in 18% (3/17) cases, MUC2 positivity in 71% (12/17) cases, and all intraductal papillary mucinous neoplasm (17/17) were MUC5AC positive. The clonality assay with the HUMARA gene revealed that the mucinous nonneoplastic cysts were of polyclonal origin. For the first time, using HUMARA assay, the authors demonstrate the nonneoplastic nature of these cysts and further characterize morphologic and immunophenotypic properties that allow differentiation from intraductal papillary mucinous neooplasm.

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Neoadjuvant peptide receptor radionuclide therapy for an inoperable neuroendocrine pancreatic tumor.

Kaemmerer D, Prasad V, Daffner W, Hörsch D, Klöppel G, Hommann M, Baum RP.

Department of General and Visceral Surgery, Zentralklinik Bad Berka. Bad Berka, Germany.

Pancreatic endocrine tumors are rare but are among the most common neuroendocrine neoplasms of the abdomen. At diagnosis many of them are already advanced and difficult to treat. The authors report on an initially inoperable malignant pancreatic endocrine tumor in a 33-year-old woman, who received neoadjuvant peptide receptor radionuclide therapy (PRRT) as first-line treatment. This resulted in a significant downstaging of the tumor and allowed its subsequent complete surgical removal. Follow-up for eighteen months revealed a complete remission. This is the first report on neoadjuvant PRRT in a neuroendocrine neoplasm with subsequent successful complete resection.

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