PANCREAS ALERTS

World J Gastroenterol 2011; 17(35):3957-61.
(PMID: 22046082)

Update on endoscopic pancreatic function testing.

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Hormone-stimulated pancreatic function tests (PFTs) are considered the gold standard for measuring pancreatic exocrine function. PFTs involve the administration of intravenous secretin or cholecystokinin, followed by collection and analysis of pancreatic secretions. Because exocrine function may decline in the earliest phase of pancreatic fibrosis, PFTs are considered accurate for diagnosing chronic pancreatitis. Unfortunately, these potentially valuable tests are infrequently performed except at specialized centers, because they are time consuming and complicated. To overcome these limitations, endoscopic PFT methods have been developed which include aspiration of pancreatic secretions through the suction channel of the endoscope. The secretin endoscopic pancreatic function test (ePFT) involves collection of duodenal aspirates at 15, 30, 45 and 60 min after secretin stimulation. A bicarbonate concentration greater than 80 mmol/L in any of the samples is considered a normal result. The secretin ePFT has demonstrated good sensitivity and specificity compared with various reference standards, including the "Dreiling tube" secretin PFT, endoscopic ultrasound, and surgical histology. Furthermore, a standard autoanalyzer can be used for bicarbonate analysis, which allows the secretin ePFT to be performed at any hospital. The secretin ePFT may complement imaging tests like endoscopic ultrasound (EUS) in the diagnosis of early chronic pancreatitis. This paper will review the literature validating the use of ePFT in the diagnosis of exocrine insufficiency and chronic pancreatitis. Newer developments will also be discussed, including the feasibility of combined EUS/ePFT, the use of cholecystokinin alone or in combination with secretin, and the discovery of new protein and lipid pancreatic juice biomarkers which may complement traditional fluid analysis.

Pancreatology 2011; 11(5):500-5.
(PMID: 22042294)

Laparoendoscopic single-site lateral pancreaticojejunostomy.

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Chronic pancreatitis is mainly managed with drugs, but surgery is required in selected groups of patients. The Partington procedure is still the procedure of choice for patients with a dilated main pancreatic duct but without an inflammatory pancreatic head mass. The same equivalent can be achieved by laparoscopic approach. Laparoendoscopic single-site surgery gained tremendous attention in the past few years. Complex surgeries are being reported using this technique. The authors report in this paper the first laparoendoscopic single-site lateral pancreaticojejunostomy (LPJ) for chronic calcific pancreatitis with dilated pancreatic duct. The procedure was performed on a 32-year-old female diagnosed to have chronic calcific pancreatitis. A single vertical 2.5 cm umbilical incision and one 10 mm and two 5 mm ports were made. The procedure was completed in 220 min without any intraoperative complication. There were no postoperative complications, and the patient was discharged on day 5 when she started taking routine diet. In conclusion, this preliminary experience suggests that single-incision laparoscopic LPJ is feasible and safe when performed by an experienced laparoscopic surgeon. It has a cosmetic advantage over laparoscopic LPJ. However, it remains to be determined if this technique offers additional advantages of decreased analgesia, decreased hospital stay or cost effectiveness. Further studies are required to analyze these factors.

Am J Physiol Gastrointest Liver Physiol 2011; Oct 28.
(PMID: 22038828)

Systemic administration of anti-NGF increases A-type potassium currents and decreases pancreatic nociceptor excitability in a rat model of chronic pancreatitis.

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The authors have previously shown that pancreatic sensory neurons in rats with chronic pancreatitis (CP) display increased excitability associated with a decrease in transient inactivating potassium currents (I(A)), thus accounting in part for the hyperalgesia associated with this condition. Because of its well-known role in somatic hyperalgesia, the authors hypothesized a role for the nerve growth factor (NGF)

in driving these changes. CP was induced by intraductal injection of trinitrobenzene sulfonic acid (TNBS) in rats. After 3 weeks, anti-NGF antibody or control serum was injected intra-peritoneally daily for one week. This protocol was repeated in another set of experiments in control rats (receiving intraductal PBS instead of TNBS). Pancreatic nociceptors labeled with the dye Dil were identified and patch-clamp recordings were made from acutely dissociated DRG neurons. Sensory neurons from anti-NGF treated rats displayed a lower resting membrane potential, increased rheobase, decreased burst discharges in response to stimulatory current and decreased input resistance as compared with those treated with control serum. Under voltage clamp condition, neuronal IA current density was increased in anti-NGF treated rats as compared with rats treated with control serum. However, anti-NGF treatment had no effect on electrophysiological parameters in neurons from control rats. The expression of Kv associated channel or ancillary genes Kv 1.4, 4.1, 4.2, 4.3, DPP6, DPP10, KCHIPs 1-4 in pancreas-specific nociceptors was examined by laser capture microdissection and real time PCR quantification of mRNA levels. No significant differences were seen among those. These findings emphasize a key role for NGF in maintaining neuronal excitability in chronic pancreatitis specifically via downregulation of IA currents by as yet unknown mechanisms.

Cell Biochem Biophys 2011; Nov 1.
(PMID: 22042732)

Resveratrol ameliorates the deleterious effect of severe acute pancreatitis.

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Resveratrol (RES) is a traditional Chinese herbal medicine having anti-inflammatory properties. The authors sought to explore the role of RES in intestinal injury during severe acute pancreatitis (SAP) in a rat model study. For this purpose, RES-treated and sham-operated (SO) SAP rat models were established, and SAP was induced in rats by injecting 4% sodium taurocholate into the biliary-pancreatic duct. In the RES group, RES was infused intravenously immediately after the SAP induction in rats; SO group served as controls. Histopathological analysis, determination of tissue levels of superoxide dismutase (SOD) and malondialdehyde (MDA) and serum levels of TNF-alpha as well as ICAM-1 and VCAM-1 expression were carried out at 3, 6, and 12 h following SAP induction. The data show that following SAP induction, SOD levels decreased and MDA levels increased along with ICAM-1 and VCAM-1 expression in the intestine. Serum TNF-alpha levels increased in the SAP group. Importantly, RES treatment significantly reversed all the pathological changes. In conclusion, this study confirmed the anti-inflammatory properties of RES and demonstrated the prevention of injury to the intestinal barrier in the rat SAP model.

J Cell Mol Med 2011; Nov 1.
(PMID: 22040127)

Activation of neurokinin-1 receptors up-regulates substance P and neurokinin-1 receptor expression in murine pancreatic acinar cells.

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Acute pancreatitis (AP) has been associated with an up-regulation of substance P (SP) and neurokinin-1 receptor (NK1R) in the pancreas. Increased SP-NK1R interaction was suggested to be pro-inflammatory during AP. Previously, the authors showed that caerulein treatment increased SP/NK1R expression in mouse pancreatic acinar cells, but the effect of SP treatment was not evaluated. Pancreatic acinar cells were obtained from pancreas of male swiss mice (25-30 g). The authors measured mRNA expression of preprotachykinin-A (PPTA) and NK1R following treatment of SP (10^{-6} M). SP treatment increased PPTA and NK1R expression in isolated pancreatic acinar cells, which was abolished by pretreatment of a selective NK1R antagonist, CP96,345. SP also time dependently increased protein expression of NK1R. Treatment of cells with a specific NK1R agonist, GR73,632, up-regulated SP protein levels in the cells. Using previously established concentrations, pre-treatment of pancreatic acinar cells with Gö6976 (10 nM), rottlerin (5 μM), PD98059 (30 μM), SP600125 (30 μM) or Bay11-7082 (30 μM) significantly inhibited up-regulation of SP and NK1R. These observations suggested that the PKC-ERK/JNK-NF-KappaB pathway is necessary for the modulation of expression levels. In comparison, pre-treatment of CP96,345 reversed gene expression in SP-induced cells, but not in caerulein-treated cells. Overall, the findings in this study suggested a possible auto-regulatory mechanism of SP/NK1R expression in mouse pancreatic acinar cells, via activation of NK1R. Elevated SP levels during AP might increase the occurrence of a positive feedback loop that contributes to abnormally high expression of SP and NK1R.

Intensive Care Med 2011; Oct 27.
(PMID: 22037716)

Soluble triggering receptor expressed on myeloid cells in severe acute pancreatitis: a biological marker of infected necrosis.

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The diagnosis and treatment of secondary infection of pancreatic necrotic tissue remain a major challenge. The level of soluble triggering receptor expressed on myeloid cells (sTREM-1) in fine needle aspiration (FNA) fluid may be a good marker of infected necrosis. Patients with a clinical suspicion of secondary infection of necrotic tissue were enrolled. The serum levels of C-reactive protein, amylase, procalcitonin (PCT), and sTREM-1 and the fluid levels of sTREM-1, PCT, interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-alpha), and amylase were examined. When infected necrosis was defined, the first step was percutaneous or endoscopic drainage. If there was no improvement after 72 h, an open necrosectomy was performed. In 30 patients with suspected infection, 18 patients were diagnosed as having secondary infection of necrotic tissue. The levels of sTREM-1 and PCT in FNA fluid were found to have the closest correlation with the diagnosis of infected necrosis (sTREM-1: area under the receiver operating characteristic curve (AUC) 0.972; 95% confidence interval (95% CI) 0.837-1.000; PCT: AUC 0.903; 95% CI 0.670-0.990, P>0.05). A fluid sTREM-1 cutoff value of 285.6 pg/mL had a sensitivity of 94.4% and a specificity of 91.7%. In a multiple logistic regression analysis, an sTREM-1 level of more than 285 pg/mL and a PCT level of more than 2.0 ng/mL in FNA fluid were independent predictors of infected necrosis. In conclusions, the fluid level of sTREM-1 will help in the rapid and accurate diagnosis of secondary infection of necrotic tissue in patients with severe acute pancreatitis (SAP).

PLoS One 2011; 6(10):e26926.
(PMID: 22046413)

Human RNA polymerase II-association factor 1 (hPaf1/PD2) regulates histone methylation and chromatin remodeling in pancreatic cancer.

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Change in gene expression associated with pancreatic cancer could be attributed to the variation in histone posttranslational modifications leading to subsequent remodeling of the chromatin template during transcription. However, the interconnected network of molecules involved in regulating such processes remains elusive. hPaf1/PD2, a subunit of the human PAF-complex, involved in the regulation of transcriptional elongation has oncogenic potential. This study explores the possibility that regulation of histone methylation by hPaf1 can contribute towards alteration in gene expression by nucleosomal rearrangement. Here, the authors show that knockdown of hPaf1/PD2 leads to decreased di- and tri-methylation at histone H3 lysine 4 residues in pancreatic cancer cells. Interestingly, hPaf1/PD2 colocalizes with MLL1 (Mixed Lineage Leukemia 1), a histone methyl-transferase that methylates H3K4 residues. Also, a reduction in hPaf1 level resulted in reduced MLL1 expression and a corresponding decrease in the level of CHD1 (chromohelicase DNA-binding protein 1), an ATPase dependent chromatin remodeling enzyme that specifically binds to H3K4 di and trimethyl marks. hPaf1/PD2 was also found to interact and colocalize with CHD1 in both cytoplasmic and nuclear extracts of pancreatic cancer cells. Further, reduced level of CHD1 localization in the nucleus in hPaf1/PD2 Knockdown cells could be rescued by ectopic expression of hPaf1/PD2. Micrococcal nuclease digestion showed an altered chromatin structure in hPaf1/PD2-KD cells. Overall, these results suggest that hPaf1/PD2 in association with MLL1 regulates methylation of H3K4 residues, as well as interacts and regulates nuclear shuttling of chromatin remodeling protein CHD1, facilitating its function in pancreatic cancer cells.

Biostatistics 2011; Oct 31.
(PMID: 22045909)

Identification of cancer genomic markers via integrative sparse boosting.

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In high-throughput cancer genomic studies, markers identified from the analysis of single data sets often suffer a lack of reproducibility because of the small sample sizes. An ideal solution is to conduct large-scale prospective studies, which are extremely expensive and time consuming. A cost-effective remedy is to pool data from multiple comparable studies and conduct integrative analysis. Integrative analysis of multiple data sets is challenging because of the high dimensionality of genomic measurements and heterogeneity among studies. In this article, the authors propose a sparse boosting approach for marker identification in integrative analysis of multiple heterogeneous cancer diagnosis studies with gene expression measurements. The proposed approach can effectively accommodate the heterogeneity among multiple studies and identify markers with consistent effects across studies. Simulation shows that the proposed approach has satisfactory identification results and outperforms alternatives including an intensity approach and meta-analysis. The proposed approach is used to identify markers of pancreatic cancer and liver cancer.

Dis Markers 2011; 31(4):241-6.
(PMID: 22045431)

A polymorphism within the connective tissue growth factor (CTGF) gene has no effect on non-invasive markers of beta-cell area and risk of type 2 diabetes.

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Chromosomal locus 6q23 is strongly linked to type 2 diabetes (T2DM) and related features including insulin secretion in various ethnic populations. Connective tissue growth factor (CTGF) gene is an interesting T2DM candidate gene in this chromosome region. CTGF is a key mediator of progressive pancreatic fibrosis up-regulated in type 2 diabetes. In contrast, CTGF inactivation in mice compromises islet cell proliferation during embryogenesis. The aim of this study was to investigate an impact of CTGF genetic variation on pancreatic beta-cell function and T2DM pathogenesis. The authors studied the effect of a common CTGF polymorphism rs9493150 on the risk of the T2DM development in three independent German cohorts. Specifically, the association between CTGF polymorphism and non-invasive markers of beta-cell area derived from oral glucose tolerance test was studied in subjects without diabetes. Neither in the Metabolic Syndrome Berlin Potsdam (MESYBEPO) study (n=1,026) (OR=0.637, CI (0.387-1.050); P=0.077) nor in the European Prospective Investigation into Cancer and Nutrition-Potsdam (EPIC-Potsdam) (n=3,049) cohort (RR=0.77, CI (0.49-1.20), P=0.249 for the recessive homozygote in general model), a significant association with increased diabetes risk was observed. The risk allele of rs9493150 had also no effect on markers of beta-cell area in the combined analysis of the MESYBEPO and Tübingen Family Study (n=1,826). In conclusion, the polymorphism rs9493150 in the 5'-untranslated region of the CTGF gene has no association with T2DM risk and surrogate markers of beta-cell area.