
Cloning of IP15, a pancreatitis-induced gene whose expression inhibits cell growth.

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The authors describe the cloning and expression of the mouse gene interferon-inducible-protein 15 (IP15), whose activation is related to the acute phase of experimental pancreatitis. Analysis of its structure indicates that it encodes a putative transmembrane protein of 137 amino acids. This gene contains a predicted IFN-stimulable-response element. In vivo studies showed that IP15 is strongly activated in pancreas early during caerulein-induced pancreatitis. In situ hybridization of IP15 mRNA showed that its expression is restricted to acinar cells. IP15 was also induced in pancreas under systemic-lipopolysaccharide treatment and in intestine under Salmonella infection. In vitro studies using NIH3T3 fibroblasts showed that IP15 is induced by IFN-alpha. Growth rate was significantly lower in cells transfected with pcDNA4/IP15 plasmid. In addition, cells expressing IP15 showed less capacity to develop colonies after antibiotic selection. In conclusion, the authors identified a new interferon-inducible gene that is activated early in pancreas with pancreatitis and whose expression inhibits cell growth.


Ethyl pyruvate ameliorates distant organ injury in a murine model of acute necrotizing pancreatitis.

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Ethyl pyruvate has been shown to be an effective anti-inflammatory agent in a variety of in vitro and in vivo model systems. Herein, the authors used a murine model of acute pancreatitis to compare the effects of treatment with either Ringer's lactate solution or ethyl pyruvate solution on several physiologic and biochemical variables related to disease severity. C57Bl/6 mice were used. Pancreatitis was induced by feeding the animals a choline-deficient diet supplemented with 0.5% ethionine for 24 hrs and then challenging the animals with seven hourly 50 microg/kg intraperitoneal injections of cerulein and a single intraperitoneal injection of Escherichia coli lipopolysaccharide (4 mg/kg). When mice were treated with ethyl pyruvate (40 mg/kg intraperitoneally every 6 hrs for 48 hrs) instead of Ringer's lactate solution starting 2 hrs after the injection of lipopolysaccharide, long-term survival was significantly improved from one of ten to six of ten (P=0.057). When mice were treated with a 40 mg/kg dose of ethyl pyruvate just before the first dose of cerulein and then injected with a second 40 mg/kg dose 6 hrs later, serum concentrations of alanine aminotransferase measured 10 hrs after the first cerulein dose were significantly lower than in mice with pancreatitis treated with Ringer's lactate solution. In this model of acute pancreatitis, the same dosing regimen for ethyl pyruvate also ameliorated bacterial translocation to mesenteric lymph nodes and leakage of fluorescein isothiocyanate-labeled albumin from blood into bronchoalveolar lavage fluid. Treatment with ethyl pyruvate decreased pancreatic expression of tumor necrosis factor and interleukin-6 messenger RNA and nuclear factor-kappaB DNA binding in nuclear extracts prepared from
pancreatic tissue. Treatment with ethyl pyruvate ameliorated the local inflammatory response and decreased local and distant organ injury in a murine model of necrotizing pancreatitis.

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To assess the effects of inhibiting both tumor necrosis factor (TNF)-alpha production and xanthine oxidase activity on the inflammatory response, mitogen-activated protein kinase (MAPK) activation and mortality in necrotizing acute pancreatitis in rats. Pancreatic injury triggers 2 major pathways involved in the systemic effects of severe acute pancreatitis: pro-inflammatory cytokines and oxidative stress. Pancreatitis was induced by intraductal infusion of 3.5% sodium taurocholate. We examined whether treatment with oxypurinol, a specific inhibitor of xanthine oxidase, and/or pentoxifylline, an inhibitor of TNF-alpha production, affects pancreatic damage, ascites, lung inflammation, and MAPK phosphorylation. Oxypurinol prevented p38 phosphorylation in the pancreas and partially avoided the rise in lung myeloperoxidase activity. Pentoxifylline prevented erk 1/2 and JNK phosphorylation in the pancreas, and it partially reduced ascites and the rise in lung myeloperoxidase activity. Combined treatment with oxypurinol and pentoxifylline almost completely abolished ascites, MAPK phosphorylation in the pancreas, and the increase in lung myeloperoxidase activity. Histology revealed a reduction in pancreatic and lung damage. These changes were associated with a significant improvement of survival. In conclusion, simultaneous inhibition of TNF-alpha production and xanthine oxidase activity greatly reduced local and systemic inflammatory response in acute pancreatitis and decreased mortality rate. These effects were associated with blockade of the 3 major MAPKs.

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Major resection for chronic pancreatitis in patients with vascular involvement is associated with increased postoperative mortality.


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The aim of this study was to evaluate the outcome of major resection for chronic pancreatitis in patients with and without vascular involvement. Of 250 patients with severe chronic pancreatitis referred between 1996 and 2003, 112 underwent pancreatic resection. The outcome of 17 patients (15.2 per cent) who had major vascular involvement was compared with that of patients without vascular involvement. The 95 patients without vascular involvement had resections comprising Beger's operation (39 patients), Kausch-Whipple pancreatoduodenectomy (28), total pancreatectomy (25) and left pancreatectomy (three). Twenty-five major vessels were involved in the remaining 17 patients. One or more major veins were occluded and/or compressed producing generalized or segmental portal hypertension, and three patients also had major arterial involvement. Surgery in these patients comprised Beger's operation (eight), total pancreatectomy (five), Kausch-Whipple pancreatoduodenectomy (two) and left pancreatectomy (two). Perioperative mortality rates were significantly different between the groups (two of 95 versus three of 17
respectively; P=0.024). There were similar and significant improvements in long-term outcomes in both groups. In conclusion, resection for severe chronic pancreatitis in patients with vascular complications is hazardous and is associated with an increased mortality rate. Vascular assessment should be included in the routine follow-up of patients with chronic pancreatitis, to enable early identification of those likely to develop vascular involvement and prompt surgical intervention.

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**An autoantibody-mediated immune response to calreticulin isoforms in pancreatic cancer.**


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The identification of circulating tumor antigens or their related autoantibodies provides a means for early cancer diagnosis as well as leads for therapy. The authors have used a proteomic approach to identify proteins that commonly induce a humoral response in pancreatic cancer. Aliquots of solubilized proteins from a pancreatic cancer cell line (Panc-1) were subjected to two-dimensional PAGE, followed by Western blot analysis in which sera of individual patients were tested for primary antibodies. Sera from 36 newly diagnosed patients with pancreatic cancer, 18 patients with chronic pancreatitis, 33 patients with other cancers, and 15 healthy subjects were analyzed. Autoantibodies were detected against either one or two calreticulin isoforms identified by mass spectrometry in sera from 21 of 36 patients with pancreatic cancer. One of 18 chronic pancreatitis patients and 1 of 15 healthy controls demonstrated autoantibodies to calreticulin isoform 1; none demonstrated autoantibodies to isoform 2. None of the sera from patients with colon cancer exhibited reactivity against either of these two proteins. One of 14 sera from lung adenocarcinoma patients demonstrated autoantibodies to calreticulin isoform 1; 2 of 14 demonstrated autoantibodies to isoform 2. Immunohistochemical analysis of calreticulin in pancreatic/ampullary tumor tissue arrays using an isoform nonspecific antibody revealed diffuse and consistent cytoplasmic staining in the neoplastic epithelial cells of the pancreatic and ampullary adenocarcinomas. The detection of autoantibodies to calreticulin isoforms may have utility for the early diagnosis of pancreatic cancer.

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**Inflammation and Cancer. V. Chronic pancreatitis and pancreatic cancer.**

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Pancreatic inflammation appears to increase the risk of pancreatic cancer. This observation is striking in the hereditary pancreatitis kindreds but also occurs in alcoholic, idiopathic, and tropical chronic pancreatitis and cystic fibrosis. However, the mutations associated with hereditary pancreatitis or cystic fibrosis are not found in sporadic pancreatic adenocarcinomas, suggesting that the effects are indirect by causing recurrent pancreatitis and chronic inflammation. The process of mutation accumulation and clonal expansion that is required for development of invasive pancreatic adenocarcinoma must therefore be accelerated in chronic pancreatitis to account for the high incidence of pancreatic cancer in these patients.
Diabetes prevention. A GAMEPLAN for success.

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Diabetes prevalence is growing at epidemic proportions, and the greatest increase in number of cases is anticipated to be among older adults. The Diabetes Prevention Program (DPP) showed that diabetes can be prevented or delayed among people with prediabetes (impaired glucose tolerance, impaired fasting glucose, or both). The National Diabetes Education Program has developed tools adapted from the DPP that primary care providers can use to counsel middle-age and older patients on diabetes prevention.

Derivatives of erythropoietin that are tissue protective but not erythropoietic.


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Erythropoietin (EPO) is both hematopoietic and tissue protective, putatively through interaction with different receptors. We generated receptor subtype-selective ligands allowing the separation of EPO's bioactivities at the cellular level and in animals. Carbamylated EPO (CEPO) or certain EPO mutants did not bind to the classical EPO receptor (EPOR) and did not show any hematopoietic activity in human cell signaling assays or upon chronic dosing in different animal species. Nevertheless, CEPO and various nonhematopoietic mutants were cytoprotective in vitro and conferred neuroprotection against stroke, spinal cord compression, diabetic neuropathy, and experimental autoimmune encephalomyelitis at a potency and efficacy comparable to EPO.

Stem-cell therapy for diabetes mellitus.

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Curative therapy for diabetes mellitus mainly implies replacement of functional insulin-producing pancreatic beta cells, with pancreas or islet-cell transplants. However, shortage of donor organs spurs research into alternative means of generating beta cells from islet expansion, encapsulated islet xenografts, human islet cell-lines, and stem cells. Stem-cell therapy here implies the replacement of diseased or lost cells from progeny of pluripotent or multipotent cells. Both embryonic stem cells (derived from the inner cell mass of a blastocyst) and adult stem cells (found in the postnatal organism) have been used to generate surrogate beta cells or otherwise restore beta-cell functioning. Recently, Andreas Lechner and colleagues failed to see transdifferentiation into pancreatic beta cells after transplantation of bone-marrow cells into mice (Diabetes 2004; 53: 616-23). Last year, Jayaraj Rajagopal and colleagues failed to derive beta cells from embryonic stem cells (Science 2003; 299: 363). However, others have seen such effects. As in every emerging field in biology, early reports seem confusing and conflicting. Embryonic and adult stem cells are potential sources for beta-cell replacement and merit further scientific investigation. Discrepancies between different results need to be reconciled. Fundamental processes in determining the differentiation pathways of
stem cells remain to be elucidated, so that rigorous and reliable differentiation protocols can be established. Encouraging studies in rodent models may ultimately set the stage for large-animal studies and translational investigation.

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Lack of insurance coverage for testing supplies is associated with poorer glycemic control in patients with type 2 diabetes.

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Public insurance for testing supplies for self-monitoring of blood glucose is highly variable across Canada. We sought to determine if insured patients were more likely than uninsured patients to use self-monitoring and whether they had better glycemic control. The authors used baseline survey and laboratory data from patients enrolled in a randomized controlled trial examining the effect of paying for testing supplies on glycemic control. The authors recruited patients through community pharmacies in Alberta and Saskatchewan from Nov. 2001 to June 2003. To avoid concerns regarding differences in provincial coverage of self-monitoring and medications, the authors report the analysis of Alberta patients only. Among our sample of 405 patients, 41% had private or public insurance coverage for self-monitoring testing supplies. Patients with insurance had significantly lower hemoglobin A(1c) concentrations than those without insurance coverage (7.1% v. 7.4%, P=0.03). Patients with insurance were younger, had a higher income, were less likely to have a high school education and were less likely to be married or living with a partner. In multivariate analyses that controlled for these and other potential confounders, lack of insurance coverage for self-monitoring testing supplies was still significantly associated with higher hemoglobin A(1c) concentrations (adjusted difference 0.5%, P=0.006). In conclusion, patients without insurance for self-monitoring test strips had poorer glycemic control.