How often are liver function tests normal in acute biliary pancreatitis?

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The biochemical markers of a biliary etiology of acute pancreatitis include an ALT elevation of more than 3 times the upper range of normal and a serum total bilirubin greater than 3 mg/dL. The authors analyzed the frequency of normal liver function tests (bilirubin, alkaline phosphatase, ALT, and AST) in patients with biliary acute pancreatitis. In this prospective study data collected for other ongoing studies on AP in the division of Gastroenterology in the last 20 years were analyzed. Serum total bilirubin, AST, ALT, and alkaline phosphatase levels in 269 patients with biliary acute pancreatitis out of 728 cases of acute pancreatitis of various etiologies were analyzed. The biliary etiology was confirmed on the basis of gallstones documented by transabdominal ultrasonography or at surgery. Normal bilirubin, AST, ALT, and alkaline phosphatase levels were found in 14.5%, 12.3%, 11.2%, and 26.4% of cases of acute biliary pancreatitis, respectively. When all the four laboratory tests were considered collectively, the incidence of normal values was 10.4%. The authors also noted an ALT elevation of less than 3 x upper range of normal in 16.7% of cases of biliary acute pancreatitis and 43.5% of cases had a total bilirubin level of less than 3 mg %. Almost 15 to 20% of patients with biliary acute pancreatitis manifest with normal liver function tests and the clinician should not exclude a biliary etiology solely on this basis.
ischemia/reperfusion-induced pancreatitis was partly reversed by administration of CGRP prior to ischemia/reperfusion. Stimulation of sensory nerves protects the pancreas against damage evoked by ischemia/reperfusion, whereas ablation of these nerves aggravates tissue damage in the pancreas exposed to ischemia/reperfusion. The authors concluded that the beneficial effect of sensory nerves is partly dependent on CGRP release.

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Alteration of somatostatin receptor subtype 2 gene expression in pancreatic tumor angiogenesis.


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The authors explored the difference of somatostatin receptor subtype 2 (SST2R) gene expression in pancreatic cancerous tissue and its adjacent tissue, and the relationship between the change of SST2R gene expression and pancreatic tumor angiogenesis related genes. The expressions of SST2R, DPC4, p53 and ras genes in cancer tissues of 40 patients with primary pancreatic cancer, and the expression of SST2R gene in its adjacent tissue were determined by immunohistochemical LSAB method and EnVision (TM) method. Chi-square test was used to analyze the difference in expression of SST2R in pancreatic cancer tissue and its adjacent tissue, and the correlation of SST2R gene expression with the expression of p53, ras and DPC4 genes. Of the tissue specimens from 40 patients with primary pancreatic cancer, 35 (88%) cancer tissues showed a negative expression of SST2R gene, whereas 34 (85%) a positive expression of SST2R gene in its adjacent tissues. Five (12.5%) cancer tissues and its adjacent tissues simultaneously expressed SST2R. The expression of SST2R gene was markedly higher in pancreatic tissues adjacent to cancer than in pancreatic cancer tissues (P<0.05). The expression rates of p53, ras and DPC4 genes were 50%, 60% and 72.5%.

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The efficacy of tyrosine kinase inhibitors on human pancreatic cancer cell lines (1).


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The authors attempted to determine potential therapeutic targets in pancreatic cancer by performing microarray analysis and targeted chemotherapy on three human pancreatic cancer cell lines. The authors used a microarray to screen 847 genes involved in cytokine signaling, signal transduction, and transcription. Tyrosine kinases represented a common target driving proliferation among the three cell types. They tested the ability of Gleevec (STI-571), Lavendustin, Herbimycin, and Genistein to inhibit the proliferation of cells in culture as assessed by the MTT assay. Eighteen genes were found to be commonly expressed by the three cell lines. Of these, six (33%) included tyrosine phosphorylation signaling as part of the pathway. The most highly expressed common transcript was the EphB3 receptor, which is a tyrosine kinase. Herbimycin and Genistein were able to inhibit the proliferation of all three cell lines in a dose dependent manner, with a mean IC(50) of 1.71 microM and 223 microM, respectively; whereas, Lavendustin and Gleevec were ineffective in the inhibition of proliferation. Transcriptional profiling yielded common targets and insights into the biology
respectively. There was a significant negative correlation of SST2R with p53 and ras genes (P<0.01), but no significant correlation with DPC4 gene (P>0.05). There was a significant difference of SST2R gene expression in pancreatic cancer tissues and its adjacent tissues, which might be one cause for the different therapeutic effects of somatostatin and its analogs on pancreatic cancer patients. There were abnormal expressions of SST2R, DPC4, p53 and ras genes in pancreatic carcinogenesis, and moreover, the loss or decrease of SST2R gene expression was significantly negatively correlated with the overexpression of tumor angiogenesis correlated p53 and ras genes, suggesting that SST2R gene together with p53 and ras genes may participate in pancreatic cancerous angiogenesis.


Red oil A5 inhibits proliferation and induces apoptosis in pancreatic cancer cells.

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The authors studied the effect of red oil A5 on pancreatic cancer cells and its possible mechanisms. Effect of different concentrations of red oil A5 on proliferation of three pancreatic cancer cell lines, AsPC-1, MiaPaCa-2 and S2013, was measured by 3H-methyl thymidine incorporation. Time-dependent effects of 1:32,000 red oil A5 on proliferation of three pancreatic cancer cell lines, were also measured by 3H-methyl thymidine incorporation, and Time-course effects of 1:32,000 red oil A5 on cell number. The cells were counted by Z1-Coulter Counter. Flow-cytometric analysis of cellular DNA content in the control and red oil A5 treated AsPC-1, MiaPaCa-2 and S2013 cells, were stained with propidium iodide. TUNEL assay of red oil A5-induced pancreatic cancer cell apoptosis was performed. Western blotting of the cytochrome c protein in AsPC-1, MiaPaCa-2 and S2013 cells treated 24 hours with 1:32,000 red oil A5 was performed. Proteins in cytosolic fraction and in mitochondria fraction were extracted. Proteins extracted from each sample were electrophoresed on SDS-PAGE gels and then were transferred to nitrocellulose membranes. Cytochrome c was identified using a monoclonal cytochrome c antibody. Western blotting of the caspase-3 protein in AsPC-1, MiaPaCa-2 and S2013 cells treated with 1:32,000 red oil A5 for 24 hours was carried out. Proteins in whole cellular lysates were electrophoresed on SDS-PAGE gels and then transferred to nitrocellulose membranes. Caspase-3 was identified using a specific antibody. Western blotting of poly-ADP ribose polymerase (PARP) protein in AsPC-1, MiaPaCa-2 and S2013 cells treated with 1:32,000 red oil A5 for 24 hours was performed. Proteins in whole cellular lysates were separated by electrophoresis on SDS-PAGE gels and then transferred to nitrocellulose membranes. PARP was identified by using a monoclonal antibody. Red oil A5 caused dose- and time-dependent inhibition of pancreatic cancer cell proliferation. Propidium iodide DNA staining showed an increase of the sub-G0/G1 cell population. The DNA fragmentation induced by red oil A5 in these three cell lines was confirmed by the TUNEL assay. Furthermore, Western blotting analysis indicated that cytochrome c was released from mitochondria to cytosol during apoptosis, and caspase-3 was activated following red oil A5 treatment which was measured by procaspase-3 cleavage and PARP cleavage. It may be concluded that red oil A5 has potent anti-proliferative effects on human pancreatic cancer cells with induction of apoptosis in vitro.
The natural history of chronic allograft nephropathy.

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With improved immunosuppression and early allograft survival, chronic allograft nephropathy has become the dominant cause of kidney-transplant failure. The authors evaluated the natural history of chronic allograft nephropathy in a prospective study of 120 recipients with type 1 diabetes, all but 1 of whom had received kidney-pancreas transplants. The researchers obtained 961 kidney-transplant-biopsy specimens taken regularly from the time of transplantation to 10 years thereafter. Two distinctive phases of injury were evident as chronic allograft nephropathy evolved. An initial phase of early tubulointerstitial damage from ischemic injury (P<0.05), prior severe rejection (P<0.01), and subclinical rejection (P<0.01) predicted mild disease by one year, which was present in 94.2 percent of patients. Early subclinical rejection was common (affecting 45.7% of biopsy specimens at three months), and the risk was increased by the occurrence of a prior episode of severe rejection and reduced by tacrolimus and mycophenolate therapy (both P<0.05) and gradually abated after one year. Both subclinical rejection and chronic rejection were associated with increased tubulointerstitial damage (P<0.01). Beyond one year, a later phase of chronic allograft nephropathy was characterized by microvascular and glomerular injury. Chronic rejection (defined as persistent subclinical rejection for two years or longer) was uncommon (5.8%). Progressive high-grade arteriolar hyalinosis with luminal narrowing, increasing glomerulosclerosis, and additional tubulointerstitial damage was accompanied by the use of calcineurin inhibitors. Nephrotoxicity, implicated in late ongoing injury, was almost universal at 10 years, even in grafts with excellent early histologic findings. By 10 years, severe chronic allograft nephropathy was present in 58.4% of patients, with sclerosis in 37.3% of glomeruli. Tubulointerstitial and glomerular damage, once established, was irreversible, resulting in declining renal function and graft failure. The authors concluded that chronic allograft nephropathy represents cumulative and incremental damage to nephrons from time-dependent immunologic and nonimmunologic causes.

Insulin signaling in health and disease.

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The signaling pathways used by insulin have been identified (M White, Insulin Signaling Pathway, Sci STKE - Connections Map, November 2003 - http://stke.sciencemag.org/cgi/cm/cmp_12069). Now the challenge is to understand how the failure of these signals is associated with obesity and the progressive failure of pancreatic beta cells that leads to diabetes. Whether better management of chronic inflammation can improve insulin action is an important area of investigation. Drugs that stimulate IRS2 (insulin receptor substrate protein 2) synthesis or signaling might be a good starting point. This knowledge will lead to rational strategies that prevent or cure diabetes.