PANCREAS ALERTS

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Human bone marrow-derived clonal mesenchymal stem cells inhibit inflammation and reduce acute pancreatitis in rats.

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Acute pancreatitis (AP) has high mortality; repetitive AP induces chronic AP and pancreatic adeno-carcinoma. Mesenchymal stem cells (MSCs) have immunoregulatory effects and reduce inflammation. The authors developed a protocol to isolate human bone marrow-derived clonal mesenchymal stem cells (hcMSCs) from bone marrow aspirate and investigated the effects of these cells in rat models of mild and severe AP. Mild AP was induced in Sprague-Dawley rats by 3 intraperitoneal injections of cerulein (100 µg/kg), given at 2-hour intervals; severe AP was induced by intraparenchymal injection of 3% sodium taurocholate solution. hcMSCs were labeled with CM-1, 1'-dioctadecyl-3, 3, 3'-tetramethylindo-carbocyanine perchloride and administered to rats through the tail vein. hcMSCs underwent self-renewal and had multi-potent differentiation capacities and immunoregulatory functions. Greater numbers of infused hcMSCs were detected in pancreas of rats with mild and severe AP than of control rats. Infused hcMSCs reduced acinar-cell degeneration, pancreatic edema, and inflammatory cell infiltration in each model of pancreatitis. The hcMSCs reduced expression of inflammation mediators and cytokines in rats with mild and severe AP. hcMSCs suppressed the mixed lymphocyte reaction and increased expression of Foxp3+ (a marker of regulatory T cells) in cultured rat lymph node cells. Rats with mild or severe AP that were given infusions of hcMSCs had reduced numbers of CD3+ T cell and increased expression of Foxp3+ in pancreas tissues. hcMSCs reduced inflammation and damage to pancreatic tissue in a rat model of AP; they reduced levels of cytokines and induced numbers of Foxp3+ regulatory T cells. hcMSCs might be developed as a cell therapy for pancreatitis.

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Hepatic arterial perfusion increases in the early stage of severe acute pancreatitis patients: evaluation by perfusion computed tomography.

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Although hepatic perfusion abnormalities have been reported in patients with acute pancreatitis, hepatic perfusion with severe acute pancreatitis (SAP) has not been quantitatively evaluated in humans. Therefore, the authors investigated hepatic perfusion in patients with SAP using perfusion CT. Hepatic perfusion CT was performed in 67 patients with SAP within 3 days after symptom onset. The patients were diagnosed as having SAP according to the Atlanta criteria. Fifteen cases were established as a control group. Perfusion CT was obtained for 54 seconds beginning with a bolus injection of 40 mL of contrast agent (600-630 mgI/kg) at a flow rate of 4 mL/s. Perfusion data were analyzed by the dual-input maximum slope method to obtain hepatic arterial perfusion (HAP) and hepatic portal perfusion (HPP). Finally, the authors compared HAP and HPP in SAP patients with those in the control group, respectively. Average HAP was significantly higher in SAP patients than in the control group (75.1±38.0 *vs*. 38.2±9.0 mL/min/100 mL; P<0.001). There was no significant difference in average HPP between SAP patients and the control group (206.7±54.9 *vs*. 204.4±38.5 mL/min/100 mL; P=0.92). Using quantitative analysis on perfusion CT, the authors demonstrated an increase of HAP in the right hepatic lobe in SAP patients.

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Deposition of complement C3c, immunoglobulin (Ig)G4 and IgG at the basement membrane of pancreatic ducts and acini in autoimmune pancreatitis.

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Deposition of complement C3c, immunoglobulin (Ig)G4 and IgG at the basement membrane of pancreatic ducts and acini in autoimmune pancreatitis. Autoimmune pancreatitis (AIP) is a type of pancreatitis whose immunopathogenesis is still unknown. It has been reported that renal biopsy specimens from patients diagnosed with both AIP and tubulointerstitial nephritis reveal deposits containing complement C3, immunoglobulin (Ig)G and IgG4 at the tubular

basement membranes (BMs). The aim was to investigate the deposition of complement and immunoglobulins in pancreatic tissue from AIP patients compared to non-AIP patients. Double immunofluorescence microscopy for C3c, IgG4 and IgG together with CK7, trypsin, collagen IV, CD31 and CD79a, as well as immunofluorescence microscopy for C1q, IgA and IgM, were performed on frozen pancreatic tissue from AIP and alcoholic chronic pancreatitis (ACP) patients. In AIP patients, complement C3c, IgG4 and IgG were deposited at the collagen IV-positive BMs of pancreatic and bile ducts and of acini. In a minority of the ACP patients, weak C3c-positive BM deposits were detected, but no IgG4- or IgG-positive BM deposits were present. The deposition of C3c, IgG4 and IgG at the BM of small- and medium-sized ducts and acini of the pancreas is characteristic of AIP. This suggests that immune complex-mediated destruction of ducts and acini play a role in the pathogenesis of AIP.

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Phenotypic changes in mouse pancreatic stellate cell Ca^{2+} signaling events following activation in culture and in a disease model of pancreatitis.

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The specific characteristics of intracellular Ca^{2+} signaling and the down-stream consequences of these events were investigated in pancreatic stellate cells (PSC) in culture and using multi-photon microscopy in situ. PSC transform from a quiescent state to a myofibroblast-like phenotype in culture which parallels the phenotype observed in chronic pancreatitis and pancreatic cancer. During culture, the cell surface receptors coupled to intracellular Ca^{2+} signaling was shown to be progressively altered. Specifically, protease activated receptors (PAR) 1 and 2, responsive to thrombin and trypsin respectively, were only expressed in activated PSC (aPSC). PAR-1 activation resulted in prominent nuclear Ca^{2+} signals. Nuclear Ca^{2+} signals and aPSC proliferation were abolished by expression of parvalbumin targeted to the nucleus. In pancreatic lobules, only quiescent PSC were present. aPSC were observed following induction of experimental pancreatitis. In contrast, in a mouse model of pancreatic disease, harboring elevated K-*ras* activity in acinar cells, aPSC were present under control conditions and their number greatly increased following induction of pancreatitis. These data are consistent with nuclear Ca^{2+} signaling generated by agents such as trypsin and thrombin, likely present in the pancreas in disease states, resulting in proliferation of "primed" aPSC to contribute to the severity of pancreatic disease.

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Increased sympathetic activity in chronic pancreatitis patients is associated with hyperalgesia.

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Pain treatment in chronic pancreatitis patients is difficult, with pain frequently relapsing or persisting. Recent studies suggest that altered central nervous system pain processing underlies the chronic pain state in these patients. There is evidence that increased sympathetic activity may also play a role in some chronic pain syndromes. This study assessed sympathetic nervous system activity and its relation to pain processing in patients with severe painful chronic pancreatitis. The authors postulated that chronic pancreatitis patients with more sympathetic activity exhibit more generalized hyperalgesia. In 16 chronic pancreatitis patients, sympathetic activity was measured via venous plasma norepinephrine (NE) levels (supine, standing). Pain processing was quantified via pressure pain tolerance thresholds (PPTs) in dermatomes T10 (pancreatic area), C5, T4, L1. Five patients showed increased supine plasma NE levels (NE equal to, or greater than, 3.0 nmol/L). PPTs were lower in patients with increased NE levels (INE) compared with patients with normal NE (NNE) (means; 95% confidence interval: INE 402 kPa; 286-517 kPa versus NNE 522 kPa; 444-600 kPa; P=0.042). In severe chronic pancreatitis patients, increased sympathetic activity and hyperalgesia appear associated, suggesting that sympathetic activity may also play a role in these patients' pain.

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Development of pancreatic cancers during long-term follow-up of side-branch intraductal papillary mucinous neoplasms.

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Side-branch intraductal papillary mucinous neoplasms (SB-IPMNs), and associated synchronous and metachronous pancreatic cancers are increasingly

detected as imaging modalities become more sensitive. The authors investigated the natural history of SB-IPMN, and the incidence and characteristics of pancreatic cancers among patients undergoing long-term follow-up. The authors reviewed the clinical, imaging, and pathological features in 103 patients, diagnosed at the Aichi Cancer Center between September 1988 and September 2006 as having SB-IPMN, and conservatively followed up for 2, or more, years (median 59 months) based on an endoscopic ultrasonography (EUS) database. Seventy-four (71.8%) patients had nonprogressive lesions. Overall, six patients (5.8%) developed pancreatic cancers during follow-up, with intraductal papillary mucinous (IPM) carcinoma in four, and ductal carcinoma of pancreas that was not IPMN in two patients. Of the six pancreatic cancers, five were diagnosed at a resectable stage. The 5-year and 10-year actuarial rates of development of pancreatic cancer were 2.4% and 20.0%, respectively. Although, at the last follow-up, cyst size, main pancreatic duct (MPD) diameter, mural nodule size, and frequency of metachronous and/or synchronous cancers of other organs were significantly higher in patients who developed IPM carcinoma, resected SB-IPMNs without mural nodules and dilated MPDs had no IPM carcinomas. The frequency of pancreatic cancers is high on long-term follow-up of SB-IPMN. Although conservative management is appropriate for selected patients, regular and long-term imaging, especially by EUS is essential, even if SB-IPMN remains unchanged for 2 years. Presence of mural nodule and dilated MPD seem to be more appropriate indicators for resection than cyst size alone for SB-IPMNs.

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The CD40-CD154 interaction would correlate with proliferation and immune escape in pancreatic ductal adenocarcinoma.

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CD40 and CD154 are associated with lymphocyte signaling pathways and they are also expressed in some malignant neoplasms, but the significance in pancreatic cancer is unknown. Eighty pancreatic cancer specimens were stained immunohistochemically, and the results were correlated with the patients' clinicopathologic features. Subsequently, *in vitro* analysis of CD40-CD154 signaling was performed. Immunohisto-chemical analysis of tumor cells showed that 29 patients (36.3%) were positive for CD40, and 17 patients (21.3%) had very high CD154 expression. The survival of patients who had very high CD154 expression was significantly better than that of others (P=0.0198). Univariate and multivariate analysis revealed that very high CD154 expression in cancer cells was not an independent, favorable prognostic factor (risk ratio, 0.493; P=0.0224). On *in vitro* proliferation assay, the growth of PK-45P and KP-4 cells was blocked by CD40 and CD154 blocking antibodies. Moreover, on *in vitro* cytokine assay, Th-2 cytokines from PK-45P and SUIT-2 were blocked by CD40 or CD154 blocking antibody. These results suggest that the CD40-CD154 interaction would correlate with cell proliferation and secretion of cytokines in PDAC cells, and CD154 overexpression could be a favorable prognostic factor in PDAC patients.

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Effect of long term, non cholesterol lowering dose of fluvastatin treatment on oxidative stress in brain and peripheral tissues of streptozotocin-diabetic rats.

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One of the main goals of treatment of diabetes mellitus is to prevent its complications. Oxidative stress is universal in diabetes, being ultimately involved with the development complications. As a result of hyperglycemia, reactive oxygen/nitrogen species are produced in various tissues that leads to tissue damage with lipid peroxidation and protein oxidation, along with disruption in cellular homeostasis and accumulation of damaged molecules. Hence, sup-plementation with antioxidant compounds may offer some protection against diabetic complications. The pleiotropic effects of statins, including antioxidant and anti-inflammatory properties, represent an area of great interest in prevention and therapy of cardiovascular and neurological disorders. Using biomarkers of oxidative stress, in this study the authors examined the effect of non cholesterol lowering dose, long term fluvastatin treatment on oxidative stress in streptozotocin-diabetic rats. Experiments were conducted in 24 Wistar adult male rats. Diabetic and non-diabetic rats were treated orally for 6 months with fluvastatin (2 mg/kg/day, p.o.) starting one week after streptozotocin injection (55 mg/kg, i.p.), (preventive study). In brain, heart, liver, pancreas and kidney homogenates malondialdehyde, lipid hydroperoxide, protein carbonyl content, advanced oxidation protein products, 3-nitrotyrosine levels and superoxide dismutase, catalase activities were measured. Hyperglycemia and dyslipidemia in diabetic groups remained unchanged after fluvastatin treatment. The drug act as antioxidant in the tissues.

Hence, antioxidant property of fluvastatin, independent of cholesterol lowering effect, may play a role in prevention of diabetic complications. Clinical relevance of this effect of fluvastatin seems worthy of further studies.

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Achievement of lipid targets with the combination of rosuvastatin and fenofibric acid in patients with type 2 diabetes mellitus.

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The objective of this study was to assess the proportion of patients with type 2 diabetes mellitus (T2DM) attaining individual and combined targets of low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), non-HDL-C, and apolipoprotein B (ApoB) after treatment with rosuvastatin (R) + fenofibric acid (FA) compared with corresponding-dose R monotherapy. This post hoc analysis evaluated data from the T2DM subset of patients with mixed dyslipidemia (LDL-C equal to, or greater than, 130 mg/dL, HDL-C <40/50 mg/dL in men/women, and TG equal to, or greater than, 150 mg/dL) from two randomized studies. Patients included in the analysis (n=456) were treated with R (5, 10, or 20 mg), FA 135 mg, or R (5, 10, or 20 mg) + FA 135 mg for 12 weeks. Attainment of LDL-C <100 mg/dL, HDL-C >40/50 mg/dL in men/women, TG <150 mg/dL, non-HDL-C <130 mg/dL, ApoB <90 mg/dL, and the combined targets of these parameters was assessed. Treatment with R + FA resulted in a significantly higher proportion of patients achieving optimal levels of HDL-C (46.8% *vs*. 20.8%, P=0.009 for R 10 mg + FA), TG (60.0% *vs*. 34.0%, P=0.02 for R 10 mg + FA; 54.0% *vs*. 26.4%, P=0.005 for R 20 mg + FA), non-HDL-C (55.1% *vs*. 36.4%, P=0.04 for R 5 mg + FA), ApoB (58.0% *vs*. 36.4%, P=0.02 for R 5 mg + FA); and the combined targets of LDL-C, HDL-C, and TG (28.3% *vs*. 8.3%, P=0.02 for R 10 mg + FA) and all 5 parameters (26.1% *vs*. 8.3%, P=0.03 for R 10 mg + FA) than corresponding-dose R monotherapies. A significantly greater proportion of T2DM patients achieved individual and combined lipid targets when treated with the combination of R + FA than corresponding-dose R monotherapies.

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