Introduction: Johanson-Blizzard syndrome (JBS; OMIM 243800), an autosomal recessive multisystem disorder, is characterized by congenital abnormalies including prenatal pancreatic inflammation and later exocrine pancreatic insufficiency. JBS is associated with mutations in the UBR1 gene on chromosome 15q14-21.1, which encodes one of the E3 ubiquitin ligases of the N-end rule pathway. UBR1 is part of the ubiquitin-dependent proteolytic pathway whose substrates include proteins with destabilizing N-terminal residues. The UBR1-dependent mechanism that causes pancreatic damage in JBS is unknown and was studied here.
Methods: *Ubr-1*-deficient mice generated by targeted disruption of the *Ubr-1* gene (Mol Cell Biol. 2001; 21:8007–21) were obtained from Y.T. Kwon, Univ. of Pittburgh, USA. Acute pancreatitis was induced by caerulein (50 μg/h, i.p.). Proteome analysis of pancreatic tissue from caerulein treated WT and UBR-1 knock-out animals was performed to identify disease associated targets and those candidates were further characterised in functional assays.
Results: Proteome analysis in UBR-1-ko and WT animals after caerulein treatment with a focus on destabilizing N-terminal residues revealed a significant accumulation of pancreatic proteases such as chymotrypsin B, anionic trypsin and pancreatic elastase. Furthermore, we found an up-regulation of ER-stress proteins and inflammation related proteins. Phenotypic characterisation of pancreatitis after 8h revealed significantly increased lipase levels in UBR-1-ko animals, a significantly increased histology score (WT 2.04+/−0,78; UBR-1 ko 2.79 +/−0.72, p = 0.023) and significantly increased elastase activity 8h after the onset of pancreatitis. In isolated pancreatic acini we found a significant increase in intracellular elastase activation upon supramaximal CCK stimulation in UBR-1 ko animals associated with a significant rise in the rate of necrosis.
Conclusion: Experimental pancreatic injury in UBR-1 ko-animals was followed by significantly greater local and systemic inflammation suggesting a vital function of UBR1 in the defense against pathologic damage - and JBS as an inflammatory disorder due to an inadequate UBR1 defense. Proteom analysis and functional data from isolated pancreatic acini showed an accumulation of activated proteases and hereby support a crucial role of proteases as underlying pathomechanism for the pancreatic phenotype in JBS.

AMPA RECEPTOR ANTAGONISM INHIBITS PANCREATIC CANCER GROWTH

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The role of the glutamate system and particularly of AMPA receptor signalling in pancreatic ductal adenocarcinoma (PDAC) has not yet been defined. We evaluated AMPA receptor expression and signalling in PDAC using immunohistochemistry and immunocytochemistry as well as proliferation, migration and invasion assays following treatment with the AMPA receptor agonist S-(-)-5-Fluorowillardiine (FW) and/or the non-competitive antagonist Sym2206 (SYM). Phosphorylation experiments were performed on MAP kinase signaling pathways. A subcutaneous pancreatic cancer model in athymic nude mice was used to assess the effects of AMPA antagonism in-vivo. AMPA1 and AMPA2/3 receptors were found to be expressed in PDAC tissues and in pancreatic cancer cell lines at different intensities. Cell proliferation, migration and invasion were increased following treatment with FW (AMPA agonist), whereas blockade of AMPA receptors using SYM resulted in a decrease of these parameters in a dose- and time-dependent manner. Analysis of MAP kinases showed increased ERK phosphorylation following treatment with FW which was reversed by pretreatment with SYM. In-vivo experiments in athymic nude mice showed that AMPA receptor antagonism reduced subcutaneous tumor growth. Thus, blockade of AMPA receptors with the non-competitive AMPA antagonist SYM reduced pancreatic cancer cell growth via modulation of the ERK1/2 pathway. AMPA receptors are therefore a potential therapeutic target in the treatment of PDAC.

EPIGENETIC CHANGES IN PANCREATIC CANCER ASSOCIATED FIBROBLASTS

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Background and Purpose: Tumor-stromal interactions are very important in pancreatic cancer development. Recently, altered gene expression signature has been reported in cancer associated fibroblasts but its mechanism remains unknown. We investigated whether epigenetic mechanisms including DNA methylation are involved in the altered gene expression in pancreatic cancer associated fibroblasts.
Methods: Using microarrays, we determined changes in gene expression profiles in fibroblasts isolated from pancreatic cancer tissue (Cancer Associated Fibroblasts, CAF) and those from normal pancreatic tissue (Normal Pancreatic Fibroblasts, NPF) treated with a DNA methylation inhibitor and a histone deacetylase inhibitor.
Results: Microarray analysis revealed different expression patterns of a number of genes between NPF and CAF. A total of 253 genes were re-expressed after treatment (epigenetic reversal) exclusively in NPF, while 265 genes were re-expressed exclusively in CAF. They included several interesting genes related to cell proliferation, invasion, and matrix remodeling.
Conclusion: The different gene expression patterns between NPF and CAF suggest that epigenetic mechanisms may be involved, at least in part, in these transcriptional changes governing tumor-stromal interactions.

CD133 POSITIVE CELLS IN PANCREATIC CANCER POSSESS INCREASED CELL PROLIFERATION, MIGRATION AND INVASION

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Purpose: Due to poor prognosis of pancreatic cancer, novel therapeutic strategies are urgently needed. Recently, cancer stem cells (CSC) have been reported as a new therapeutic target in pancreatic cancer, but the specific role of the cells is not fully understood. We investigated the functional roles of CD133 positive ($CD133^+$) cells as a candidate of pancreatic CSC.
Experimental Design: CD133 expression was assessed in pancreatic cancer cells by real-time RT-PCR and flow cytometry. We compared the ability of cell proliferation, migration and invasion between $CD133^+$ and $CD133^-$ cells in two pancreatic cancer cell lines (KP-2 and SUIT-2).
Results: CD133 was expressed in 67% and 53% of KP-2 and SUIT-2, respectively, whereas not expressed in primary normal pancreatic duct and stromal cells. $CD133^+$ cells, isolated by cell sorting, indicated increased cell proliferation under anchorage independent condition ($P < 0.01$), and increased migratory and invasive ability especially when co-cultured with primary pancreatic stromal cells ($P < 0.001$). CXCR4, markedly overexpressed in $CD133^+$ cells, may be responsible for the increased invasive ability of the cells co-cultured with SDF-1 positive pancreatic stromal cells.
Conclusions: These data suggest that $CD133^+$ cells possess more malignant behavior such as increased cell proliferation, migration and invasion. The targeting therapy for $CD133^+$ cells may be a new possible approach for the treatment of pancreatic cancer.

USEFULNESS OF SERUM IgG4 IN THE DIAGNOSIS AND FOLLOW-UP OF AUTOIMMUNE PANCREATITIS (AIP): A META-ANALYSIS

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Context: High circulating IgG4 levels have been proposed as a marker of AIP.
Objective: To review the data existing in the English literature on the usefulness of the serum levels of IgG4 in the diagnosis and follow up of patients with AIP.
Study population: 7 selected papers report the usefulness of serum IgG4 in diagnosing AIP in 159 AIP patients and 1,099 controls (304 pancreatic cancer;