Methyl Donor Deficiency Induces Small Intestinal Crypt Hypertrophy in Mice and Murine Enteroids

Background & Aims: Previous studies show dietary fat composition affects body fat composition. BACKGROUND: Previous studies show dietary fat composition affects body fat composition. Pancreatitis (AP) Outcomes At Lower Body Mass Index (BMI)

Methods: We generated pancreatic acinar cell lineages from wild-type, ATG7KO, and ATG5KO mice. Results: Pancreatic acinar cell in mice induces accumulation of zymogen granules and apoptosis in acinar cell followed by severe atrophic change in pancreas similar with chronic pancreatitis. Exosomes Derived From Pancreatic Stellate Cells: microRNA Signature and Effects on Pancreatic Cancer Cells
Exosomes derived from PSCs induced chemokine expression and proliferation in pancreatic cancer cells, suggesting the exosomes have a role in the interactions between PSCs and cancer cells.

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Intrapancreatic Transforming Growth Factor beta (TGF-β) Induces Pain Behavior and Pancreatic Nociceptor Excitability: Mimicking the Effects of Chronic Pancreatitis

Yaohui Zhu, Liansheng Liu, Qian Li, Pankaj J. Pasricha

Introduction. TGF-β is upregulated in chronic inflammation and it has been associated with nociceptive sensitization in several somatic pain models. It is also a key factor in the pathogenesis of fibrosis in chronic pancreatitis and pancreatic cancer. We therefore hypothesized that increased levels of TGFβ within the pancreas may result in pain through sensitization of pancreatic nocceptors in dorsal root ganglia (DRG). Methods. TGFβ 1 was infused in different concentrations into the duet of adult male rats 3 weeks after injection of Dil into the pancreas to retrogradely label sensory neurons in pancreas-specific DRG (Figure). Results. TGFβ 1 at a dose of 1 mg, but not 100 ng, displayed hypersensitivity to graded pancreatic electrical stimulation, with significantly more pain behaviors (Figure, P<0.01 by two-way ANOVA). Further, pancreatic-specific DRG neurons displayed evidence of increased neural excitability in rats receiving 400 ng (a dose that is also associated with increased pain behavior) of intrapancreatic TGFβ 1 as compared with rats receiving vehicle alone, as follows: resting membrane potential: 49±1.6 versus 57±3.9 mV (P<0.05), rheobase: 0.2±0.4 versus 0.36±0.3 mA (P=0.1), number of action potentials at 1x rheobase: 1±0.22 versus 1±0.22 (P=0.4) and 1x rheobase: (P=0.80) at 2x rheobase. A significant decrease was seen in the transverse 'A-type' current (IA) potassium currents (35±1 vs 9.63, P<0.05) but not in 'sustained delayed rectifier type' (IK) currents. Conclusions. The results of this study are consistent with a role for TGFβ in mediating pain and nociceptive sensitization in the pancreas. Induction of TGFβ mimics the behavioral and neurochemical changes that are characteristic of chronic pancreatitis. These results provide a novel therapeutic target for pain in pancreatic disorders where TGFβ expression is prominent such as chronic pancreatitis and pancreatic cancer.

Nocifensive response to electrical stimulation of the pancreas in rats receiving different doses of TGFβ into the pancreas

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The Impact of Bcl-xL Upregulation in Kras-mutated Pancreatic Neoplasia

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Background and aims: Kras mutation is observed in almost all pancreatic ductal adenocarcinoma (PDAC) and occurred in early phase among multicentric carcinogenesis towards PDAC. On the other hand, Bcl-xL, an anti-apoptotic Bcl-2 family protein, is reported to be overexpressed in 90% of PDAC. However, the impact of Bcl-xL overexpression in PDAC or pancreatic intraepithelial neoplasias (PanINs), which are pre-cancerous lesions of PDAC, still remains unclear. In this study, we examined the significance of Bcl-xL in the development of Kras mutation-derived pancreatic neoplasia. Methods: We used KrasG12D mice as a model of PanIN and PDAC, dependent on Kras mutation. To examine the impact of Bcl-xL, Bcl-xL was knocked down by Pdx1-Cre driven Cre-loxP expression in Kras(x1/x2) mice, and Bcl-xL deficient (Bcl-xL-/-) mice were generated by crossing KrasG12D mice with Bcl-xL-/- mice. To address the mechanisms by which Bcl-xL is overexpressed in Kras-mutated cells, PanIN1 and MIA PaCa2 cells (Kras-mutated pancreatic cancer cells) or BxPC3 cells (wild-type Kras) were transfected with siRNAs of Kras. Results: Bcl-xL knockdown downregulated Bcl-xL expression in Kras-mutated cells, but not in wild-type cells (BxPC3). MIE1 knockdown increased the expression of Bcl-xL in Kras-mutated cells, but not in wild-type cells (BxPC3). MIEX1 knockdown decreased the expression level of Bcl-xL, as well as phosphorilated ERK in Kras-mutated cells. Conclusions: Resident bacteria stimulate development of 10-secretory immune cells, especially CD+ T cells in a MyD88-dependent manner. Figure, B cells isolated from WT but not Bcl-xL or MyD88- mice significantly attenuated histologic intestinal inflammation (p<0.05) and decreased IFN-γ secretion by colonic tissue explants (p<0.01). Summary: Resident bacteria stimulate development of 10-secretory immune cells, especially CD+ T cells in a MyD88-dependent manner, which could play a key role in regulating intestinal inflammation and maintaining homeostasis.

Lack of TLR-signaling negates the bacteria-stimulated development of inducible, but not naturally-occurring, mucosal IL-10-secreting B cells in a TLR2/MyD88-dependent manner

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