Interleukin 22: A Novel Mediator of Inflammatory Inhibition and Tissue Damage in Acute Pancreatitis

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Acute Pancreatitis remains a major clinical challenge

- Acute pancreatitis (AP) is responsible for 100,000 hospitalizations and 2,000 deaths per year in the U.S.

- Partially due to the poorly understood mechanisms of pancreatic damage and inflammation
Pancreatitis Associated Proteins (PAPs)

- Family of stress-response proteins mainly secreted by acinar cells and conserved between humans and rodents

- Upregulated during AP, IBD, hepatobiliary cancer and colon cancer

- PAP family in rodents consists of PAP₁, PAP₂ and PAP₃
PAPs regulate inflammation and tissue damage

- PAP1 KO mice show increased inflammation but decreased necrosis during AP

- PAP2 KO mice show increased inflammation during AP
  - Huan et al. Experimental Acute Pancreatitis in Reg3a (PAP2) Knockout Mice and Reg1 Knockout Mice. Pancreas, Vol 39, Number 8, Nov 2010

- PAP1-3 are antibacterial in the small intestine against VRE
  - science
PAP expression is induced by Interleukin-22 (IL-22)

- Acinar cells *in vitro* exposed to IL-22 express PAP 1-3

- IL-22 is required for intestinal production of PAP 1-3 during bacterial infection

- Exogenous PAP restores antimicrobial activity in IL-22 KO mice
  - Zheng et al. Interleukin-22 mediates early host defense against attaching and effacing bacterial pathogens, Nature Medicine, vol 14, Number 3, March 2008
Interleukin-22 (IL-22)

- IL-22 is a cytokine that belongs to the IL-10 family
- Produced by immune cells and involved in the process of inflammation via induction of acute phase reactants (PAPs)
- Conveys inflammatory signals from immune cells to non-immune cells
IL-22 receptors are most abundant in acinar cells
Hypothesis

- IL-22 mediates pancreatic inflammation and damage via induction of PAPs
Experimental strategies

- Measure IL-22 levels in the pancreas and identify tissue source of IL-22 during AP

- Characterize the effects of IL-22 on inflammation and tissue damage during AP

- Establish that IL-22 induces expression of PAPs in AP using IL-22 KO mice

- Rescue IL-22 KO phenotype with exogenous PAP protein
Mouse acute pancreatitis was induced by intraperitoneal injections of cerulein given hourly for a total of seven hours.

- Each dose = 50 micrograms/kilogram/hour
IL-22 is rapidly expressed by intestine

- Real time RT-PCR analysis of mRNA from spleen, peripheral blood, pancreas, and small bowel mucosa
IL-22 protein accumulates in the pancreas during AP

- ELISA of pancreatic lysate shows increased IL22 protein at 16 and 24 H
IL-22 increases tissue damage in AP

- IL22 KO mice have less serum amylase and lipase, indicating less tissue injury
IL-22 is anti-inflammatory in AP

- IL-22 KO mice have enhanced pancreatic inflammatory infiltration
IL-22 reduces inflammation but enhances tissue damage

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<th>Edema</th>
<th>Acinar necrosis</th>
<th>Inflammatory infiltration</th>
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<td>IL22 WT</td>
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<td>IL22 KO</td>
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PAP mRNA expression is delayed in the absence of IL-22 during AP

- Real time RT-PCR of pancreatic tissue shows delayed expression of PAP mRNA in IL-22 KO mice
IL-22 KO mice have decreased levels of PAP proteins.
IL-22 KO phenotype is rescued by PAP supplementation

- Exogenous PAPs increase tissue damage in IL-22 KO mice
Conclusions

- IL22 contributes to tissue damage and plays an anti-inflammatory role during acute pancreatitis.

- IL22 appears to induce changes via induction of PAP expression.

- IL22 induction during pancreatitis may involve the interplay of multiple organs.
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