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
  - Gironella et al. Experimental acute pancreatitis in PAP/HIP knock-out mice. Gut 2007;56;1091-1097
- 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
  - Brandl et al. Vancomycin-resistant enterococci exploit antibiotic-induced innate immune deficits. Nature 455, 804-807 (9 Oct 2008)
  - science

PAP expression is induced by Interleukin-22 (IL-22)

- Acinar cells *in vitro* exposed to IL-22 express PAP 1-3
  - Aggarwal et al. Acinar Cells of the Pancreas are a Target of Interleukin-22, Journal of Interferon and cytokine Research, Dec 2001, 21(12): 1047-1053

- 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

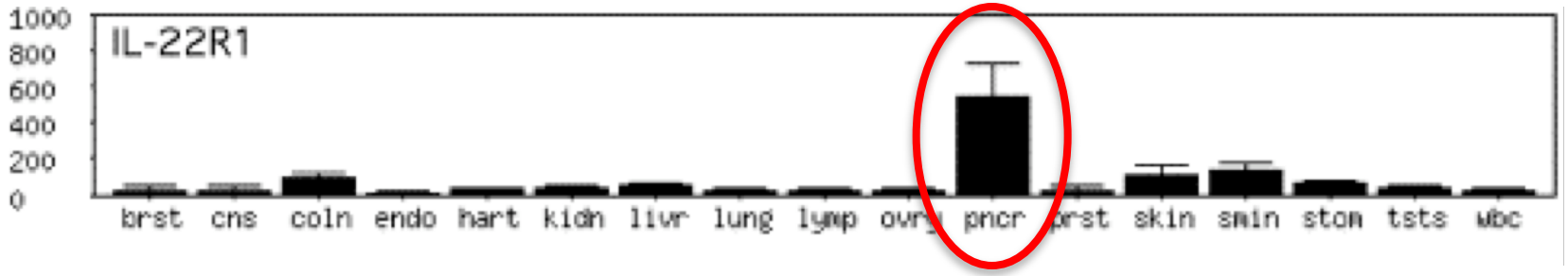
Interleukin-22 (IL-22)

- 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

Pancreas

Relative Microarray signal



Hypothesis

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

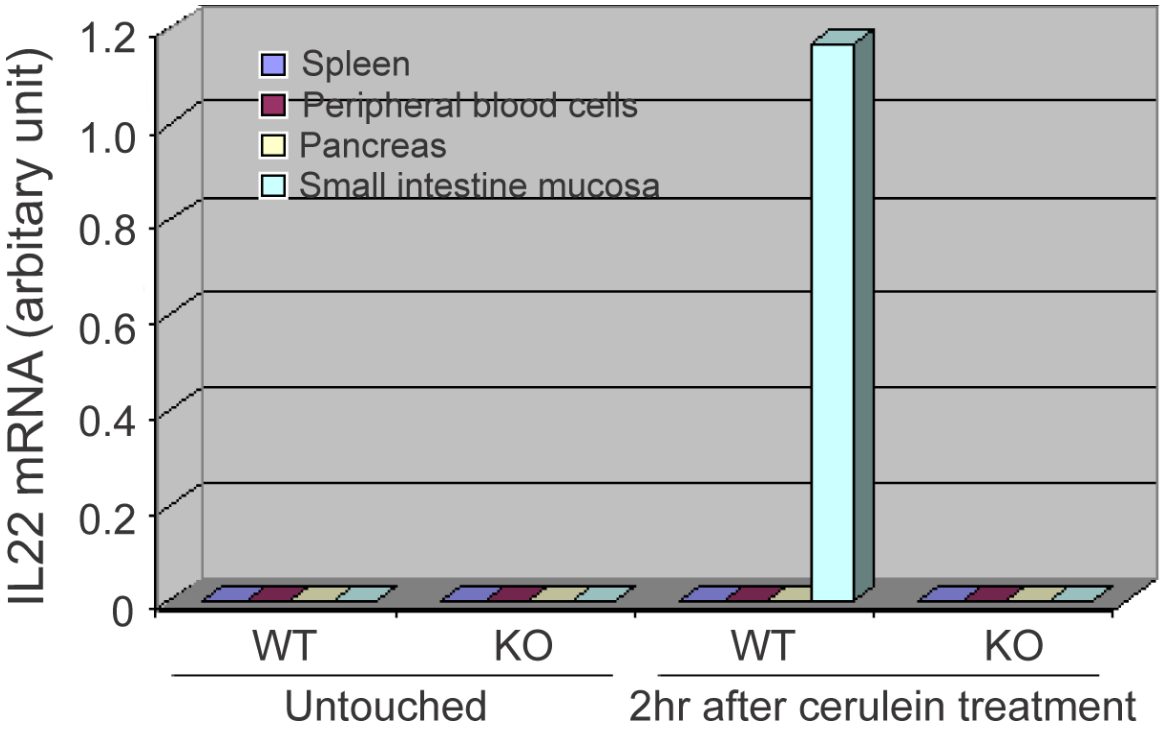
Experimental strategies

- 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

Protocol of Acute Pancreatitis Induction

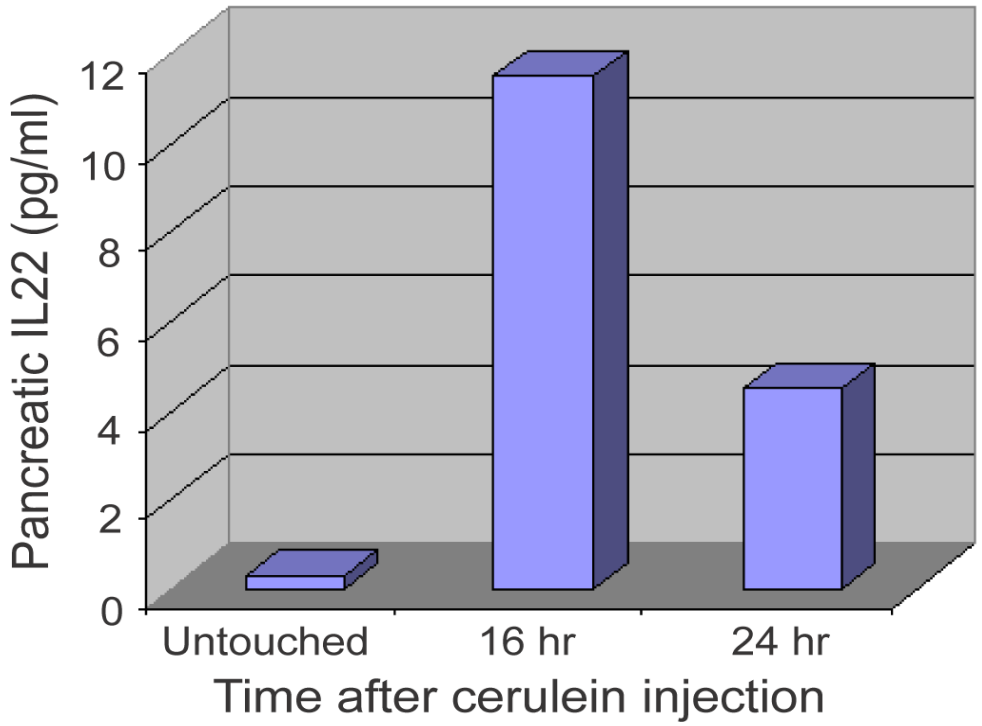
- Mouse acute pancreatitis was induced by intraperitoneal injections of cerulein given hourly for a total of seven hours
  - Each dose = 50 micrograms/kilogram/hour

IL-22 is rapidly expressed by intestine



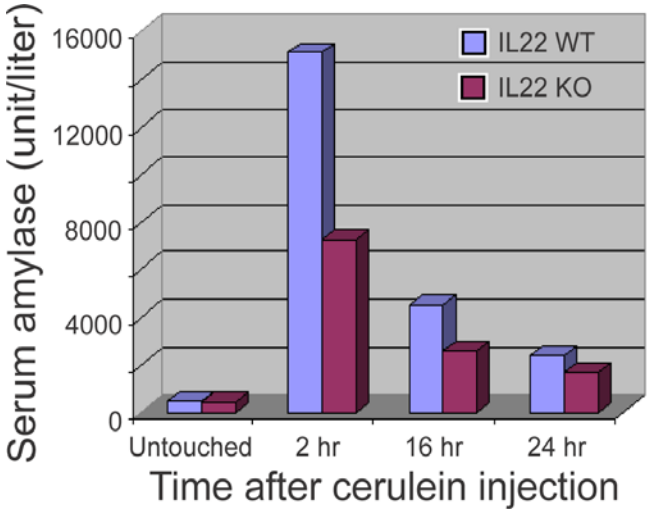
- Real time RT-PCR analysis of mRNA from spleen, peripheral blood, pancreas, and small bowel mucosa

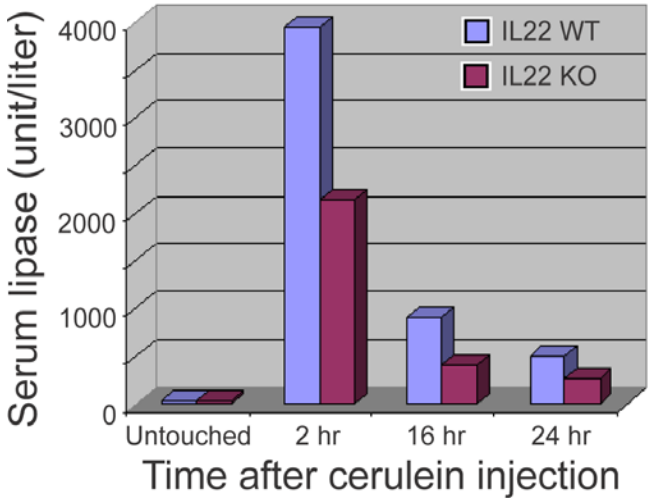
IL-22 protein accumulates in the pancreas during AP



- ELISA of pancreatic lysate shows increased IL22 protein at 16 and 24 H

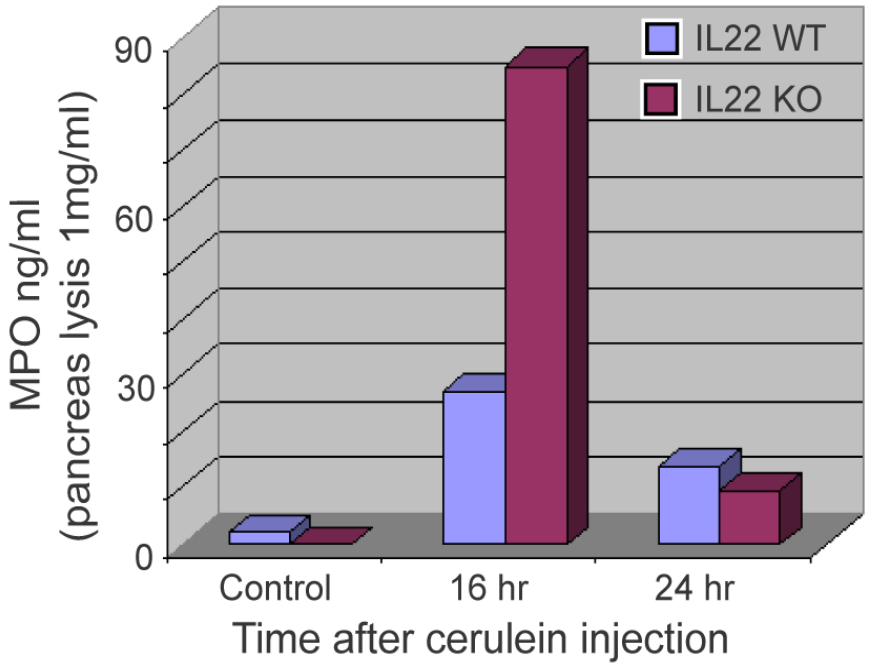
IL-22 increases tissue damage in AP





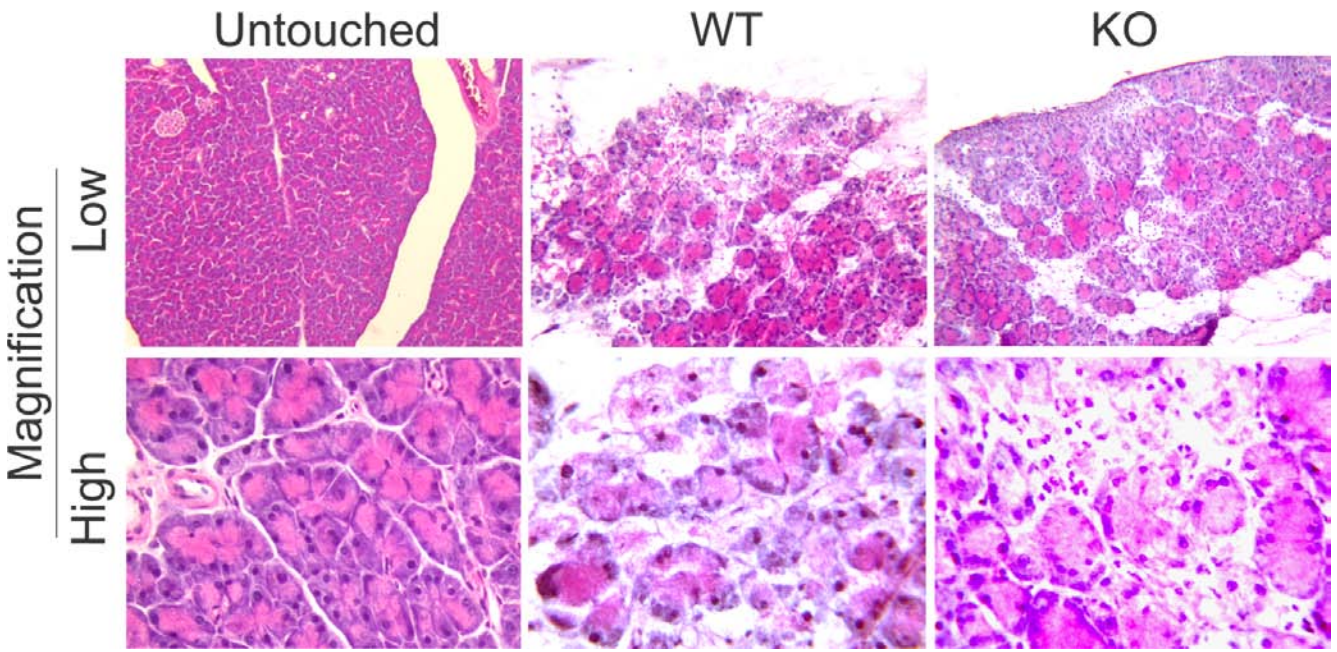
- IL22 KO mice have less serum amylase and lipase, indicating less tissue injury

IL-22 is anti-inflammatory in AP



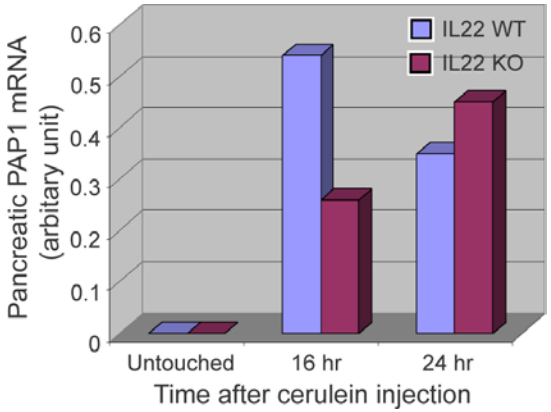
- IL-22 KO mice have enhanced pancreatic inflammatory infiltration

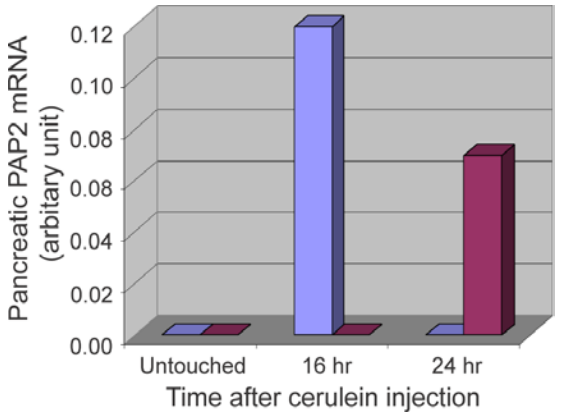
IL-22 reduces inflammation but enhances tissue damage

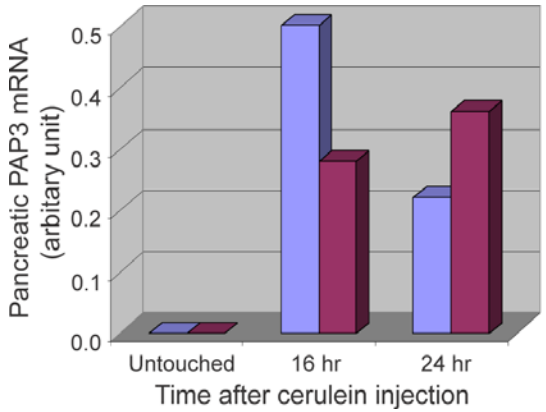


	Edema	Acinar necrosis	Inflammatory infiltration
IL22 WT	+++	+++	+
IL22 KO	++	+	++++

PAP mRNA expression is delayed in the absence of IL-22 during AP

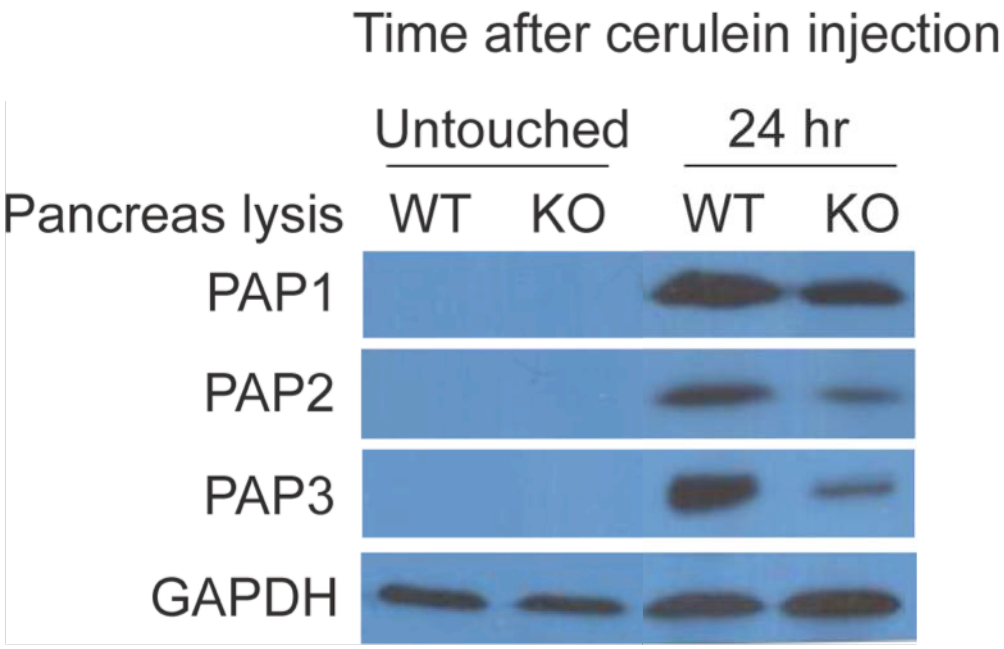






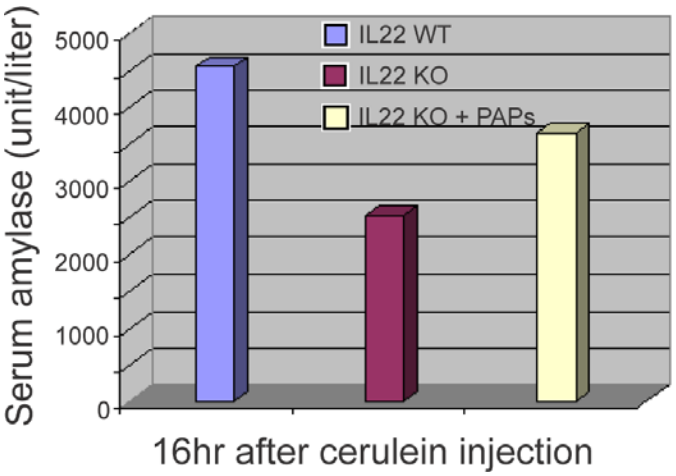
- Real time RT-PCR of pancreatic tissue shows delayed expression of PAP mRNA in IL-22 KO mice

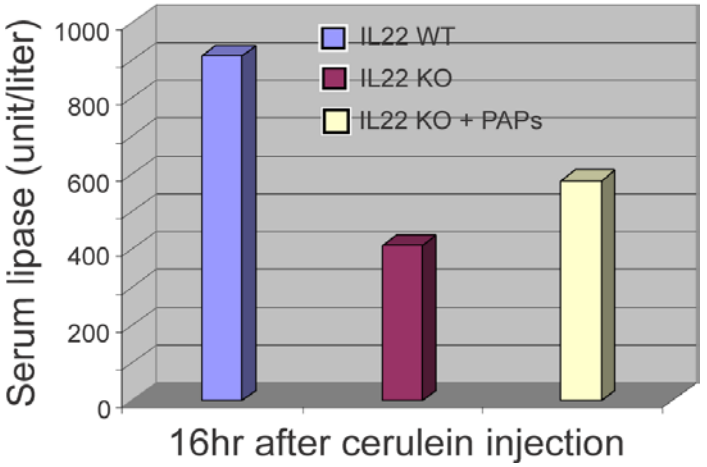
IL-22 regulates PAP expression in AP



- 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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