Targeting pancreatic calcineurin to prevent post-ERCP pancreatitis

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Post-ERCP pancreatitis (PEP) is still a problem

- Despite recent preventative modalities, PEP still occurs with a frequency of 3-8%
- Why does ERCP cause pancreatitis?

Both pressure & radiocontrast contribute to PEP
Why does radiocontrast exposure cause PEP?

Radiocontrast on Ca\textsuperscript{2+} and Ca\textsuperscript{2+} targets

- Aberrant Ca\textsuperscript{2+} is an early pathologic signal in pancreatic acinar cell injury
- A key Ca\textsuperscript{2+} target in pancreatitis is calcineurin
  - Ca\textsuperscript{2+}-activated serine/threonine phosphatase

Does radiocontrast trigger aberrant acinar cell Ca\textsuperscript{2+} signals?

Radiocontrast induces high amplitude Ca\textsuperscript{2+} signals in pancreatic acinar cells

![Peak fluorescence graph]
Do these Ca$^{2+}$ signals activate the phosphatase calcineurin?

The phosphatase calcineurin is a target of Ca$^{2+}$

Calcineurin (Cn)
- **Activators**
  - Ca$^{2+}$
  - Calmodulin (CaM)
- **Inhibitors**
  - FK506, CsA
- **Targets**
  - NFAT, several others

Radiocontrast induces calcineurin activation
Radiocontrast causes NF-κB activation

Radiocontrast causes acinar cell injury through a calcineurin dependent pathway

Inhibition or deletion of calcineurin attenuates in vivo PEP in mice
Which cellular source of calcineurin is involved in PEP? 

- Acinar cells?
- Duct cells?
- Immune cells?

Designing an acinar cell-specific calcineurin knockout

Acinar cell calcineurin mediates PEP

<table>
<thead>
<tr>
<th>Score</th>
<th>Histological Severity</th>
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</thead>
<tbody>
<tr>
<td>2.5</td>
<td>CnB1^{floxfloxflox}</td>
</tr>
<tr>
<td>2.0</td>
<td>CnB1^{A/A}</td>
</tr>
</tbody>
</table>

- Low pressure NS infusion
- CnB1^{floxfloxflox}
- CnB1^{A/A}

- #
Intraductal administration of calcineurin inhibitors prevents PEP

<table>
<thead>
<tr>
<th>NS</th>
<th>RC + High Press.</th>
<th>+ ID FK506</th>
<th>+ ID CsA</th>
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<td></td>
<td>1</td>
<td>2</td>
<td>3</td>
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*Histological Severity Score#

Serum Amylase (U/L)

-30000
-20000
-10000

Summary

- First demonstration that post-ERCP pancreatitis (PEP) signals through Ca²⁺, calcineurin, NF-κB.
- Acinar cell calcineurin mediates PEP.
- Implications for targeted delivery of Cn inhibitors
- Mechanism for radiocontrast-induced injury in other organs?

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25% Omnipaque-300, 10 min exposure followed by a washout. Collect cells at 5 hours.