Solving a pediatric dilemma: Drug-induced pancreatitis (DIP)

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In the past 12 months, I have had no relevant financial relationships with the manufacturer(s) of any commercial product(s) and/or provider(s) of commercial services discussed in this CME activity.
Learning objectives

• Recognize the problem of drug-induced pancreatitis (DIP)

• Discuss insight into novel mechanisms underlying DIP

• Understand how to devise strategies to prevent DIP
Bridging the gap between basic science and clinical application
Etiologies of Acute Pancreatitis

Adults
- Alcoholic
- Biliary
- Idiopathic
- Other

Children
- Idiopathic 19%
- Systemic 9%
- Trauma 8%
- Viral 7%
- Metabolic 4%
- Other 5%
- Biliary 27%
- Medication 21%

AGA, 2006
*Park A, *Latif SU, JPGN, 2009
What qualifies as DIP?

<table>
<thead>
<tr>
<th>Category</th>
<th>Reasonable temporal sequence</th>
<th>Follows a known response pattern</th>
<th>Could not be explained by other factors</th>
<th>Relieved by cessation of the drug</th>
<th>Recurs after a repeat challenge</th>
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</thead>
<tbody>
<tr>
<td>Definite</td>
<td>❑</td>
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<td>Probable</td>
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<td>Possible</td>
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</tbody>
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Karch and Lasagna, Adverse drug reactions, JAMA, 1974
Problem of drug-induced pancreatitis

- ~21% of all cases
Pressing questions about DIP

• Why do some patients develop DIP?

• Can we identify patients who are at risk before they receive the drug and prevent DIP?

• Can DIP instruct us about pancreatic physiology and disease?
Concomitant etiologies identified in childhood cases of drug-associated pancreatitis
IBD pharmacogenomics

- Pancreatitis and IBD in children (comprehensive review)
  - Medications are likely the major contributor to this association

Heap et al., Nat Genetics, 2014
- A class II HLA haplotype
  - Heterozygotes had a 9% risk of developing pancreatitis with thiopurines
  - Homozygotes had a 17% risk

- Not there yet in making clinical changes to care with just this info.

- But likely with another one or a few additional genetic or environmental discoveries?

- Computational risk modeling
Two short stories about unraveling the mechanism of DIP and one worthy of mention

• #1 Valproic acid

• #2 Radiocontrast

• Asparaginase
Story #1: Valproic acid (VPA)-associated pancreatitis

• “Worst case of acute pancreatitis I saw as a fellow”

• 5 yo dev. delayed child with epilepsy, taking VPA for 6 months
How does VPA predispose some patients to pancreatitis?

• VPA by itself doesn’t cause pancreatitis

• VPA is an histone deacetylase inhibitor (HDACi)
HDACs remove acetyl groups from histone tails, resulting in chromatin compaction and gene repression.

Closed chromatin = repressed gene expression

Open chromatin = Active gene expression

HDACs, epigenetics, pancreatitis, and pancreatic recovery

- **Epigenetics** is the study of the molecules that determine when, where, and how much of our DNA is used

- HDACs are a major epigenetic regulator through modifying histones

- HDACs are upregulated during pancreatic development

- Elements of pancreatic development recap. during pancreatic recovery

- **Hypothesis**: HDACs are crucial for activating the programs necessary for pancreatic recovery and regeneration after pancreatic injury
Devised a machine learning tool to quantify pancreatic acinar content

Amy Davis, MD
Valproic acid (VPA) limits pancreatic recovery following injury

Valproic acid (VPA)

Day # -2 -1 0 1 3 7

Caer Caer Euthanize Euthanize Euthanize

Vehicle VPA

Baseline Day 3 Day 7

Acinar content

% content

0 20 40 60 80 100

Vehicle VPA

* *

acH3

Vehicle VPA VPD

Total H3

Acinar content

% content

0 20 40 60 80 100

Vehicle VPA VPD

*

DAY 7

Vehicle-treated VPA-treated VPD-treated
HDACs are upregulated within the pancreas during recovery following injury.
HDACi with VPA causes the persistence of regenerative acinar to ductal metaplastic complexes (ADMs) during pancreatic recovery.
HDACi with VPA causes the persistence of regenerative acinar to ductal metaplastic complexes (ADMs) during pancreatic recovery.
What is the mechanism by which HDACs allow pancreatic recovery to run to completion?
Hypothesis
HDACs facilitate the repression of β-catenin signaling in the pancreas
VPA-associated pancreatitis:
Opened up a new paradigm to examine whether epigenetic processes that enhance recovery during pancreatic injury can tip the balance in pancreatic health
Story #2: Radiocontrast, ERCP, Ca2+, and post-ERCP pancreatitis (PEP)

• “Sohail, it’s interesting that patients taking Cn inhibitors don’t seem to develop PEP.” –Dr. Priya Jamidar, Yale

• PEP is still a problem

• Over a quarter million ERCPs performed in the US; a bulk of them by community GIs

• What is the pathophysiology of PEP?
PEP = pressure + radiocontrast (RC)

Histological Severity

- Clues to Ca$^{2+}$: Pressure = Ca$^{2+}$; RC ≈ Ca$^{2+}$ (renal)

Jin, Gastro, 2015
Radiocontrast (RC) selectively induces acinar cell Ca\textsuperscript{2+} signals

Jin, Gastro, 2015
A target of the RC-induced Ca\(^{2+}\) is the Ca\(^{2+}\)-activated phosphatase calcineurin (Cn)

**Graphs:**
- **Ad-NFAT-luciferase**
  - Mouse acinar cells
  - Human acinar cells
  - Fold increase above control

*Kissinger, Nature, 1995*

*Jin, Gastro, 2015*
RC-induced NF-κB activation is Cn-dependent

Ad-NF-κB-luciferase

Acinar cell line

Fold increase above control

RC (%)

FK506 (µM)

CsA (µM)

AAV6-NF-κB-luciferase

(NS) (RC+high press) (+FK506)

Jin, Gastro, 2015
CnAb\(^{-/-}\)-deficient mice protected against PEP

Jin, Gastro, 2015
In vivo

Cn mediates PEP: Cn inhibitors

B

Normal Saline  RC + high pressure  + FK506

C

Histological Severity

Serum Amylase

Jin, Gastro, 2015
Summary: RC on Ca$^{2+}$/Cn in PEP

- Ca$^{2+}$/Cn are critical mediators of pancreatic injury

- Ca$^{2+}$/Cn pathways appear to mediate RC-induced injury and PEP

- These pathways can be harnessed as pancreatitis therapies
Current questions

• How does RC exposure to the pancreas induce Ca^{2+} and Cn?

• How does Cn activation by RC induce NF-κB and pancreatic injury?

• Are pancreatic acinar cells a critical site of Cn activation during *in vivo* PEP?

• Would targeted *in vivo* delivery of Cn inhibitors to the pancreas prevent PEP?
Summary of drug-induced pancreatitis (DIP)

- DIP is a major pediatric dilemma
- VPA predisposes to pancreatitis by inhibiting HDACs and the redifferentiation programs during pancreatic recovery
- RC exposure is a risk factor for PEP through inducing pancreatic Ca\(^{2+}\) and Cn
- Understanding the mechanisms underlying DIP will be crucial for preventative and therapeutic strategies

We will need to cross more bridges between science and medicine
Acknowledgments: Building bridges

Current Lab Members
- Shunqian Jin
- Abraham Orabi
- John Eisses
- Tanveer Javed
- Kristy Boggs
- Fateema Turay
- Judy-April Oparaji

Former Members
- Tianming Le
- Swati Sah
- Sheharyar Sarwar
- Katie Lemon
- Zachary Dionise
- Kamaldeen Muili

Mark Lowe
- Farzad Esni
- Angela Criscimanna

Maching Learning Group
- Gustavo K. Rohde
- John Ozolek
- Amy W. Davis
- Burak Tosun
- (Paul) Satdarshan Monga

NIH National Institute of Diabetes and Digestive and Kidney Diseases

INSPIRE

Pitt/Children’s Joint Pancreatic Research Group