Immunology of Chronic Pancreatitis
PancreasFest: July 26, 2019

Aida Habtezion
Ballinger-Swindells Scholar
Associate Professor of Medicine
Division of Gastroenterology & Hepatology
Institute for Immunity, Transplantation, and Infection
School of Medicine, Stanford University
Incidence Rates: Pancreatitis and Pancreatic Cancer

- Acute pancreatitis (non-gallstone) (25)
- Acute pancreatitis (gallstone) (15)
- Recurrent acute pancreatitis (10)
- Chronic pancreatitis (8)
- Pancreatic cancer (13)

Yearly incident rates per 100,000 persons

Yadav & Lowenfels, Gastroenterology 2013
Chronic Pancreatitis

Etiologies

Alcohol abuse/Cigarette smoking

Idiopathic

Other

Cystic fibrosis
Hereditary pancreatitis
Hypertriglyceridemia
Autoimmune
Tropical (fibrocalcific)
Chronic Pancreatititis (CP)

- Risk factor for developing pancreas cancer

- Smoking an independent risk factor for developing CP

- How does smoking increase or promote CP progression?

- Are there immune mediated mechanisms?
CHEMICAL COMPOUNDS IN CIGARETTE SMOKE

ESTIMATED NUMBER OF CHEMICAL COMPOUNDS IN CIGARETTE SMOKE

7,357

70

NUMBER OF THESE COMPOUNDS WITH CONFIRMED CARCINOGENIC ACTIVITY

http://www.compoundchem.com/2014/05/01/the-chemicals-in-cigarette-smoke-their-effects/
AhR ligands in cigarette smoke promote fibrosis in CP

Xue*, Zhao* et al Gastroenterology 2016
Editorial: Kumar & Batra, Gastroenterology 2016
AhR ligands in cigarette smoke promote fibrosis in CP

Figure 5. Circulating IL-22 is elevated in CP and associated with cigarette smoking among CP patients

HC Non Current Ex

- P<0.001
- P<0.05
- P<0.01
- P<0.01
- P<0.001

Xue*, Zhao* et al Gastroenterology 2016
Editorial: Kumar & Batra, Gastroenterology 2016
Macrophage and PSCs interaction in CP

IL-4, IL-13

Th2 / other cells

IL-4Rα

STAT6

M2 genes

IL-4

IL-13

Activated PSCs

Sustained Activation

TGFβ

PDGF

Activated PSCs

Sustained Activation

TGFβ

PDGF

Fibrogenesis

TIMPs

ECMs

Xue et al Nat Commun 2015
Macrophage and PSCs interaction in CP

IL4/IL13 BP

IL-4
IL-13

Th2 / other cells

STAT6

M2 genes

Activated PSCs

TGFβ
PDGF

Sustained Activation

Fibrogenesis

TIMPs

ECMs

Con       IL4/13BP

H&E

Trichrome

Xue et al Nat Commun 2015
Acinar-Immune Cell Interaction

Injury

DNA

cGAS
STING
IRF3, NF-κB

TNFα
IFNβ

Nucleus

Acinar cell

Macrophage

Zhao et al, Gastroenterology 2018
STING signaling in CP
STING signaling in CP

A

Relative pancreas weight (mg/g)

WT KO

P = .004

B

WT KO

P = .0422

C

α-SMA mRNA level (fold change)

WT KO

P = .0226

Fibronectin mRNA level (fold change)

WT KO

P = .0199

D

Relative mRNA level (fold change)

WT KO

IRF7

P = .019

IRF3

P = .0422

E

Relative mRNA level (fold change)

cGAS STING

Con CP

P = .002

P = .003

F

Con CP

cGAS STING P-IRF3 IRF3 Actin

P = .0071
STING signaling in CP

A

Irradiation

WT/KO

8 weeks

Cerulein induced CP

WT

B

WT → WT

KO → WT

Fibrosis (%)

WT-WT

KO-WT

P = 0.0429

C

α-SMA mRNA level

(fold change)

WT-WT

KO-WT

P = 0.383

Fibronectin mRNA level

(fold change)

WT-WT

KO-WT

P = 0.0298

D

Gated on CD45+CD4+CD44+CD45RB- cells

Isotype

WT-WT

KO-WT

IFNγ

0.34%

0.27%

4.04%

3.60%

4.11%

9.04%

IL-17A

E

IL-17A+ cells (% of CD4)

WT-WT

KO-WT

P = 0.0302

IFNγ+ cells (% of CD4)

WT-WT

KO-WT

ns

Zhao*, Manohar* et al Gut 2019
STING signaling in CP

A

Relative pancreas weight (mg/g)

B

WT/anti-IgG1  KO/anti-IgG1  WT/anti-IL17A  KO/anti-IL17A

C

Fibrosis (%)

D

α-SMA mRNA level (fold change)

Fibronectin mRNA level (fold change)

Zhao*, Manohar* et al Gut 2019
STING signaling in CP

D Primary mPSCs

mIL-17A (100ng/ml) 0 5 15 30 (min)

IL-17RA
p-ERK1/2
ERK1/2
aSMA
Actin

P=0.343

E

Relative mRNA level (fold change)

- Con P<.0001
- IL-17A

P=0.0003

F

Th17

cGAS STING IL-17A RORγt

Fibrosis related genes

ECM production

Activated PSCs

Zhao*, Manohar* et al Gut 2019
Immune Cell Interactions in Pancreatitis

Acinar Cells

AP

IL-22/HO-1

DNA/STING

PSCs

CP

IL-4R signaling

AhR/IL-22R

STING/IL-17 signaling

Leukocytes

Habtezion et al. Gut 2011
Xue et al. Gastroenterology 2012
Zhao et al. Gastroenterology 2018

Xue et al. Nat Commun 2015
Xue*, Zhao* et al. Gastroenterology 2016
Zhao*, Manohar* et al. Gut 2019
Relevance to human disease?
Access to human pancreas tissues from deceased organ donors and CP patients

- **Control pancreas** from organ donors (UCSF)
- **CP pancreas** from patients (UMN)
- **Total Pancreatectomy with Islet Isolation** (TPIAT)
- Exocrine compartment for immune profiling (Stanford U)

*Bellin D. M. American J Gastroenterology (2018)*
Thank you!