

Immunology of Chronic Pancreatitis

PancreasFest: July 26, 2019



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Ballinger-Swindells Scholar

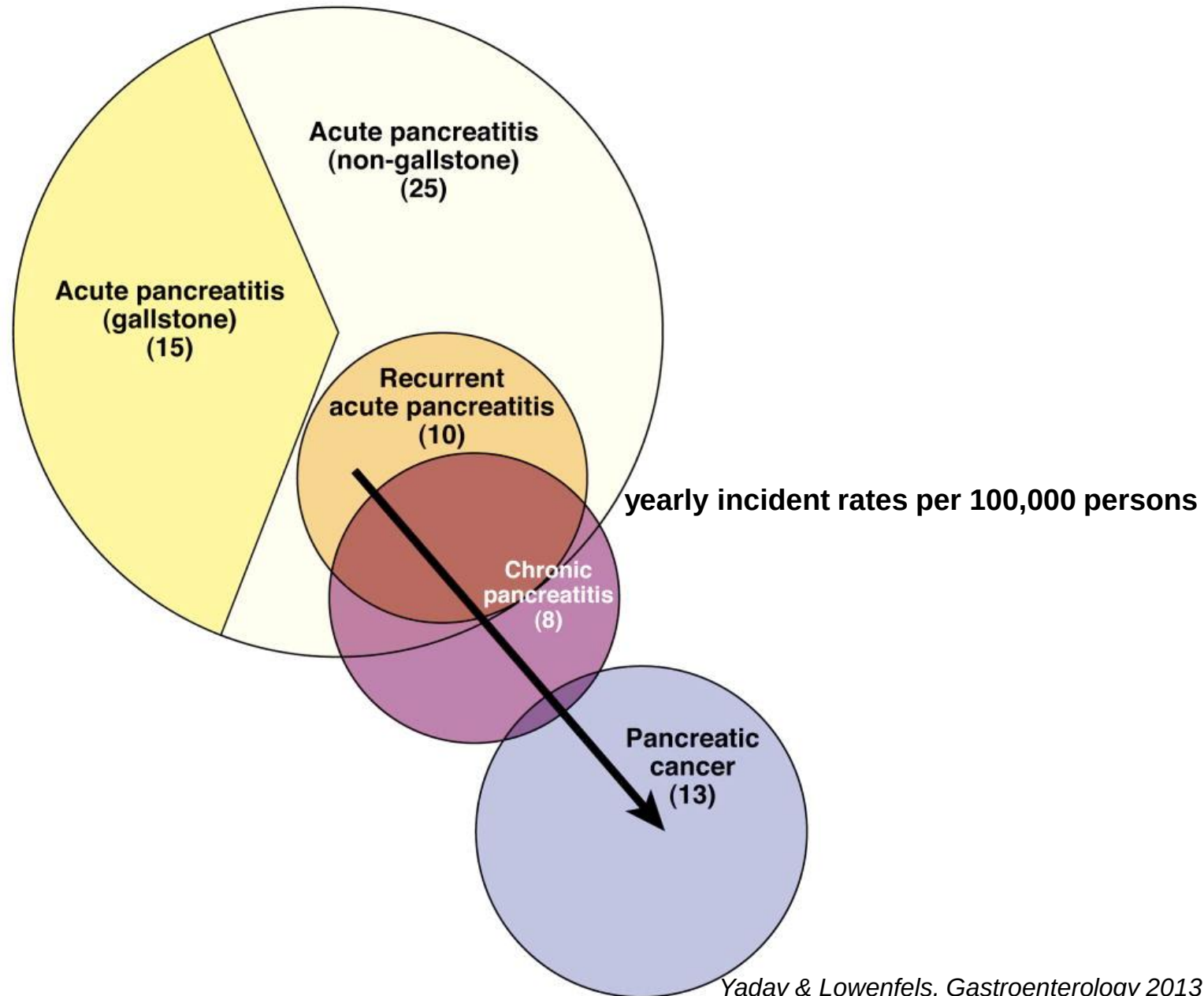
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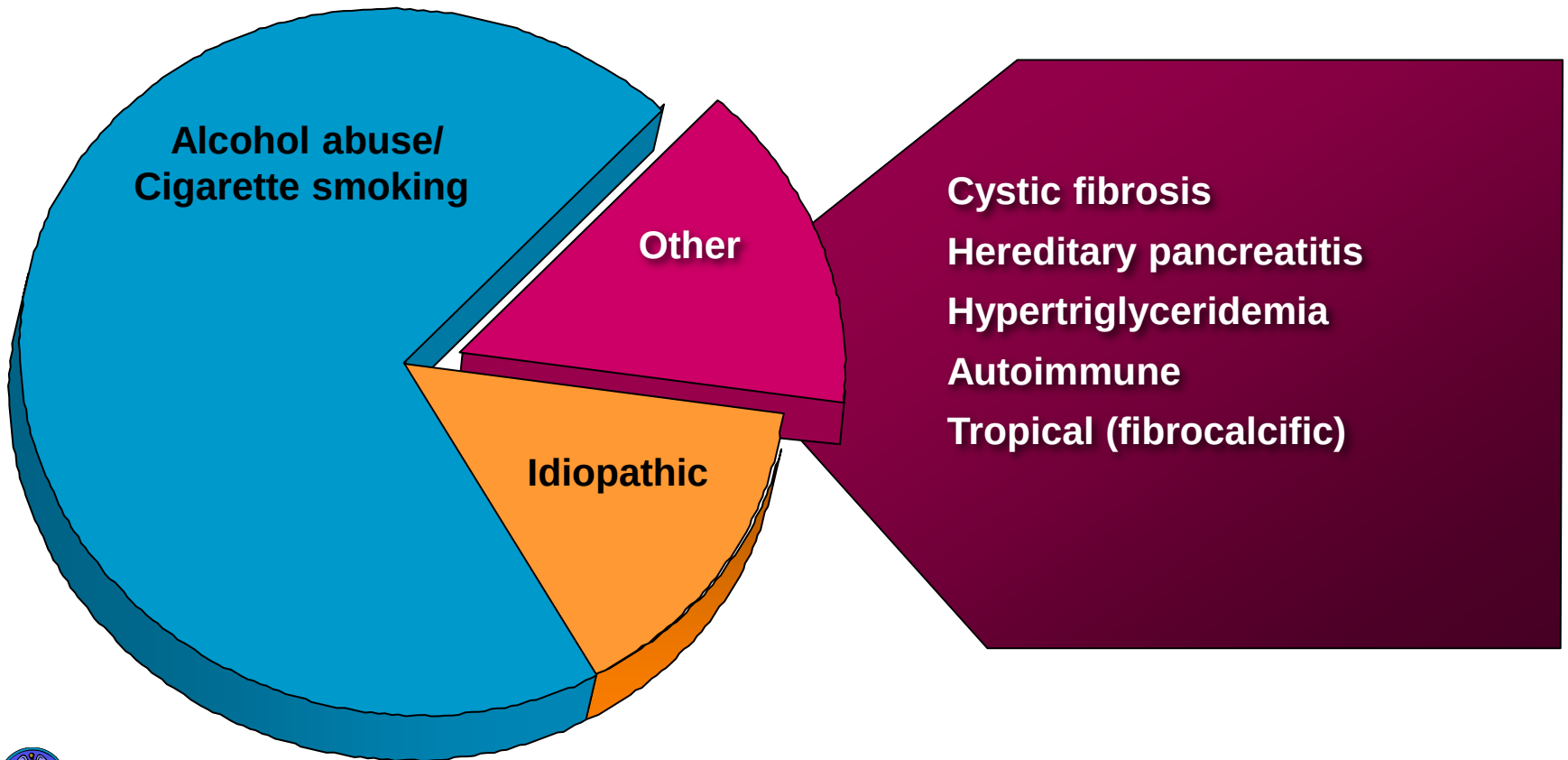
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Incidence Rates: Pancreatitis and Pancreatic Cancer



Chronic Pancreatitis

Etiologies



Chronic Pancreatitis (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

THIS GRAPHIC OFFERS A SUMMARY OF A SELECTION OF HAZARDOUS COMPOUNDS IN CIGARETTE SMOKE & THEIR EFFECTS

ESTIMATED NUMBER OF CHEMICAL COMPOUNDS IN CIGARETTE SMOKE

7,357

70

NUMBER OF THESE COMPOUNDS WITH CONFIRMED CARCINOGENIC ACTIVITY

The compounds shown below are all found in cigarette smoke. The mass figures, given in µg, take into account both mainstream (inhaled) and sidestream smoke. 1 µg is equal to 1 millionth of a gram. Amounts of these compounds vary in different brands of cigarettes - these figures are approximate.

NICOTINE



- Approx. 919µg per cigarette
- Addictive
- Increases heart rate
- Increases blood pressure
- Increases blood glucose
- Lethal dose: around 500-1000mg

N-NITROSAMINES



- Large class of compounds
- Several are tobacco-specific
- Known human carcinogens
- Most carcinogenic: NNK & NNN
- NNK approx. 0.3µg per cigarette
- NNN approx. 2.50µg per cigarette
- May cause reproductive damage

BENZENE



- Approx. 46-272µg per cigarette
- Known human carcinogen
- Damages bone marrow
- Lowers red blood cell count
- May harm reproductive organs

AROMATIC AMINES



- Large class of compounds
- Includes 2-aminonaphthalene:
- Known human carcinogen
- Linked with bladder cancer
- Approx. 0.04µg per cigarette

ACETALDEHYDE



- Approx. 680-1571µg per cigarette
- Known animal carcinogen
- Probable human carcinogen
- Irritant to skin & eyes
- Irritant to respiratory tract

1,3-BUTADIENE



- Approx. 36-191µg per cigarette
- Known human carcinogen
- Suspected human teratogen
- Irritant to eyes & skin
- Irritant to upper respiratory tract

ACROLEIN



- Approx. 69-306µg per cigarette
- Possible human carcinogen
- Known DNA mutagen
- Irritant to skin & nasal passages
- May contribute to heart disease

POLYAROMATICS

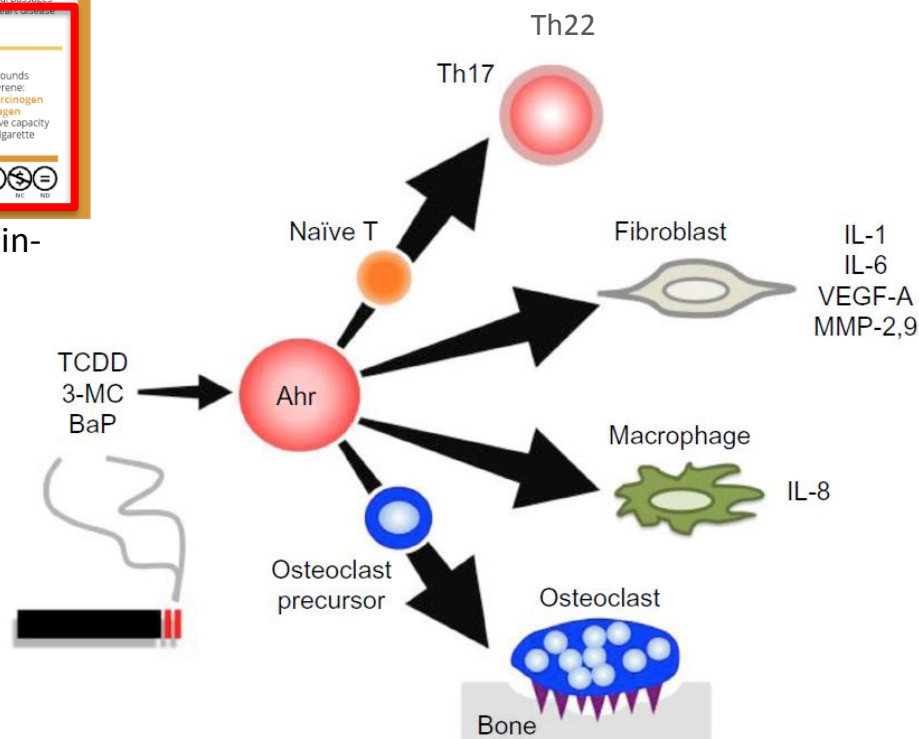


- Large class of compounds
- Includes benzo[a]pyrene:
- Known human carcinogen
- Known DNA mutagen
- Affects reproductive capacity
- Up to 0.14µg per cigarette

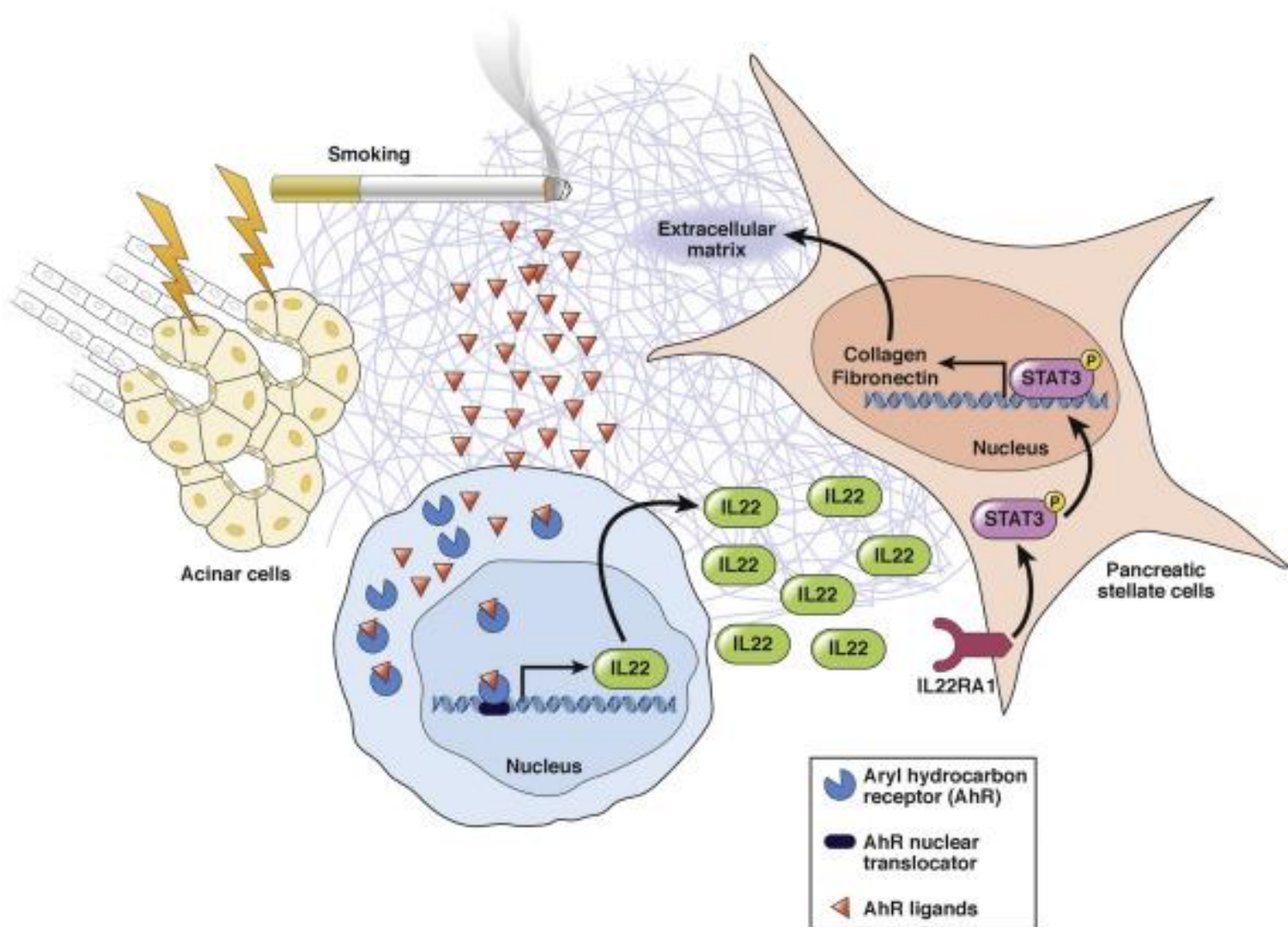
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<http://www.compoundchem.com/2014/05/01/the-chemicals-in-cigarette-smoke-their-effects/>



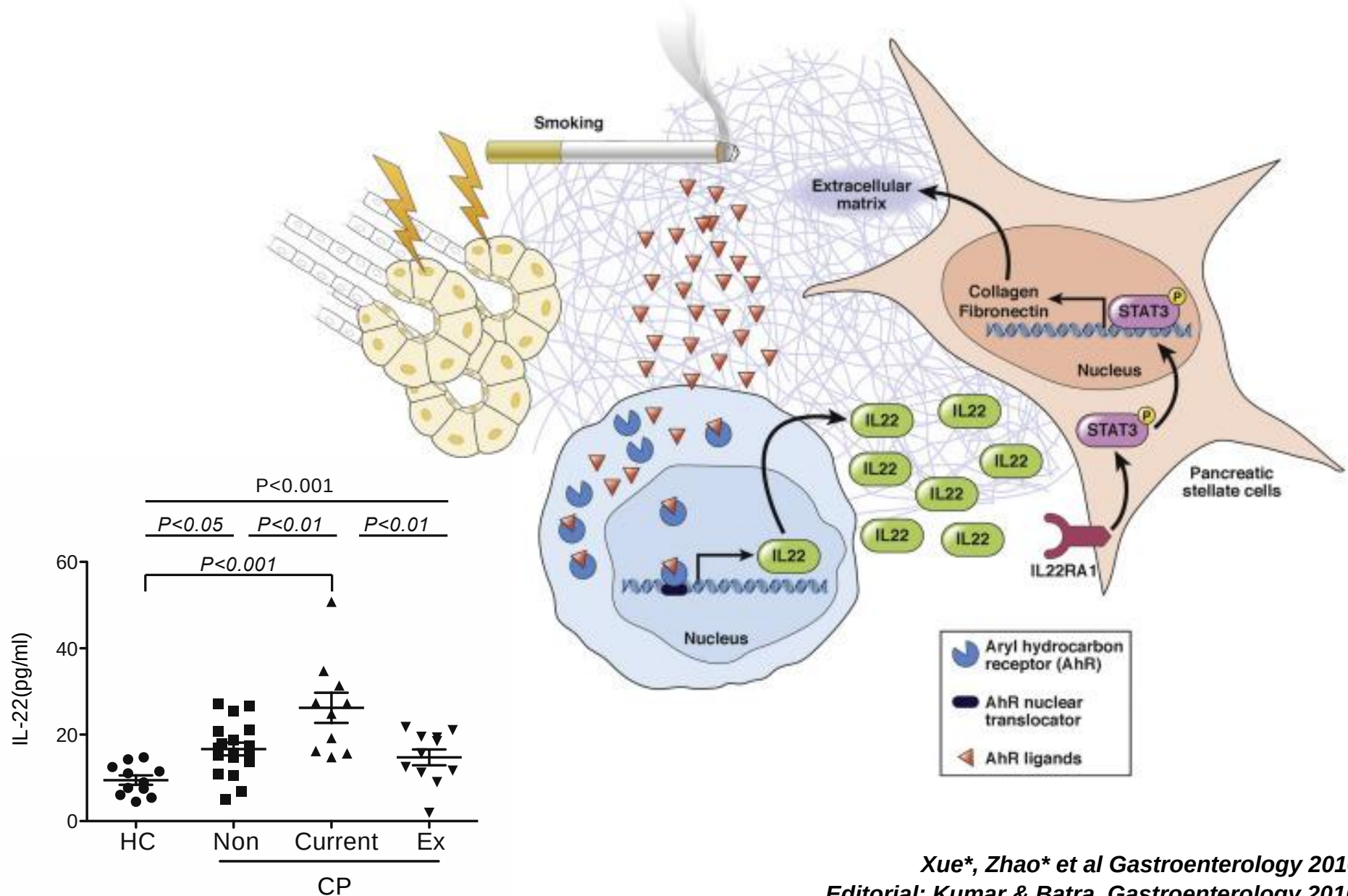
AhR ligands in cigarette smoke promote fibrosis in CP



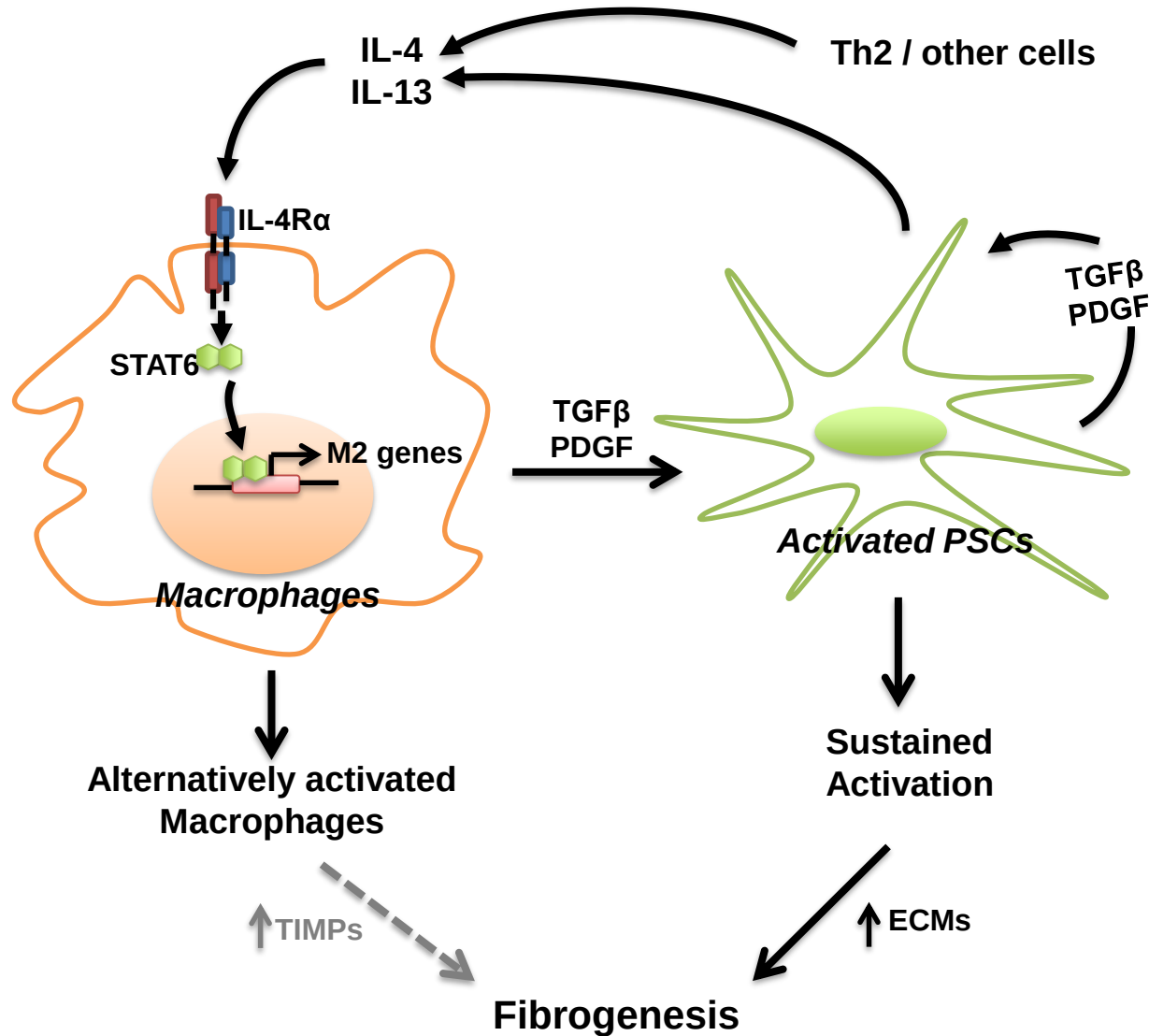
Xue*, Zhao* et al *Gastroenterology* 2016

Editorial: Kumar & Batra, *Gastroenterology* 2016

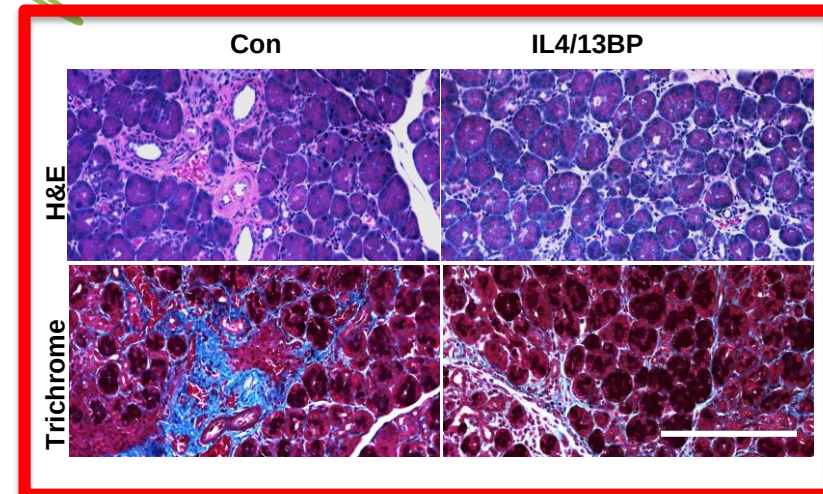
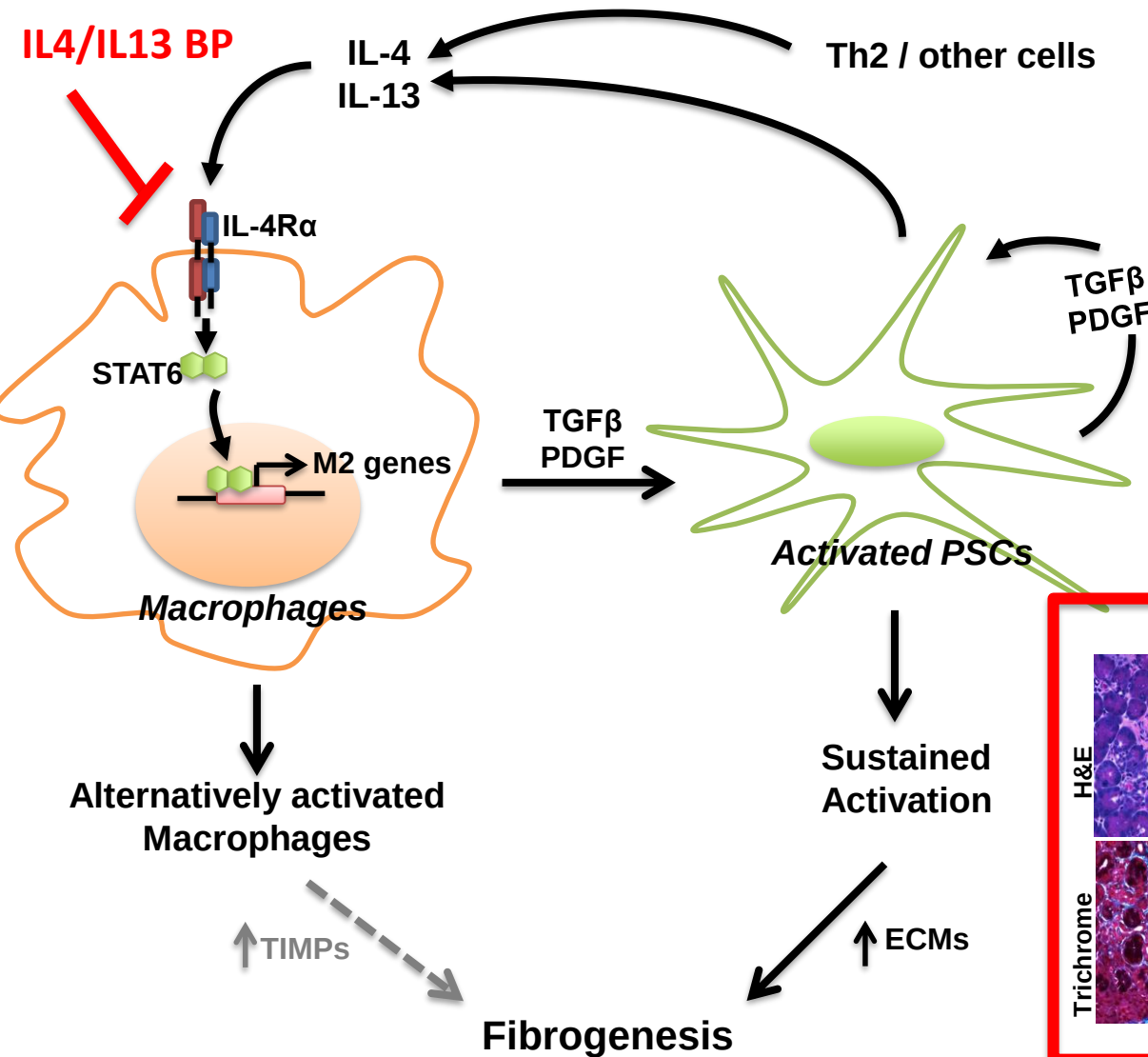
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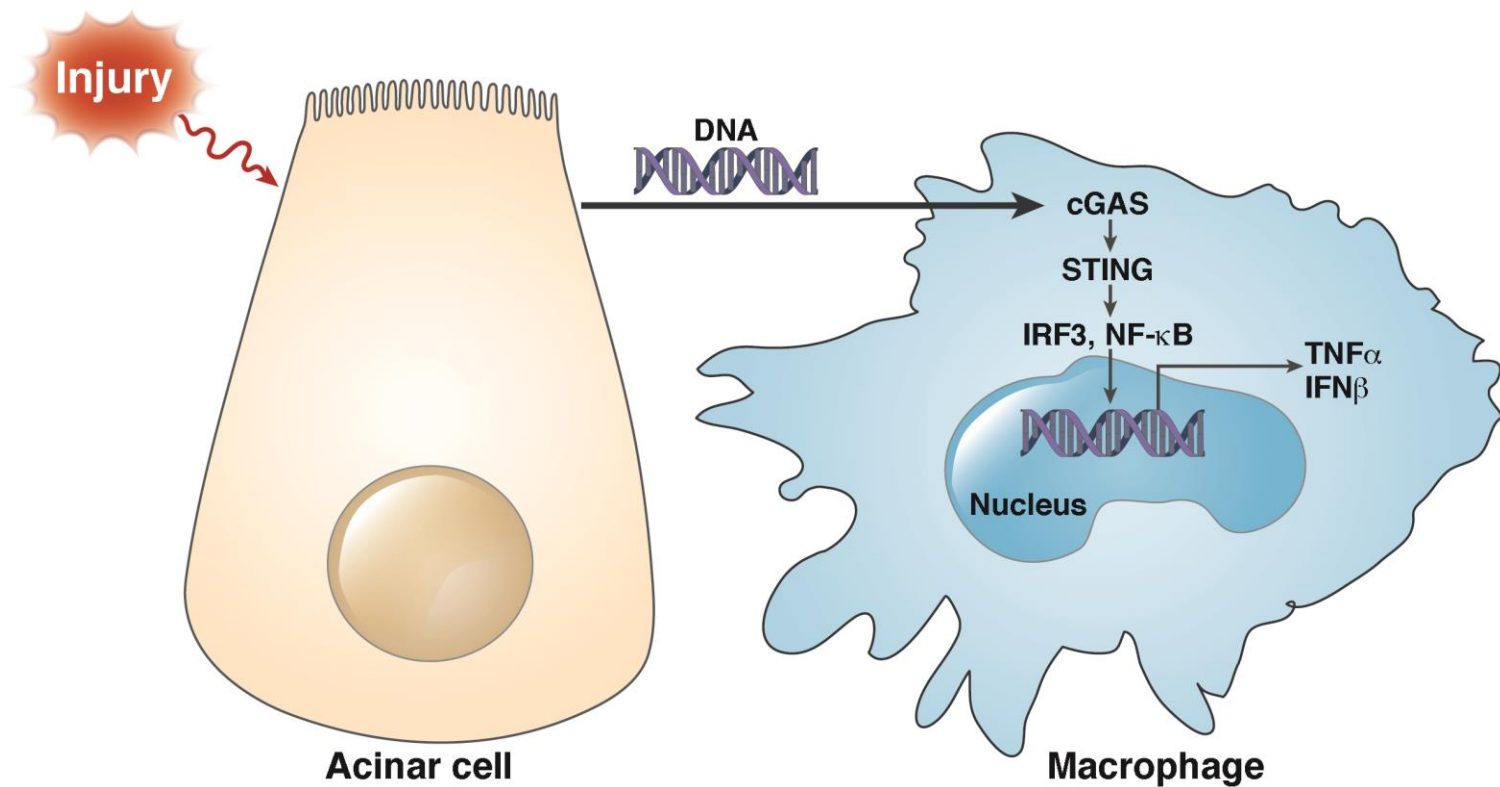
Macrophage and PSCs interaction in CP



Macrophage and PSCs interaction in CP

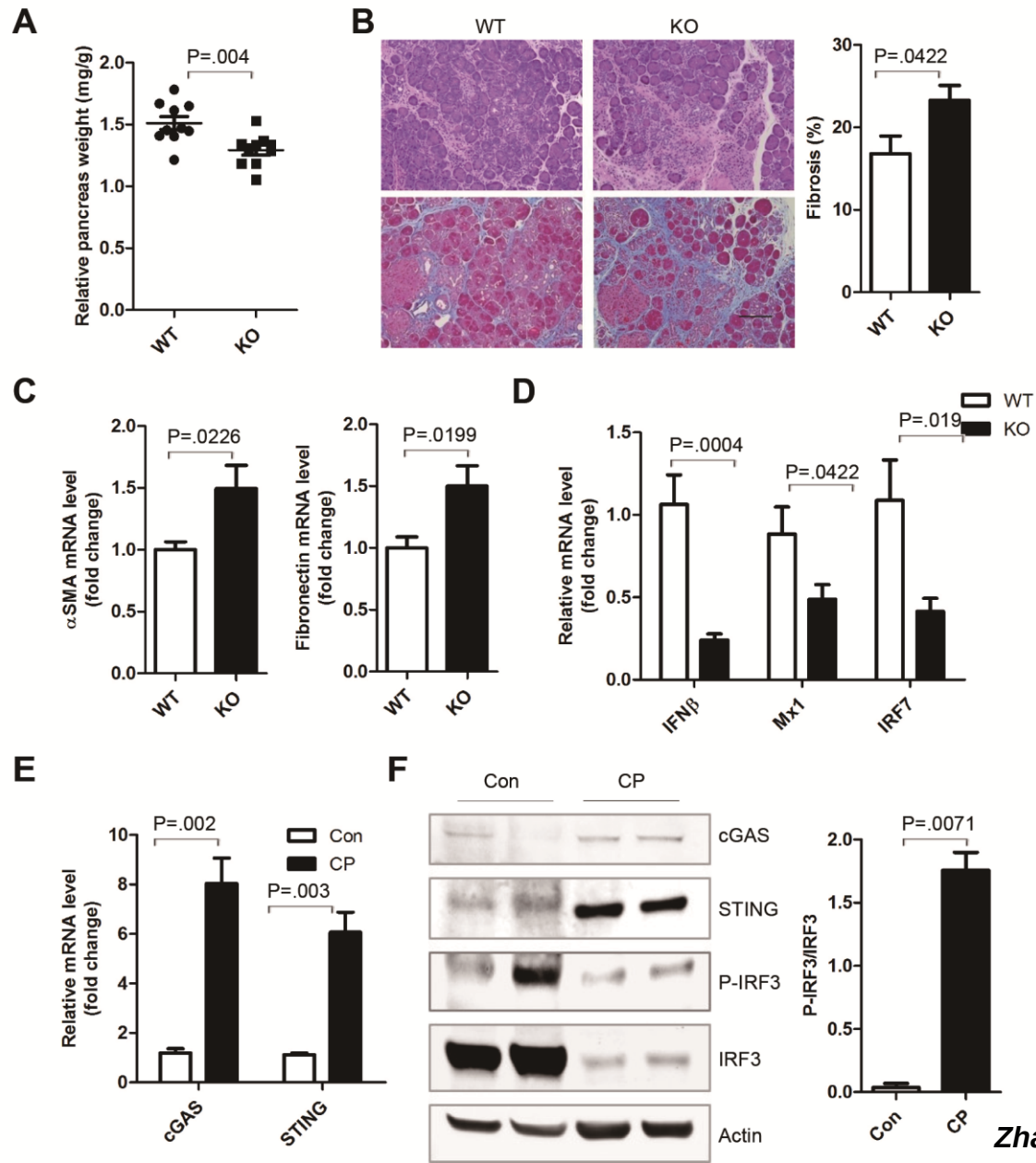


Acinar-Immune Cell Interaction

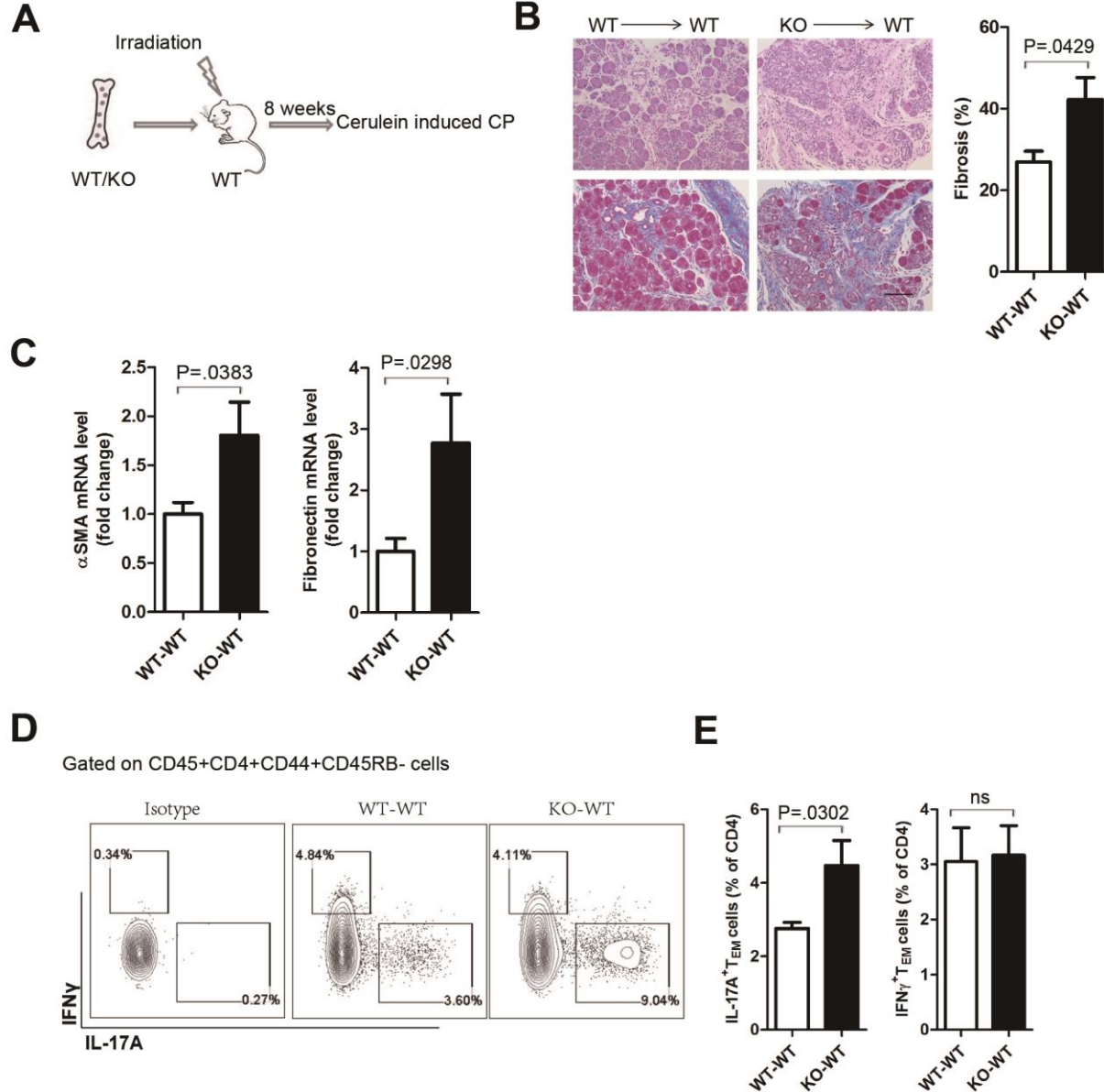


STING signaling in CP

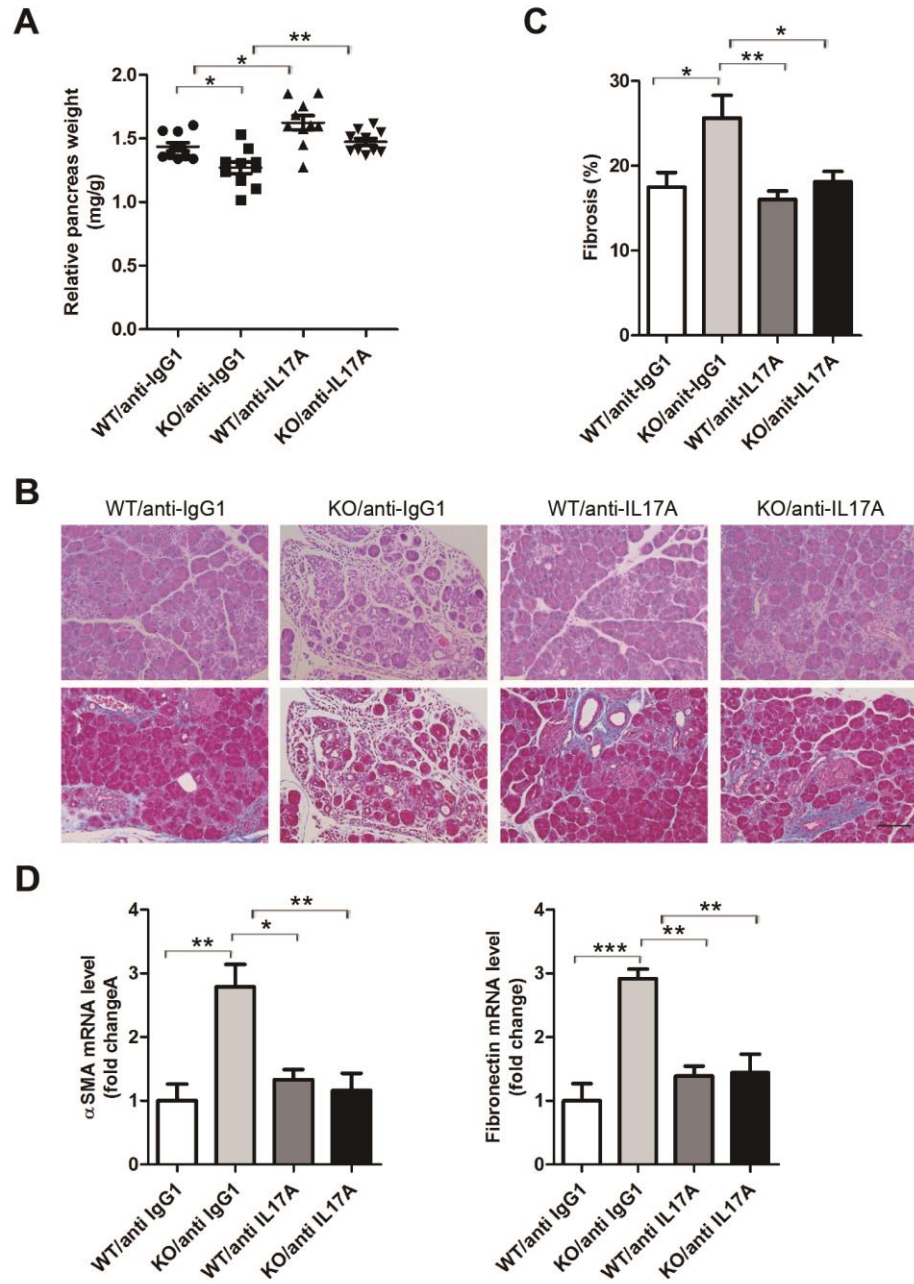
STING signaling in CP



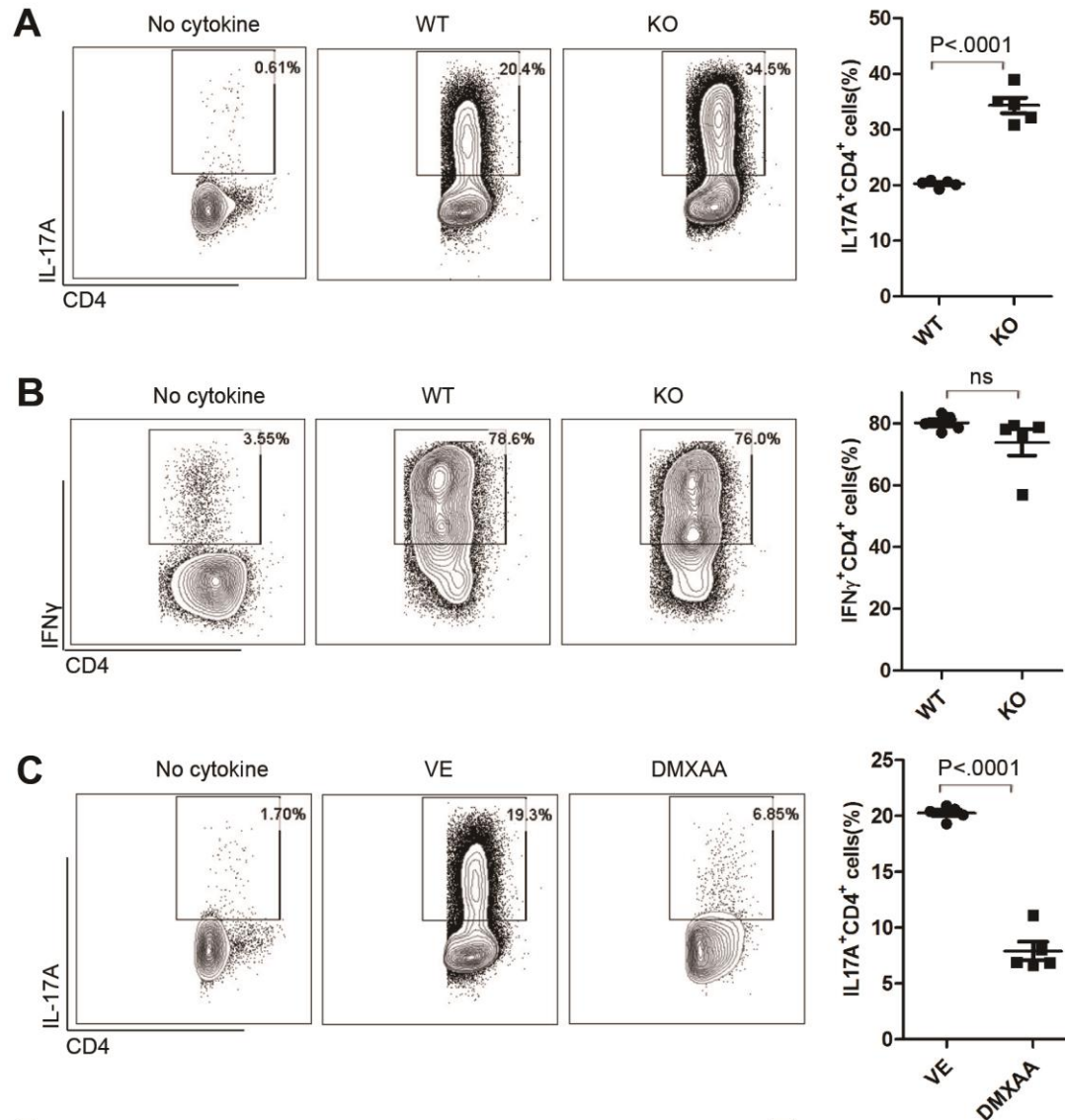
STING signaling in CP



STING signaling in CP

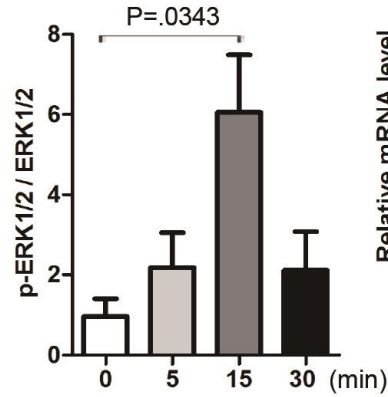
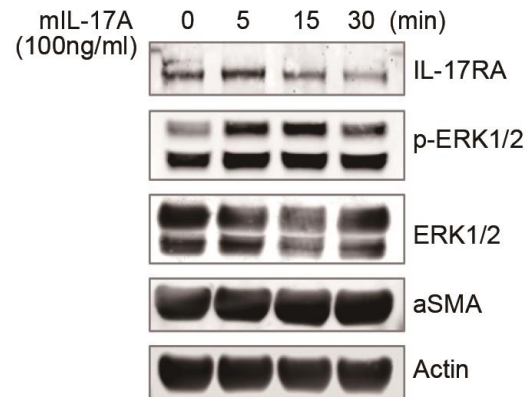


STING signaling in CP

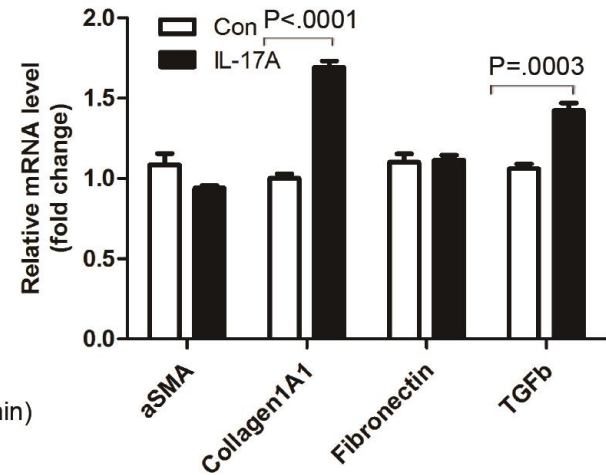


STING signaling in CP

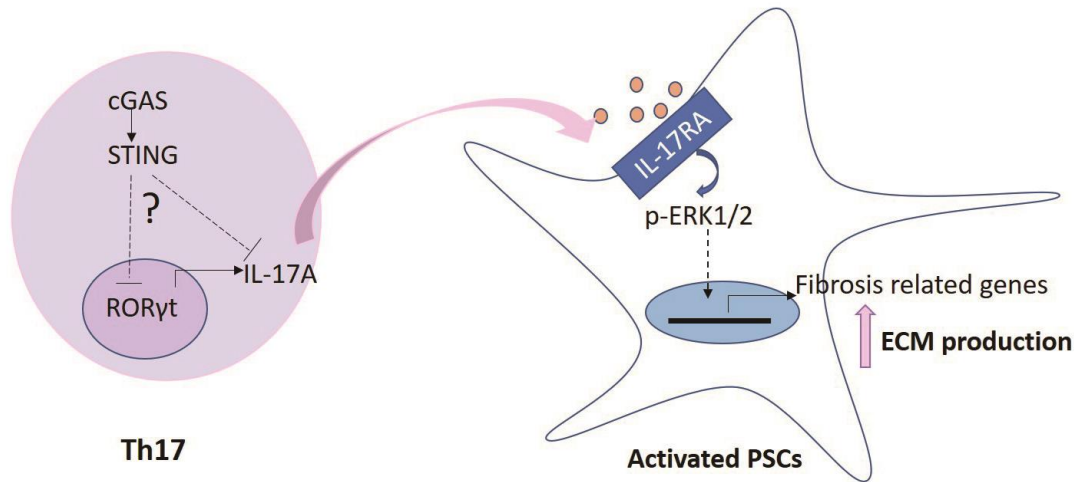
D Primary mPSCs



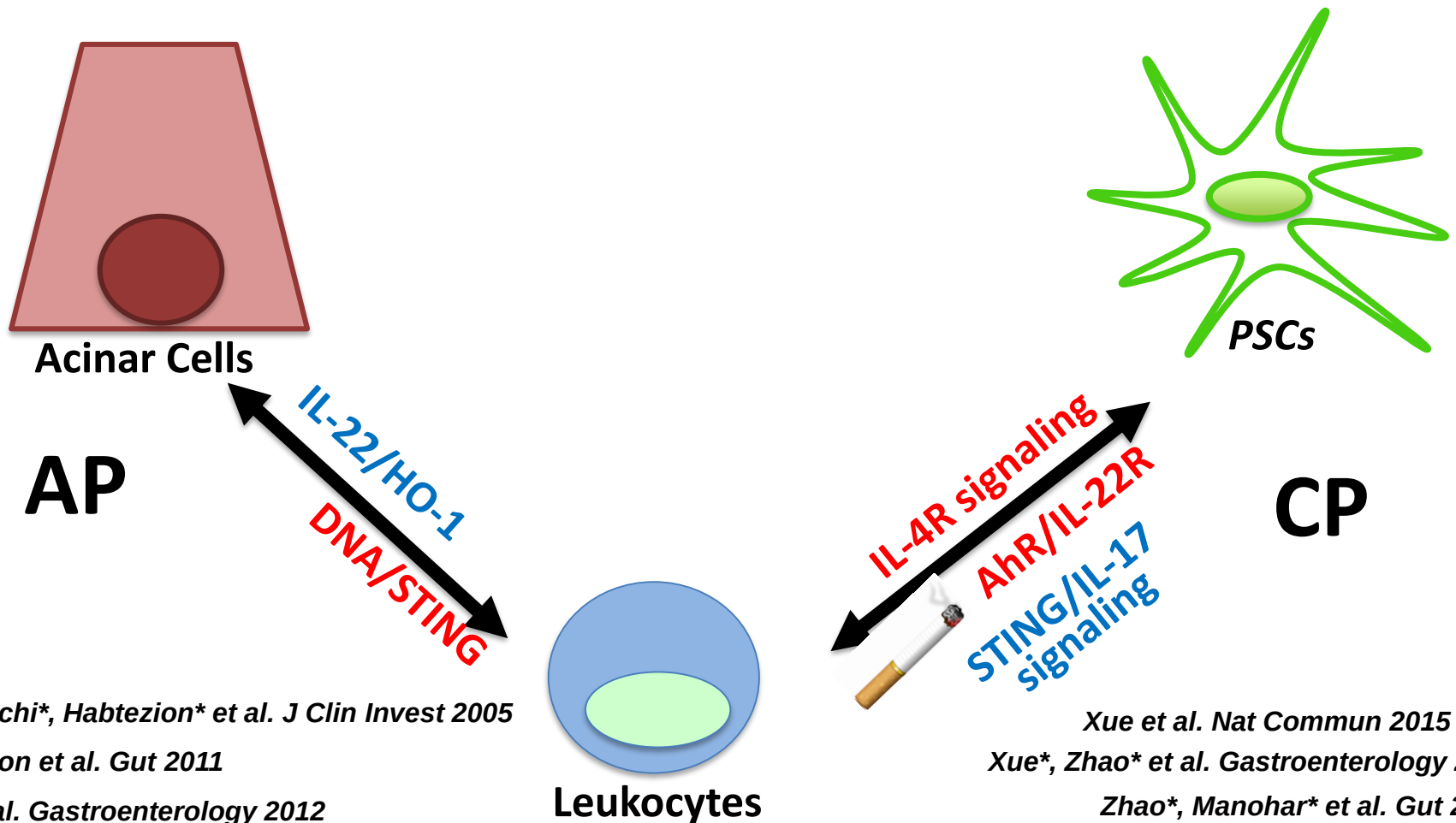
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Immune Cell Interactions in Pancreatitis



Nakamichi, Habtezion* et al. J Clin Invest 2005*

Habtezion et al. Gut 2011

Xue et al. Gastroenterology 2012

Xue & Habtezion. J Clin Invest 2014

Zhao et al. Gastroenterology 2018

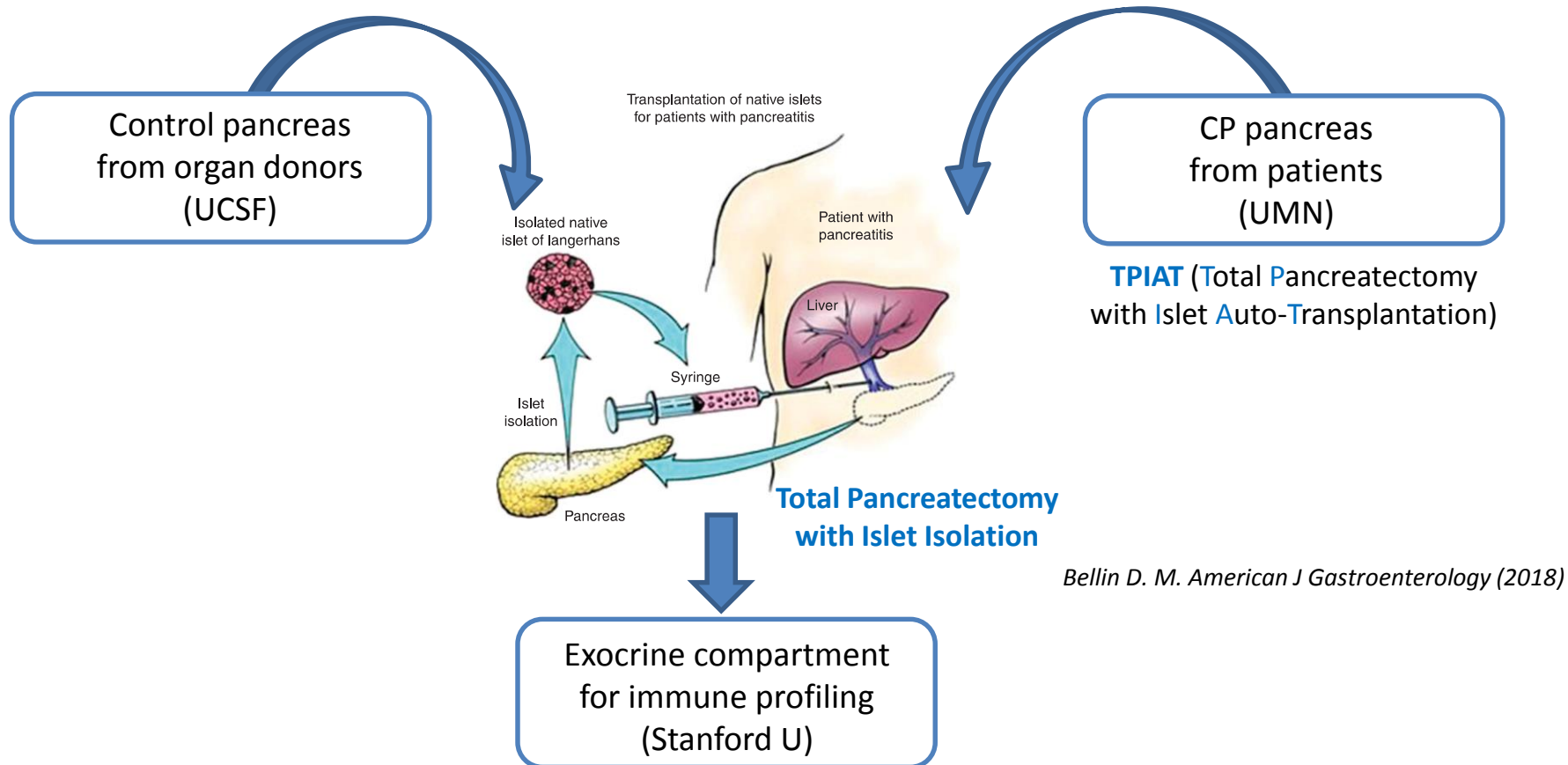
Xue et al. Nat Commun 2015

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



Thank you!

