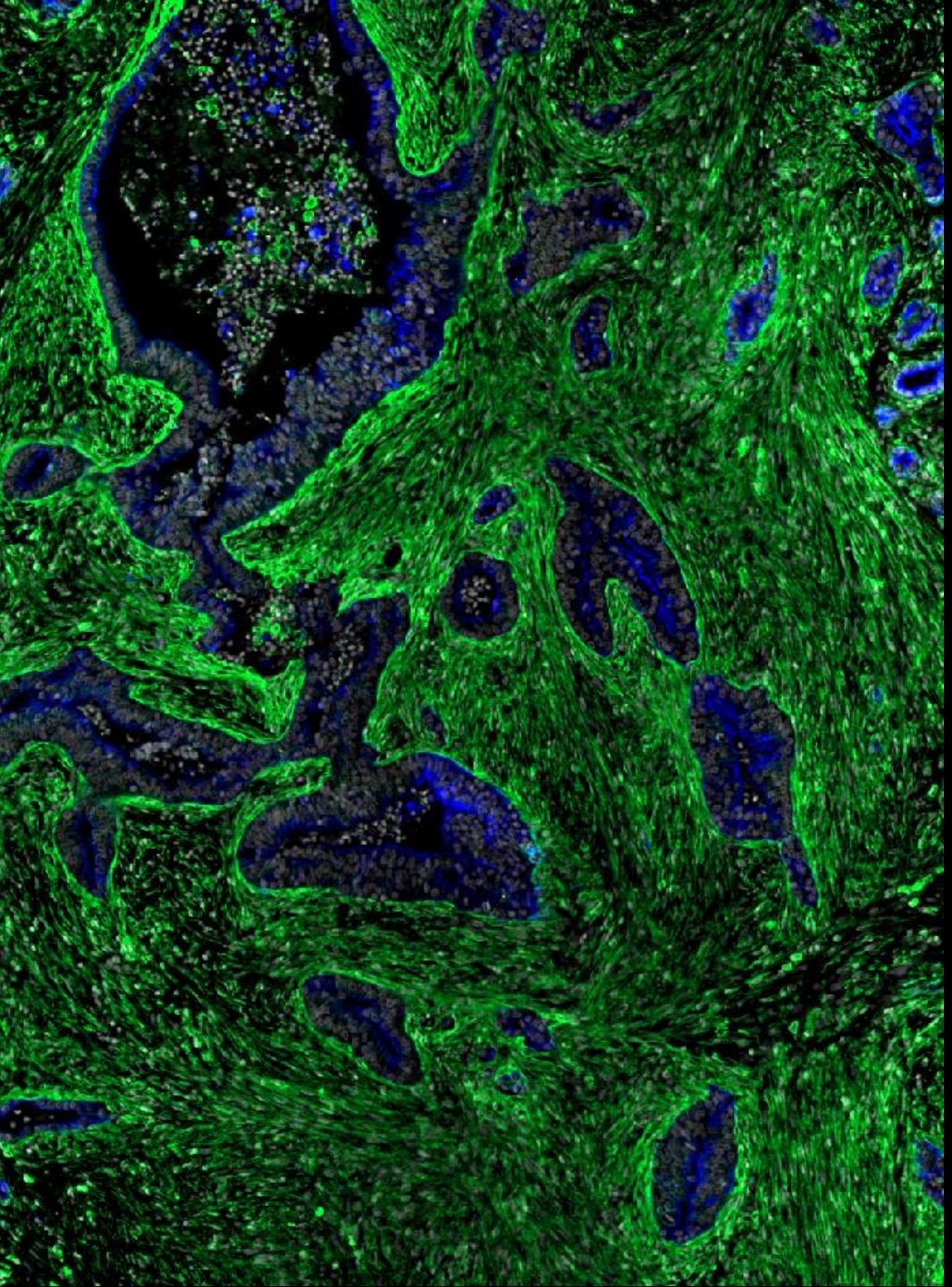

Mechanisms and consequences of pancreatic cancer stromal evolution

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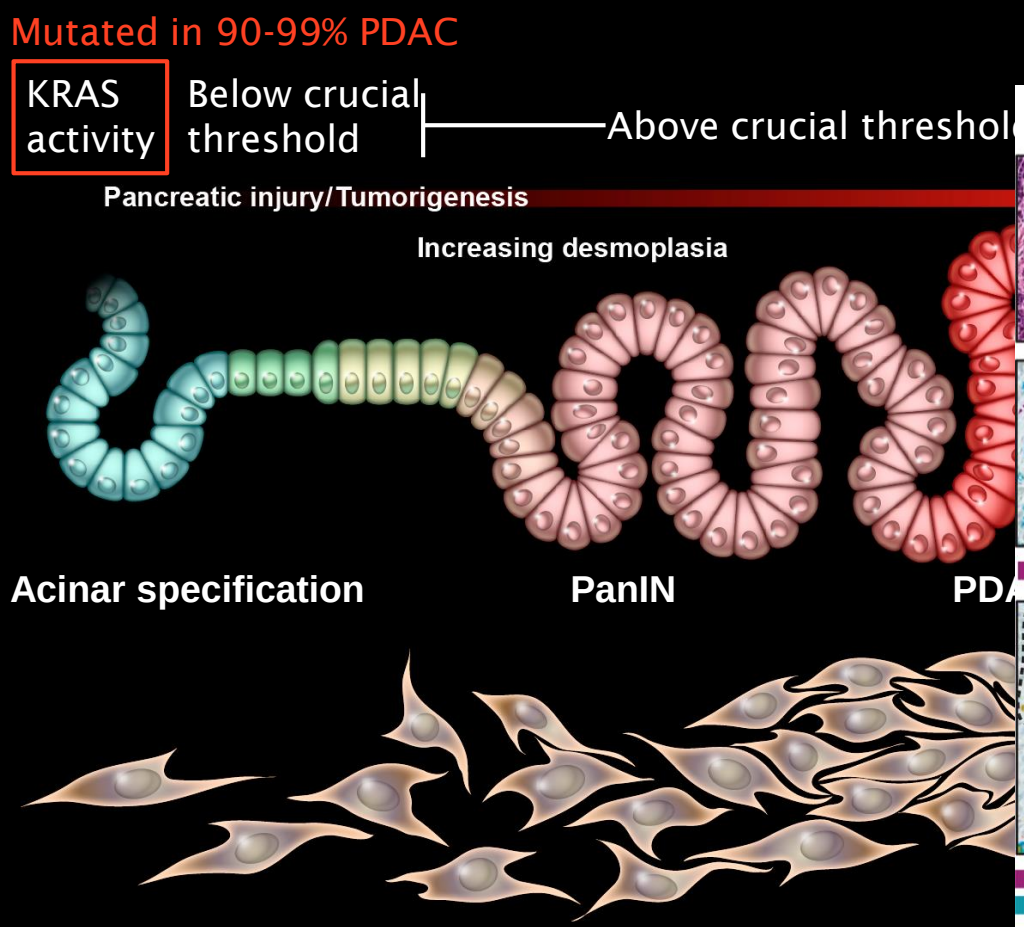
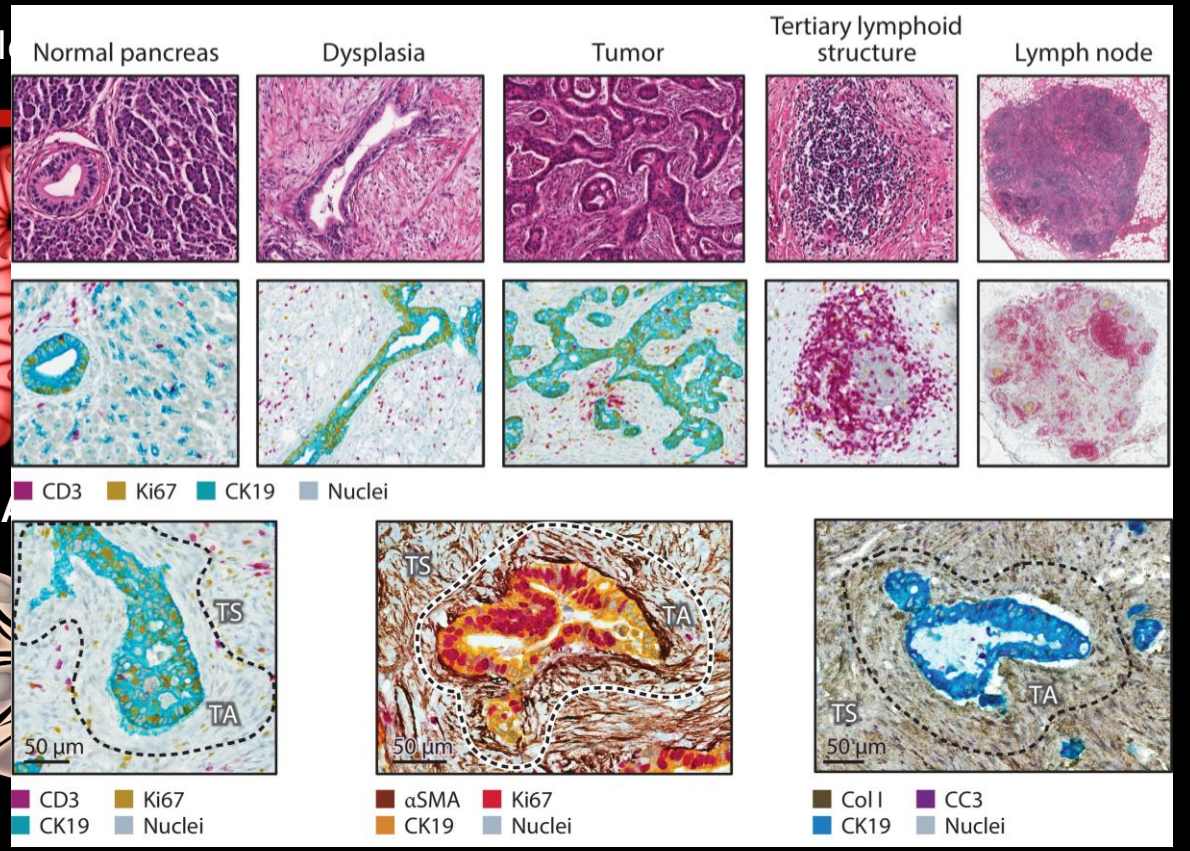
Pancreatic ductal adenocarcinoma (PDAC) features *causally linked* KRAS activation and a prominent desmoplastic stroma

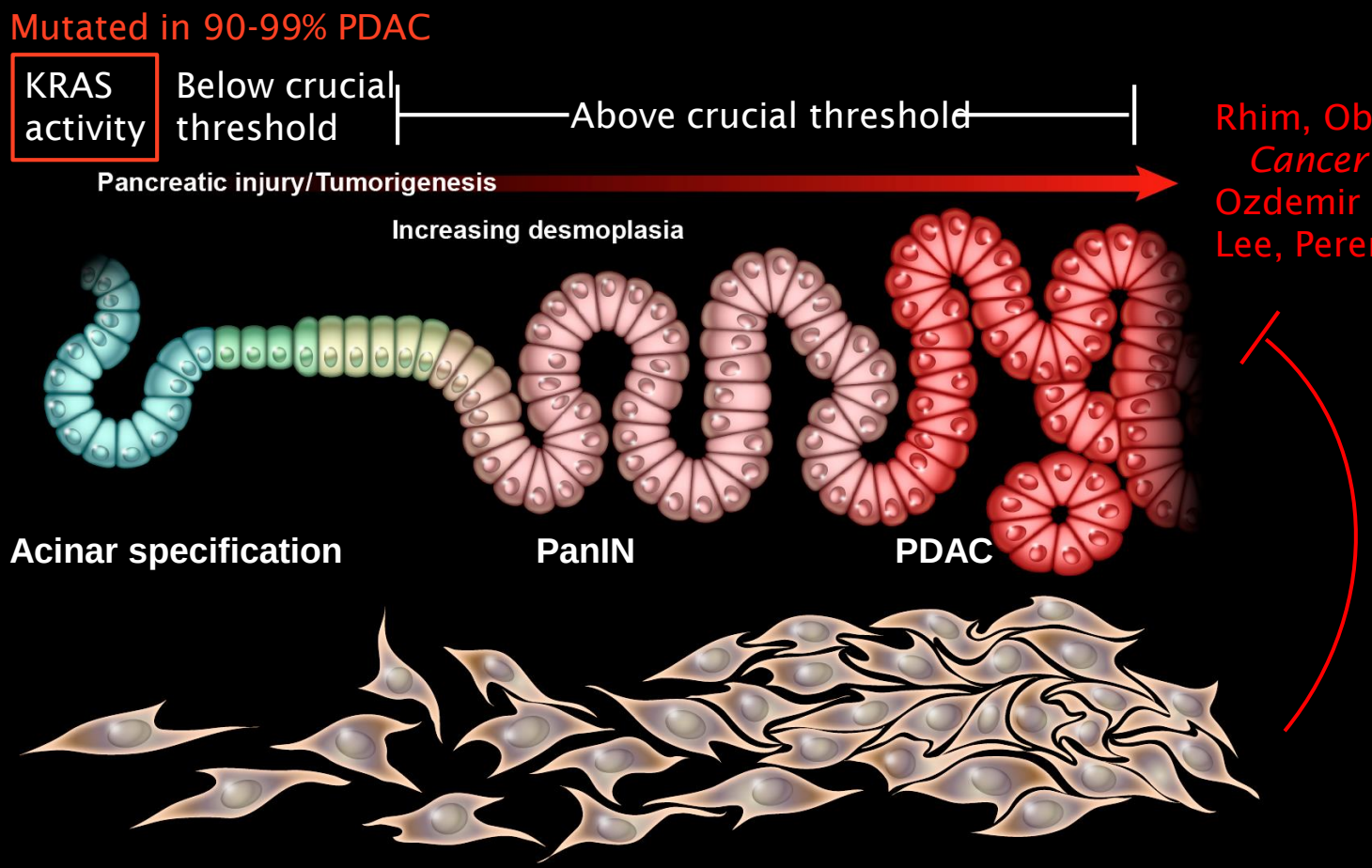




Sherman & Beatty, Annu Rev Pathol, 2023

Adapted from Liot S et al., *Front Immunol*, 2021

Pancreatic ductal adenocarcinoma (PDAC) features *causally linked* KRAS activation and a prominent desmoplastic stroma



Rhim, Oberstein, Thomas et al., *Cancer Cell*, 2014
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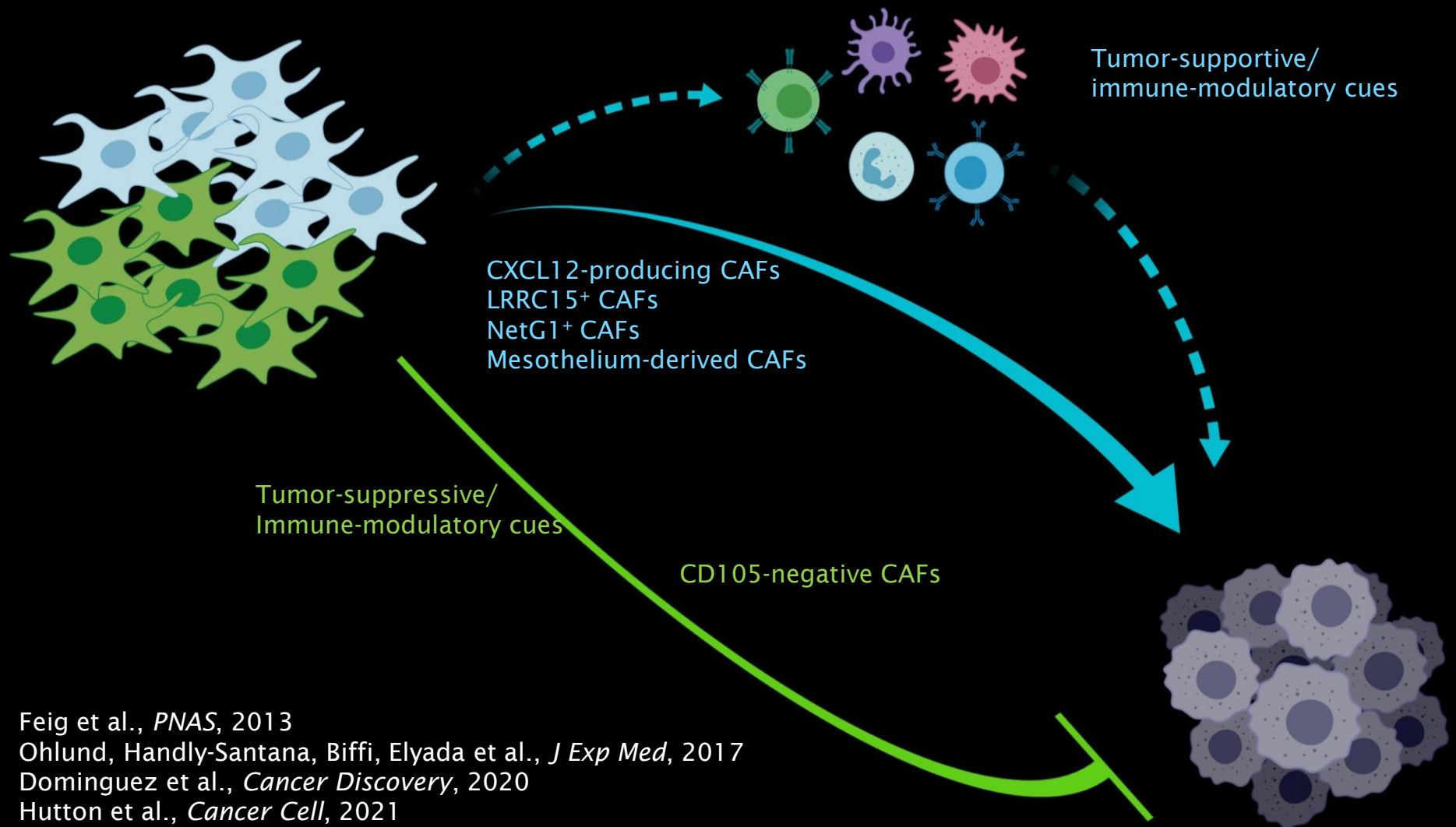
Lee, Perera et al., *PNAS*, 2014

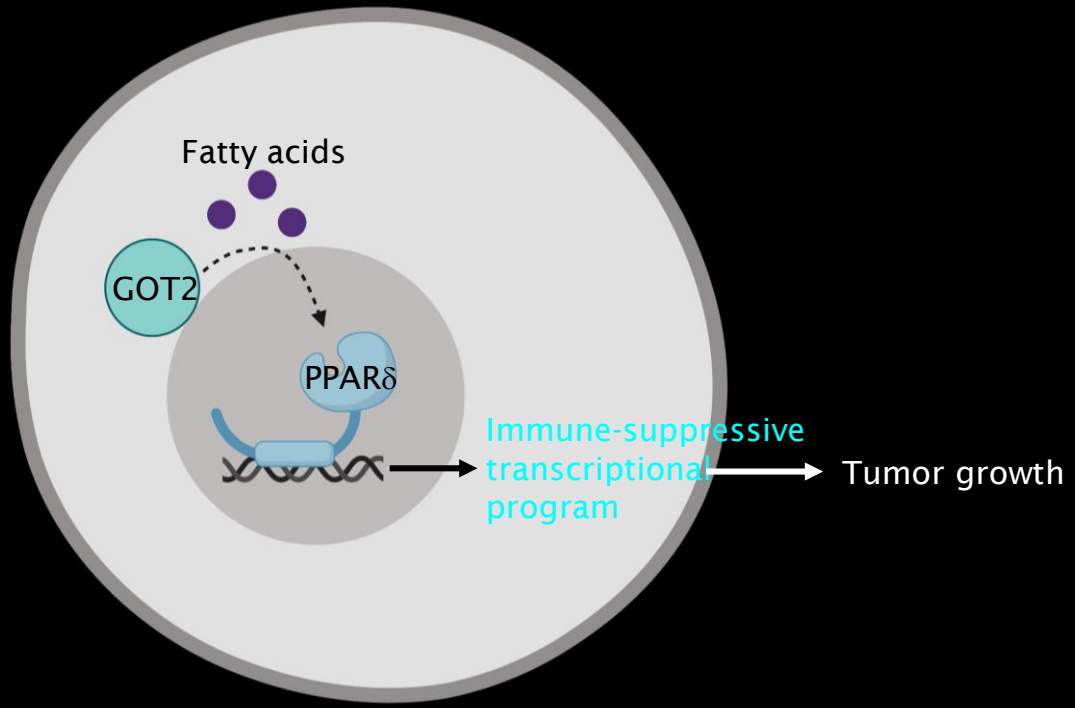
Adapted from Liot S et al., *Front Immunol*, 2021

CAFs are heterogeneous, including distinct pro- and anti-tumorigenic subsets which act via immune modulation



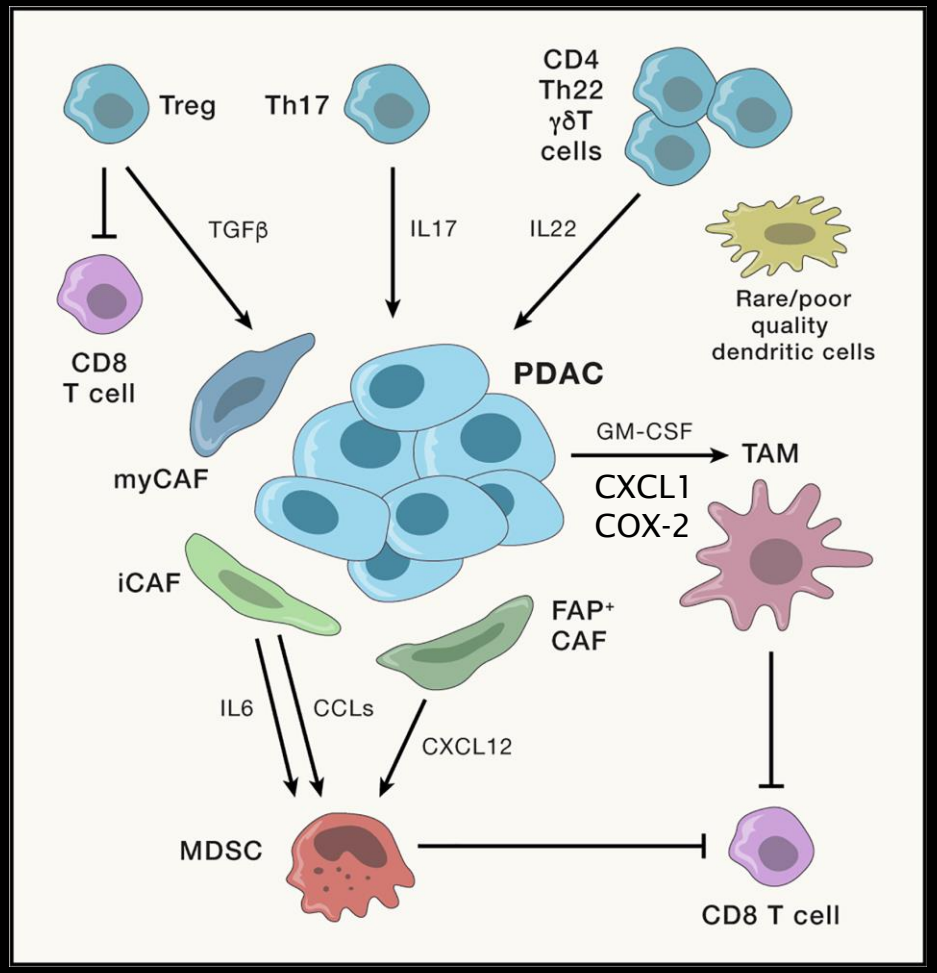
Feig et al., *PNAS*, 2013
Ohlund, Handly-Santana, Biffi, Elyada et al., *J Exp Med*, 2017
Dominguez et al., *Cancer Discovery*, 2020
Hutton et al., *Cancer Cell*, 2021
Francescone, Vendramini-Costa et al., *Cancer Discovery*, 2021
Huang et al., *Cancer Cell*, 2022

KRAS-transformed pancreatic epithelium drives immune suppression via multiple mechanisms



Abrego, Sanford-Crane et al., *Cancer Discovery*, 2022

Genetic inhibition of the GOT2-PPARδ axis:
*Increased DC, T cell infiltration; antitumor T cell fxn
*Induction of PD-L1 throughout the TME



Adapted from Halbrook, Lyssiotis, Pasca di Magliano, & Maitra, *Cell*, 2023

Key question and future directions

- What are the cellular hierarchies driving immune suppression in pancreatic cancer?
- What are the *targetable* cues, if any, that promote spatial restriction of T cells from the PDAC core?
- KRAS inhibitors are here. How will these inhibitors change the abundance and spatial distribution of immune cells in human PDAC, as well as their phenotypes? Combination therapies??
- To what extent are the spatial and cellular hallmarks of immune suppression reflected across anatomic sites in the setting of metastatic disease? Are there conserved mechanisms that may unleash antitumor immunity against both primary tumors and distant metastases upon inhibition/perturbation?