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.

Mutated in 90-99% PDAC

**KRAS activity**

Below crucial threshold

Above crucial threshold

Pancreatic injury/Tumorigenesis

Increasing desmoplasia

Acinar specification PanIN PDAC


Adapted from Liot S et al., *Front Immunol*, 2021
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Rhim, Oberstein, Thomas et al., *Cancer Cell*, 2014
Ozdemir et al., *Cancer Cell*, 2014
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
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

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

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

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?