Immunological Mechanisms in Pancreatic Cancer

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Key Objectives

- Etiology and common treatment options for pancreatic ductal adenocarcinoma
- Challenges imposed by tumor microenvironment
- Novel approaches to immunotherapy in pancreatic cancer

Types of pancreatic cancer

- Endocrine (5%)
- Exocrine (95%)

- Pancreatic ductal adenocarcinoma
- Acinar cell carcinoma
- Pseudopapillary
- Pancreaticoblastoma
Pancreatic cancer
2nd leading cause of death

Pancreatic ductal adenocarcinoma

The exocrine pancreas
Why is pancreatic cancer such a difficult problem?
- Diagnosed late
- Difficult to see on imaging
- Difficult to biopsy
- Cystic neoplasms
  - When are they malignant?
- Biopsies may have few tumor cells
- Metastasizes early
- Surgery is a big deal
- Few therapies
  - Drugs don’t penetrate?
  - Drugs don’t work?

Challenges
PDAC: Stage at Diagnosis
Human
PanIN-1A  PanIN-1B  PanIN-2  PanIN-3  PDAC  Metastasis

Histopathological and genetic evolution of pancreatic ductal adenocarcinoma

Yeh & Der (2007) Expert Opin Ther Targets 11:673

Histopathological and genetic evolution of pancreatic ductal adenocarcinoma

Adapted from A. Maitra and R. Hruban, 2008

Pancreatic ductal adenocarcinoma (PDAC)

- 230,000 cases worldwide (2% of cancers)
- Greater than 90% mortality
- Late diagnosis
- 4 year survival rate after treatment <8%
- >95% harbor KRAS mutations: currently UNDRUGGABLE!!
If the cancer is detected at an early stage when surgical removal of the tumor is possible, the 5-year survival rate is 32%.

About 10% of people are diagnosed at this stage.

If the cancer has spread to surrounding tissues or organs, the 5-year survival rate is 12%.

For the 52% of people who are diagnosed after the cancer has spread to a distant part of the body, the 5-year survival rate is 3%.
Challenges: Tumor stroma barrier
just a physical barrier?

Figure 1. The stromal landscape in HCC. Both human hepatocellular carcinoma (HCC) and murine hepatocellular carcinomas (HCC) show distinct collagen deposits and activated fibroblasts. (a) HCC shows collagen deposits and activated fibroblasts. (b) HCC shows collagen deposits and activated fibroblasts. (c) HCC shows collagen deposits and activated fibroblasts. (d) HCC shows collagen deposits and activated fibroblasts. (e) HCC shows collagen deposits and activated fibroblasts. (f) HCC shows collagen deposits and activated fibroblasts. (g) HCC shows collagen deposits and activated fibroblasts. (h) HCC shows collagen deposits and activated fibroblasts. (i) HCC shows collagen deposits and activated fibroblasts. (j) HCC shows collagen deposits and activated fibroblasts. (k) HCC shows collagen deposits and activated fibroblasts. (l) HCC shows collagen deposits and activated fibroblasts. (m) HCC shows collagen deposits and activated fibroblasts. (n) HCC shows collagen deposits and activated fibroblasts. (o) HCC shows collagen deposits and activated fibroblasts. (p) HCC shows collagen deposits and activated fibroblasts. (q) HCC shows collagen deposits and activated fibroblasts. (r) HCC shows collagen deposits and activated fibroblasts. (s) HCC shows collagen deposits and activated fibroblasts. (t) HCC shows collagen deposits and activated fibroblasts. (u) HCC shows collagen deposits and activated fibroblasts. (v) HCC shows collagen deposits and activated fibroblasts. (w) HCC shows collagen deposits and activated fibroblasts. (x) HCC shows collagen deposits and activated fibroblasts. (y) HCC shows collagen deposits and activated fibroblasts. (z) HCC shows collagen deposits and activated fibroblasts.

Provenzano et al., 2013
Most blood cells act to fight infection

- Dendritic cells and macrophage: directly kill microbes by phagocytosis and other mechanisms.
- They also help to activate T cells (connection between innate and adaptive immunity)
- T helper cells: regulate other immune cells
- T cytotoxic (killer) cells: kill infected cells
- B cells: produce antibodies (immunoglobulin)
1. A bacterium phagocytosed by an APC is enclosed in a vacuole.

2. Lysosomes fuse with the vacuole and bacterium is digested.

3. Antigens from digested bacterium are presented with MHC II.

Mechanisms of antigen presentation

1. Direct presentation

2. Cross-presentation

Mechanisms of T cell activation by antigens

1. Direct presentation

2. Cross-presentation
The 3 E’s of cancer immunoediting

- Recognition of cancer cells by immune system:
  - Mutant antigen
  - Ectopic expression of a normal protein

How does cancer escape immune surveillance?

- Altering characteristics of a cancer cell:
  - Loss of antigen
  - Downregulation of MHC I

- Suppressing the immune response:
  - T cell anergy
  - Release of immunosuppressive cytokines by tumor or stromal cells

Challenges: Tumor stroma barrier

- Immunotherapy
  - Strategies to improve the tumor-associated immune response by either boosting components of the immune system that produce an effective immune response or by inhibiting components that suppress the immune response.
**Current Immunotherapy approaches in pancreatic cancer**

- To boost immune system:
  - Checkpoint blockade antibody therapy
  - Vaccination
  - "Designer" T cells (CAR T cells, enhanced TCR cells)

- Block suppressive mechanisms:
  - Block or deplete regulatory T cells and MDSC
  - Block suppressive cytokines

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Proposed vaccine benefits in pancreatic cancer

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  - Checkpoint blockade antibody therapy (anti-PD-1, CTLA-4)

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Johnson et al., 2017

Wolchok and Chan, Nature, 2014
Basic mechanisms of T cell stimulation and inhibition

T cell activation

T cell activation is limited by CTLA-4

Current Immunotherapies that induce effector T cell function

Use of anti-CTLA-4 and anti-PD-1 allows for sustained T cell response

For Educational Use Only
Germline mutations as predictors of checkpoint blockade responsiveness

References

- A. Maitra and R. Hruban, 2008
- Moore et al. JCO 2007
- Conroy et al. NEJM 2011
- Von Hoff NEJM 2013