Investigating genetic and environmental contributors to pancreatic cancer progression

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• None
Pancreatic cancer: the problem

- Large disease burden
  - 55,440 new cases/year
  - 44,330 deaths/year
- Metastatic disease common at diagnosis (~50%)
- Standard of care: combination chemo
  - FOLFIRINOX
  - Gemcitabine + abraxane
- 5-year survival: 8%
- Unmet challenges
  - Prevention/interception
  - Better treatments for advanced disease
Pancreatic Cancer Progression

Inherited mutations:
- DNA repair (BRCA)
- Cell cycle (p16)
- Inflammation (PRSS1)

Somatic mutations:
- KRAS (>90%)
- p53 (75%)
- p16 (50%)
- SMAD4 (40%)

Prevention

Interception

Treatment

Targeting KRAS in pancreatic cancer

KRASmut

VS

KRAS

CRISPR screens identify targets in KRAS mutant pancreatic cancer cells
Pancreatic Cancer Progression

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Normal → Initiation → Precancer → Progression → Cancer

Prevention → Interception → Treatment

Tracing tumor-progression in *KRAS* mutant cancers

Pancreas

Lung


*p53* normal

*p53* mutated
Tracing tumor-progression in \textit{KRAS} mutant cancers

Sort out Red and Green cells

Progressing cells

1000s of DNA-barcoded single-cell transcriptomes
Pancreatic Cancer Progression

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Risk Factors
- Smoking
- Obesity
- Diabetes
- Age

Prevention
- Inherited mutations

Interception
- Somatic mutations

Treatment
- Prevention

Obesity as a risk factor for PDAC

Obesity is associated with an increased risk of developing pancreatic cancer.

Changes in % adult obesity prevalence over time in selected countries around the world.

Pancreatic Cancer Incidence Predictions (Globocan) to 2030.
Modeling obesity and pancreatic cancer

**KC model recapitulates human pancreatic cancer**
- Genetics (*Kras* mutation)
- Microscopic appearance (early to advanced progression)
- Metastatic behavior
- Response to chemotherapy

**Leptin deficiency: obesity model**
- Very obese (dose-response)
- Fast onset
- Reversible (leptin restoration)
Obesity induced shortened survival in *KRAS* mutant mice

![Graph showing percent survival over days for non-obese KC, obese KC, and KC (p53 mutation)]
Obesity promotes tumor progression

3 months

KC; +/+  
KC; ob/+  
KC; ob/ob

Tumor burden (% area disease/total)

**  
****

NS

**p<0.01, ****p<0.0001
Early obesity reversal impedes tumor progression

6 weeks post-AAV infection

- Graph showing change in weight over time (weeks 0, 6, 12) for GFP and Leptin groups.
- Bar graph comparing tumor burden (% area disease/total) between GFP and Leptin groups, with significance indicated by **.
Late obesity reversal has no impact on survival
CCK-driven inflammatory/fibrotic circuit drives tumor progression in obesity

CCK is the top upregulated gene in pancreas of obese mice.

CCK is aberrantly expressed in pancreas of obese mice with tumors.
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Prevention
- Normal
- Precancer

Interception
- Cancer

Treatment
- ?

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http://medicine.yale.edu/lab/muzumdar/