Heterogeneous Tumor Stroma and Prostate Carcinogenesis

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Composition of the Tumor Microenvironment

Franco et al. In Mouse Models of Stromal Epithelial Interactions 2008
Cancer = Wound

“Wounds that never heal”
Dvorak (1986)

Virchow (1863): “inflammation and cancer”
Composition of the Tumor Microenvironment

Carcinoma Associated Fibroblasts

Activated Fibroblasts

Tumor associated fibroblasts

Myofibroblasts

Reactive Stroma

Franco et al. In Mouse Models of Stromal Epithelial Interactions 2008
Tissue Recombination (TR) and Renal Xenograft

Enzymatic Digestion

Reporter Cell (BPH1)

Culture <P8

TR (Fibroblasts + BPH1) in collagen

SCID Mice

Tissue Harvest @12 weeks
Renal Xenograft

- Implantation of cell lines
  - Benign
  - Malignant

- Human explants
  - PDX (Patient-derived Xenograft)

- Tissue Recombination
  - Normal Development
  - Carcinogenesis

- Tissue Rescue
  - Embryonic lethal

- Advantages
  - Time/cost effective alternative to GEM
  - High uptake

- Drawbacks
  - Technically challenged
  - Unnatural site?
# CAF Induces Malignant Transformation Of Benign Prostate Epithelial Cells

<table>
<thead>
<tr>
<th>Patient #1</th>
<th>Patient #2</th>
<th>Patient #3</th>
<th>Patient #4</th>
</tr>
</thead>
</table>

- **Patient #1**
  - [Image of tissue section]
  - [Histology image]

- **Patient #2**
  - [Image of tissue section]
  - [Histology image]

- **Patient #3**
  - [Image of tissue section]
  - [Histology image]

- **Patient #4**
  - [Image of tissue section]
  - [Histology image]

**Tumor Induction (Growth + Invasion)**
Heterogeneous TGFβ signaling in mouse prostatic stromal cells induces oncogenic effects

Wyld 100%  Wt 50% : TGFβRKO 50%

Normal Mouse Prostate  Mouse Prostate Cancer

Bhowmick et al. Science 2004
Heterogeneous TGFβ Signaling in Prostate Tumor Stroma

Normal Prostate

Prostate Cancer

PZ Stroma

Stromal pSmad2
SCORE

The University of Utah
Department of Pathology
Heterogeneous TGFβ Signaling in CAF Cells

Percentage of positive cells over total population

Serum(-)  TGFβ(+)  Serum(+)

Serum(-)  TGFβ(+)  Serum(+)

BHPrS

CAF

Serum (+)

pSmad2 / αSMA/DAPI

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Heterogeneous TGFβ Signaling in Normal Fibroblasts Increases Proliferation of Prostate Epithelial Cells
and Malignant Transformation… and Malignant Transformation
Identification of Paracrine Mediators

Locally Growing Prostate Tumor

Aberrant Paracrine Signaling

Smooth muscle

Altered stromal TGFβ response

Juxtacrine Signaling

TGFβ1

SDF1α

NorthShore University HealthSystem
Induction of CAF phenotype by over-expression of TGF-β1 and SDF1α in normal prostate fibroblasts

Franco et al. Cancer Research 2011
TGF-β1 and SDF1α induces malignant transformation
• CAF induces **malignant transformation** of benign prostate epithelial cells

• Prostate Cancer Stroma shows **heterogeneous** TGFβ signaling

• Experimental model: loss of TGFβ signaling in 50% of fibroblasts induces malignant transformation

• Paracrine factors such as TGFβ1 and SDF1α are potential mediators