Tumor Stroma

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Outline

• Overview of stroma composition
• Focus on Cancer Associated Fibroblasts (CAFs)
  – Origins of CAFs
  – Stromal – epithelial interaction
  – Genetics and Epigenetics of CAFs
  – Prognostic value of CAFs
  – Significance of CAFs in tumor progression and metastasis
• Therapeutic implications and results
Practical questions about the cancer associated stroma

• Chicken and Egg dilemma
  – Do cancer cells induce a desmoplastic reaction or does an altered microenvironment provide a permissive milieu for tumor formation?

• Friend or Foe (or Frenemy?)
  – Does ablation or reduction of tumor stroma benefit

• Primary Therapeutic Target or Adjunct?
Components of the tumor stroma or tumor microenvironment

• Components of the stroma
  • Vascular cells
    – Endothelial cells
    – Pericytes
  • Leukocytes
    – Myeloid
    – Lymphoid
  • Neural cells
  • Extracellular Matrix
  • Mesenchymal cells
    – (Myo)fibroblasts/Cancer Associated
    – Mesenchymal stem cells
    – Fibroblasts
Tumors are “non-healing wounds”
Fibroblasts and Myofibroblasts

• The major stromal cell type in most cancers
• Slender fusiform smooth nucleus
• Cancer Associated Fibroblasts (CAFs) are often equated with activated fibroblasts or myofibroblasts
  – The cancer stroma does contain both fibroblasts and myofibroblasts
• Myofibroblasts are capable/responsible for tissue contraction and secretion of ECM
  – The hallmark is αSMA expression
A nearly ubiquitous feature of most solid cancers

<table>
<thead>
<tr>
<th>Tissue Type</th>
<th>Estimated % stroma</th>
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</thead>
<tbody>
<tr>
<td>Esophagus (mostly SCC)</td>
<td>50-82%</td>
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<tr>
<td>Gastric</td>
<td>34%</td>
</tr>
<tr>
<td>Liver</td>
<td>50%</td>
</tr>
<tr>
<td>Pancreas</td>
<td>83%</td>
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<tr>
<td>Colon</td>
<td>34%</td>
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<tr>
<td>Breast</td>
<td>41-66%</td>
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<tr>
<td>Prostate</td>
<td>40%</td>
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<tr>
<td>Renal</td>
<td>10%</td>
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<tr>
<td>Glioblastoma</td>
<td>10%</td>
</tr>
</tbody>
</table>

Liu L et al PLOS One 2016
Gonda et al Cell Dev 2010
Significant organ specific differences exist between CAFs.
Markers of CAFs

Other cells that express these markers:
- Pericytes (smooth muscle cells)
- Neural cells
- Macrophages

Terminology:
- Myofibroblasts
- Fibroblasts
- Cancer-associated fibroblasts

Molecular markers:
- $\alpha$-SMA
- FAP$\alpha$
- NG2
- PDGFR-\(\beta\)
- Fibroblast-associated antigen
- Prolyl 4-hydroxase
- FSP-1

Positive Marker
- $\alpha$-SMA
- Fibroblast activation protein
- Tenascin-C
- Periostin
- Neuron glial antigen-2
- Vimentin
- Desmin
- Platelet derived growth factor receptor
- Fibroblast specific protein-1

Negative Marker
- Cytokeratin
- CD31

Ohlund et al JEM 2014
Stromal cells are present in the premalignant lesions

Origins of CAFs

• Activation or transformation of resident cells in the tumor
  – Activation of fibroblasts, smooth muscle cells, endothelial cells/pericytes
  – Epithelial mesenchymal Transformation

• Recruitment of bone marrow derived cells
Origins of CAFs

- Endothelial cells
- Epithelial cells
- Bone marrow derived hematopoietic stem cells
- Bone marrow derived mesenchymal stem cells
- Adipocyte

- Resident fibroblasts
- Cancer associated fibroblasts

- endMT
- EMT
Activation of fibroblasts - tumor cell derived paracrine signals

α-SMA⁻

Tumor

TGF-β, PDGF, Shh, Wnt7a, Exosomes

α-SMA⁺

IL-1β, LIF

α-SMA⁻

Mezawa Cel Tiss Res 2016
Gonda Semin Cell Dev 2012
Activation of fibroblasts - tumor cell derived & autocrine signaling

MCF7 + fibroblasts -> CAF

CAF (+/- CXCR4 shRNA + MCF7)

Kojimo PNAS 2010
Epithelial Mesenchymal Transformation (EMT)

- Observed in normal development/wound healing and cancer

- Possibly reversible (E->M->E; EMT to MET)

- Phenotypic similarities with CSCs

- Significant epigenetic regulation of EMT-TFs

Kalluri Weinberg JCI 2009