Angiogenesis and Inflammation in the Tumor Microenvironment
Tumors are not bags of cancer cells but rather “outlaw” complex organs

TUMOR: Cancer cells + Stromal cells + ECM
Stromal cell components of carcinomas

**Invasive breast carcinoma**

Cancer cells: brown (arrows)

Stromal cells / ECM: blue.

Note the very abundant tumor stroma in this invasive carcinoma. Single cancer cells invade the stroma (arrowhead).

Figure 13.1a  *Weinberg, The Biology of Cancer* (© Garland Science 2007)
Multiple “normal” cell types are present in tumors

- Cancer Stem Cell (CSC)
- Cancer Cell (CC)
- Inflammatory Cells
- Local & Bone-marrow Derived Stromal cells
- Endothelial Cell (EC)
- Pericyte (PC)
- Cancer-Associated Fibroblast (CAF)

Hanahan & Weinberg, Cell, 2011
Stromal cell components of carcinomas

- **Fibroblasts (alpha-SMA+)**
- **T lymphocytes (CD4+)**
- **Monocytes/macrophages (CD11b+)**

*Figure 13.3a  Weinberg, The Biology of Cancer (© Garland Science 2007)*
The tumor microenvironment evolves during malignant progression

Hanahan & Weinberg, Cell, 2011
Stromal cells modulate the hallmarks of cancer

Hanahan & Coussens, Cancer Cell, 2012
Inflammation and Cancer
Some basic concepts in immunology....
Functions of antibodies (immunoglobulins)

antigen-binding domains
variable region
light (L) chain
constant region
heavy (H) chain
disulfide bonds

antibody prevents viral adsorption

antibody prevents bacterial adherence

Figure 15.2b  *The Biology of Cancer* (© Garland Science 2007)
Coating of pathogens or cells by antibodies stimulates their elimination by INNATE IMMUNE CELLS

Phagocytosis by macrophages (antibody-directed cellular phagocytosis, ADCP)

Lysis by NK cells

Figure 15.3b  *The Biology of Cancer* (© Garland Science 2007)
Antigen uptake by APCs like DCs stimulates T-cells to mount ADAPTIVE IMMUNE RESPONSES.

 APCs present antigens via MHCII.
T-cells

humoral

cellular
Adaptive humoral responses

Figure 15.8b  The Biology of Cancer (© Garland Science 2007)
Adaptive cytotoxic responses

ALL CELLS can present antigens via MHCI

Lytic granules (perforin, granzymes) are scattered in the T_C cell cytoplasm.

Upon contact with the target cell, the lytic granules localize at the cells’ contact, are released, and kill the target cell.
Tumor initiators and promoters

**Tumor initiator**: Generally a mutagen, causes genetic or epigenetic changes (mutations) in normal cells that are necessary (but often not sufficient) for tumor development.

**Tumor promoter**: Fosters the growth (proliferation) of “initiated” cancer cells, enabling their acquisition of additional features, also genetic, leading to cancer. A tumor promoter may not be a mutagen. **Inflammation** is a typical tumor promoter.
Virchow first noted the association of tumors with chronically inflamed tissues (tissues characterized by unusually high numbers of infiltrating inflammatory cells, or leukocytes)
Human tumors are heavily infiltrated by leukocytes (inflammatory/immune cells)

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<th>human breast</th>
<th>human prostate</th>
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<td>‘normal’</td>
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<td>malignant</td>
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- **H&E**
  - Human breast: ‘normal’
  - Human breast: malignant
  - Human prostate: ‘normal’
  - Human prostate: malignant

- **anti-CD45**
  - Human breast: ‘normal’
  - Human breast: malignant
  - Human prostate: ‘normal’
  - Human prostate: malignant

**CD45: total leukocytes**

Adapted from van Kempen et al., *Eur J Cancer*, 2006
H. pylori $\rightarrow$ Gastritis

Gastric Cancer

Viral hepatitis / Liver cirrhosis $\rightarrow$ Hepatocellular Carcinoma

Reflux $\rightarrow$ Esophagitis

Esophageal Cancer

Recurrent cholangitis

Cholangiocellular Carcinoma

Recurrent gallstones

Gallbladder Carcinoma

Inflammation & Cancer

Inflammmatory bowel disease

Colorectal Cancer

HPV-16 / 18

Cervical Cancer

Chronic pancreatitis

Pancreatic Cancer
Inflammation, the Janus of cancer: Pro- versus anti-tumor effects

T-cells
NK cells

Macrophages
Immature myeloid cells

Immunosurveillance

Tumor-promoting inflammation

Cytokines
IFNγ, IL-17, GM-CSF, IL-12

Cytokines
FasL, TNF, TRAIL, IFNαβ

Cytotoxic effectors
Perforin
Granzyme
TRAIL

Cytokines
IL-10
ROS RNOS

Cytokines
IL-1, IL-6
IL-17, IL-23

Tumor

Adapted from Grivennikov et al., Cell 2010
Cross-talk between cancer and inflammatory cells fosters cancer-cell evolution and malignant progression.
Tumor angiogenesis
Tumor-associated stromal cells: vascular endothelial cells and angiogenesis

Joyce et al., Nat. Rev. Cancer, 2009
Tumor blood vessels differ from “normal” vessels.
Features of tumor blood vessels

Because of these features, tumor blood vessels are poorly functional, leaky and provide inadequate oxygen and nutrient levels to the tumor mass.
Excessive amounts of proangiogenic growth factors (over endogenous inhibitors) activate the angiogenic switch and sustain relentless tumor angiogenesis.

Does tumor inflammation influence angiogenesis?