Tumor Microenvironment: Complexity of Cells and Molecules Regulating Intratumoral Immunity

Victor Engelhard, PhD
Carter Immunology Center
Department of Microbiology, Immunology, and Cancer Biology
University of Virginia School of Medicine
Perspectives

• Focus entirely on solid tumors
• Focus on stromal cell interactions with immune cells
• Discuss similarities and differences between cancer growth and wound healing
• Tumor microenvironments originate and evolve distinctly based on:
  – Predominant driver mutations in transformed cells
  – Distinct environments of different tissue sites
  – Co-regulation and co-evolution of stromal and immune cells
Fibroblasts

- **Normal fibroblasts**
  - Principal components of connective tissue, embedded within extracellular matrix (ECM)
  - Produce ECM/basement membrane, provide structure to tissue
  - Secrete matrix remodeling factors (matrix metalloproteinases)
  - Regulate epithelial differentiation and inflammation through secreted factors and direct contact

- **Activated (Myo)fibroblasts**
  - Develop in response to TGFβ, PDGF, FGF2, chemokines, ECM degradation
  - Increased proliferation, synthesis of ECM components, α-SMA, VEGF
  - Important in wound closure, tissue remodeling, angiogenesis
  - If unresolved in chronic inflammation, leads to fibrosis
Cancer-associated myofibroblasts (CAFs)

Products of Cancer Associated Fibroblasts (CAF)

- Accumulate in and around tumors and secrete abundant collagen (reactive or desmoplastic stroma)
  - Traps immune cells
  - High interstitial pressure
- Produce factors that promote initial tumorigenesis of epithelial cells, support tumor invasiveness
- Promote angiogenesis
- Recruit and regulate immune cells associated with wound healing
- Enable dormancy?
Tumor Angiogenesis and Neovascularization

A. Small tumor

B. Sprouting capillary

C. Growing tumor

Angiogenic factors

Nutrients from blood

Metastatic spread
Disregulated Angiogenesis in Tumors

Normal colorectal mucosa

Nearby colorectal cancer

VEGF blockade: Relief of Immunosuppression

Differences in Immune Cell Infiltrates Influence Tumor Control

- Immunotypes correlate with “inflamed” gene signatures and “hot” and “cold” tumors
- Clinical responses to immunotherapy are associated with pre-existing infiltrates and inflamed gene signatures
- What underlies poor infiltration?

Determinants of Immune Cell Composition and Function in Tumors

• Tissue resident cells that become included in outgrowing tumor
• Antigen driven immune responses in secondary lymphoid organs
• Recruitment of immune cells through blood vasculature
• Retention/sequestration of immune cells based on intercellular interactions
• Differentiation/exhaustion/death of immune cells due to mechanisms operating within tumors
Extravasation into Inflamed Tissue is Enabled by "Activation" of Vascular Endothelium
The Tumor Vasculature Forms Barriers to Immune Cell Entry

Stromal Organization and Impact on Tumor Perfusion and Immune Cell Entry
Cancer Cell-intrinsic Signaling Pathways Shape the Tumor Immune Landscape through Recruitment and Differentiation

↑ macrophage/monocyte, CD4 T, neutrophil
↓ CD8

↑ neutrophil, block CD8

↑ neutrophil

↑ neutrophil

↑ neutrophil, block CD8

↑ neutrophil

↑ CD8 and CD4

↑ macrophage, CD4 Treg, neutrophil

↓ dendritic cells, thus T cells

Alternate Effector Cell Programming Of Adaptive And Innate Immune Cells

- Differentiation of adaptive and innate immune cells is driven by environmental cytokines
- Sources of these cytokines include tumor, stromal cells, and other immune cells
- System can be self-reinforcing over time
Gene sets identify common immune signatures among 10,000 tumors representing 33 cancer types

Prognostic Significance of Infiltrate Components Has Both General and Tumor Specific Aspects (18,000 tumors, 39 malignancies)
Activities of Tumor-Associated Neutrophils (TANs) Favor Tumor Initiation and Growth

Regulation of tumor associated TLS by B-cell fibroblast interaction
Immune Responses to Cancer Involve Interactions Among Adaptive, Innate, and Non-immune Cells and Molecules

- Tumor microenvironment is determined by cellular composition and cellular activities, often associated with production of cytokines and chemokines.
- Tumors, fibroblasts, and endothelial cells all regulate immune microenvironment towards something with characteristics of wound healing, chronic fibrosis.
- However, there is substantial heterogeneity that depends on the tissue origin of the tumor cell, activated oncogenic pathways, and mutational burden.
- Transcriptome analyses are providing insight that enables classification of tumors based on immune profile, and illuminates unexpected roles for some immune cell populations that requires further investigation and may enable new forms of immunotherapy.