Tumor Microenvironment: Complexity of Cells and Molecules Regulating Intratumoral Immunity

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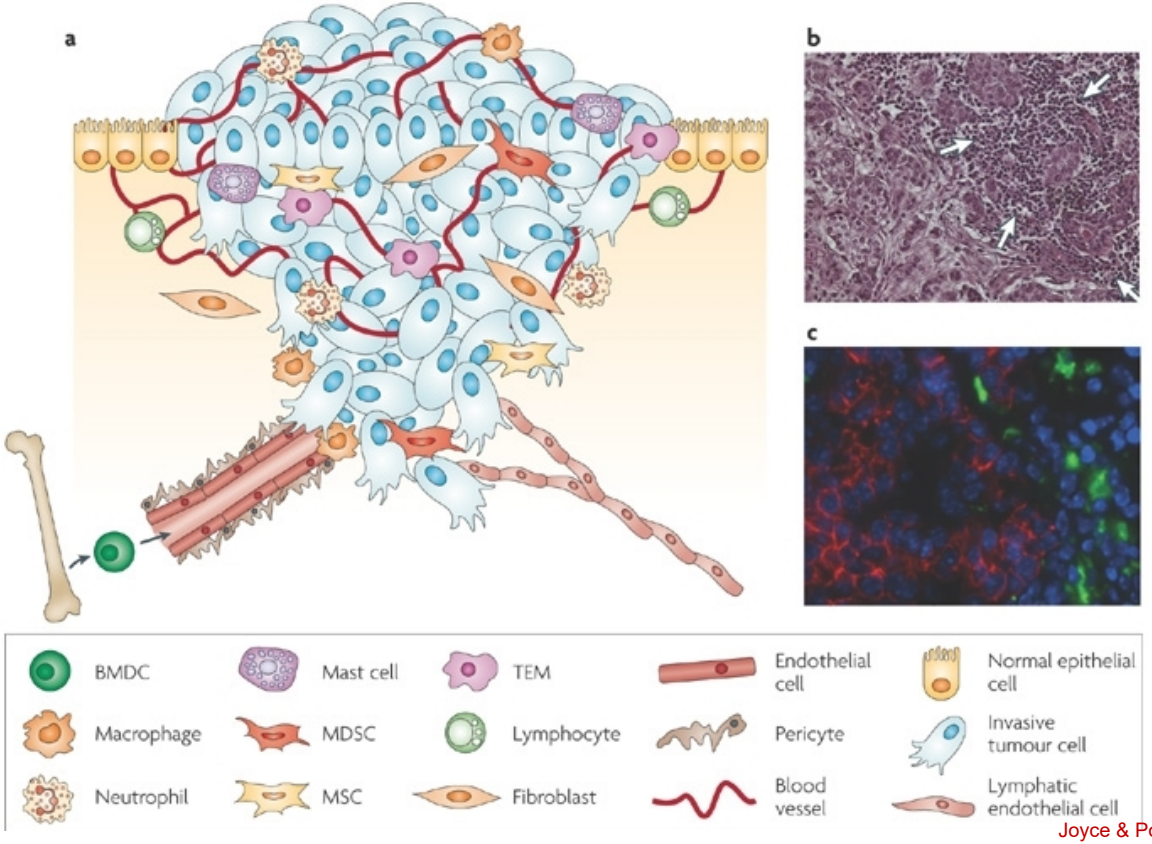
Tumors are Communities of Different Cell Types



Joyce & Pollard *Nature Rev Cancer* 9:239 (2009)

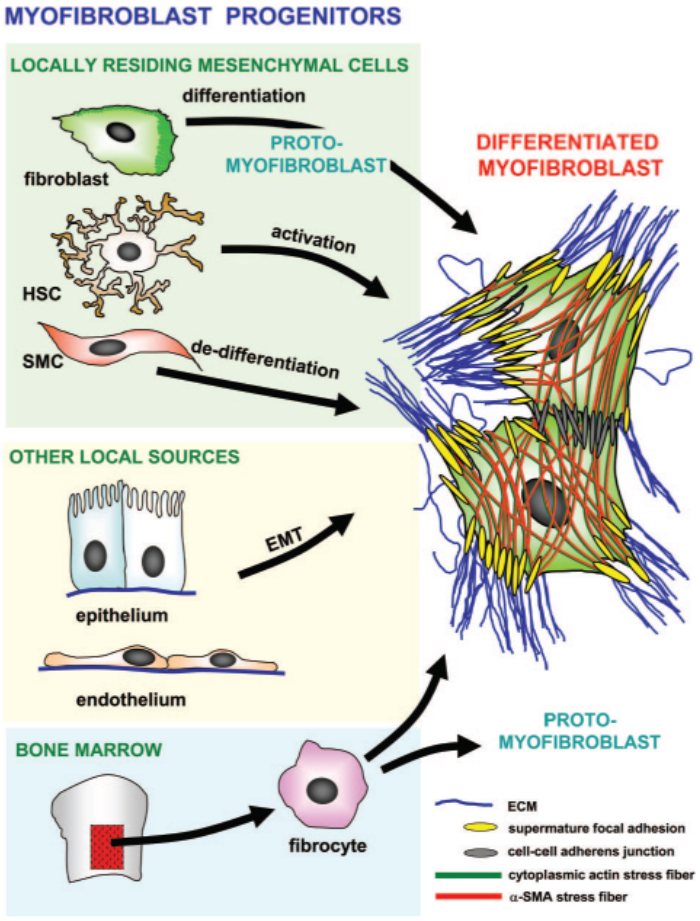
Perspectives

- 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

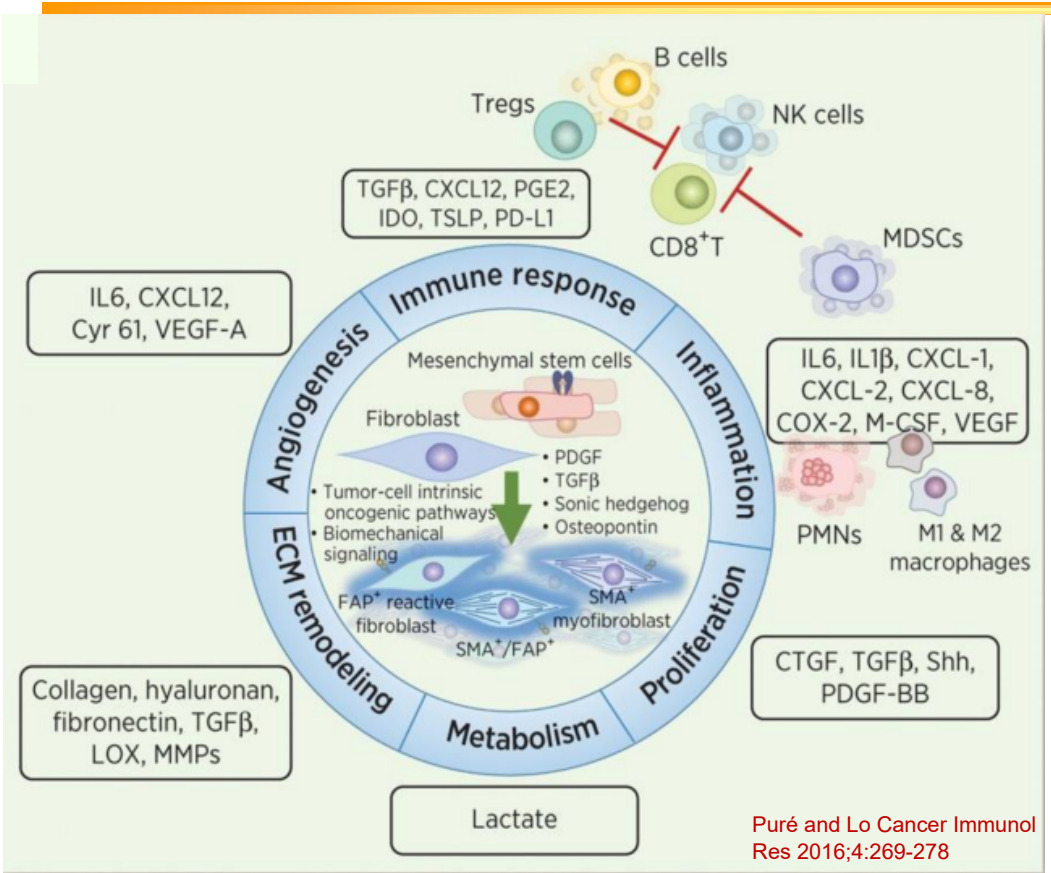
- Normal fibroblasts
  - Principal components of connective tissue, embedded within extracellular matrix (ECM)
  - Produce ECM/basement membrane, provide structure to tissue
  - Secrete matrix remodeling factors (matrix metalloproteinases)
  - Regulate epithelial differentiation and inflammation through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



Hinz et al. *Am J Pathol* 170:1807 (2007)

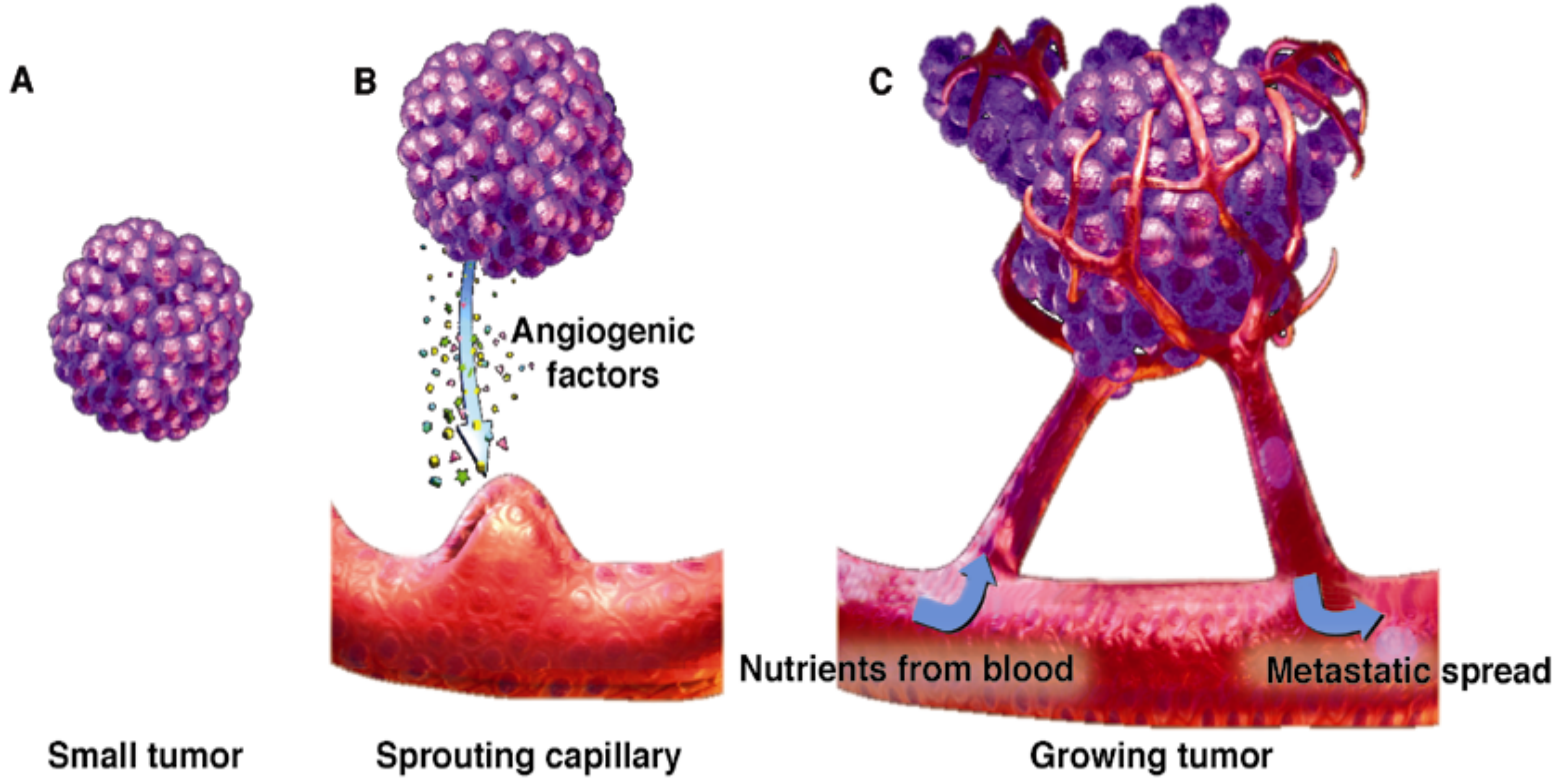
Products of Cancer Associated Fibroblasts (CAF)



Puré and Lo Cancer Immunol Res 2016;4:269-278

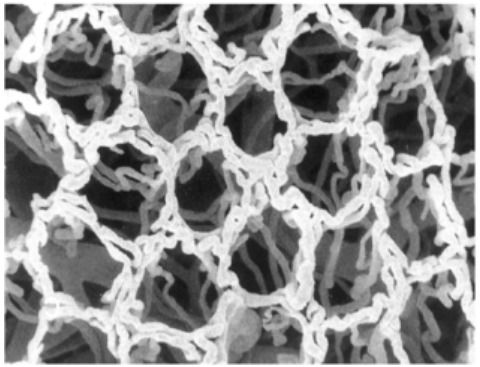
- Accumulate in and around tumors and secrete abundant collagen (reactive or desmoplastic stroma)
  - Traps immune cells
  - High interstitial pressure
- Produce factors that promote initial tumorigenesis of epithelial cells, support tumor invasiveness
- Promote angiogenesis
- Recruit and regulate immune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

Tumor Angiogenesis and Neovascularization

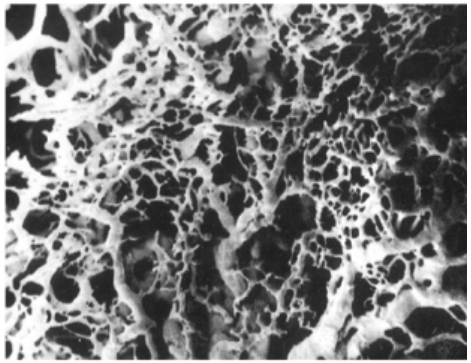


Disregulated Angiogenesis in Tumors

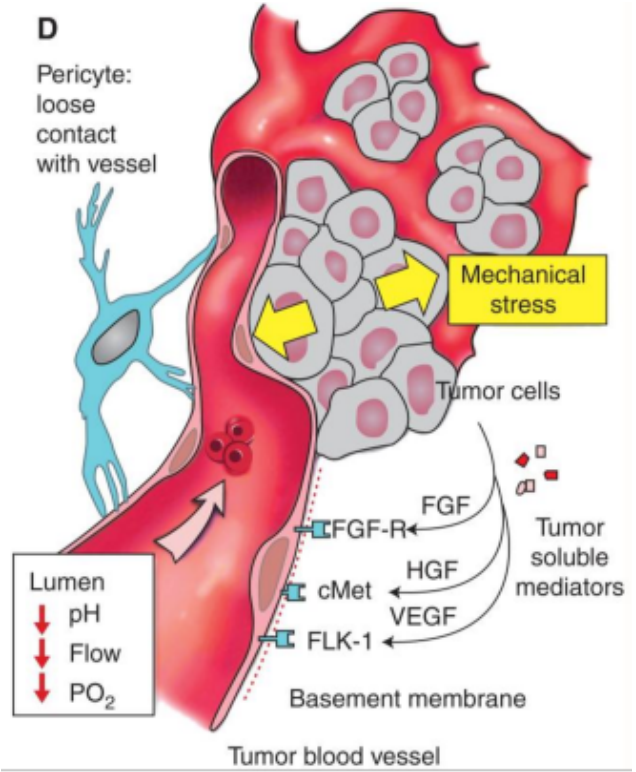
Normal colorectal mucosa



Nearby colorectal cancer

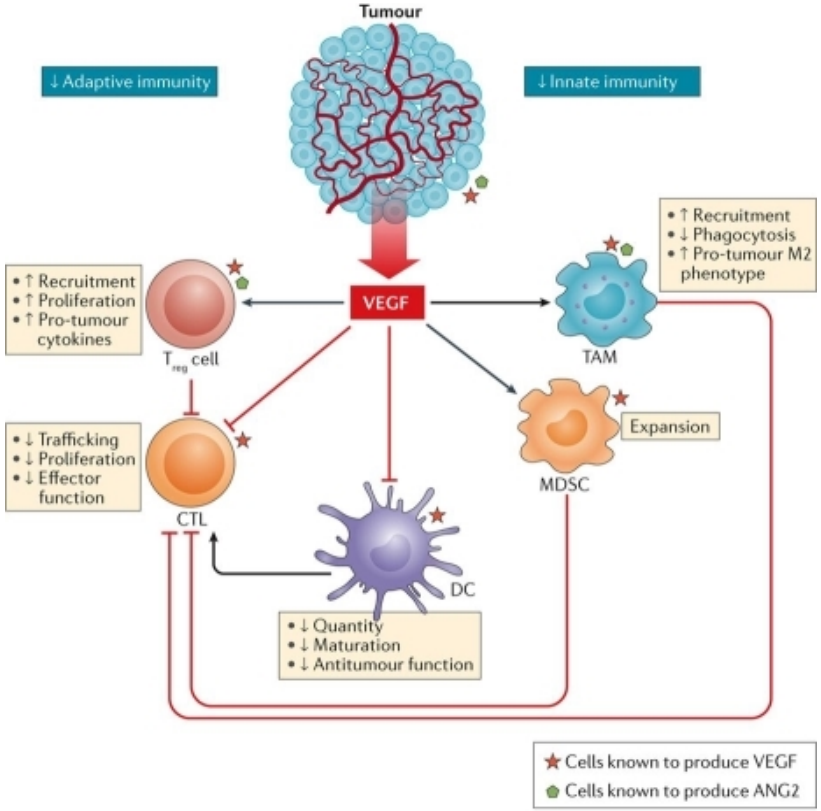


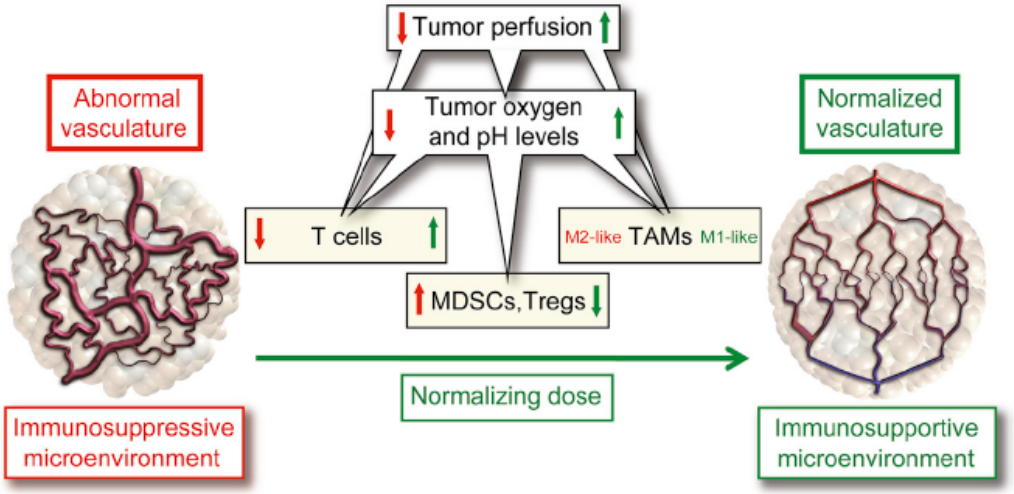
Konerding et al. In Molls and Vaupel, eds. *Blood Perfusion and Microenvironment of Human Tumors*, 2002



Aird *Cold Spring Harb Perspect Med* 2012:2:a006429

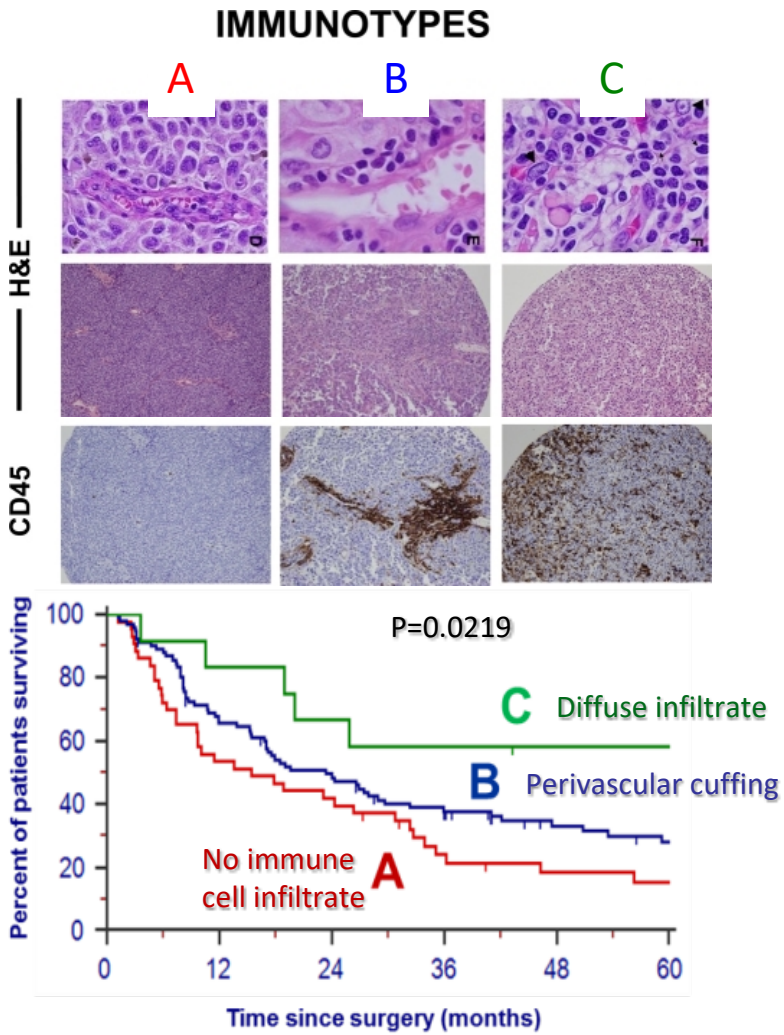
VEGF blockade: Relief of Immunosuppression





Fukuma et al. Nature Rev Clin Oncol 15:325 (2018)

Differences in Immune Cell Infiltrates Influence Tumor Control



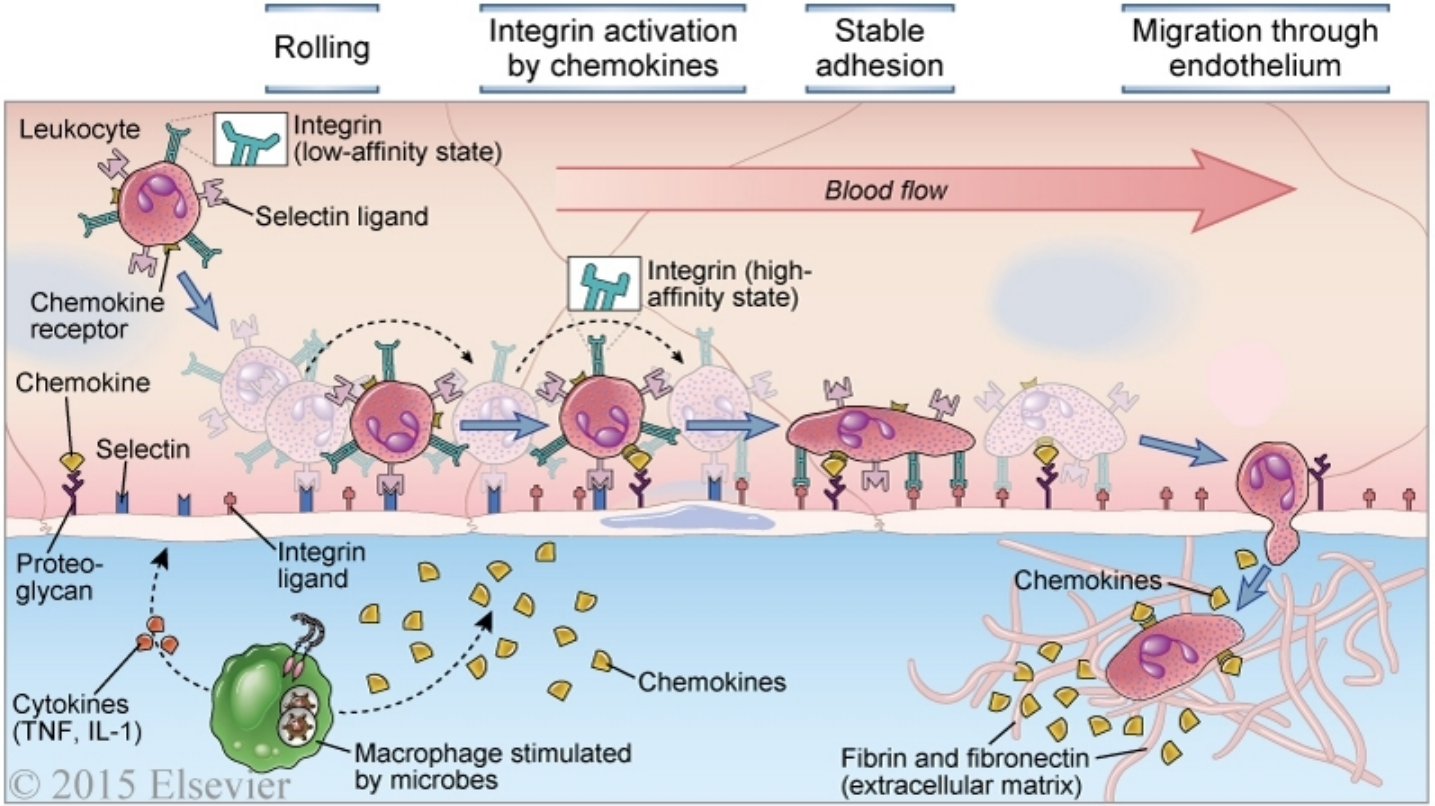
- Immunotypes correlate with “inflamed” gene signatures and “hot” and “cold” tumors
- Clinical responses to immunotherapy are associated with *pre-existing* infiltrates and inflamed gene signatures
- What underlies poor infiltration?

Erdag et al *Cancer Res* 72:1010 (2012)

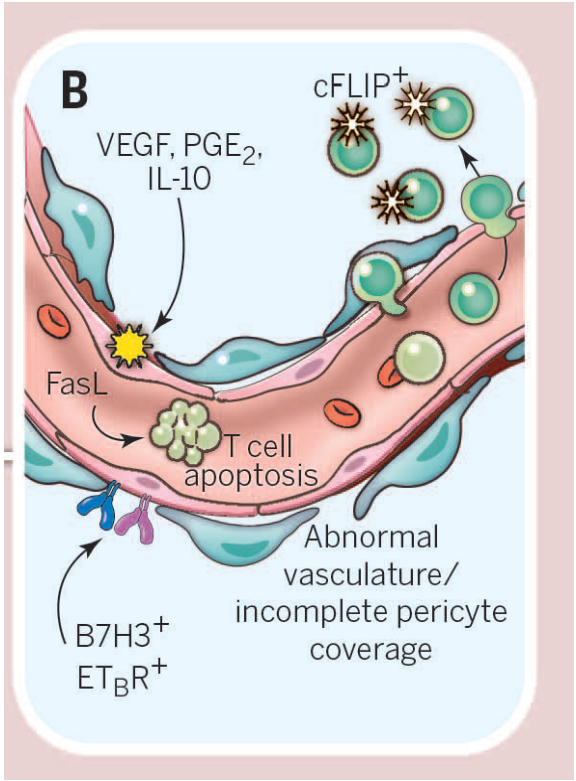
Determinants of Immune Cell Composition and Function in Tumors

- 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

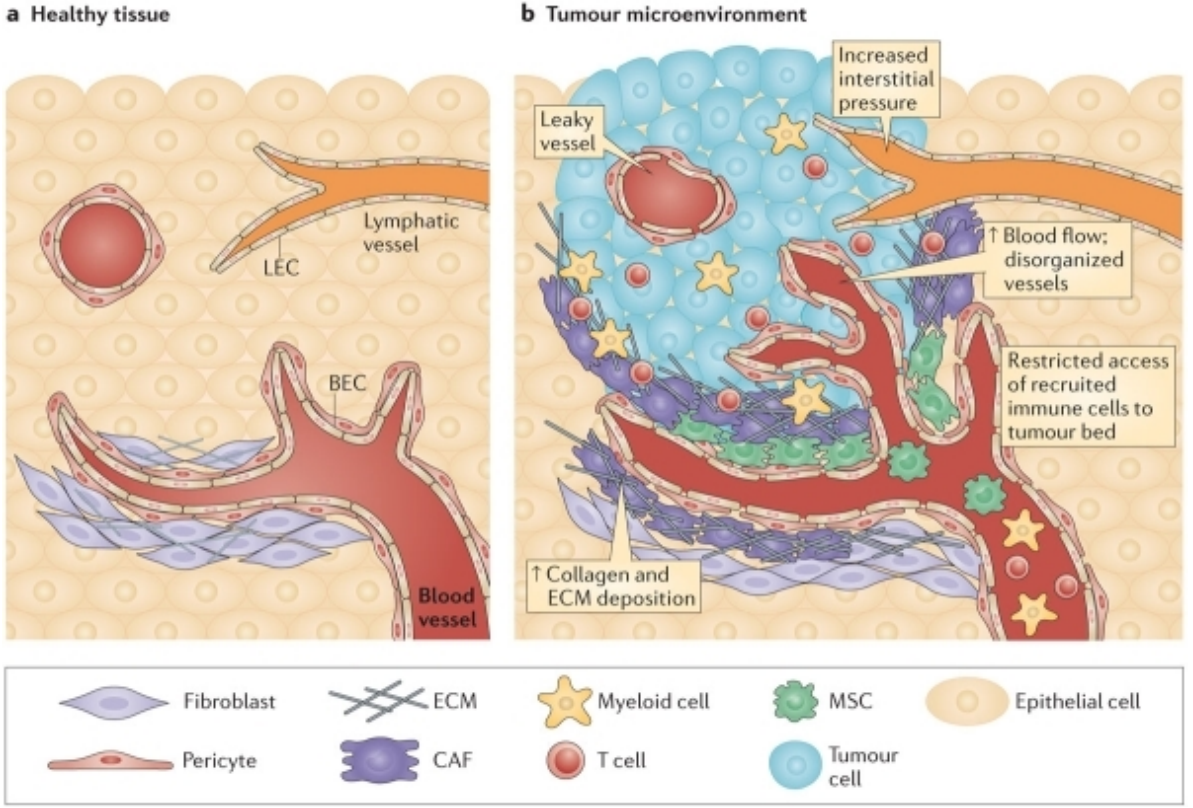


The Tumor Vasculature Forms Barriers to Immune Cell Entry

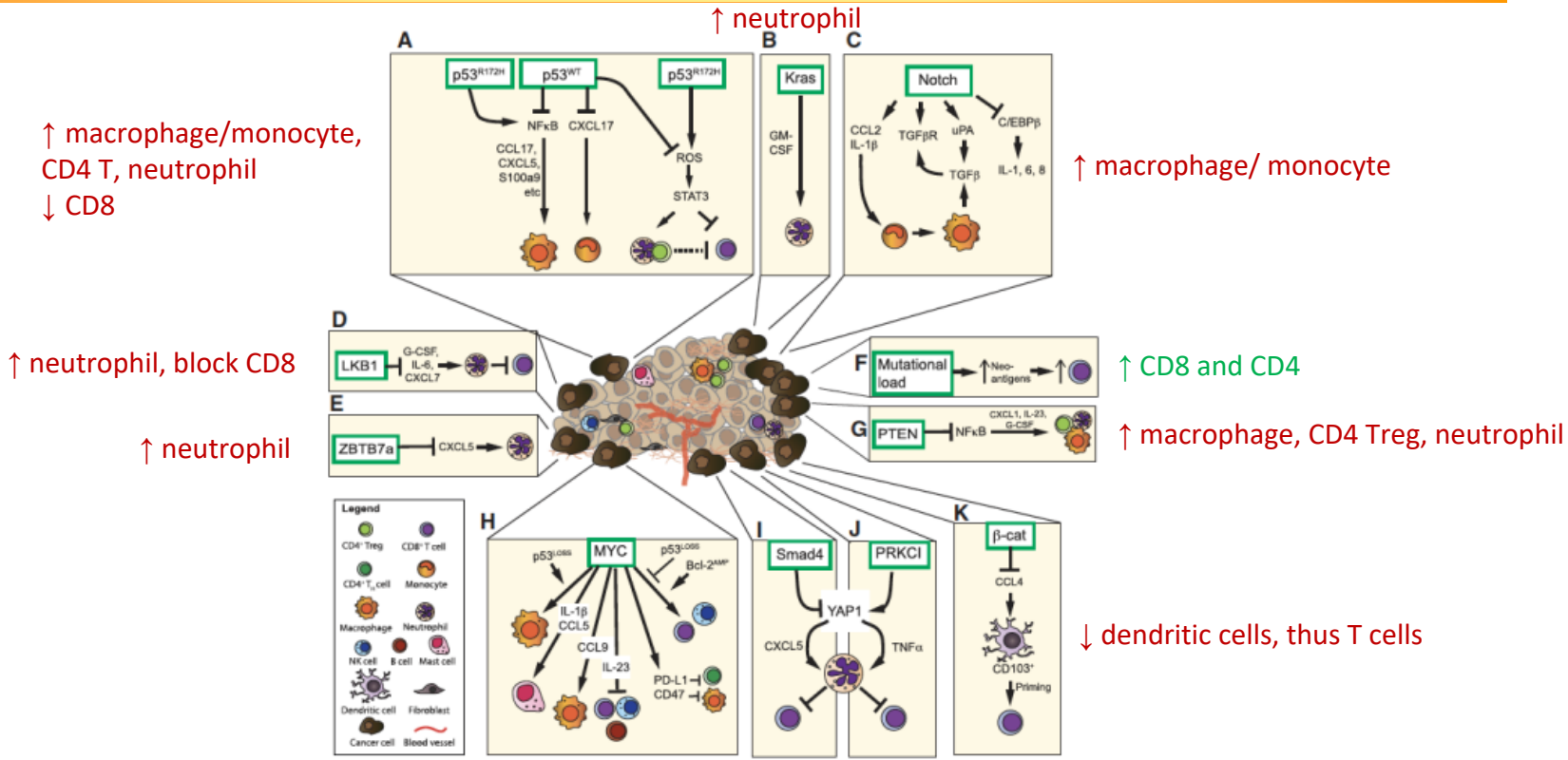


Joyce & Fearon. *Science* 348:74 (2015)

Stromal Organization and Impact on Tumor Perfusion and Immune Cell Entry

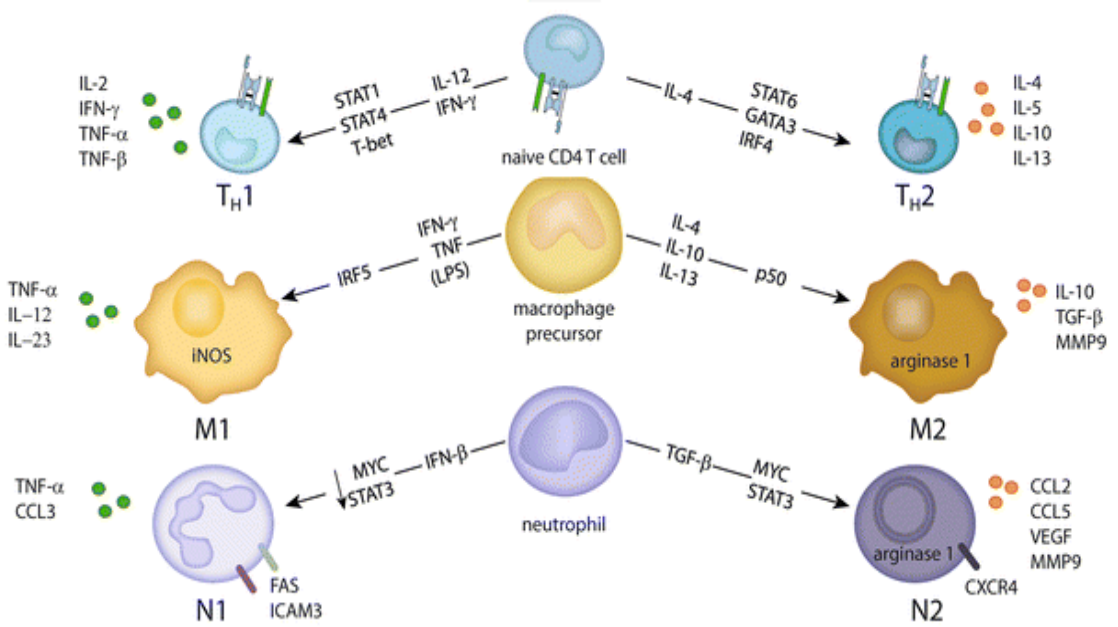


Cancer Cell-intrinsic Signaling Pathways Shape the Tumor Immune Landscape through Recruitment and Differentiation



Wellenstein & de Visser, Immunity 48:399 (2018)

Alternate Effector Cell Programming Of Adaptive And Innate Immune Cells

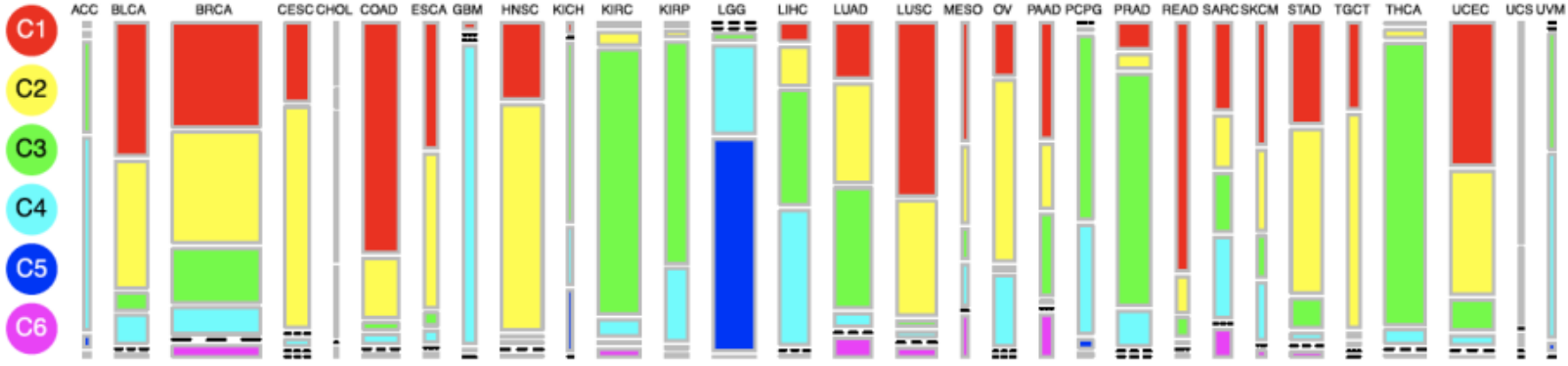


- Differentiation of adaptive and innate immune cells is driven by environmental cytokines
- Sources of these cytokines include tumor, stromal cells, and other immune cells
- System can be self-reinforcing over time

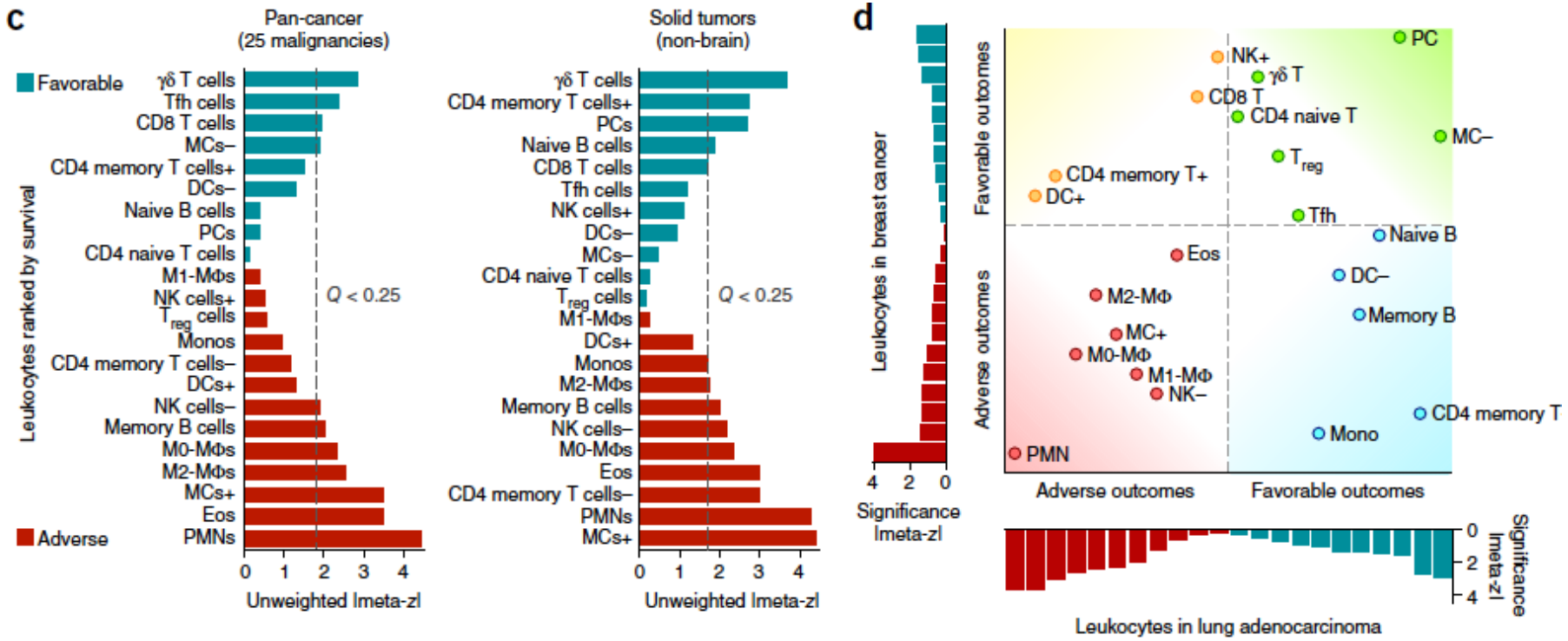
Gene sets identify common immune signatures among 10,000 tumors representing 33 cancer types

	Macrophage: lymphocyte	Th1:Th2	Proliferation	Intratumoral heterogeneity	Other
Wound healing	Balanced	Low	High	High	
IFN-γ dominant	Lowest	Lowest	High	Highest	Highest M1 and highest CD8 T cells
Inflammatory	Balanced	High	Low	Lowest	Highest Th17
Lymphocyte depleted	High	Minimal Th	Moderate	Moderate	
Immunologically quiet	Highest	Minimal Th	Low	Low	Highest M2
TGF-β dominant	High	Balanced	Moderate	Moderate	Highest TGF-β signature

Vesteinn et al. *Immunity* 48:812 (2018)

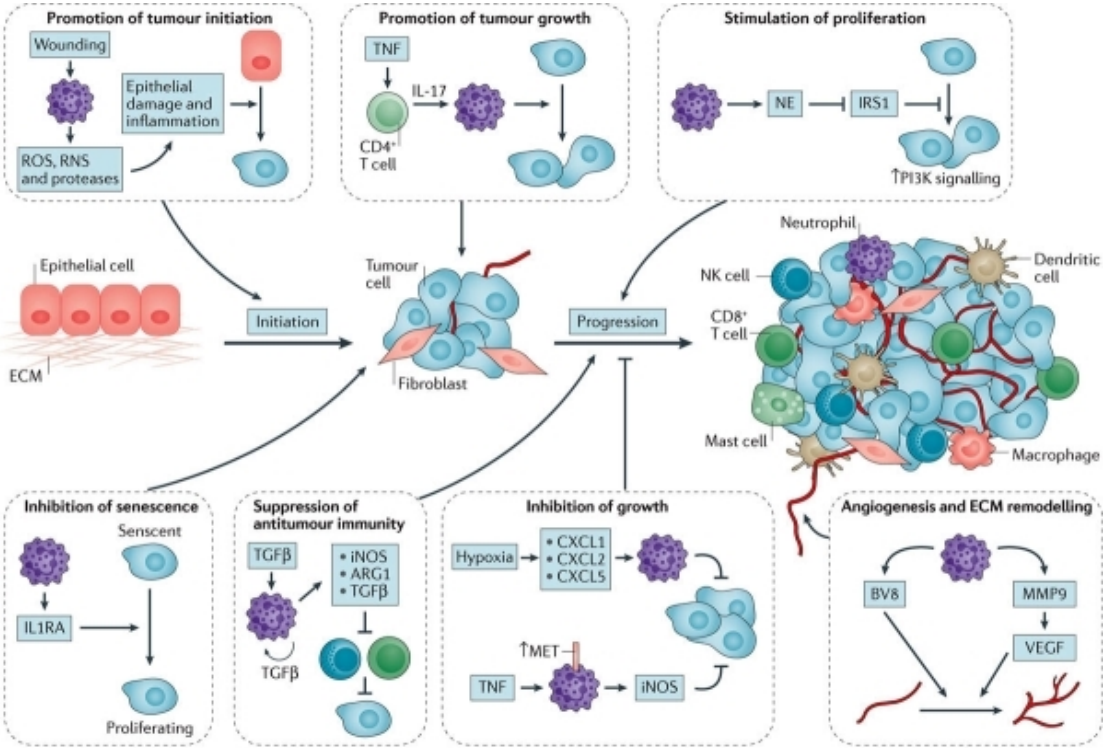


Prognostic Significance of Infiltrate Components Has Both General and Tumor Specific Aspects (18,000 tumors, 39 malignancies)



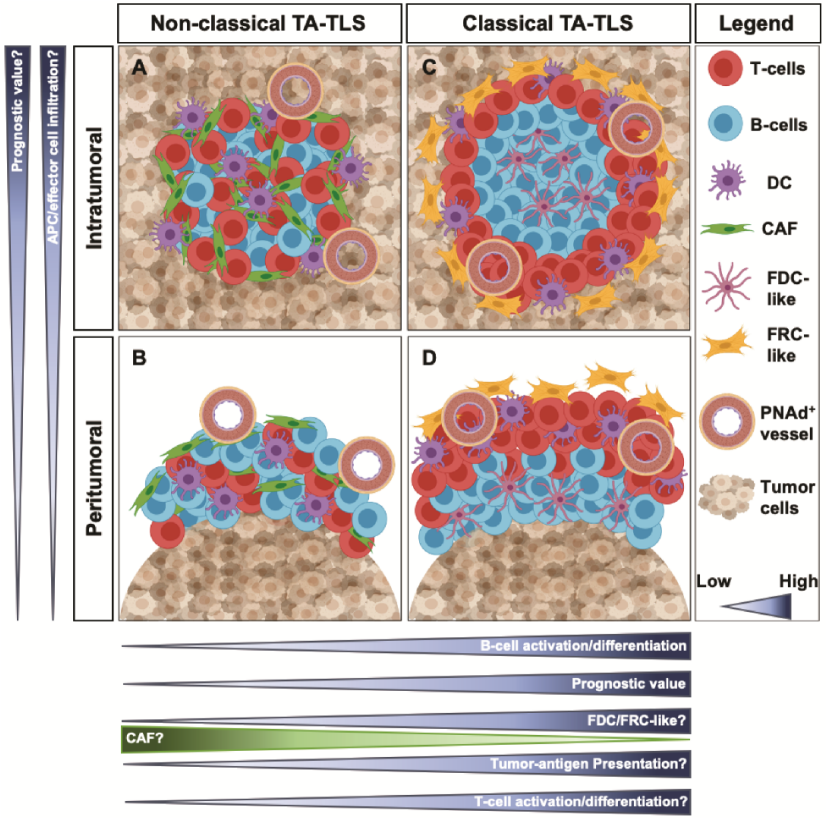
Gentles et al, *Nature Med* 21:938 (2015)

Activities of Tumor-Associated Neutrophils (TANs) Favor Tumor Initiation and Growth

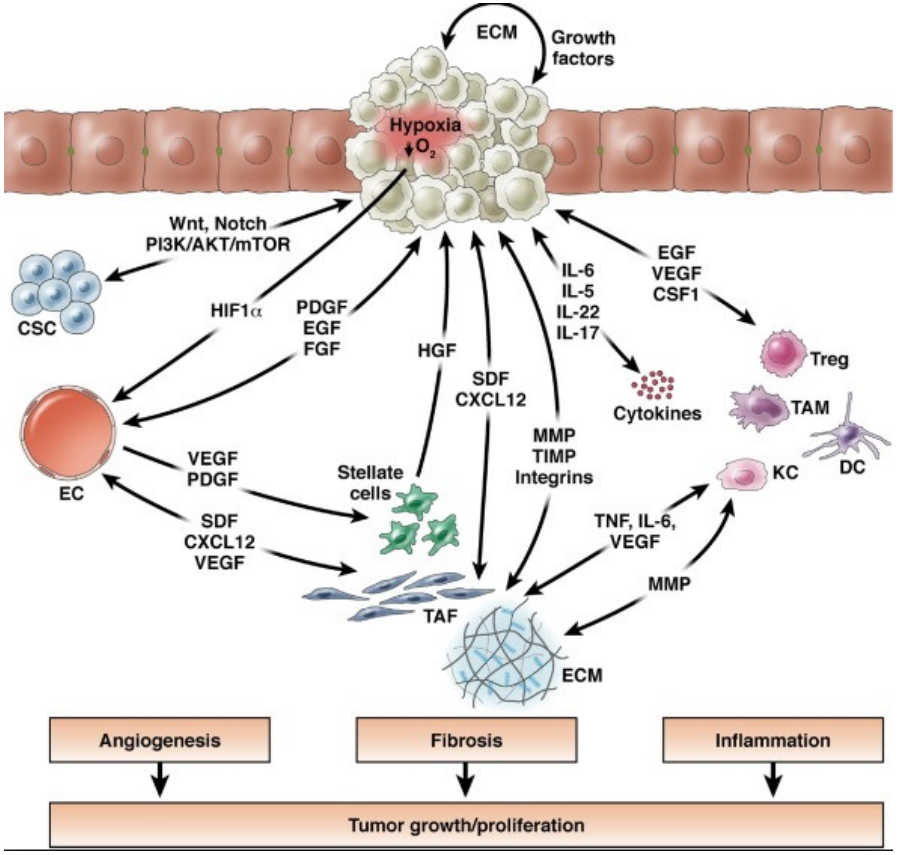


Coffelt et al, Nature Rev Cancer 16:431 (2016)

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