The Tumor Microenvironment (TME):

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- and –

I will not discuss off label use and/or investigational use in my presentation.
Properties of the TME are associated with prognosis

Type, Density, and Location of Immune Cells Within Human Colorectal Tumors Predict Clinical Outcome

Galon et al., Science, 2006

Specific recruitment of regulatory T cells in ovarian carcinoma fosters immune privilege and predicts reduced survival

Curiel et al., Nat. Med., 2004
The cancer immunoediting hypothesis: How tumor cells evade the immune system

Elimination
Tumor cells recognized by immune cells are killed

Equilibrium
Tumor cells are selected that can suppress immune activity

Escape
Edited tumor cells evade immune responses and continue growing

Schreiber, Old and Smyth, Science, 2011
Solid tumors are complex tissues with a broad diversity of cell types.

Representative HNSCC

dsDNA, Keratin, E-Cadherin, CD45, Vimentin, CD31

Maha Rahim, Kyle Jones
Advances in single cell analysis provide new perspectives on this diversity

High-Dimensional Cytometry (CyTOF, spectral flow)

Single-Cell Sequencing (RNA, ATAC, multi-modal)

Multiplexed Imaging (MIBI, IMC, CODEX, MERSCOPE)

Nieto et al., Genome Res., 2021
Different tumors have unique TMEs

Allen, Hiam et al., Nat. Med., 2020
Human TME archetypes defined by patterns of the cellular infiltrate

- Measuring the composition of immune cells in the tumor can classify into 12 groups
- These groups are independent of the cancer tissue-of-origin
- Associations with prognosis within the same tumor type

Combes and Samad et al., Cell, 2022
Defining T cell subsets in the TME

- Single-cell RNA-sequencing of tumor-infiltrating T cells
- Integrative analysis across 21 different tumor types
- The subsets of T cells are conserved across cancers, but significant variability across tumors

Zheng et al., Science, 2021
Many CD8 T cells in the TME are bystanders

- Most predicted neoantigens did not have detectable T cell responses
- T cells specific to unrelated viruses can be abundant
Tissue resident memory T cells ($T_{RM}$) and newly infiltrating CD8 T cells

- $T_{RM}$ express molecules that mediate retention in tumors
  - CD103
  - CD69
- Recent studies suggest recirculation into lymph nodes after activation
- Cell trafficking dynamics between TME and periphery is under active investigation.

Okla et al., J. Exp. Med., 2021
Tumors can evolve to evade CD8 T cell responses

- Mutations, silencing, or degradation of MHC class I
- Loss of immunogenic neoantigens
- Mutations in antigen processing machinery
- Mutations in IFNγ signaling pathway

Modified from Kalbasi and Ribas, Nat. Rev. Immunol., 2020
CD4 T cells in the TME

- Different CD4 T cell subsets have opposing functions in the TME
- Recent studies identified importance for effective immunotherapy
- Direct recognition (MHC class II+ tumors) and “helper” functions

CD4 T cells in the TME:
Opposing functions and cross-regulation

- Treg depletion enables cDC2 trafficking to the lymph node
- Antigen presentation drives a CD4 effector cell response
Dendritic cells: Functions in the TME and in the tdLN

- Antigen uptake in TME and presentation in lymph nodes
- New studies identifying roles for supporting T cell responses in the TME
Unique functions of dendritic cell subsets in the TME

- **cDC1s** specialized in antigen cross-presentation
- **cDC2s** are better at priming CD4 T cell responses
- **cDC3s** recently described but may be a subset of cDC2s
- **pDCs** can make type 1 IFN but mixed functions

Kvedaraite and Ginhoux, Sci. Immunol., 2022
NK cells can drive a cDC1-CD8 T cell circuit in the TME

Bottcher et al., Cell, 2018; Barry et al., Cancer Cell, 2018

Figure from review: Peterson and Barry, Front. Immunol., 2021
Macrophages in the TME: The M1/M2 Paradigm

- Classically defined from in vitro polarization studies
- Extrapolation to in vivo immune responses

Wu et al., Front. Immunol., 2020
Macrophage ontogeny: tissue- or bone marrow-derived?

- Macrophages can be replenished from bone marrow-derived monocytes

- Early tissue macrophages are derived from embryonic sources

- The balance of these sources of cells is highly tissue-specific

Ginhoux and Guilliams, Immunity, 2016
Revisiting Macrophages in the TME:
A diversity of cell states

Wagner et al., Cell, 2019
Neutrophils in the TME

- Inflammatory functions can be pro- or anti-tumor
- Cytokines can promote tumor cell growth
- Other mechanisms can be tumoricidal
- Suppression of T cell responses
Fibroblasts in the TME

- Substantial focus on tumor-promoting properties of cancer-associated fibroblasts (CAFs)
- Data suggest that fibroblasts can play anti-tumor roles in some contexts
Dissecting fibroblast diversity in the TME

Buechler and Pradhan et al., Nature, 2021;

Dominguez et al., Cancer Discov., 2020
Soluble factors in the TME

• Complex cytokine networks mediate cell-cell communication and migration in the TME

• Shape the polarization, differentiation and effector function of each cell type

Abousaway et al., Nanotheranostics, 2021
The metabolic environment of the TME

- **Hypoxia**
  - Induces HIF1α

- **Nutrient poor**
  - e.g., glucose consumption, arginine and tryptophan depletion

- **Immunomodulatory metabolites**
  - e.g., kynurenine, adenosine
The spatial organization of the TME is associated with prognosis

*Triple-negative breast cancer:*
TGFβ is a regulator of the “excluded” phenotype

Mariathasan et al., Nature, 2018
The spatial organization of the TME is associated with prognosis.

Keren et al., Cell, 2018
Cellular hubs with coordinated activity in the TME

Pelka et al., Cell, 2021
Tertiary lymphoid structures in the TME

- TLS are lymph node-like structures that form ectopically in inflamed tissues
- Variable in their composition, localization and maturation state
- Poorly modeled in mice

Schumacher and Thommen, Science, 2022
Tertiary lymphoid structures associate with response to checkpoint inhibitor immunotherapy

Cabrita et al., Nature, 2020 (figures)
Helmink et al., Nature, 2020
Petitprez et al., Nature, 2020
The “Cancer Immunity” cycle connects the TME with the rest of the body

Chen and Mellman, Immunity, 2013
The “Cancer Immunity” cycle connects the TME with the rest of the body

Chen and Mellman, *Immunity*, 2013
The TME communicates with the rest of the body

- Different mouse models of cancer change the peripheral immune system in distinct ways
- Some have dramatic effects across all tissues, while some predominantly impact the tumor-draining lymph node

Allen, Hiam et al., Nat. Med., 2020
Tumors can alter immune cell development in the bone marrow

Casbon et al., PNAS, 2015; Meyer et al., 2018, Nat. Comm.
Figure from review: Hiam-Galvez et al., Nat. Rev. Cancer, 2021
Tumors can alter new immune responses

Allen, Hiam et al., Nat. Med., 2020

- Mice with established cancers make poor T cell response to new stimuli, such as pathogens.
Tumors can alter new immune responses

Allen, Hiam et al., Nat. Med., 2020
Pre-metastatic niches create a hospitable environment for tumor cells to disseminate

- Before tumor cells metastasize, targeted tissues begin to change

- Infiltration of myeloid cells that drive inflammation and suppress T cells

- Remodeling of ECM and vasculature

Liu and Cao, Cancer Cell, 2016
Questions?