Tumor Microenvironment and Immune Suppression

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Hallmarks of Cancer: The Next Generation
Role of the Immune System

Douglas Hanahan, Robert A. Weinberg, Cell, 2011, 244: 646 - 674

Immune Suppression in the TME
The Cancer-Immunity Cycle and Tumor Microenvironment (TME)

1. Release of cancer cell antigens (cancer cell death)
2. Cancer antigen presentation (dendritic cells/ APCs)
3. Priming and activation (APCs & T cells)
4. Trafficking of T cells to tumors (CTLs)
5. Infiltration of T cells into tumors (CTLs, endothelial cells)
6. Recognition of cancer cells by T cells (CTLs, cancer cells)
7. Killing of cancer cells (immune and cancer cells)
Cellular Infiltrates Within the TME

Stromal Cells
- Tumor-associated Fibroblasts
- Endothelial Cells
- Pericytes

Effector T cells
- Cytotoxic T cells: CTL
- CD4+ T cells

Others
- Granulocytes
- Eosinophils
- Mast cells
- Platelets

Immunoregulatory Pathways Inhibit antigen-specific T Cell Function during Chronic antigen exposure

**Inhibitory receptors**
- PD-1, CTLA-4, LAG-3
- 2B4, CD160, etc
- Tim-3

**Immunoregulatory cytokines**
- IL-10, TGF-β, others?
- IDO, arginase

**Suppressive/Regulatory Cells**
- Natural Treg
- Adaptive Treg
- CD8 Treg?
- Myeloid suppressors?

**Tumor Cells**
- Altered antigen-presenting cell
  - Dendritic cell loss or dysfunction
  - Nonprofessional antigen-presenting cell

**CTL**

**Dendritic cell**
Regulatory T cells: Tregs

- Natural and Induced Tregs (tumor antigen-specific Tregs)
- Can produce IL-10 and TGF-β
- Markers:
  - Transcription factor forkhead box Foxp3,
  - CTLA-4, GITR, CD39, Tim-3, VEGFR...
- Suppress T and NK functions through multiple mechanisms (IL-2 deprivation, IL-10 and TGF-b secretion, granzyme-dependent cytolysis, adenosine production, DC crosstalk).
- Targeting Tregs: anti-CD25, anti-CTLA-4 (ADCC), anti-GITR, TKis
**Myelosuppressive Dendritic Cells: MDSCs**

- Immature dendritic cells
- Lin-, HLA-DR-, CD33+ cells?
- Suppress T cell
  - though cell-to-cell contact
  - Produce NO (nitration and nitrolysisation of aa) and arginase 1 (arginine depletion)
- IL-10 and reactive oxygen species production
- Favor Treg differentiation
Tumor cells and Immune Escape

- Loss of peptide-MHC complexe expression with downregulation of antigen processing machinery
- Express surface molecules that can kill CTLs: FasL, Trail
- Secrete immunosuppressive cytokines/molecules promoting T cell dysfunction: IL-10, TGF-β, IDO, TDO, adenosine, PGE2, galectin 3
- Hypoxia and tumor lactic acidosis can suppress CTLs
- They can upregulate inhibitory receptor ligands including PD-L1, HVEM, galectin 9 and HLA-DR.
Other Tumor-infiltrating Cells

- **Tumor-Associated Macrophages**
  - Secrete immunosuppressive factors
  - Recruit Tregs via CCL2
  - Produce Arginase 1 and iNOS

- **Mast cells recruit MDSCS and Tregs**

- **Cancer-Associated Fibroblasts**
  - Recruit MDSCS
  - Produce TGF-β

- **Abnormal tumor vasculature** with absence of high endothelial veinules limit mass transit of CTLs and represent an active barrier to tumor-reactive T cells
  - May express FasL, Trail, PD-L1, IL-10, TGF-β....
  - Maintained by tumor cells through paracrine mechanisms
  - Targeting tumor microvasculature: VEGF blockade
Immunoregulatory Pathways Inhibit T Cell survival and function in the TME

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Immunosuppressive Effects of IDO in the TME

**a**
- **IDO^+ tumour cell**
- Tryptophan
- IDO1
- Kynurenines
- NK cell
- Cytotoxic T cell
- Downregulation of activating NK receptors
- Apoptosis
- Cell cycle arrest
- Decreased activation
- Apoptosis

**b**
- Cytotoxic T cell
- Cell cycle arrest
- Downregulation of TCR ζ-chain expression
- Apoptosis
- Areactivity
- Naive CD4^+ T cell
- Cell cycle arrest
- Apoptosis
- Areactivity
- Conversion into T_{reg} cell
- Decreased production of IFNγ
- Increased production of IL-4
- Increased production of IL-13
- Invariant NK cell
- Bystander suppression
- Plasma cell
- Decreased antibody production
- Apoptosis

*Nature Reviews Cancer*
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** CTL **
PD-1/B7-H1 (PD-L1) pathway

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CCR Focus
T Cell Dysfunction/Exhaustion Upon Chronic Antigen Exposure

Highly polyfunctional memory T cells

**CHARACTERISTICS**

<table>
<thead>
<tr>
<th>IFN-γ</th>
<th>TNF</th>
<th>CTL</th>
<th>IL-2</th>
<th>Proliferative potential</th>
<th>Apoptosis</th>
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- e.g., T cells specific for vaccinia virus, yellow fever vaccine, acute LCMV

Hierarchical loss of T cell function during chronic infections

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<td>Apoptotic T cell</td>
<td>+/−</td>
<td>−</td>
<td>−</td>
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</tbody>
</table>
T Cell Targets for Immunoregulatory Antibody Therapy

I Mellman et al. Nature 480, 480-489 (2011)
Multiple co-stimulatory and inhibitory interactions regulate T cell responses.
Stimulatory and Inhibitory Factors in the Cancer-Immunity Cycle and Tumor Microenvironment

Cytotoxic T cell (CTL) Cell Death or CTL Dysfunction
Manipulating the TME with Potent Immunotherapies of Cancer

Daniel S. Chen and Ira Mellman, Immunity, 2013, 39, 2013: 1 - 10
Manipulating the TME with Therapeutic Targeting of the Hallmarks of Cancer

- EGFR inhibitors
- Cyclin-dependent kinase inhibitors
- Aerobic glycolysis inhibitors
- Sustaining proliferative signaling
- Evading growth suppressors
- Deregulating cellular energetics
- Avoiding immune destruction
- Genomic instability & mutation
- Enabling replicative immortality
- Resisting cell death
- Inducing angiogenesis
- Activating invasion & metastasis
- Tumor-promoting inflammation
- Telomerase inhibitors
- Selective anti-inflammatory drugs

Immunotherapy
Question 1

What receptor in the list below is not an inhibitory receptor expressed by T cells in the TME?

- PD-1?
- BTL-A
- Tim-3
- LAG-3
- CD28
Please indicate the wrong answer:
Dysfunctional/exhausted CTLs in the TME
• Upregulate PD-1 expression
• Loose their capacity to produce cytokines
• Loose their capacity to proliferate
• Occur in the TME upon chronic antigen stimulation
• Can potently lyse tumor cells
Question 3

Please indicate the wrong answer:

Tregs in the TME

• Express Foxp3
• Upregulate CD39
• Suppress T cell functions
• Do not express CTLA-4
Question 4

Please indicate the wrong answer below
Tumor cells in the TME may escape T cell destruction by the following mechanisms:
• Loss peptide-MHC complex expression with downregulation of antigen processing machinery
• PD-L1 expression
• Production of IL-10, TGF-β and galectin 3
• Expressing MHC class I molecules