Principles of tumor immunity

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Lecture outline

• Role of the immune system in defending against cancers
  • Initiating anti-tumor immune responses

• Tumor antigens

• Immune evasion by cancers

• Immune cells that promote cancers

• New therapeutic approaches
General principles

• The immune system recognizes and reacts against cancers (immune surveillance)

• The immune response against tumors is often dominated by regulation or tolerance
  – Evasion of host immunity is one of the hallmarks of cancer (Hanahan and Weinberg Cell 144:646, 2011)

• Some immune responses promote cancer growth

• Immunotherapies have revolutionized the care of cancer patients
T cell responses to tumors
Initiating CD8+ T-cell responses to tumors

• To initiate T cell responses, dendritic cells capture antigens from site of production and take the antigens to secondary lymphoid organs (e.g., lymph nodes) through which naïve T cells recirculate
  – DCs are located in the correct place (tissues where tumors grow) and migrate to the correct place (co-localize with naïve T cells)
  – Are antitumor responses also initiated in the tumor environment?
Initiating CD8+ T-cell responses to tumors

- CD8+ T cells recognize antigens present in the cytosol of cells → proteasomal processing and presentation by class I MHC

- But antigens captured by DCs are ingested into vesicles (the common pathway of class II MHC-associated antigen presentation)

- Specialized DCs transfer antigens from vesicles into the cytosol: the pathway of cross-presentation
  - Need to optimize this pathway for promoting anti-tumor immunity
Cross-presentation of tumor antigens

Type 1 conventional DCs (cDC1) are the most potent cross-presenting APCs. Once functional CTLs are generated, they can kill tumor cells producing tumor antigens in the cytosol (peptides presented on class I MHC).
T cell infiltrate in tumor predicts survival

Analysis of T cell infiltrate in colon cancers

In some cancers, “immunoscore” is as good at predicting outcome as histologic grade and clinical stage of tumor
T cell phenotypes that predict better survival

Analysis of 124 published articles on correlation of T cell subsets and prognosis of 20 cancer types

Prognostic significance of other immune cell types

- **B cells**
  - No prognosis: 19
  - Poor prognosis: 16
  - Good prognosis: 39

- **NK cells**
  - No prognosis: 24
  - Poor prognosis: 5
  - Good prognosis: 38

- **Dendritic cells**
  - No prognosis: 21
  - Poor prognosis: 123
  - Good prognosis: 19
Types of tumor antigens

- **Neoantigens**
  - Generated by mutations unrelated to tumorigenesis
  - Examples: Random passenger mutations in common cancers

- **Aberrantly expressed normal proteins**
  - Example: Cancer testis antigens in many tumors

- **Amplified genes/overexpressed normal proteins**
  - Example: HER2/neu in breast cancers

- **Protein antigens expressed by an oncogenic virus**
  - Example: EBV nuclear antigens in EBV+ Lymphomas

- **Normal proteins expressed by tissue of tumor origin**
  - Example: Tyrosinase in melanomas; CD20 on B cell lymphomas
Types of tumor antigens

• Tumor antigens:
  – Must be tumor-specific (not in normal cells)
  – Must be capable of stimulating CD8 T cell responses in patients

• Most tumor antigens that elicit immune responses are neoantigens
  – Produced by mutated genes that are usually not involved in oncogenesis and reflect environmental carcinogen exposure and genomic instability (passenger mutations)
  – Cytosolic proteins so presented by class I MHC
  – Mutations have to be in MHC-binding epitopes
  – Not present normally, so no tolerance
Other tumor antigens

• **Viral proteins**
  - Only in tumors caused by oncogenic viruses (HPV, EBV)

• **Unmutated proteins (tyrosinase, cancer-testis antigens)**
  - Derepressed (because of epigenetic changes) or over-expressed (gene amplification)

• **Cell surface antigens are often differentiation antigens that are also present in normal cells**
  - Major challenge for CAR-T therapy for solid tumors
Identification of tumor neoantigens

1. Obtain tumor material
2. Identify tumor-specific mutations within expressed genes
   - Next gen sequencing and/or RNA-seq
3. Filter in silico
   - Identification of HLA-binding peptides
   - Filter by MS analysis
4. Assess T cell recognition
   - MHC-peptide multimer and/or functional assays

Ton N. Schumacher, and Robert D. Schreiber Science 2015;348:69-74
From M. DuPage, UC-Berkeley
Cell types that may promote cancers

- **Foxp3+ regulatory T cells (Tregs)**
  - Variable results in humans

- **Alternatively activated (M2) macrophages**
  - Mechanism of action?

- **Myeloid-derived suppressor cells (MDSC)**
  - Poorly defined markers

- **B cells**
  - In experimental models only
Manipulating the tumor microenvironment

- **Goal:** stimulate protective (anti-tumor) cells and disable or eliminate pro-tumor cells

- **Challenges:**
  - Heterogeneity (TME varies in the same tumor type in different individuals and sometimes at different sites in the same patient)
  - Lack of markers for cell type-specific deletion (e.g., MDSCs)
  - Systemic depletion can cause serious adverse effects (e.g., Tregs)
Tumor immune evasion mechanisms

• Loss of MHC and proteins involved in antigen processing
  – Mutations in β2-microglobulin

• T cell exhaustion
  – Repeated stimulation of T cells

• Expression of PD-L1
  – PD-L1 is also induced on myeloid cells in the tumor microenvironment

• Secretion of immunosuppressive molecules
  – TGF-β, others
The same principle applies to stimulation by tumors
Harnessing the immune system to combat cancer

Cancer vaccines

Antigen presentation

Tumor cell

T cell

Infuse into patient

Adoptive cellular therapy

Dendritic cell

Blockade of checkpoint molecules

Vanneman and Dranoff, Nat Rev Can, 2012
Cancer vaccines

• Which antigens?

• How to induce potent CTL responses?

• Avoiding immune evasion by tumors

• Overcoming tumor-induced immune regulation (e.g., checkpoints)

• Changes in tumor antigens with clonal evolution
Adoptive cellular therapy

• Limiting factor is frequency of tumor-specific T cells
  – Initial attempts with cells from patients had mixed success (too few tumor-specific T cells?)
  – Rationale of CAR-T

• Challenges with CAR-T therapy
  – Toxicity (strong T cell activation)
  – Immune evasion mechanisms of tumors
  – T cell exhaustion
  – Unable to target tumor-specific antigen for solid tumors
Checkpoint blockade therapy

- Based on defining checkpoints (brakes) in immune responses
  - CTLA-4: removes B7, competitive inhibitor of CD28
  - PD-1: signaling inhibitor
  - Others: not well defined
## Functions of CTLA-4 and PD-1

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<tr>
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<th>CTLA-4</th>
<th>PD-1</th>
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<tr>
<td><strong>Major site of action</strong></td>
<td>Lymphoid organs</td>
<td>Peripheral tissues</td>
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<tr>
<td><strong>Stage of immune response suppressed</strong></td>
<td>Induction</td>
<td>Effector phase</td>
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<tr>
<td><strong>Mechanism of action</strong></td>
<td>Removes B7, out-competes CD28</td>
<td>Signaling inhibitor of CD28 and TCR</td>
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<td><strong>Cell type suppressed</strong></td>
<td>CD4+ &gt; CD8+</td>
<td>CD8+ &gt; CD4+</td>
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Challenges in checkpoint blockade

• Effective in only a minority of patients
  – Combination strategies to increase the frequency of responders; so far, only successful combination is blocking CTLA-4 and PD-1

• Toxicity: autoimmune reactions
  – Cannot separate anti-tumor effect from autoimmunity

• Lack of predictive biomarkers
  – Which patients will respond?