Tumor Immunity and Immunotherapy

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Lecture Outline

- Evidence for tumor immunity
- Types of tumor antigens
- Generation of anti-tumor T cell responses
- Tumor immune evasion mechanisms
- Tumor immunotherapy
General principles

• The immune system recognizes and reacts against cancers

• The immune response against tumors is often dominated by regulation or tolerance
  – Evasion of host immunity is one of the hallmarks of cancer

• Some immune responses promote cancer growth

• Defining the immune response against cancers will help in developing new immunotherapies
T lymphocytes infiltrate tumors and their presence improves prognosis.

Rodent Work in Tumor Immunology
Established Importance of T Cells


Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2015
Cancer Patients' T cells Respond to Tumor Specific Antigens Derived from Mutated Proteins (neoantigens) and Oncogenic Viruses

Normal self peptides displayed on MHC; no responding T cells due to tolerance

Mutation-generated neoantigens; T cell response (mostly random, unrelated to malignant phenotype)

Peptide from a protein encoded by an oncogenic virus; T cell response

Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017
Cancer Patients’ T cells Respond to Unmutated Protein Antigens that are Aberrantly Expressed by Tumor Cells

De-repressed expression (e.g. cancer-testis antigens)

Overexpression of oncogenic protein due to gene amplification (e.g. HER2/nu in breast CA)

Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017
Cancer Patients’ T Cells Respond to Unmutated Protein Antigens Typical of Cell Type of Origin

Increased number of cells expressing tissue specific protein breaks tolerance (e.g. tyrosinase in melanomas)

Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017
Steps in the Generation of an Anti-Tumor CD8+ T Cell Response

Cell injury/death at tumor site will generate DAMPs that activate DCs

CD4+ T cell responses will also occur; most evidence indicates CTLs are the most important effectors

Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017
Cross-presentation of tumor antigens
Tumors Have Many Ways of Evading the Immune System


Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017
The Immunosuppressive Tumor Microenvironment

Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017
The history of cancer immunotherapy: from empirical approaches to rational, science-based therapies
Harnessing the Immune System to Fight Cancer

Vanneman and Dranoff, Nat Rev Can, 2012
Dendritic Cell Vaccines Against Tumors

Dendritic cells pulsed with tumor antigens

Vaccinate with tumor-antigen pulsed dendritic cell

Tumor antigen presentation to patient’s tumor-specific T cells

CD8+ T cell

Activation of tumor-specific T cells and killing of tumor cells
Identification of tumor neoantigens to use for tumor vaccines

Next gen sequencing and/or RNA-seq

Identification of HLA-binding peptides

Validate that patients mount T cell responses to these peptides with MHC-peptide multimer and/or functional assays

Ton N. Schumacher, and Robert D. Schreiber Science 2015;348:69-74
Checkpoint Blockade Immunotherapy

A. Induction of anti-tumor immune response in lymph node

- Tumor peptide-MHC
- Tumor peptide-MHC
- Dendritic cell
- CD8+ T cell
- B7
- CTLA-4
- CD28
- No costimulation
- Anti-CTLA-4
- Primed CTL capable of killing tumor cells
- Costimulation

B. CTL-mediated killing of tumor cells

- Tumor peptide-MHC
- Inhibited CTL
- Activated CTL
- Dead tumor cell
- Tumor cell
- PD-L1
- PD-1
- PD-L1
- Anti-PD-L1
- Anti-PD-1
FDA-Approved Checkpoint Blockade Drugs for Cancers

- Anti-PD-1 (pembrolizumab): Metastatic cancers with microsatellite instability (2017): *Landmark*—treat tumors based on genetics, not tissue/histological type
- ...more to come
Targeting inhibitory receptors for cancer immunotherapy

• Blocking inhibitory receptors induces tumor regression
  – Partial or complete responses in up to 40%
  – Biomarkers for therapeutic responses?

• May be more effective than vaccination
  – Vaccines have to overcome tumor-induced regulation/tolerance

• Adverse effects (inflammatory autoimmune reactions)
  – Typically manageable (risk-benefit analysis)
Adverse Effects of Checkpoint Blockade

- Pneumonitis (2.0%); Colitis (2%); Hepatitis (1%); Hypophysitis (anterior pituitary) (0.8%); Hyperthyroidism (3.3%); Type 1 diabetes mellitus (0.1%); Nephritis (0.4%);
- Exfoliative dermatitis, Bullous pemphigoid, Uveitis, Myocarditis, Myositis, Guillain-Barré syndrome, Myasthenia gravis, Vasculitis, Pancreatitis, Hemolytic anemia
- Grade 3 and 4 adverse events for anti-PD-1/anti-CTLA-4 combination ~ 55 percent

*Normal heart*  
*Anti-PD-1/CTLA-4 Myocarditis*
The landscape of T cell activating and inhibitory receptors

Inhibitory receptors (coinhibitors)
- CTLA-4
- PD-1
- TIM-3
- TIGIT
- LAG-3
- BTLA

Activating receptors (costimulators)
- CD28
- ICOS
- OX40
- GITR
- CD137 (4-1BB)

T cell

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T cell
Why do tumors engage CTLA-4 and PD-1?

• *CTLA-4*: tumor induces low levels of B7 costimulation $\Rightarrow$ preferential engagement of the high-affinity receptor CTLA-4

• *PD-1*: tumors may express PD-L1

• Remains incompletely understood
  - These mechanisms do not easily account for all tumors
Chimeric antigen receptors

- Remarkable success in B cell acute leukemia (targeting CD19); up to 90% complete remission
- Risk of cytokine storm
- Outgrowth of antigen-loss variants of tumors?
Development of chimeric antigen receptors
Limitations and challenges of CAR-T cell therapy

• **Cytokine storm** – many T cells respond to target antigen
  – Requires anti-inflammatory therapy (anti-IL-6R)
  – Risk of long-term damage (especially brain)
• **Unclear how well it will work against solid tumors**
  – Problem of T cells entering tumor site and immunosuppressive tumor microenvironment
• **Will tumors lose target antigen and develop resistance?**
Limitations and challenges of CAR-T cell therapy -- 2

• Technical and regulatory challenges of producing genetically modified CAR-T cells for each patient
  – Prospect of gene-edited "universal" CAR-T cells?

• Exhaustion of transferred T cells
  – Use CRISPR gene editing to delete PD-1 from T cells
  – Increased risk of autoimmune reactions from endogenous TCRs
  – Use CRISPR to delete TCRs
  – Result is PD-1- T cells expressing tumor-specific CAR
Is checkpoint blockade more effective than vaccination for tumor therapy?

- Tumor vaccines have been tried for many years with limited success

- Immune evasion is a hallmark of cancer
  - Multiple regulatory mechanisms

- Vaccines have to overcome regulation
  - Tumor vaccines are the only examples of therapeutic (not prophylactic) vaccines
  - Vaccination after tumor detection means regulatory mechanisms are already active
Combination strategies for cancer immunotherapy

• Combinations of checkpoint blockers, or bispecific antibodies targeting two checkpoints
  • Already done with CTLA-4 and PD-1

• Checkpoint blockade (anti-PD1 or -CTLA-4) + vaccination (DCs presenting tumor antigen)

• Checkpoint blockade + agonist antibody specific for activating receptor

• Checkpoint blockade + kinase inhibitor to target oncogene
Cancer immunotherapy-based combination studies underway in 2016

Chen and Mellman, Nature 2017
Checkpoint blockade: prospects and challenges

- Exploiting combinations of checkpoints
  - Poor biology underlying choice of combinations to block
  - Difficult to reliably produce agonistic antibodies

- Typically, 20-40% response rates; risk of developing resistance?
Checkpoint blockade: prospects and challenges

• Possible biomarkers of response vs resistance:
  - Nature of cellular infiltrate around tumor
  - Expression of ligands for inhibitory receptors (e.g. PD-L1) on tumor or DCs
  - Frequency of neoantigens (HLA-binding mutated peptides) in tumors from different patients
  - Frequency of tumor-specific “exhausted” T cells