T Cell Mediated Immunity: 
Selected Features Relevant to Cancer Immunotherapy

Andrew Lichtman M.D., Ph.D. 
Dept. of Pathology 
Brigham and Women’s Hospital 
Harvard Medical School
Lecture Outline

• Overview of T cell functions
• T cell antigen recognition/ MHC restriction
• Antigen receptor signaling
• Costimulation
• Effector T cell subsets (Th subsets and CTLs)
• Molecules that inhibit T cells (CTLA-4, PD-1, others)
• Cells that inhibit T cells (Treg)
Types of T Cell–Mediated Immune Reactions

**CD4+ helper T cells (Th)**
- Microbes that live inside phagocytes
- Microbes that are readily killed by phagocytes

**Phagocytes with ingested microbes in vesicles**
- CD4+ effector T cells (Th1 cells)
- CD4+ effector T cells (Th17 cells)

- Cytokine secretion

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<th>Macrophage activation</th>
<th>Killing of ingested microbes</th>
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<tbody>
<tr>
<td>Inflammation, killing of microbes</td>
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**CD8+ Cytotoxic T lymphocytes (CTL)**
- Microbes that live inside tissue cells

**Infected cell with microbes or antigens in cytoplasm**
- CD8+ T cells (CTLs)

- Killing of infected cell
Sequence of events in T cell responses

Antigen recognition

Lymphocyte activation
- CD4 help
- Cytokines (e.g., IL-2)

Proliferation

Differentiation
- Effector CD4+ T cell
- Memory CD4+ T cell

Effector functions
- Activation of macrophages, B cells, other cells; inflammation
- Killing of infected cells; macrophage activation

Lymphoid organ

Peripheral tissue

Naive CD8+ T cell
CD4+ and CD8+ T cells
Antigen recognition/ MHC Class Restriction

CD4+ T cells (helper T cells) recognition is class II MHC restricted

CD8+ T cells (cytotoxic T lymphocytes) recognition is class I MHC restricted

Peptide from phagocytosed, lysosome-processed protein (microbial, tumor, normal self)

Peptide from cytosolic, proteasome-processed protein (microbial, tumor, normal self)
The signals generated by antigen recognition require the participation of cytoplasmic tails of:

- The co-receptor (CD4 or CD8)
- Signaling proteins associated with the TCR (CD3 and zeta)

Relevant to activation of naive T cells (initiation) and activation of effector T cell
TCR signaling: Protein tyrosine kinase (PTK)-mediated ITAM phosphorylation, recruitment and activation of other enzymes

Active ZAP-70
Active PLCγ1
Inactive PLCγ1

Immunoreceptor tyrosine activation motif (ITAM)

Inactive ZAP-70
SH2 domain for docking
PTK domain for further signaling

Downstream signaling; Gene expression; proliferation, differentiation, effector functions

Adaptor protein

PI3K
GTP/GDP exchange factor
Antigen recognition-Signal 1: Costimulation-Signal 2

- TCR binding to pMHC antigen to MHC is necessary to generate intracellular signals that activate the naïve T cell, but is not sufficient. ("Signal 1")
- Additional signals generated by the binding of molecules called costimulators on the APC to costimulatory receptors on the naïve T cell are also necessary for naïve T cell activation. ("costimulatory signals" or "Signal 2")
- Signal 1 without signal 2 leads to anergy, death or Treg differentiation: peripheral tolerance
Proteins of the B7 and CD28 families: Costimulatory and inhibitory functions

- All are members of Ig superfamily
- B7-1, B7-2 and ICOS-L are costimulators
- CD28 and ICOS are costimulatory receptors
- B7-1 (CD80) and B7-2 (CD86) are the best characterized and probably most important costimulators for naïve T cells
  - B7-1 and B7-2 are highly homologous, with similar functions.
  - B7-1 and B7-2 are highly expressed on activated DCs
  - B7-1 and B7-2 bind to the same receptor on T cells, called CD28
  - CD28 is expressed on most T cells
Other T Cell Costimulatory Molecules

- TNF/TNFR super family
  - 4-1BBL
  - GITRL
  - MHC I
  - CD70
  - OX40L
  - CD40

- B7/CD28 family
  - IL-15Rα + IL-15
  - MHC I
  - PD-L1
  - CD80
  - CD86

- B7/CD28 family
  - B7/CD28 family
  - Type I IFNγ R
  - IFN-α
  - IL-2
  - IL-7
  - IL-12
  - IL-21
  - IL-7R
  - IL-12R
  - IL-21R

TCR + CD8 +
CTL A-4 +
CD28 +
CD40L +
OX40 +
CD27 +
CD8 +
CD12 +
PD-L1 +
Relevance of TCR and costimulatory signaling to immunotherapy

- Chimeric antigen receptors (CARs) make any T cell specific for a tumor antigen
- CARs use TCR complex and costimulatory signaling motifs to activate the T cells
Properties of the major subsets of CD4+ helper T cells

<table>
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<th>Effector T cells</th>
<th>Defining cytokines</th>
<th>Principal target cells</th>
<th>Major immune reactions</th>
<th>Host defense</th>
<th>Role in disease</th>
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<td>Th1</td>
<td>IFN-γ</td>
<td>Macrophages</td>
<td>Macrophage activation</td>
<td>Intracellular pathogens</td>
<td>Autoimmunity; chronic inflammation (Blocks tumor growth)</td>
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<tr>
<td>Th2</td>
<td>IL-4, IL-5, IL-13</td>
<td>Eosinophils</td>
<td>Eosinophil and mast cell activation; alternative macrophage activation</td>
<td>Helminths</td>
<td>Allergy (Promotes tumor growth)</td>
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<tr>
<td>Th17</td>
<td>IL-17, IL-22</td>
<td>Neutrophils</td>
<td>Neutrophil recruitment and activation</td>
<td>Extracellular bacteria and fungi</td>
<td>Autoimmunity; inflammation</td>
</tr>
<tr>
<td>Tfh</td>
<td>IL-21 (and IFN-γ or IL-4)</td>
<td>B cells</td>
<td>Antibody production</td>
<td>Extracellular pathogens</td>
<td>Autoimmunity (autoantibodies)</td>
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- DC: Dendritic cell
- B cell: B lymphocyte
- Naïve CD4+ T cell: T lymphocyte
- Activated CD4+ T cell: Activated T lymphocyte

IL-4: Interleukin-4
IFN-γ: Interferon-γ
IL-12: Interleukin-12
IL-6: Interleukin-6
TGF-β: Transforming growth factor-β
Differentiation and function of CD8+ T cells

Two main functions:
1. Direct killing of target cells
2. Secretion of inflammatory cytokines: IFNγ and TNFα
Putting it all together: CD8+ T cell response to tumor

1. Tumor antigens are picked up by host dendritic cells
2. DCs process the antigens and transport to lymph nodes
3. DCs present tumor peptide antigens to naïve T cells, and provide costimulation
4. Tumor specific effector T cells (CTLs) are generated
5. Migration of tumor-specific CTL to tumor
6. CTL killing of tumor cell

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

(CD4+ T cell responses will also occur)
CTLA-4 Inhibits T cell Activation: Competitive Blockade of CD28–B7 Costimulation

- CTLA-4 binds B7’s with higher affinity than CD28; acts as a competitive inhibitor of CD28 costimulation
- CTLA-4 is most effective when B7 expression is low
- CTLA4 may also deliver inhibitory signals into the T cells it is expressed on
PD-1 Inhibits T cell Activation: Inhibitory Signals Block Effector T Cell Activation

Activated CD8+ CTL cell

Inhibited CD8+ CTL

Reduced TCR and CD28 signaling, causing reduced cytokine production and target cell lysis

Annu. Rev. Immunol. 34:539–73
PD-1 Inhibits Both TCR and CD28 Signaling

Roles of PD1 in acute infection, tolerance and cancer

**a Differentiation in lymphoid organs**

**Role of PD1 pathway in priming to foreign antigen:**
- Limit overactivation during initial priming
- Fine-tune effector T cell differentiation

**b Acute infection**

**State of tissue:**
- Pro-inflammatory
- Antipathogen

**Role of PD1 pathway:**
- Fine-tune effector responses
- Temper over-activation
- Protect tissue from immunopathology
- Regulate memory formation
- Return to homeostasis

**c Cancer**

**State of tissue:**
- Hijacking immune suppression
- Physiologically stressed (hypoxic, nutrient-deprived)

**Role of PD1 pathway:**
- Inhibit conventional T cell effector functions
- Promote T cell exhaustion
- Contribute to adaptive resistance

**d Autoimmunity**

**State of tissue:**
- Reacting to aberrant immune attack
- Inducing tissue repair and tolerance mechanisms

**Role of PD1 pathway:**
- Inhibit conventional T cell effector functions
- PDL1 acts as a molecular shield for self tissue
Many T cell inhibitory/regulatory molecules
Regulatory T Cells

- Thymus
- Recognition of self-antigen in thymus
- Regulatory T cells
- Recognition of antigen in peripheral tissues
- Inhibition of T cell responses
- Inhibition of other cells
- NK cell
- B cell

Cytokines (IL-10, TGF-β)
IL-2 sequestration
CTLA-4
Others

CD4
CTLA-4
CD25
Thymic Treg
Peripheral Treg

Costimulation blockade

Abbas, Lichtman, Pillai. Cellular and Molecular Immunology. Elsevier. 2017