T Lymphocyte Activation and Costimulation

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Lecture outline

• T cell activation

• Costimulation, the B7:CD28 family

• Inhibitory receptors of T cells

• Targeting costimulators for therapy
The life history of T lymphocytes

Precursors mature in the thymus

Naïve CD4+ and CD8+ T cells enter the circulation

Naïve T cells circulate through lymph nodes and find antigens

T cells are activated and develop into effector and memory cells

Effector T cells migrate to sites of infection

Eradication of infection

Principles of lymphocyte activation

• Lymphocytes are normally in a resting state in lymphoid organs and circulation

• Rapid response to antigen (activation) --> proliferation, change to functionally active effector cells (differentiation)

• Migration to tissues, where they perform their function of eliminating infections

• Multiple possible steps for therapeutic targeting

Take home messages
Functional responses of T lymphocytes

From: Abbas & Lichtman, Cellular & Molecular Immunology 5th ed 2003
Molecules involved in T cell activation

- **CD3:** signaling molecule attached to the TCR on all T cells; anti-CD3 MAb to deplete T cells (transplants)

- **Integrins** (LFA-1, VLA-4, others): adhesion to APCs, endothelium; anti-integrin MAb’s to block leukocyte migration

- **“Costimulators”:** CD28, others; costimulatory blockade

Therapeutic targeting of molecules involved in T cell responses
Principal signaling pathways in T cell activation

- Membrane signal (TCR complex, other receptors) -> biochemical intermediates -> transcription factors
- Calcium -- calcineurin -> NFAT
- Ras/MAP-kinase -> AP-1
- PKC -- CARMA/BCL-10 -> NFκB
- PI3-kinase -- Akt -> NFκB
- Cytokines -> Jak-Stat

The innate immune system provides second signals required for lymphocyte activation

Second signals for T cells: "costimulators" induced on APCs by microbial products, during early innate response

Second signals for B cells: products of complement activation recognized by B cell complement receptors

Take home messages
The role of costimulation in T cell activation.

<table>
<thead>
<tr>
<th>Antigen recognition</th>
<th>T cell response</th>
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</thead>
<tbody>
<tr>
<td>&quot;Resting&quot; (costimulator-deficient) APC</td>
<td>Naive T cell</td>
</tr>
<tr>
<td>Activation of APCs by microbes, innate immune response</td>
<td>Effector T cells</td>
</tr>
<tr>
<td>Activated APC: increased expression of costimulators, secretion of cytokines</td>
<td>T cell proliferation and differentiation</td>
</tr>
<tr>
<td>Cytokines (e.g., IL-12)</td>
<td>IL-2</td>
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</tbody>
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Costimulation

- Required for initiating T cell responses (activation of naïve T cells)
- Ensures that T cells respond to microbes (the inducers of costimulators) and not to harmless antigens
  - Source of costimulation during responses to tumors, transplants, self antigens?
- Targets for therapeutic blockade of T cell responses

[Take home messages]
## Complexities of B7:CD28 costimulation

- **Initiation of T cell responses requires B7:CD28**
  - Other costimulators may function at different stages of immune responses

- **Different T cell populations vary in their dependence on B7:CD28:**
  - Naïve > activated > memory
  - CD4 > CD8
  - Regulatory T cells (controllers of immune responses) are also B7-dependent

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**Take home messages**
Knockout of CTLA-4 results in autoimmune disease:
- multi-organ lymphocytic infiltrate, lethal by 3-4 weeks
- lymphadenopathy, splenomegaly

Blocking CTLA-4 promotes tumor rejection:
CTLA-4 limits immune responses to tumors

Administration of antibody that blocks CTLA-4 in
tumor-bearing mouse
The PD-1 inhibitory pathway

- PD-1 recognizes two widely expressed ligands (PD-L1, PD-L2)
- Knockout of PD-1 leads to autoimmune disease
- Role of PD-1 in T cell suppression in chronic infections?
Inhibitory role of PD-1 in a chronic infection

Virus-specific T cell response

Residual virus

In chronic LCMV infection in mice, virus-specific T cells become paralyzed; express high levels of PD-1; function is restored by blocking PD-1.

R. Ahmed lab, Nature 2006

Roles of inhibitory receptors of the CD28 family

- Maintenance of self-tolerance
- Immune evasion in tumors, chronic infections (e.g. HCV, HIV)
  - How have microbes and tumors evolved to use a pathway of normal immune regulation?
- Exploiting inhibitory pathways for therapy?

Take home messages
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Therapeutics based on the B7:CD28/CTLA-4 family

1. Costimulatory blockade

CTLA-4.Ig is being tested in diseases caused by excessive T cell activation -- rheumatoid arthritis (FDA approved), psoriasis, graft rejection

Costimulatory blockade therapy

- B7-antagonist (CTLA-4.Ig, Abatacept) approved for RA, psoriasis; ongoing trials in transplantation (Belatacept)
  - Risks:
    - Reducing responses against infections
    - Possibility of depleting regulatory T cells or blocking inhibitory pathways? -- may exacerbate disease??
Therapeutics based on the B7:CD28/CTLA-4 family
2. Inhibiting the inhibitors

Anti-CTLA-4 antibody is used for tumor immunotherapy (enhancing immune responses against tumors)
Potential of anti-PD1 for chronic infections, tumors?

Risks of blocking CTLA-4

- Autoimmune diseases
  - Prostatitis, vitiligo
  - Use of pulse therapy based on cancer progression?
Costimulators as therapeutic targets

• Blocking the B7-CD28 interaction for inflammatory diseases, graft rejection

• Blocking inhibitors (CTLA-4, PD-1?) for boosting responses against tumors and persistent infections

• Complexities of the pathways create challenges and potential risks

• Role of molecules other than B7:CD28 -- TNF-receptor family members, others?

Take home messages

T cell expansion and contraction (decline)

Many aspects of T cell responses and functions are mediated by cytokines: initial activation -- IL-2; maintenance of memory cells -- IL-7; effector functions -- various