Topics

• T cell mediated immunity Part II
  – Effector T cells
  – Binding and secretion of effector molecules
  – CD8 T cell function
  – CD4 T cell function
  – Cytokines
  – TH1 effector functions
• Adhesion molecules allow for longer cell-cell interaction
• CD4 cells bind to target cells for a long time
• CD8 T cells bind to target cells for short periods, kills target cell, then detaches and binds to another cell

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- Binding leads to clustering of receptors
- Polarization:
  1. Reorganization of cortical actin cytoskeleton at site of contact
  2. Reorientation of microtubule reorganizing center
  3. Relocalization of Golgi apparatus
  4. Exocytosis at site of contact (tight space)
- Detachment
Two types of effector molecules:

1. Cytotoxins
2. Cytokines

Cytotoxins

- Soluble secreted factors
  1. perforin
  2. granzyme
- Membrane associated factors
  1. Fas Ligand
Cytokines

- Small secreted soluble molecules that can change the behavior or properties of the cell itself or of another cell
- Multiple effects in different types of cells
- Synergism

- Lymphocytes = lymphokines
- T cell = Interleukines
- Chemoattractants = chemokines

- Studied by in vitro assays or gene disruption

Types of effector T cells

- **CTL**
  - Cytotoxic T cells
  - CD8
  - MHC I recognition
  - Kill viral infected cells
  - Kill Transformed cells

- **Th1**
  - CD4
  - MHC II recognition
  - Activation of macrophages

- **Th2**
  - CD4
  - MHC II recognition
  - Activation of B cells
Effector Molecules

CD8 T cells: peptide + MHC class I
- Cytotoxic (killer) T cells
  - CTL
  - Cytotoxic molecules:
    - Perforin
    - Granzymes
    - Granulysin
    - Fas ligand
  - Virus-infected cell

CD4 T cells: peptide + MHC class II
- T$_{h1}$ cells
  - Cytokines
    - IFN-γ
    - TNF-β
    - CD40 ligand
  - Macrophage
    - IL-3
    - TNF-β
    - IL-12 (CI): CXCL2
  - Others
    - IL-4
    - IL-5
    - IL-15
    - CD40 ligand

- T$_{h2}$ cells
  - Cytokines
    - IFN-γ
    - TNF-β
    - IL-10
  - Macrophage
    - IL-3
    - GM-CSF
    - IL-10
    - TGF-β
    - CD11 (corticin)
    - CCL17 (TARC)

Figure 8:31 Immunobiology, 6/e, (c) Garland Science 2005

CD8 T cells
The kiss of death

- CTL recognizes and binds virus-infected cell
- CTL programs target for death, inducing DNA fragmentation
- CTL migrates to new target
- Target cell dies by apoptosis

CTL effector molecules

- Perforin: forms a pore in membrane
- Granzymes: Serine proteases, activate apoptosis
- Fas ligand: activates apoptosis
- IFN-γ: inhibits viral replication, up-regulate MHC I expression, activates macrophages
- TNF-α, TNF-β: synergizes with IFN-γ, induce apoptosis
Cytotoxic T cells are selective

CD4 T cells

\[ \text{TH} 0 \quad \text{TH} 1 \quad \text{TH} 2 \]
Differentiation of CD4 cells

- Initial response mounted by the innate non-specific immune response is important in this process

1. Cytokines elicited by infectious agents

2. Molecules used for co-stimulation

3. Nature of MHC:peptide ligand

Main Th1 cytokines

- IL-2 (Th 0, Th1, CTL)
  - Growth of T cells
  - Growth of NK cells

- IFN-γ (Th1, CTL)
  - Increase MHC I & II
  - Inhibits Th2 cell growth
  - Activates macrophages
  - B cell differentiation, IgG2a synthesis
  - Activates NK cells

Figure 8:31, appendix 2
Main Th2 cytokines

- **IL-4 (Th2)**
  - B cell activation and growth
  - Th2 growth and survival
  - Increase MHC II
  - IgG1, IgE
  - Decreases macrophage activation

- **IL-5 (Th2)**
  - IgA
  - increase eosinophils

- **IL-10 (Th2)**
  - Increase MHC II
  - Inhibit Th1 cell growth

other cytokines

- **IL-3 (Th1, Th2, CTL)**
  - Stimulates hematopoiesis

- **TNF-α (Th1, some Th2, CTL)**
  - Activates macrophages (synergy with IFN-γ)
  - production of NO

- **GM-CSF (Th1, Th2, CTL)**
  - Increase granulocyte production
  - Increase macrophage and dendritic cell production
### Cytokine Effects

<table>
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<th>Cytokine</th>
<th>T-cell source</th>
<th>Effects on</th>
<th>Effect of gene knockout</th>
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<tr>
<td></td>
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<td>B cells</td>
<td>T cells</td>
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<tr>
<td>Interleukin-2 (IL-2)</td>
<td>naive T cells, some CD8</td>
<td>stimulates growth and IgM synthesis</td>
<td>growth</td>
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<tr>
<td>Interferon-γ (IFN-γ)</td>
<td>T&lt;sub&gt;α&lt;/sub&gt;, CTL</td>
<td>differentiation IgG2A synthesis (mouse)</td>
<td>inhibits T&lt;sub&gt;α&lt;/sub&gt;2 cell growth</td>
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<tr>
<td>Lymphotoksin (LT, TNF-β)</td>
<td>T&lt;sub&gt;α&lt;/sub&gt;, some CTL</td>
<td>inhibits</td>
<td>kills</td>
</tr>
</tbody>
</table>

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Figure 8.22 part 1 of 3: Immunobiology, 6th ed. (Garland Science 2005)
Consequences of Th1 or Th2

Leishmania sp

Th1

Resistant

IL-4

Th2

Susceptible

Leishmania sp

Anti-IL-4

Th1

Resistant

Th2

Susceptible
Macrophage activation

- Requires 2 signals:
  - IFN-\(\gamma\)
  - CD40 or
  - membrane bound TNF alpha or beta

- Stimulation via TCR triggers novo protein synthesis

- Proteins are delivered to the site of contact by vesicles

- Signals are delivered directly to that macrophage

Activated macrophage

1. Increase fusion of lysosomes and phagosomes to form phagolysosomes
2. Increase oxygen radicals and Nitric Oxide production
3. Increase expression of B7, CD40, MHC II & TNF receptors
4. Production of IL-12 (stimulates Th1 cells)
5. Recruitment of other cells
6. More effective killing
7. Better APC
Activated T_{H1} cell

IL-3 + GM-CSF
- Induces macrophage differentiation in the bone marrow

TNF-\alpha + TNF-\beta
- Activates endothelium to induce macrophage binding and exit from blood vessel at site of infection
- Diapedesis
  - Blood vessel lumen

CCL2
- Causes macrophages to accumulate at site of infection
- Chemotaxis
  - Site of infection

2/7/2005 [Figure 8-41 part 2 of 2: Immunobiology, 6th Ed. (Garland Science 2005)]