Cell Mediated Immunity: Effector Mechanisms

Cytolytic T cell attacking targeted cells (T cell shown in red & blue).
Objectives

• Describe the process of T cells homing to sites of injury or infection
• Identify effector functions of CD8+ T cells
• Describe how CD4+ helper cells regulate the immune system
• Identify effector functions of Th1 CD4+ cells
• Identify effector functions of Th2 CD4+ cells
• Identify examples of regulation of the immune response
• Identify examples of cell-mediated immunopathology
**Effector Functions**

- **Antigen recognition** has occurred in lymphoid organs.
- Activated T cells to **expand & differentiate into effector cells**.
- Effector cells **migrate into tissues**.
- Th1 CD4 cells & CD8 cytotoxic T cells **perform cell-mediated targeting of the microbes**.
T Cell Homing

- T cells exit nodes & are attracted to site of infection with **adhesion molecules** (homing)
- Activated **T cells that recognize antigen** are retained to battle the infection
- Other T cells that are **not** ag specific continue to circulate
Focus on CD8+ cells

- CD8 cells primarily respond to intracellular pathogens (restricted to MHC I)
- Once activated, CD8 cells proliferate into antigen specific effector cells
- Effector cells leave the peripheral lymphoid organs to migrate to the site of infection
- Major effector function: recognize & kill infected host cells
- CD8+ cells provide the major cellular response to viral infections
CD8+ T cells: Differentiation

- First signal: recognize antigen peptide on surface of host cell displayed by MHC I
- Second signal: need costimulators (B7 – CD28) to trigger activation
- Differentiation into effector cells leads to specific targeting of any other cell infected with same microbe (ag specificity)
**CD8+ T cells: Deadly Consequences**

- CD8+ cells then **release granules** that kill the organism
  - **Perforin** punches holes through the targeted cell membrane
  - **Granzymes** then enter the cell, activate caspases which induces apoptosis
- Infected cell is killed, CD8 T cell also can produce **IFN γ** to recruit macrophages
- Apoptotic (dead) cells are quickly phagocytosed & removed

*Watch an excellent animation on how effector Tc cells kill targets with perforin.*
Focus on CD4+ cells

- CD4 cells primarily respond to extracellular antigens (restricted to MHC II)
- Once activated, CD4 cells differentiate into effector cells
- Primarily function to release cytokines that activate B cells & macrophages
- Two subsets of CD4 cells:
  - Th1
  - Th2

**Also, Th0 (T reg cells – discussed in Block 5)**
# A Delicate Balance

**CD4+ Cells Polarize the Immune System**

<table>
<thead>
<tr>
<th>Th1 Cells</th>
<th>Th2 cells</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cytokines: Ifnγ, IL-12, IL-2</td>
<td>Cytokines: IL-4, 9, 10, 13</td>
</tr>
<tr>
<td>IgG2a antibodies</td>
<td>IgG4 and IgE antibodies</td>
</tr>
<tr>
<td>Pro-inflammatory</td>
<td>Anti-inflammatory</td>
</tr>
<tr>
<td>Cell mediated Immunity</td>
<td>Humoral Immunity</td>
</tr>
</tbody>
</table>
Dual Purpose:

- CD4+ T Cells Influence CMI

- CD4+ T Cells Influence AMI
CD4: Type 1 Helper cells (Th1)

- Cytokines influence immune response
- **Th1** cells release interferon y, a potent activator of macrophages
- This also stimulates expression of MHC II on APCs, which amplifies the T cell response
- May result in tissue injury
- Improves cell-mediated response
Th1 cells have a tremendous influence on other cell types to generate a large & multiple cell-mediated attack on an antigen (virus, etc.).

Check out the action of these activated cytolytic T cells in a real-time “video”! Watch as the smaller T cell (arrow) destroys a larger cell infected by influenza virus by clicking on the 640K movie link located on this page: Cytolytic T Cell Death
Example of CD4 Th1 cells assisting cytolytic CD8 cells to enhance the immune response & improve lysis of the infected cell.
**Th1 Activation of Macrophages**

- **Activation of macrophages**
  - CD40
  - CD40L
  - Macrophage with ingested microbes
  - IFN-γ
  - CD4+ effector T cell (TH1 cell)

- **Responses of activated macrophages**
  - Killing of phagocytosed microbes
  - Increased expression of MHC molecules and costimulators (B7 molecules)
  - ROI, NO
  - Secretion of cytokines (TNF, IL-1, chemokines, IL-12)
**Th1 Cells & Leprosy**

- **M. leprae** bacteria lives inside macrophages (immune evasion strategy!) & causes leprosy
  - Destructive lepromatous form (right) can occur in individuals that do not mount a strong cell-mediated immune response
- **Defect in Th1 cell activation** prevents macrophages from becoming activated to destroy bacteria

Photos of active lepromatous leprosy cases, with significant physical disfigurement.
**CD4: Type 2 Helper Cells (Th2)**

- **Th2** cells release **interleukin 4 (IL-4)**, which stimulates **B cell responses**
- Th2 cells **also activate eosinophils** to defend against parasites via IgE antibodies
- Can also dampen the Th1 response to limit tissue damage (anti-inflammatory)
- Improves **humoral immunity**
CD4+ Helper (Th2) cells especially promote B cell growth and differentiation to stimulate antibody production.

A B cell will differentiate into a plasma cell after receiving 2 signals:
1) antigen binding
2) t cell help
Th1 and Th2 pathways are mutually antagonistic. These pathways serve to regulate each other, so that both parts are kept in balance.
Regulation of the Immune Response

- Regulation by antigen
- Regulation by Antigen Presenting Cell (APC)
- Regulation by antibody
- Regulation by lymphocytes
- Regulation by neuroendocrine modulation
- Genetic control of immune response
Regulation by Antigen

- T & B cells; Antigen receptors, Class 1 & 2 MHC proteins
- Nature of the Antigen: chemical, intracellular or extracellular
- Antigen dose
- Route of administration of antigen (mucosa, skin, blood)
Regulation by Antigen Presenting Cell (APC)

- Antigen recognition with MHC proteins or tolerance induction
- APC can up-regulate the expression of MHC on surface by cytokine induction
Regulation by Antibody

- Feedback control of response

- Antibody blocking; competition for antigen

- Receptor cross-linking; Fc & Ag receptor inhibits Ab synthesis

- Immune complex; inhibition or augmentation
Regulation by T Lymphocyte

- Th1 & Th2 choose nature of immune responses (CMI or Ab)
- CD4+ T cells can prevent induction of autoimmunity
- Cross-regulation of Th1 & Th2 responses by cytokines
- CD8+ T cells can be suppressive
Regulation by Neuroendocrine Modulation

• Direct sympathetic innervation of lymphoid tissues
• Lymphocytes have receptors for hormones such as corticosteroids
• Stress can modulate immune system, especially leading to immunosuppression during stress
Genetic Control of Immune Responses

- **Inherited ability** to make immune responses to given Ag
- Influence of **MHC haplotypes**
- Influence of non-MHC linked genes
- **T cells** recognize Ag only in MHC context
- **Thymus selection** for self-recognition
- **MHC linked** (inflammatory bowel disease, psoriasis, diabetes, etc) and **autoimmune disease** [Block 5]
- Non-MHC linked genes and susceptibility to infection
Cell-Mediated Immunopathology

- **Cell-Mediated Immune Response** causes tissue damage
- **Cytotoxicity**: essential cells are killed with a resultant deficit, autoimmunity
- **Chronic inflammation**: autoantigens, cross-reactive Ags, lysosomal enzyme release
- **Space-Occupying lesion**: granulomas, impaired functions of organs
- **Excessive cytokine release**: Toxic Shock Syndrome, Schwartzman Reaction, Hemorrhagic Necrosis (TNF)
- **Type 4 Delayed Hypersensitivity**
Cell-mediated cytotoxicity

effector cells

- Tc (CD8, MHC class I)
- Tc (CD4, MHC class II)
- NK (NK receptor, MHC class I determinant)
- K (ADCC)

Tumor cell

Target cells (MHC class I)
Chronic Inflammation in Joints
To be continued ...

- **T cells** also have been shown to be important causes of immunopathologies in several other diseases.
- Diabetes, autoimmune diseases [i.e. multiple sclerosis, lupus, myasthenia gravis], and delayed type hypersensitivity will be covered in **Block Five**.
Cell Mediated Immunity Summary

• “Transferred” by T lymphocytes, and is cell-based (NOT antibody)
• T cells provide Ag specificity (TcR)
• Cells exert effector functions (macrophages & T cells)
• Major Histocompatibility Restriction controls type of T cell involved
• Th1 & Th2 cells “choose” & regulate response
Summary

- **AMI & CMI**: Two sides of the same coin
- **Adaptive** immune response mediated by B & T cells
- Both have **specific effector functions** to protect against different types of pathogens
- **Work together** to produce a strong response, memory, and elimination of antigens
In Summary

• CD8+ effector mechanisms
• CD4+ effector mechanisms (Th1 & Th2)
• How T cells help B cells

• Macrophage activation
• Cytokines that control the immune response
• Regulation of the immune response
• CMI immunopathology
Self-Test Questions

• How do T cells find the site of injury? Include specific adhesion molecules that attract them to the area & those that keep them at the site (hint: see text).

• Describe how CD8+ T cells kill infected cells. What does granzyme do?

• Describe the effector functions of CD4+ Th1 cells. Th2 cells.

• What cytokines are involved in the regulation of the immune system? What cytokines stimulate CMI? Humoral immunity?

• Name 3 examples of CMI immunopathology.