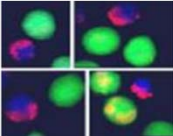


**Foundations of Public Health Immunology**

**Cell Mediated Immunity: Effector Mechanisms**



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

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**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

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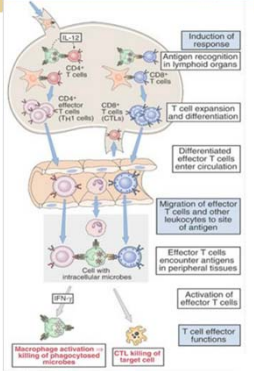
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**Effector Functions**

- **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



The diagram illustrates the following steps: 1. Induction of response (Antigen recognition in lymphoid organs) involving CD4+ T cells and CD8+ T cells. 2. T cell expansion and differentiation. 3. Differentiated effector T cells enter circulation. 4. Migration of effector T cells and other leukocytes to site of antigen. 5. Effector T cells encounter antigens in peripheral tissues. 6. Activation of effector T cells. 7. T cell effector functions, including CTL killing of target cells and Macrophage activation leading to killing of intracellular microbes.

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**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  $\gamma$**  to recruit macrophages
- Apoptotic (dead) cells are quickly phagocytosed & removed

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

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**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

CD4+ T cells are especially susceptible to infection with HIV. The image on the top are **healthy** T cells, **compared** to those below that have been infected.

\*\*Also, Th0 (T reg cells – discussed in Block 5)

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**A Delicate Balance**

**CD4+ Cells Polarize the Immune System**

<ul style="list-style-type: none"> <li><b>Th1 Cells</b></li> <li>Cytokines: Ifn <math>\gamma</math>, IL-12, IL-2</li> <li>IgG2a antibodies</li> <li>Pro-inflammatory</li> <li><b>Cell mediated Immunity</b></li> </ul>	<ul style="list-style-type: none"> <li><b>Th2 cells</b></li> <li>Cytokines: IL-4, 9, 10, 13</li> <li>IgG4 and IgE antibodies</li> <li>Anti-inflammatory</li> <li><b>Humoral Immunity</b></li> </ul>
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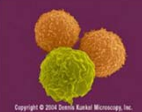






### CD4: Type 2 Helper Cells (Th2)

- 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**



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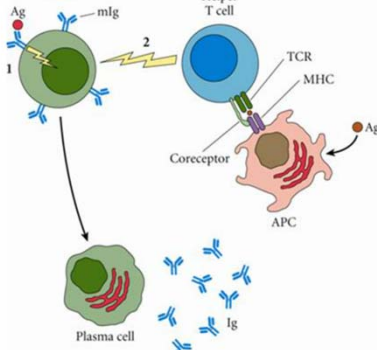
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**CD4+ Helper (Th2) cells especially promote B cell growth and differentiation to stimulate antibody production.**



A B cell will differentiate into a plasma cell after receiving 2 signals:  
 1) antigen binding  
 2) t cell help

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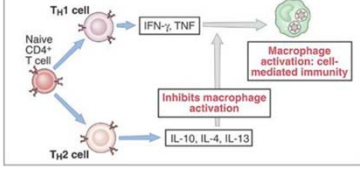
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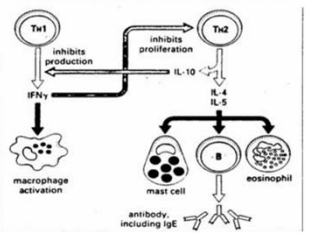
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**Selection of effector mechanisms by Th1 and Th2 cells**



Th1 and Th2 pathways are mutually antagonistic. These pathways serve to regulate each other, so that both parts are kept in balance.

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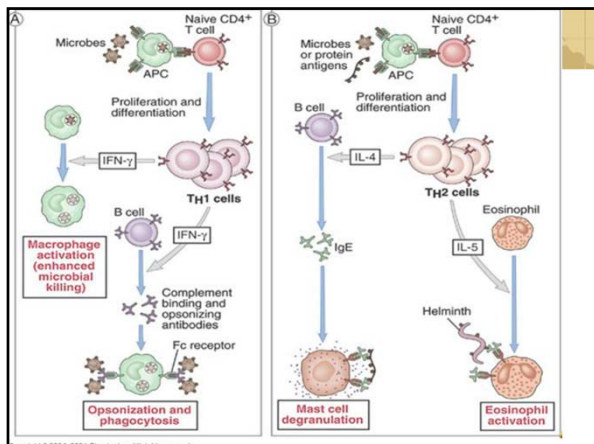
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**Regulation of the Immune Response**

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

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**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)

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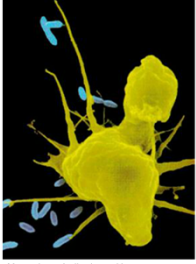
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 *Regulation by Antigen Presenting Cell (APC)*

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

  
Macrophage (yellow) attacking bacteria (blue).

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 *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



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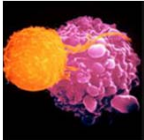
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 *Regulation by T Lymphocyte*

- 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



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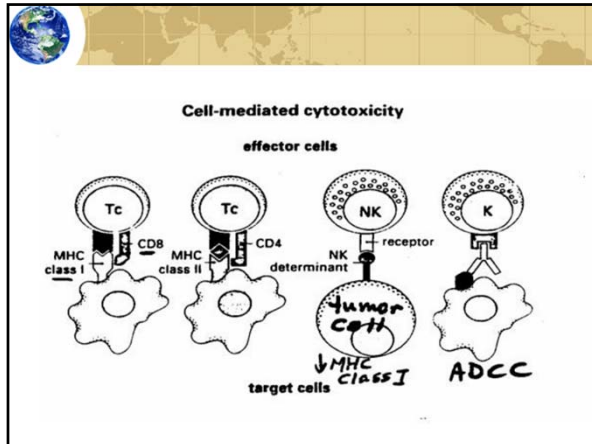
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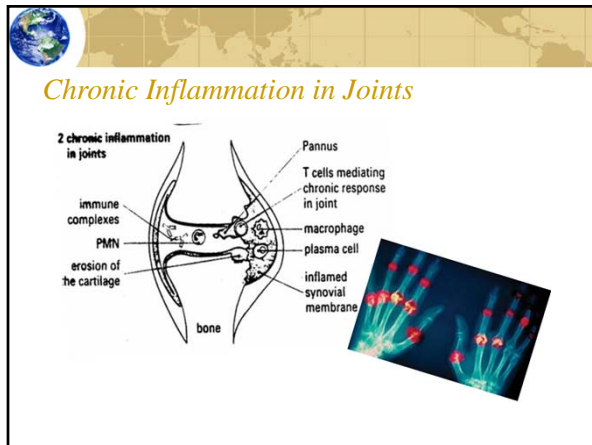
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*To be continued ...*

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

NERVE CELL T-CELLS ATTACK MYELIN MONOCYTES ALSO ATTACK

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### 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

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### 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

	Humoral immunity	Cell-mediated immunity
Microbe	Extracellular microbes	Phagocytosed microbes in macrophage Intracellular microbes (e.g., viruses) replicating within infected cell
Responding lymphocytes	B lymphocyte	Helper T lymphocyte Cytotoxic T lymphocyte
Effector mechanism	Secreted antibody	
Functions	Block infections and eliminate extracellular microbes	Activate macrophages to kill phagocytosed microbes Kill infected cells and eliminate reservoirs of infection

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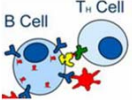
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### In Summary

- 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




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*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.

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