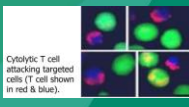



Slide 1

FOUNDATIONS OF PUBLIC HEALTH
IMMUNOLOGY



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

Cell Mediated Immunity:
Effector Mechanisms



Slide 2

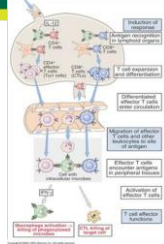
USF UNIVERSITY OF SOUTH FLORIDA OBJECTIVES

- 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 effector functions of Th17 cells
- Identify examples of regulation of the immune response
- Identify examples of cell-mediated immunopathology

Slide 3

USF UNIVERSITY OF SOUTH FLORIDA 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**



Slide 4

USF T CELL HOMING

Increased expression of adhesion molecules on endothelium at site of infection allows homing of activated T cells

Effector T cells enter peripheral tissues

Antigen recognition by T cells specific for microbe

Effector T cells recognize and kill infected cells

Activated T cells recognize and kill infected cells

Activated T cells recognize and kill infected cells

Slide 5

USF 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 in red.

Slide 6

USF CD8+ T CELLS: DIFFERENTIATION

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

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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 γ** to recruit macrophages
- Apoptotic (dead) cells are quickly phagocytosed & removed

The diagram illustrates the following steps: 1. Antigen recognition and endocytosis by the CTL. 2. CTL activation. 3. CTL granule exocytosis. 4. Killing of target cell. 5. Granzymes enter through perforin holes, activation of caspases. 6. Phagocytosis of the apoptotic cell.

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MECHANISM OF KILLING BY CD8+ T CELLS

The diagram is divided into three stages: 1. Antigen recognition and binding of CTL to target cell, showing CD8+ CTL and CD8+ T cell interacting with a target cell. 2. CTL activation and granule exocytosis, showing the release of Granzymes and Perforin. 3. Apoptosis of target cell, where Perforin facilitates the entry of granzymes into the cytosol, activating apoptosis. Adhesion molecules ICAM-1 and LFA-1 are also shown.

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Cooperation between CD4+ and CD8+ T cells in eradication of intracellular infections.

The diagram shows: 1. Phagocytosed microbes in vesicles and cytosol. 2. A CD4+ cell releasing IFN- γ to activate a CD8+ CTL. 3. Killing of microbes in phagolysosomes. 4. Killing of the infected cell. A viable microbe in the cytosol is also shown.

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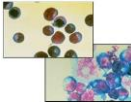
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FOCUS ON CD4+ CELLS

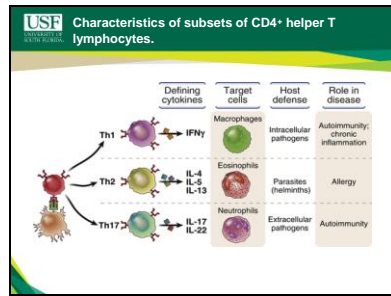
- CD4 cells primarily respond to **extracellular antigens** (restricted to MHC II)
- Once activated, CD4 cells differentiate into **effector cells**
- Primarily function to **release cytokines that activate B cells & macrophages**
- Three subsets of CD4 cells:
 - Th1
 - Th2
 - Th17

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

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.



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A DELICATE BALANCE

CD4+ Cells Polarize the Immune System

<ul style="list-style-type: none">• Th1 Cells• Cytokines: IFN-γ, IL-12, IL-2• IgG2a antibodies• Pro-inflammatory• Cell mediated Immunity	<ul style="list-style-type: none">• Th2 cells• Cytokines: IL-4, 9, 10, 13• IgG4 and IgE antibodies• Anti-inflammatory• Humoral Immunity
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CD4: TYPE 1 HELPER CELLS (TH1)

- Secretes cytokines that influence immune response
- Secretes IFN- γ , a potent activator of macrophages
- Stimulates expression of MHC-II on APCs, which amplifies the T cell response
- Improves cell mediated response
- Pro-inflammatory – result in tissue injury

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Functions of Th1 cells.

The diagram illustrates the following process: Bacteria are taken up by an APC. A Naive T cell interacts with the APC. This interaction leads to the differentiation of Th1 cells. Th1 cells then secrete IFN- γ , which acts on a Macrophage to cause Classical macrophage activation, resulting in enhanced microbial killing.

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Activation of macrophages by Th1 lymphocytes.

A Activation of effector cell: A CD4⁺ effector T cell (Th1 cell) interacts with a Macrophage with ingested bacteria via an IFN- γ receptor.

Activation of macrophage: The interaction leads to the activation of the macrophage.

Responses of activated macrophages:

- Killing of phagocytosed bacteria
- Secretion of cytokines (TNF, IL-1, IL-12) and chemokines
- Increased expression of MHC and costimulators (B7 molecules)

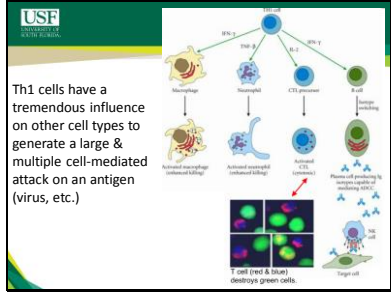
Macrophage response:

- Production of reactive oxygen species, nitric oxide, increased lysosomal enzymes
- Secretion of cytokines (TNF, IL-1, IL-12) and chemokines
- Increased expression of B7 costimulators, MHC molecules

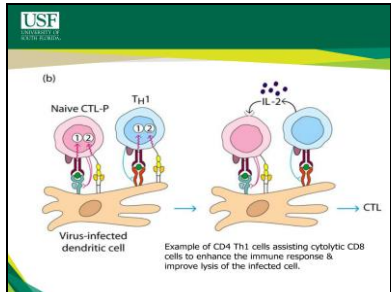
Role in cell-mediated immunity:

- Killing of microbes in phagolysosomes (effector function of macrophages)
- TNF, IL-1, chemokines: leukocyte recruitment (inflammation)
- IL-12: Th1 differentiation, IFN- γ production
- Increased T cell activation (amplification of T cell response)

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Slide 17



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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.

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CD4: TYPE 2 HELPER CELLS (TH2)

- Th2 cells secrete IL-4 – stimulates B cell response
- Th2 cells secrete IL-5 – activates eosinophils to defend against parasites via IgE antibodies
- Secretes IL-4 and IL-13- alternate macrophage activation which dampens the Th1 response and limit tissue damage.
- Improves humoral immunity.

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Functions of Th2 cells.

Naive CD4⁺ T cell

Macrophage

Th2 Cells

IL-4

IL-5

IL-13

Alternative macrophage activation (enhanced fibrosis, tissue repair)

Eosinophil

Helminth

Intestinal mucus secretion and peristalsis

Mast cell degranulation

Antibody production

IgG4 (human), IgE1 (mouse)

B cell

Proliferation and differentiation

Antigen Presenting Cell (APC)

Helminth

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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

B cell

Helper T cell

APC

Ag

TCR

MHC

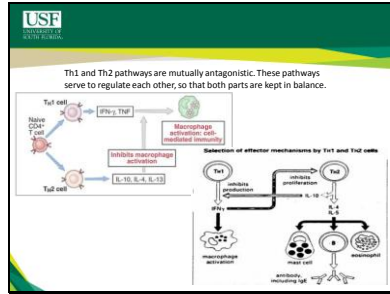
Co-receptor

Ag

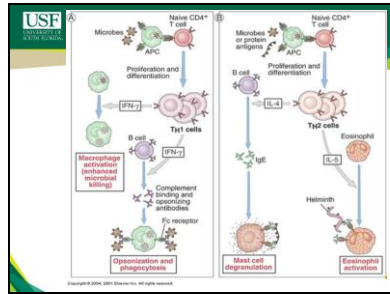
Plasma cell

Ig

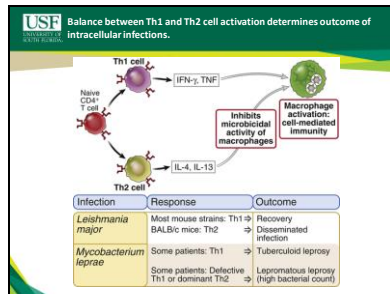
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CD4: TYPE 17 HELPER CELLS (TH17)

- Secretes IL-17 which recruitment of neutrophils and monocytes (lesser extent).
- Secretes IL-22 which maintains the integrity of epithelial barriers and promote repair of damaged epithelia.
- Stimulate the production of defensins – antimicrobial peptides.

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Functions of Th17 cells.

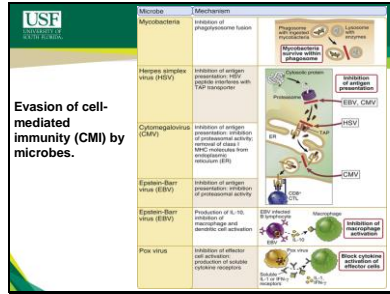
Bacteria, APC, Naive CD4⁺ T cell, Proliferation and differentiation, Th17 cells, Leukocytes and tissue cells, Epithelial cells, Chemokines, TNF, IL-1, IL-6, CSFs, Antimicrobial peptides, Inflammation, neutrophil response, Increased barrier integrity.

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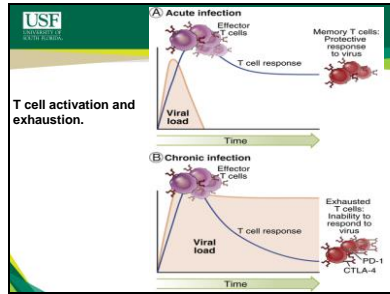
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Development of Th1, Th2, and Th17 effector cells.

(A) Dendritic cell, Intracellular mycobacteria (mycobacteria), NK cell, IL-12, IFN- γ , STAT1, STAT4, Antigen-activated T cell, Th1 cell.
(B) Dendritic cell, Helminths, Mast cells, eosinophils, IL-4, STAT3, STAT6, Antigen-activated T cell, Th2 cell.
(C) Dendritic cell, Extracellular large bacteria, IL-17, IL-1, IL-6, IL-23, TGF- β , STAT3, ROR- γ , Antigen-activated T cell, Th17 cell.

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Slide 30

- 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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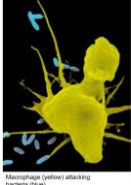
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REGULATION BY ANTIGEN

- 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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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



Micrograph (yellow) attacking bacteria (blue)

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Slide 34



Slide 35



Slide 36



Slide 37



Slide 38



Slide 39



Slide 40



Slide 41



Slide 42



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