

# Immune System

**NONSPECIFIC**  
(or innate)  
and  
**SPECIFIC**  
(or adaptive)

## Pathways of Defense

This animation posted by Harvard Life Sciences, Outreach Program discusses:  
Physical Barriers  
Innate Immunity  
Adaptive Immunity



## Fighting the Common Cold

This video posted by Harvard Life Sciences, Outreach Program is an introductory discussion to innate immunity, infection, and adaptive immunity.



# NON-SPECIFIC DEFENSES

- Protect against a **wide variety** of pathogens (disease causing organisms)
  - protecting our body **against entry** (barriers)
  - help **prevent spread** of pathogen

# Forms of Non-Specific Defenses

- Include
  - Physical barriers
  - Phagocytes
  - Immunological Surveillance
  - Interferon
  - Complement
  - Inflammation
  - Fever

# Surface Barriers

- Two major physical barriers are
  - **Skin**
  - **Mucous membranes** (membranes which open to the outside of the body)
- **Skin** (in addition to physical barrier)
  - pH is acidic (3 - 5)
- **Mucous membranes** (in addition to physical barrier)
  - traps pathogens
  - pH destroys pathogen (stomach)
  - contains enzymes that destroy pathogen (saliva)

# Phagocytes

- **Microphages** originate from neutrophils and become phagocytic when they encounter pathogens or are **stimulated** by cytokines (eosinophils and basophils may also be classified as microphages)
- **Macrophages** originate from monocytes and are highly phagocytic
  - Fixed macrophages are permanently associated with certain tissues or organs (Kupffer and microglia)
  - Free macrophages are mobile and highly phagocytic (alveolar macrophages)
- Destroy by
  - internal digestion (lysosomes)
  - release toxins from a “respiratory burst”
  - release defensins or oxidizing chemicals

## Natural Killer (NK) Cells

- Unique population of cells designed to attack
  - cancer cells
  - virus infected cells
- Detect abnormal cells by differences in surface membrane proteins
- Kill by interaction of target cell (not phagocytic) which leads to destruction of target cell's membrane – release of perforins

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## Interferon (IFNs)

- Produced by cells invaded by viruses.
- Diffuses to cells and inhibits proteins synthesis; thus, viral replication
- Not viral specific
- *Alpha IFN* used to treat genital warts and hepatitis C

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## Complement

- Complement (20 plasma proteins)
  - complements activity of antibody (specific) or certain cell wall polysaccharides of various pathogens (non-specific)
  - enhances inflammation by promoting release of histamine, enhances blood vessel permeability, promotes chemotaxis, enhances phagocytosis
  - Terminates by insertion of complement proteins (MAC) into membrane of target cell and lysis of that cell

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## Inflammation

- Tissue response to injury
  - Promotes healing at the local level
    - Increased capillary permeability
    - Increased blood flow
    - Prevents spread of damaging agent
    - Activates macrophages -disposal of debris and pathogens
    - Prevents blood loss (clotting)
    - Possible limitation of movement (swelling)
    - Complement activation
    - Regional temperature increase
    - Activation of specific defenses

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## Signs of Inflammation

- Four signs of inflammation are
  - heat
  - redness
  - swelling
  - pain

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## Start of Inflammation

- Chemical mediators released by damaged tissues - fibrocytes, phagocytes, mast cells, etc.
- Chemicals include:
  - histamine, kinins, prostaglandins, complement, etc.
    - all promote vasodilation of arterioles and increased capillary permeability. Kinins result in attraction of leukocytes (chemotaxis).

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## Vasodilation of Arterioles

- Leads to local **hyperemia** (increased blood flow) which results in redness and heat.
- Increased temperature **increases cell metabolism** which promotes healing.

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## Increased Capillary Permeability

- Results in **swelling (edema) and pain**
- Leads to increased oxygen and nutrient delivery through interstitial spaces
- May lead to limitation in joint mobility
- May lead to clotting to prevent blood loss
- Chemical mediators (kinins) result in local attraction of leukocytes (chemotaxis) to area
  - phagocytosis of cell debris and pathogens

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## Fever

- Hypothalamus controls body temperature. **Pyrogens**, a variety of chemicals produced by active leukocytes and macrophages, reset body's thermostat.
- Fever (mild to moderate) promotes healing by
  - increasing metabolism, speeds repair and defense
  - causes spleen and liver to sequester iron and zinc which "starves" bacteria.
- High fever denatures enzymes and may be fatal

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## SPECIFIC BODY DEFENSES

### Adaptive Immunity

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## SPECIFIC BODY DEFENSES

- Immune response **recognizes specific foreign substances (antigens) and mounts a response against them.**
- Response includes
  - cell to cell interaction (cell mediated, or cellular)
    - usually involves direct cell-to-cell interaction and the release of cell-to-cell chemical mediators
  - production of antibodies (humoral)

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## Specific Immunity

(adaptive)

Define the following terms:

- Specific Immunity
  - Innate immunity
  - Acquired immunity
    - Active immunity
      - Naturally acquired immunity
      - Induced active immunity
    - Passive immunity
      - Induced passive immunity
      - Natural passive immunity

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## Specific Immunity

### The Body's Guard

(Animation from Rockefeller University presenting response to antigens- dendritic cells, lymph node, T cell response, etc.)



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## Properties of Immunity

- **Specificity**
  - Targets a specific antigen. Activation of specific lymphocytes and production of specific antibodies.
- **Versatility**
  - Defends against any antigen at any time. Many different lymphocytes and variations in antibodies
- **Memory**
  - Memory cell production allows a stronger and longer lasting second response to antigen
- **Tolerance**
  - Responds to antigens that are considered foreign. Tolerance for normal proteins.

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### Phagocyte Chemotaxis

(Animation from Wisconsin Online Resource Center)



### Inflammatory Response

(Animation from Sumanasinc.com presenting the non-specific inflammatory response (splinter, attraction of phagocytes);



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## T Cells and Cell Mediated Immunity

### THREE MAJOR TYPES OF T CELLS

- **Cytotoxic T cells**
  - Cell mediated immunity
- **Helper T cells**
  - Stimulate both T and B cells. Essential in stimulating activated B cells to produce antibody
- **Suppressor T cells**
  - Inhibit both T and B cells and moderate and suppress the immune response

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## ANTIGEN PRESENTATION

- T cells are activated by exposure to antigen  
Antigen presentation is usually by presentation of antigen on the surface of infected cell or by **antigen presenting cell (APC)**  
(Exposure of T cell is seldom by direct antigen to T cell exposure)

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## Antigens (Ags)

- **Mostly large complex molecules**
  - Mostly proteins and polysaccharides
- **Complete Antigens exhibit**
  - **Immunogenicity** the ability to stimulate specific lymphocytes for
    - **cell-to-cell interactions**
    - **antibody production**
  - **Reactivity** the stimulated cells and antibodies must be capable of interaction with the antigen

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## Antigens (Ags)

- Antigens that enter the body
  - Inhaled
  - Ingested
  - Injected (breaking skin or mucous membrane)
- Antigens produced by the body
  - Proteins encoded by viruses
  - Proteins encoded by mutant cells such as cancer

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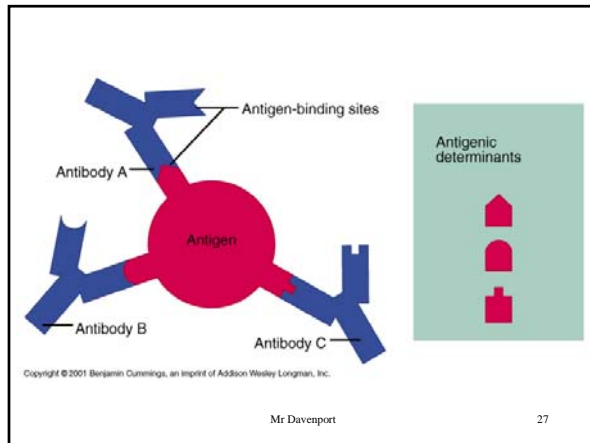
## Antigenic Determinates



- Parts of the complete antigen which are **immunogenic**. Provide binding sites for lymphocytes or antibodies
- Most antigens have many **antigenic determinates (epitopes)**; thus, many different lymphocytes and antibodies may react with the same antigen.
- Ideal implant materials would have no antigen determinates; thus, no immunogenicity.

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## Cellular Response

(Cancer Research Institute's animation explaining activation and effector phases of cellular immunity.)



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## HLA Complex (Human Leukocyte Antigen Complex), Mosby's Medical Dictionary, 8th edition. © 2009, Elsevier.

HLA complex, antigens in the region of chromosome 6 containing genes that code for proteins that enable the immune system to differentiate tissues or proteins between "self" and "nonself." These loci are identified by numbers and letters, such as HLA-B27. Antigens are divided into three classes. **Class I** antigens (HLA-A, -B, and -C) occur on the surface of all nucleated cells and platelets and are important in tissue transplantation. If donor and recipient HLA antigens do not match, the nonself antigens are recognized and destroyed by killer T cells. **Class II** antigens occur only on immunocompetent cells and normally recognize foreign proteins. **Class III** antigens are nonhistocompatibility antigens, such as some complement components, that map in the HLA complex. Also called **major histocompatibility complex**.

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## HLA or Major Histocompatibility Complex

- MHC proteins are membrane glycoproteins
- Unique to an individual because they are a result of gene expression.
- Two major classes of MHC proteins are
  - Class I are present in all nucleated cells (and platelets)
  - Class II are present only in antigen presenting cells (APCs) (macrophages, Kupffer cells, and microglia) and lymphocytes (immunocompetent cells)

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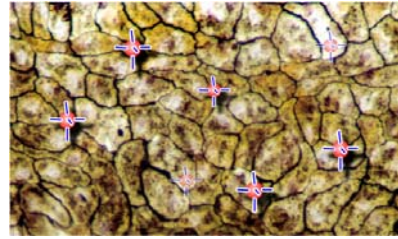
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## Class I MHC

- Proteins in membranes of all nucleated cells
- Continual synthesis and incorporation into cell membrane
- Incorporation of abnormal peptides into MHC I (because of infected cell) results in identification and activation of T cells.

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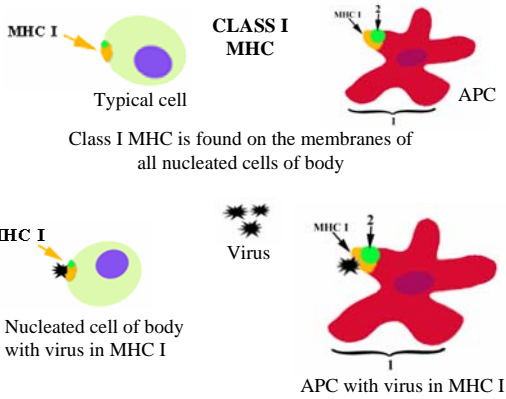


This is a surface-photo of squamous epithelium (similar to the surface cells at the back of the throat). How would your immune system know if this tissue was infected by a virus?

Virus

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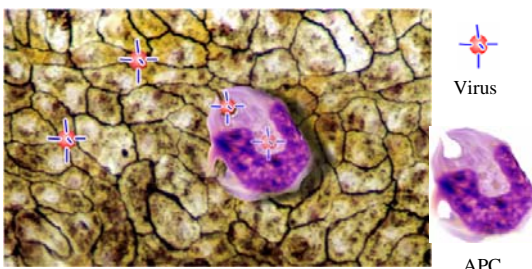
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## Class II MHC

- Present in membranes of antigen presenting cells, or APCs, which include macrophages, Kupffer cells, and microglia) and lymphocytes (T cells and B cells)
- APCs engulf and destroy antigen. Antigenic fragments are incorporated into class II MHC and are presented on membrane of APC.

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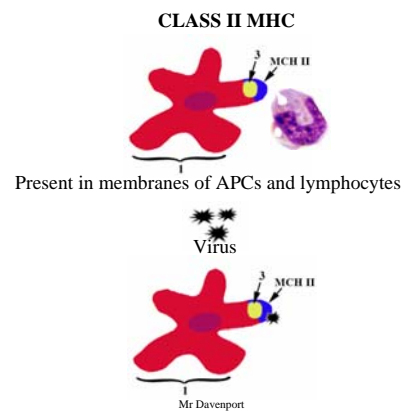
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The pathogen (virus) is phagocytized by the APC. What is an APC? What happens to the antigenic fragments?

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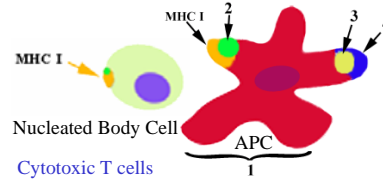
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## Antigen Recognition- T cells

- Inactive T cells have receptors that recognize either Class I or Class II MHC proteins
- Antigen recognition occurs when specific T cells contact MHCs that the T cell is genetically determined to detect
- T cell receptors are CD markers and are called either CD8 or CD4 markers.
  - CD8 are found on cytotoxic T cells (and suppressor T cells). **CD8 T cells respond to antigens presented by Class I MHC**
  - CD4 are found on helper T cells. **CD4 T cells respond to antigens presented by Class II MHC**
- Costimulation occurs when the presenting cell releases costimulation chemicals (cytokines). Results in T cells becoming active in cell division and differentiation.
- Active CD8 T cells and memory cells (inactive) are produced.

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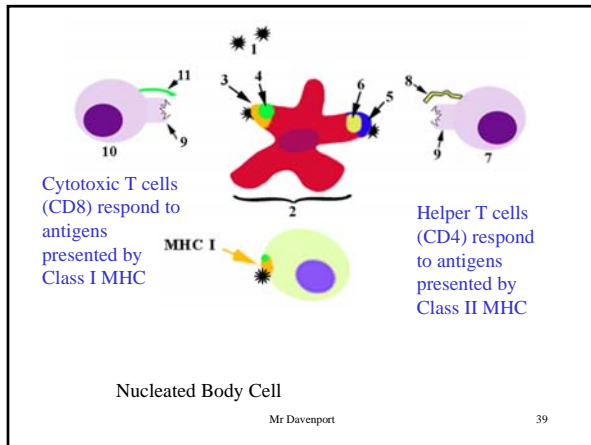


Cytotoxic T cells (CD8) respond to antigens presented by Class I MHC which is found on all nucleated cells.

Helper T cells (CD4) respond to antigens presented by Class II MHC which is found only on APCs (immunogenic cells).

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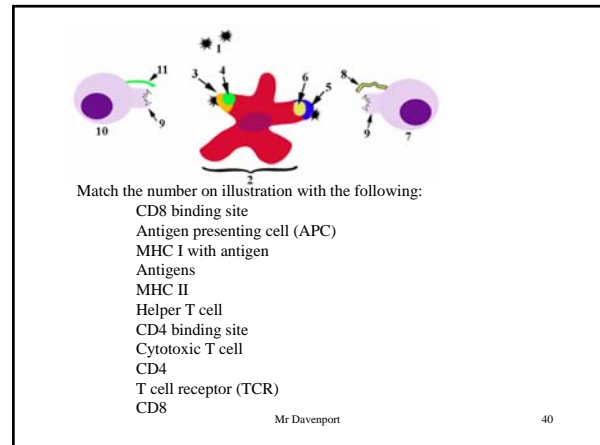
Cytotoxic T cells (CD8) respond to antigens presented by Class I MHC

Helper T cells (CD4) respond to antigens presented by Class II MHC

Nucleated Body Cell

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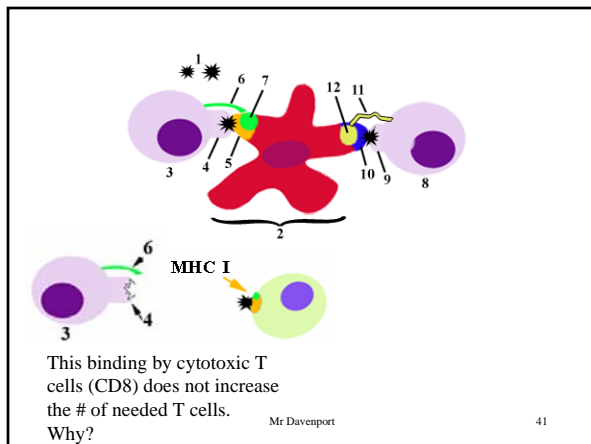


Match the number on illustration with the following:

- CD8 binding site
- Antigen presenting cell (APC)
- MHC I with antigen
- Antigens
- MHC II
- Helper T cell
- CD4 binding site
- Cytotoxic T cell
- CD4
- T cell receptor (TCR)
- CD8

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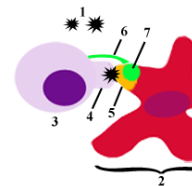


This binding by cytotoxic T cells (CD8) does not increase the # of needed T cells. Why?

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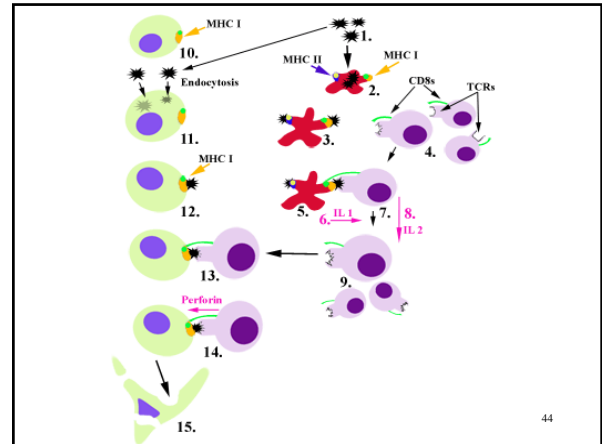
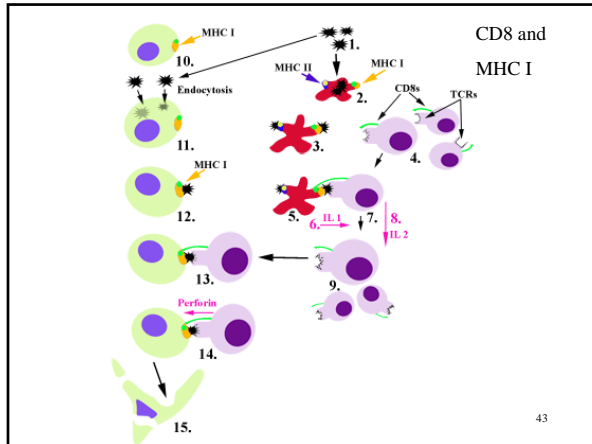
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## Activation and Role of CD8 (cytotoxic T cell)



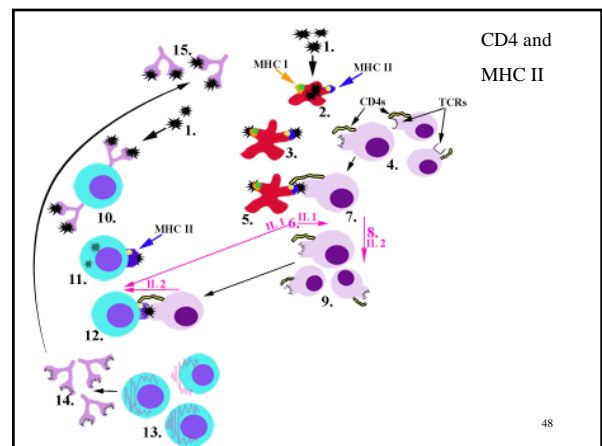
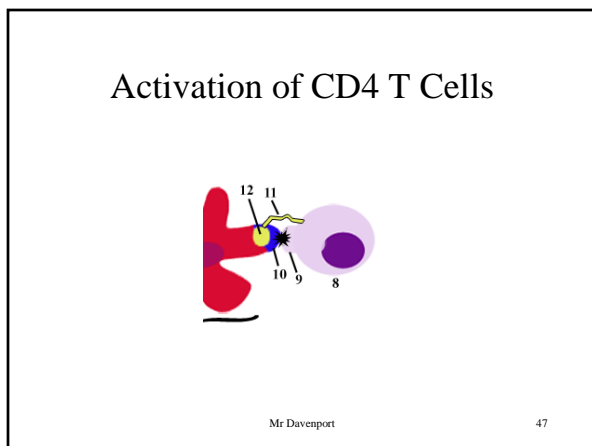
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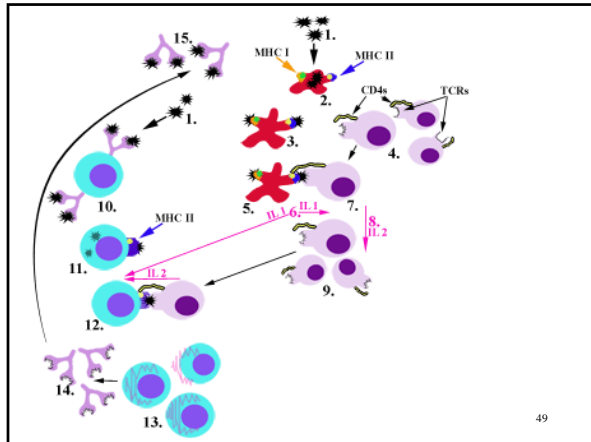
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- Antigen presenting cell showing antigen associated with MHC I (and MHC II)
- Antigen presenting cell with phagocytized antigen and normal MHCs
- APC bound to cytotoxic T cell (at MHC I and CD8)
- Antigen
- Immature cytotoxic T cells
- Cytotoxic T cell bound to MHC I and CD8 receptor of APC
- Released from APC and stimulates cytotoxic T cell to secrete interleukin 2
- Clone of mature (capable of releasing perforin) cytotoxic T cells
- Released from bound cytotoxic T cell and promotes cytotoxic T cell development and cloning.
- Endocytosis of antigen (typically a virus)
- Normal nucleated cell of body with normal MHC I (and associated CD8 receptor)
- Binding of mature cytotoxic T cell with antigen-bound MHC I (and binding of CD8 with receptor)
- Antigen expression on MHC I.
- Target cell lysis
- Mature cytotoxic T cell releases perforin on target cell


- ### Activation of CD4 T Cells
- Produces helper T cells (clones)
  - Helper T cells (CD4 cells) produce cytokines that
    - Stimulate T cell division
    - Enhance nonspecific immune defenses
    - Attract NK cells
    - Promote activation of B cells
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




- Immature helper T cells
- Antigen presenting cell with phagocytized antigen and normal MHCs
- APC bound to helper T cell (at TCR and CD4)
- Antigen presenting cell showing antigen associated with MHC II (and MHC I)
- Antigen
- Helper T cell bound to MHC II and CD4 receptor of APC
- Clone of mature helper T cells
- Released from APC and stimulates helper T cell to secrete interleukin 2 and promotes B cell development
- B cell with surface receptors for antigen (soluble)
- Released from bound helper T cell and promotes helper T cell development and cloning.
- Plasma cells develop after helper T cell binding.
- Activation of cytotoxic T cells
- B cell with endocytosis on antigen-bound receptors and antigen expression on MHC II.
- Antibodies agglutinate antigens.
- Mature helper T cell binding to B cell MHC II with antigen and binding to CD4 receptor.
- Antibodies (against the antigen) are secreted from plasma cells

## B Cells and Antibody Mediated Immunity

**Specific Immunity, Antibodies** 

**Macrophages, B-cells, Pathogens, Antibody Immune Response** 

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- ## B Cell Sensitization and Activation
- B cells have receptors (antibodies) in cell membrane that bind to corresponding antigens – sensitization
  - Bound antigens undergo phagocytosis and cell is activated.
  - Activated B cell binds to helper T cell that promotes B cell division and differentiation by the secretion of cytokines.
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- ## Antibodies
- Antibodies, or immunoglobulins (Igs), are component of plasma produced by plasma cells (or activated B cells)
  - Consist of four polypeptide chains which when joined produce a “T” or “Y” shape
  - Consist of one pair of heavy chains and one pair of light chains.
  - 5 types of constant segments of heavy chains thus 5 types of antibodies
  - Heavy chains also contain binding sites for complement system. Binding sites are uncovered when antibody binds to antigen. Thus, complement system is activated.
  - Light chains contain antigen binding sites.
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- ## Antigen-Antibody Complex
- Antibodies bind to antigenic determinate sites.
  - Complete antigen has at least two antigenic determinate sites and bind to each antigen binding site on the antibody molecule.
  - Antibodies may eliminate antigen by
    - Neutralization Attract phagocytes
    - Agglutination and Precipitation Opsonization
    - Complement Inflammation
    - Prevention of adhesion
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## Neutralization

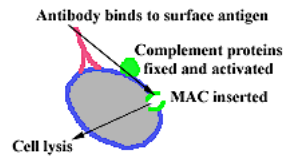


- Binding of antibodies blocks binding sites on pathogen (or toxin); thus, tissue cells are not subjected to injury

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## Complement Fixation



- Binding of antibody to antigen causes antibody to change shape. Thus, a region of the constant portion is exposed and allows the binding of a complement protein. Cascading events leads to the insertion of complement proteins, the membrane attack complex (MAC) and the lysis of the target cell.

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## Precipitation

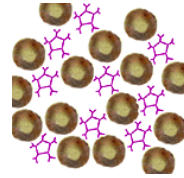


- Soluble molecules are cross-linked to form larger complexes. Complexes are easily captured for phagocytosis

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## Agglutination



- Cell antigens are cross-linked by antibodies. Typical in cross-reaction in mismatched blood. Complexes are easily captured for phagocytosis

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## Primary and Secondary Responses to Antigen Exposure

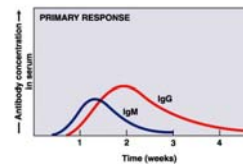
Applies to both Humoral and Cell-Mediated Memory

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## Primary Response

- Response to first encounter with an antigen
  - Typical lag period of 3 – 6 days
  - Antibody levels (titer) peak in about 10 days

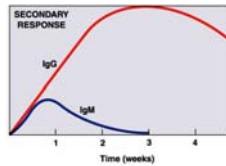


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## Secondary Response

- Subsequent encounter with the antigen
  - Within 2 – 3 days antibody level (titer) is higher than that reached in primary response
  - Antibody level can remain higher for a longer period of time
  - Memory cell population may last for a life time



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## Monoclonal Antibodies

- Pure antibody preparations specific for a single antigenic determinant
- Antibody producing cell is produced by fusing tumor cells with specific B lymphocytes. Thus, resulting hybrid cell
  - Divides indefinitely
  - Produces a single type of antibody
- Uses include
  - diagnosis of pregnancy, STDs, hepatitis, certain types of cancer, rabies, blood typing sera, RhoGam
  - injection of antibodies helps fight diseases such as leukemia and lymphomas

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## Anaphylaxis

- Exposure to allergen results in production of IgE antibodies
- IgE antibodies attach to mast cells and basophils
- Subsequent exposure to antigen binds to “antibodies” on mast cells and basophils which result in release of histamine (prostaglandins, cytokines)
- Histamine causes
  - Dilation of blood vessels and increased permeability which promotes edema
  - Stimulates the secretion of mucus
  - Stimulates the contraction of smooth muscles (in airways causes asthma)

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## Anaphylaxis

- Anaphylaxis may be local or systemic
  - Skin, gastrointestinal tract, and respiratory are local
  - Systemic typically involves allergen entering the blood such as bee stings. Circulatory collapse and restricted breathing may result in death.

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