Innate immunity
(nonspecific or natural)

- **Born with it,** do not need **prior exposure**
- The effectiveness of the immune response varies with age.

1. **First line of defense:** Designed to keep microorganisms out.
   - **A. Physical barriers,** such as epithelial cells (intact skin), trapping of bacteria in m
   - **B. Chemicals** secreted by cells and tissues, such as acidic pH of skin surface, complement, interferons, lysozymes.
2. **Second line of defense:**
   - **A. Phagocytosis:** The process of a white blood cell (WBC) engulfing bacteria.
   - **B. Inflammation:** Nonspecific response to tissue damage that includes:
     - Chemical release.
     - Cellular movement.
     - Elimination of foreign material.
     - Tissue repair.

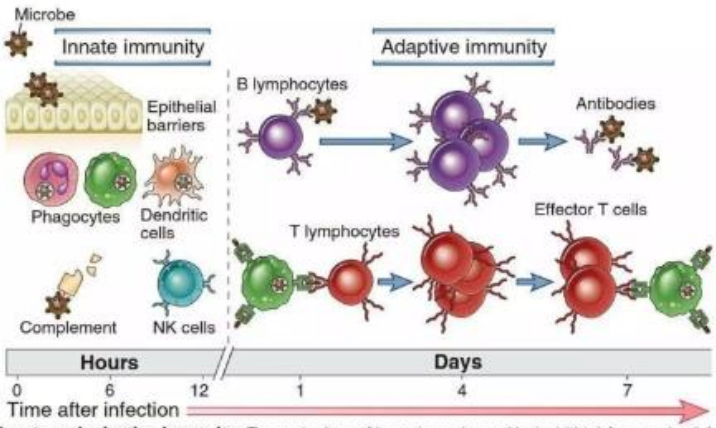


FIGURE 1–1 Innate and adaptive immunity. The mechanisms of innate immunity provide the initial defense against infections. Adaptive immune responses develop later and consist of activation of lymphocytes. The kinetics of the innate and adaptive immune responses are approximations and may vary in different infections.

The Immune System		
Innate (nonspecific) defense mechanisms		Adaptive (specific) defense mechanisms
First line of defense	Second line of defense	Third line of defense
• Skin • Mucous membranes • Secretions of skin and mucous membranes	• Phagocytic cells • Natural killer cells • Antimicrobial proteins • The inflammatory response	• Lymphocytes • Antibodies • Macrophages and other antigen-presenting cells

Type	Mechanism
Anatomic barriers	
Skin	Mechanical barrier retards entry of microbes. Acidic environment (pH 3–5) retards growth of microbes.
Mucous membranes	Normal flora compete with microbes for attachment sites and nutrients. Mucus entraps foreign microorganisms. Cilia propel microorganisms out of body.
Physiologic barriers	
Temperature	Normal body temperature inhibits growth of some pathogens. Fever response inhibits growth of some pathogens.
Low pH	Acidity of stomach contents kills most ingested microorganisms.
Chemical mediators	Lysozyme cleaves bacterial cell wall. Interferon induces antiviral state in uninfected cells. Complement lyses microorganisms or facilitates phagocytosis. Toll-like receptors recognize microbial molecules, signal cell to secrete immunostimulatory cytokines. Collectins disrupt cell wall of pathogen.
Phagocytic/endocytic barriers	Various cells internalize (endocytose) and break down foreign macromolecules. Specialized cells (blood monocytes, neutrophils, tissue macrophages) internalize (phagocytose), kill, and digest whole microorganisms.
Inflammatory barriers	Tissue damage and infection induce leakage of vascular fluid, containing serum proteins with antibacterial activity, and influx of phagocytic cells into the affected area.

- ***Inflammation***
- *Cardinal signs: Redness (rubor), Swelling (tumor), Heat (calor), Pain (dolor), Loss of functio (functio laesa).*
- *Sequenced events following tissue damage that protect the host from foreign invaders and att to minimize tissue damage*
- ***Increased vascular permeability***
  - *a. Upon injury, capillaries, arterioles, and venules are dilated to* ***increase blood flow*** *to i site of the injury.*
  - *b. Because of increased vascular permeability, fluid moves from the circulation to the spa around the injury, bringing fibrinogen and PMNs to the injury site.*
- ***Migration of neutrophils***
  - *After the injury,* ***chemotaxins*** *and* ***endothelial activating factors*** *are released.*
  - *PMNs adhere to activated* ***endothelial cells.***
  - *PMNs move between the endothelial cells to the site of tissue damage by a process called* ***diapedesis.***
  - *Chemicals are released and more PMNs are released from the storage pool, and the injury site is flooded with PMNs.*
- ***Migration of mononuclear cells***
  - *The macrophages release IL-1, which attracts monocytes, macrophages, and lymphocytes to the injury site.*
  - *About 4 hours after the injury, mononuclear cells migrate to the site of damage.*
  - *Cellular proliferation and repair: Fibroblasts help repair the damage and return the injury site to normal.*

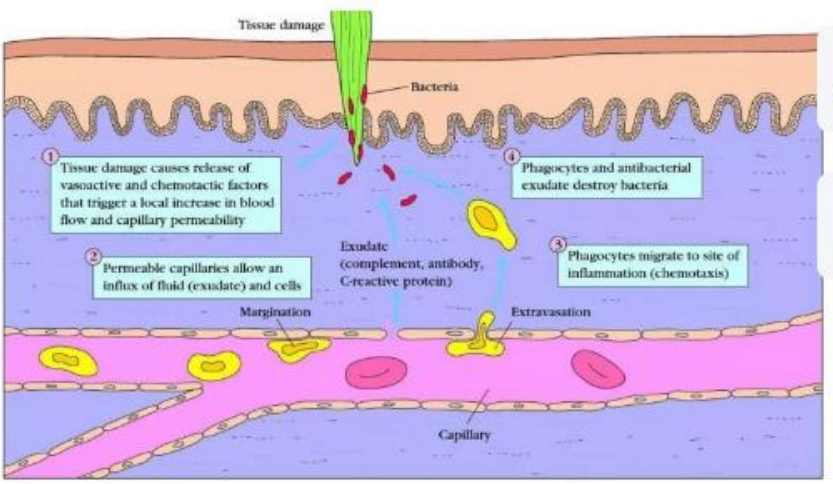
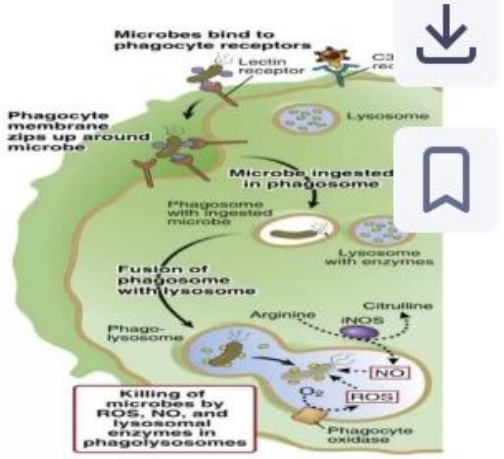


FIGURE 1-4 Major events in the inflammatory response. A bacterial infection causes tissue damage with release of various vasoactive and chemotactic factors. These factors induce increased blood flow to the area, increased capillary permeability, and an influx of white blood cells, including phagocytes and lymphocytes, from the blood into the tissues. The serum proteins contained in the exudate have antibacterial properties, and the phagocytes begin to engulf the bacteria, as illustrated in Figure 1-3.

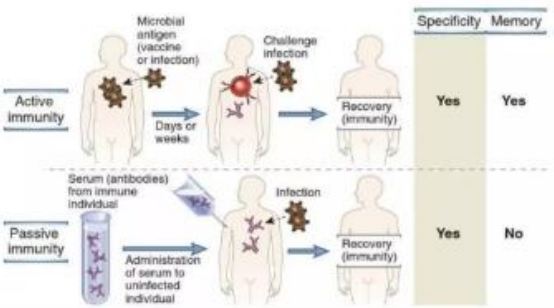
- *Phagocyte oxidase(phox), killing by reactive oxygen species, ROS,(NO, H2O2).*

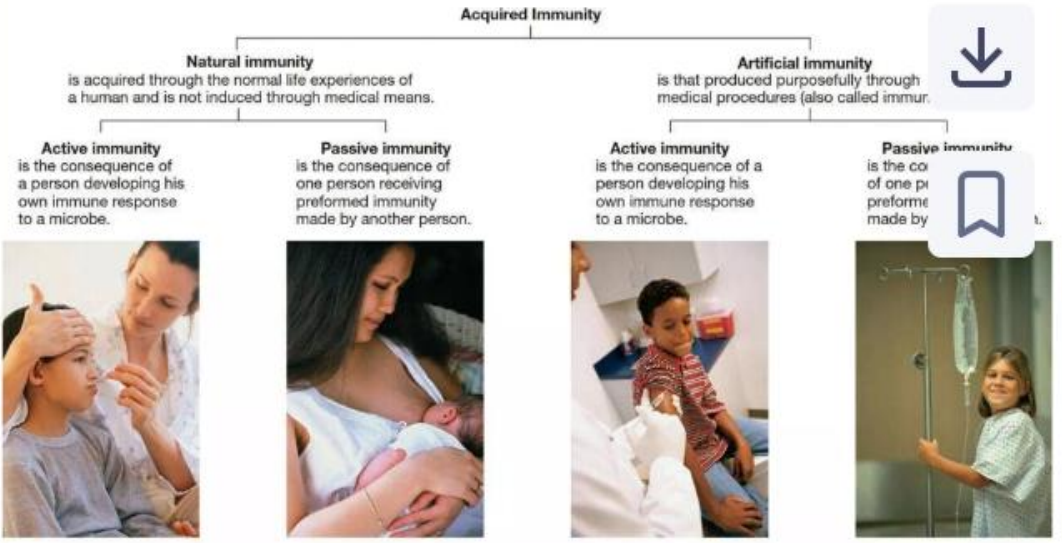


Adaptive
(specific or acquired)

- Acquired only after a **specific challenge** is encountered and responds specifically to the challenge.
- Two responses:
- **1. Humoral-mediated immunity (HMI)**
  - Against **extracellular** pathogens.
  - B lymphocyte activated **by T helper-2 cells** (Th-2) to plasma cell.
  - **Antibody** production by plasma cells.
- **2. Cell-mediated immunity (CMI)**
  - Against **intracellular** pathogens
  - **T helper-1 cells (Th-1).**
  - **Natural killer (NK) cells:** against viral and tumor cells
  - **Cytotoxic T lymphocytes** (CTLs)

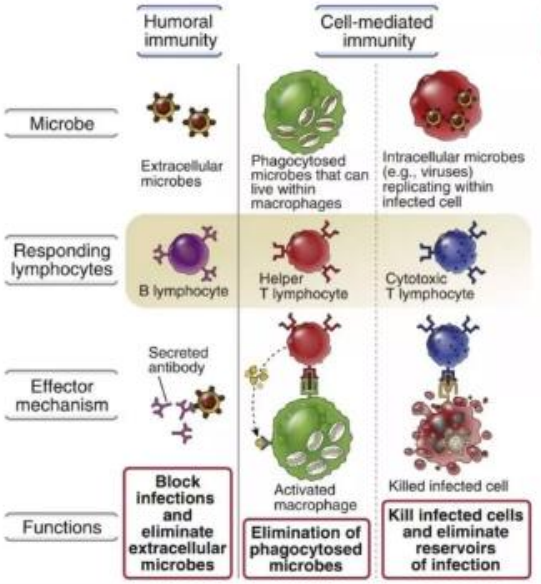
- **Adaptive immunity can be passive or active.**
- **Active immunity:**
  - **Natural:** The host is exposed **to foreign immunogen as a result of infection**, and the immune cells manufacture specific products to eliminate foreign immunogen.
  - **Artificial: Vaccination**; immune system responds to an **altered (noninfectious)** organ
  - Active immunity generally **endures for life.**
- **Passive immunity:**
  - **Natural: Maternal antibodies** crosses placenta to protect infant
  - **Artificial: Immune products** from another animal injected into the host (e.g., pooled gamma-globulin).
  - Passive transfer of lymphocytes is referred to as **adoptive transfer**.
  - Passive immunity **short term**; no memory cells produced

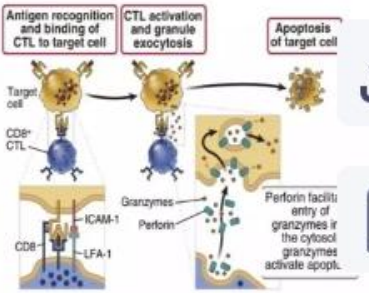


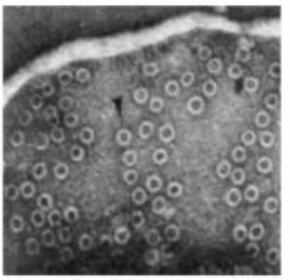


- **Cell-Mediated Immunity**
  - Mediated by TH 1 cells, a subset of T helper cells, that secrete cytokines that activ other cells involved in the response
  - Monocytes and macrophages are stimulated by cytokines from TH 1 cells, inflammatory reaction cells that are activated by cytokines.
  - CTLs are activated by cytokines from TH 1 cells and then destroy targets by cell-to contact. The main function of CTLs is to destroy virus infected
  - cells.
  - NK cells kill target cells without being previously sensitized. NK cell activities are governed by cytokines.
- **Humoral-Mediated Immunity**
  - B cell activation begins when antigen binds to antibody on B cell surface and the antigen is internalized and linked to an MHC II molecule on the cell's surface.
  - T and B cell interactions
    - B cell processes and presents the antigen, stimulating the TH 2 cell to produce cytokines.
    - The cytokines stimulate the B cell to divide and differentiate into a memory B cell or a plasma cell that will synthesize antibody.

- ***Antibody production:***
- *Primary and secondary antibody responses:*
  - ***1. Primary antibody response:***
    - *Produced when host first encounters antigen*
    - *During the latent phase, no antibody is produced for about 5-7 days. During thi time, the host is producing plasma cells that will secrete antibodies.*
    - *IgM is the first antibody produced.*
    - *Antibody production starts slowly, peaks, levels off, then declines.*
  - ***2. Secondary (anamnestic) response:***
    - *Produced after the host has previously been exposed to an antigen*
    - *Short latent phase (3-5 days)*
    - *Higher antibody concentration*
    - *IgG produced due to class switching*
    - *IgG antibodies persist longer in circulation than IgM.*
- ***Antibody-dependent cell-mediated cytotoxicity (ADCC):*** *Cytolytic effector cells (e.g., NK cells and PMNs) can lyse antibody coated target cells if there is direct contact.*





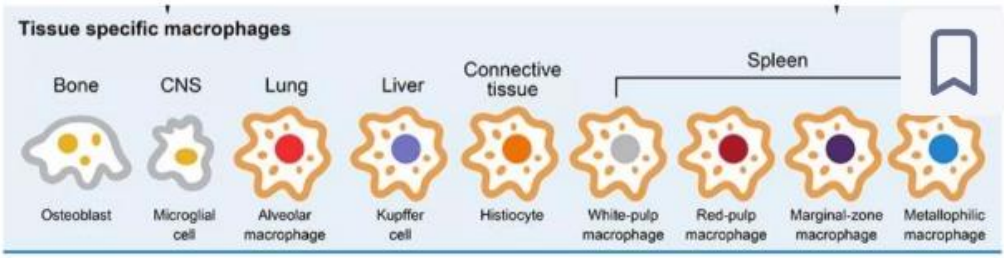


Cells and tissues of the immune system

- ***Cells of the Immune System***
  - *Phagocytes*
  - *Mast cells, Basophils, and Eosinophils*
  - *Antigens-Presenting Cells (APCs)*
  - *Lymphocytes*
- ***Lymphoid Tissues and Organs***
  - *Primary Lymphoid Organs*
  - *Secondary Lymphoid Organs*

- ***Phagocytes:***
  - *Phagocytes, are the cells whose primary function is to identify, ingest, and destroy microbes.*
  - *They comprise neutrophils and macrophages.*
  - *They are also called "professional phagocytes".*
- ***Neutrophils (PMNs):***
  - *The most abundant population of circulating leukocytes.*
  - *They are the cells of acute inflammatory immune response.*
  - *They have a segmented nucleus, hence the synonym "polymorphonuclear neutrophil*
  - *They have two types of granules; specific ones, which are filled with enzymes such lysozyme, and azurophilic granules (lysosomes).*
- ***Mononuclear phagocytes:***
  - *This system is composed of the less-differentiated, circulating monocytes, and the mature tissue macrophages.*
  - *MØs are given special names according to their tissue of location, e.g. Kupffer cells in the liver and microglial cells in the CNS.*
  - *MØs perform several important functions in innate and adaptive immunity:*
    1. *Phagocytosis*
    2. *They clean dead cells and tissue debris (act as scavengers)*
    3. *They secrete cytokines (monokines), such as TNF-α and IL-1*
    4. *They function as APCs*

- *Macrophages have major histocompatibility complex (MHC) class II, complement, and antibody Fc receptors on their surface.*



- ***Mast cells, Basophils and Eosinophils:***
  - *They have cytoplasmic granules filled with various inflammatory and antimicrobial medi*
  - *They are involved in immune responses that protect against helminths and immune responses that cause allergic diseases.*
  - *They work in cooperation with IgE, since they have FcεR.*
- *Platelets (mediators): release substances that mediate immune reactions.*
- *The mediators produce increased vascular permeability, smooth muscle contraction, chemotaxins for phagocytes, and increased inflammatory response.*
- **Antigen-Presenting cells (APCs):**
- signature molecules in microbes, PRR).
  - *Are cell population that are specialized in capturing Ags, displaying them to lymphocytes to stimulate their proliferation and differentiation.*
  - *Macrophages, B-cells, and dendritic cells (DCs) express MHC class II and function as APCs.*
  - *These cells represent the link between innate and adaptive immune responses.*

- *DCs are the most important APCs, being capable of presenting Ags to naïve T-cells.*

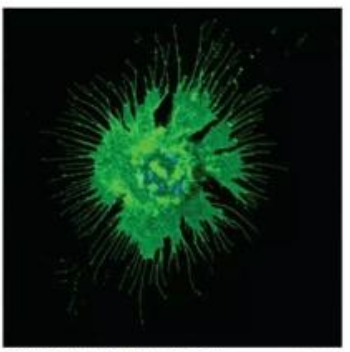


FIGURE 2–4 A dendritic cell. The fluorescence photomicrograph shows a bone marrow–derived dendritic cell in which class II MHC molecules appear green, highlighting the fine cytoplasmic processes characteristic of dendritic cells, and the nucleus appears blue. Class II MHC molecules are highly expressed in dendritic cells and are important for their function (see Chapter 6). *(Courtesy of Scott Loughhead and UA Von Andrian, Harvard Medical School, Boston, Massachusetts.)*

- ***LYMPHOCYTES:***
  - *Are the cells of the adaptive immunity.*
  - *The only cells in the body that express "antigen-specific" receptors.*
  - *They are said to be clonally distributed and antigenically committed.*
  - *Morphologically, all lymphocytes are similar, but they differ in terms of their function and surface markers.*
- ***B lymphocytes (Bursa of Fabricius, Bone Marrow-derived):***
  - *They express mIgM (BCR), and MHC class II.*
  - *They secrete Abs, and differentiate into* ***plasma cells*** *(i.e. involved in humoral immunity).*
  - *Memory cell.*
- ***T lymphocytes (Thymus-derived)***
  - *They express TCR and CD3.*
  - *Have two major subdivisions; CD4+ cells (helper T cells), and CD8+ cells (cytotoxic T cells).*
  - *Stimulate (Th cells) or suppress (Ts cells).*
- ***Non-T non-B lymphocytes (Natural Killer cells or Null cells):***
  - *NK cells are large granular lymphocytes (LGL).*
  - *Guard the body against viral infection and tumor growth.*
  - *They are* ***non-specific****.*

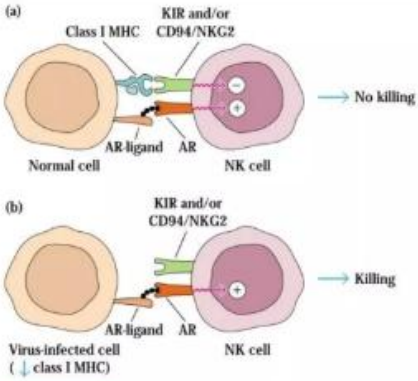


FIGURE 14.14 Opposing-signals model of how cytotoxic activity of NK cells is restricted to altered self-cells. An activation receptor (AR) on NK cells interacts with its ligand on normal and altered self-cells, inducing an activation signal that results in killing. However, engagement of inhibitory NK cell receptors such as KIR and CD94/NKG2 by class I MHC molecules delivers an inhibitory signal that counteracts the activation signal. Expression of class I molecules on normal cells thus prevents their destruction by NK cells. Because class I expression is often decreased on altered self-cells, the killing signal predominates, leading to their destruction.

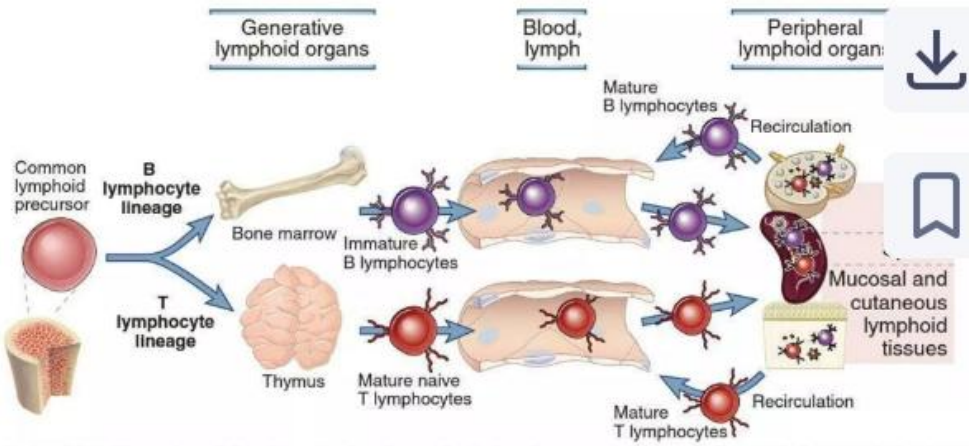


FIGURE 2-5 Maturation of lymphocytes. Lymphocytes develop from bone marrow stem cells and mature in the generative lymphoid organs (bone marrow and thymus for B and T cells, respectively) and then circulate through the blood to secondary lymphoid organs (lymph nodes, spleen, regional lymphoid tissues such as mucosa-associated lymphoid tissues). Fully mature T cells leave the thymus, but immature B cells leave the bone marrow and complete their maturation in secondary lymphoid organs. Naive lymphocytes may respond to foreign antigens in these secondary lymphoid tissues or return by lymphatic drainage to the blood and recirculate through other secondary lymphoid organs.

LYMPHOID TISSUES AND ORGANS:

- ***Generative (primary, or central) lymphoid organs*** *where lymphocytes develop and m and express Ag-specific receptors (bone marrow and thymus gland).*
- ***Peripheral or secondary lymphoid organs*** *where lymphocytes respond to Ags. These i lymph nodes, spleen, mucosa-associated lymphoid tissue (MALT).*
  - ***. Lymph nodes:*** *B cells migrate to the cortex and T cells to the paracortex.*
    - ***Primary follicle:*** *Many small B cells*
    - ***Secondary follicle:*** *After stimulation, primary follicle becomes a secondary fol The germinal center has small and large lymphocytes, blast cells, macrophages, dendritic cells. The medulla contains plasma cells and large lymphocytes.*
  - ***. Spleen***
    - *Purpose: Filter blood*
    - *Contains both T and B cells*

  Mucosal-associated lymphoid tissue (MALT)
    - *Gut-associated lymphoid tissue-GALT).*
      - ***Peyer's patch:*** *Specialized MALT found in the lower ileum.*
    - *Respiratory tract (bronchus-associated lymphoid tissue-BALT, nasal-associated lymphoid tissue (NALT).*
    - *Urogenital tract (UGALT).*
    - *Cutaneous-associated lymphoid tissue (CALT).*

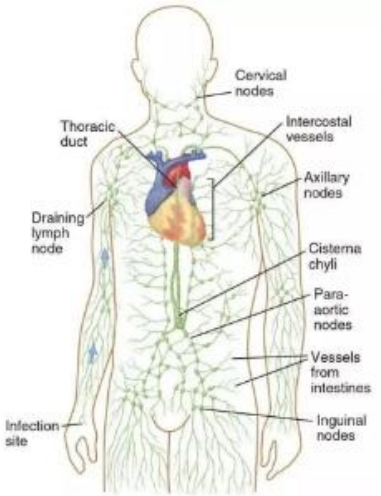


FIGURE 2–11 The lymphatic system. The major lymphatic vessels, which drain into the inferior vena cava (and superior vena cava, not shown), and collections of lymph nodes are illustrated. Antigens are captured from a site of infection and the draining lymph node to which these antigens are transported and where the immune response is initiated.

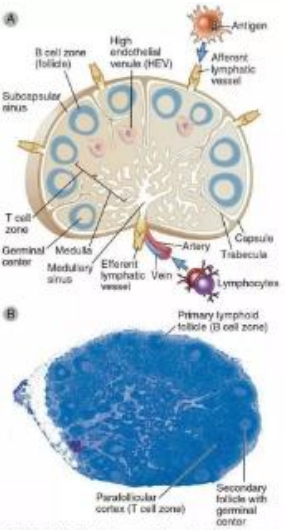


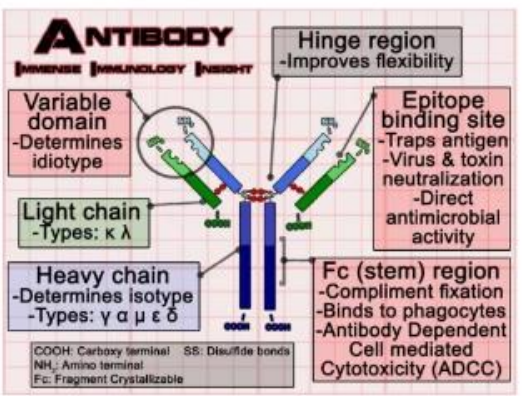
FIGURE 2–12 Morphology of a lymph node. A, Schematic diagram of a lymph node illustrating the T cell–rich and B cell–rich zones and the routes of entry of lymphocytes and antigen (shown captured by a dendritic cell). **B,** Light micrograph of a lymph node illustrating the T cell and B cell zones. (Courtesy of Dr. James Gulizia, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)

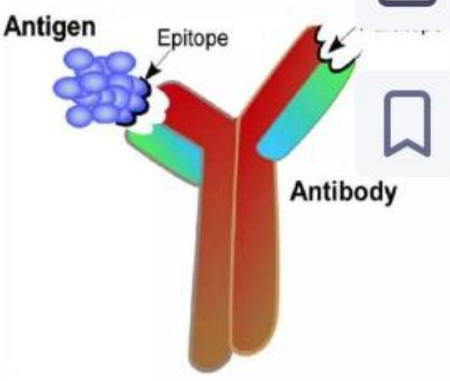
- ***Antigens and immunogens:***
  - *Self Ag: not induce immune response (auto tolerance).*
  - ***Immunogen:*** *A substance capable of inducing an immune response*
  - ***Antigen:*** *A substance that specifically interacts with cells or substances of the immune system. Immunogens are also antigens, but not all antigens produce a immune response.*
  - *A* ***hapten*** *is a low-molecular-weight molecule that alone is too small to stimula immune response but can combine with another molecule (a carrier) to induce response.*
  - ***Adjuvant*** *is a compound that enhances an immune response. It is not immunogenic and cannot induce an antibody response alone.*
  - ***Epitope:*** *The portion of a molecule (i.e., antigen) that binds to an antibody or T cell receptor.*
  - ***Thymic-dependent immunogens:*** *Molecules that require T helper cells to stimulate antibody formation.*
  - ***Thymic-independent immunogens:*** *Molecules that initiate antibody production without stimulating T helper cells.*

- ***Immunogenicity characteristics:***
  - ***Foreignness:*** *Must be recognized by the body as "nonself"*
  - ***Size:*** *Greater than 10 kilodaltons*
  - ***Chemical composition:*** *Proteins and carbohydrates are the most immunogenic, whereas lipids and nucleic acids are weakly immunogeni*
  - ***Complexity:*** *The more complex a molecule, the more immunogenic it becomes.*
  - *Route of entry into the host also determines immunogenicity.*
  - *Dose of immunogen affects immunogenicity.*
  - ***Degradability:*** *The immunogen needs to be degraded and presented to cells of the immune system.*

Antibody (immunoglobulin [Ig] or gammaglobul

- *A proteins that binds to antigens. There are five classes:* ***IgG, IgM, IgE, IgA,*** *and* ***IgD.***
- *Antibodies primarily migrate in the beta and gamma regions during protein electrophoresis.*
- *Antibodies are composed of* ***two heavy*** *polypeptide chains and* ***two light*** *polypeptide chains*
- ***Light chains:***
  - *Two types:* ***kappa*** *and* ***lambda.***
- ***Heavy chains:***
  - *Immunoglobulin classes are defined by a unique heavy chain: IgM-mu, IgG-gamrna, IgA-alpha, IgD-delta, IgE-epsilon.*
- *Every heavy chain and light chain consists of one* ***variable domain*** *and one or more* ***constant domain.***
- *The variable domain defines the specificity of an antibody. This portion of the molecule is referred to as the* ***fragment of antigen binding (Fab).***
- *The* ***crystalline fragment (Fc)*** *of the antibody is located at the carboxy-terminus. It is responsible for the biological activity of the molecule, including activating complement, binding phagocytic cells.*
- *J* ***(joining) chain:*** *Multiple monomers of IgM and IgA are linked by a J chain. One J chain is needed for each IgM or IgA molecule that is linked together.*





Antibody classes:

1. IgG:

- **Predominant serum antibody,** approximately **75%** of immunoglobul in the blood
- **Subclasses** include IgGl, IgG2, IgG3, and IgG4.
- **Only immunoglobulin that crosses the placenta**
- Produced in **secondary (anamnestic)** antibody response
- IgG I, IgG2, and IgG3 activate the classical complement pathway.

2. IgM:

- **Five monomers** linked together by a J chain and interchain disulfide bonds
- 10% of total serum immunoglobulins
- **First antibody produced against an immunogen**
- Produced in both primary and secondary immune responses
- It is the **best activator of the classical pathway of complement-only** one molecule of IgM is required.

3. lgA:

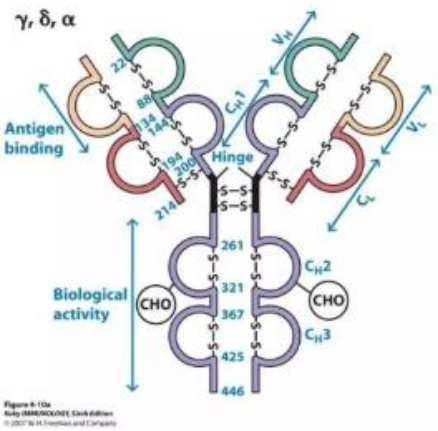
- **Serum and secretory forms:** Serum IgA is a single immunoglobulin molecule whereas secretory IgA is a dimer held together by a J chain.
- Two **subclasses:** IgAI and IgA2
- Accounts for 15-20% of total serum antibody
- The functions of serum IgA are antigen clearance and immune regulation.
- The function of IgA in mucous membranes is to block attachment of viruses, bacteria, and toxins to host cells.

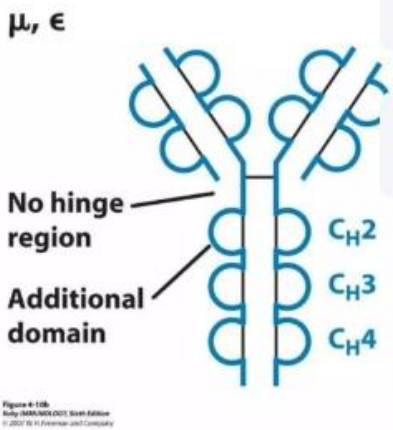
4. IgD:

- Primarily a cell membrane surface component of B lymphocytes
- Short half-life (2-3 days)

5. lgE:

- **Responsible for allergic (type I hypersensitivity) reactions**
- **The Fe portion binds to receptors on mast cells and basophils.**
- Once attached to mast cells, IgE binding an allergen triggers degranulation of the cell and release of allergic mediators such as histamine and leukotrienes.
- Elevated lgE concentrations are often found during parasitic infections.





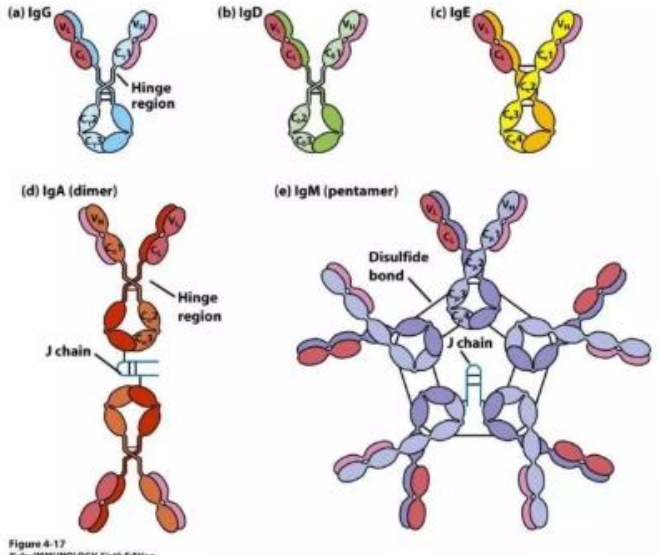


Figure 4-17
Kuby IMMUNOLOGY, Sixth Edition

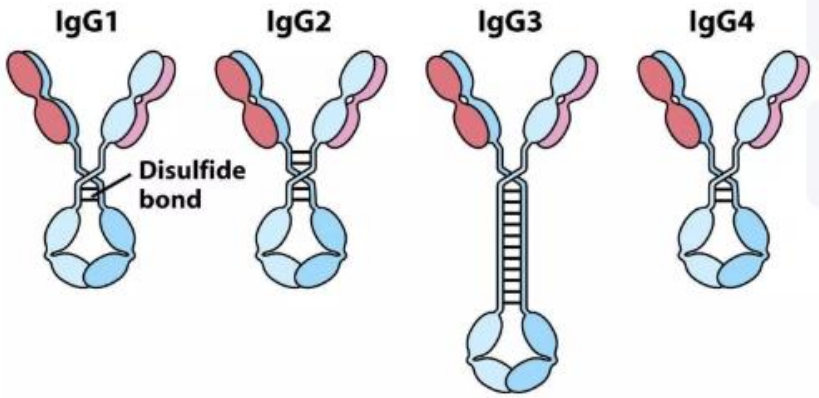


Figure 4-18
Kuby IMMUNOLOGY, Sixth Edition

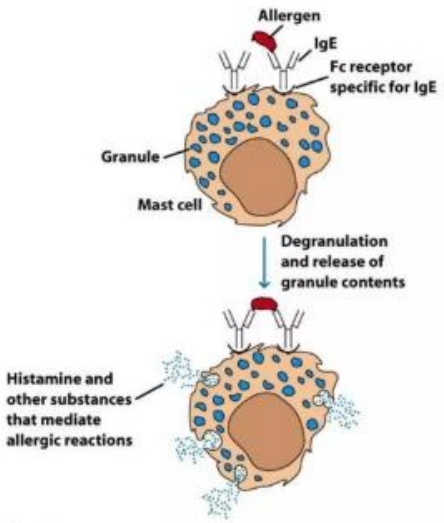


Figure 4-20
Kuby IMMUNOLOGY, Sixth Edition

- *Immunoglobulins when injected into another species can be immunogenic.*
- *Isotypic: differences in constant region from one species to another.*
- *Allotypic: differences (alleles) that occur in some individuals.*
- *Idiotypic: differences in variable regions, will differ even on Abs of same isotype.*
- *Affinity: strength of the interaction between single epitope and single paratope.*
- *Avidity: overall strength of antigen-antibody complex.*

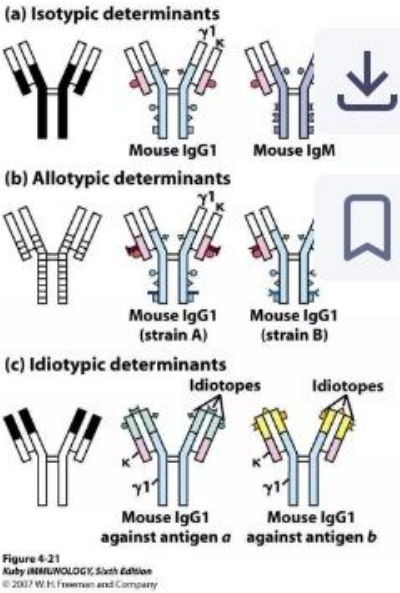
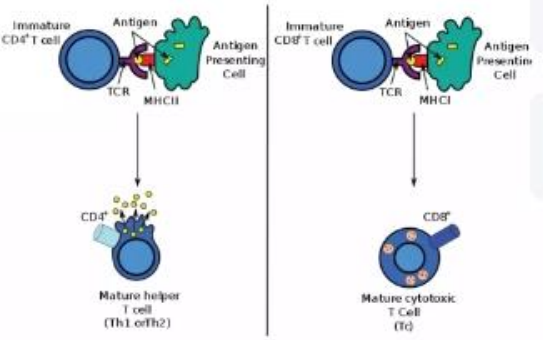


Figure 4-21
Kuby IMMUNOLOGY, Sixth Edition
© 2007 W.H. Freeman and Company

MAJOR HISTOCOMPATIBILITY COMPLEX
Human Leukocyte Antigens

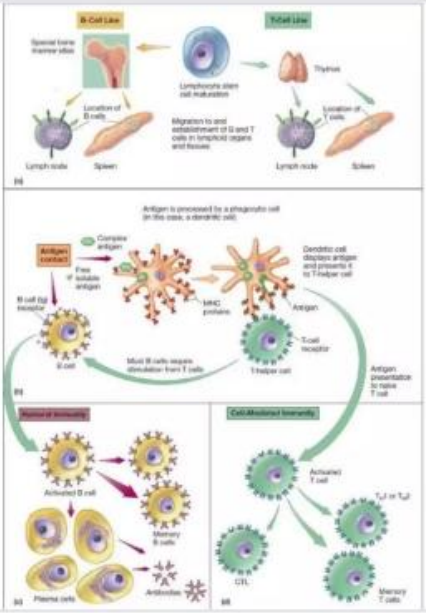
- *Human leukocyte antigens (HLAs) are **cell surface markers** that allow immune cells to distinguish "self' from "nonself."*
- *These antigens were first described on white blood cells (leukocytes) and are coded for b genes in the **MHC** located on chromosome six.*
- ***Three Classes of MHC Products***
  - ***Class I***
    - ***loci:** HLA-A, HLA-B, HLA-C, HLA-E, HLA-F, HLA-G, and HLA-J*
    - *Molecules found on nearly every nucleated cell surface*
    - *Antigen-presenting cells with MHC I molecules present antigens to CTLs.*
  - ***Class II:***
    - *13 loci, including HLA-DM, HLA-DO, HLA-DP, HLA-DQ, and HLA-DR*
    - *Molecules located on the surface of monocytes, macrophages, B cells, activated T cells, dendritic cells, Langerhans' cells, and some epithelial cells*
    - *Antigen-presenting cells with MHC II molecules present antigens to T helper cells.*
  - ***Class III** products:*
    - *Complement proteins, TNFa and 13, and other proteins (e.g., heat shock protein) not associated with cell membrane surfaces*

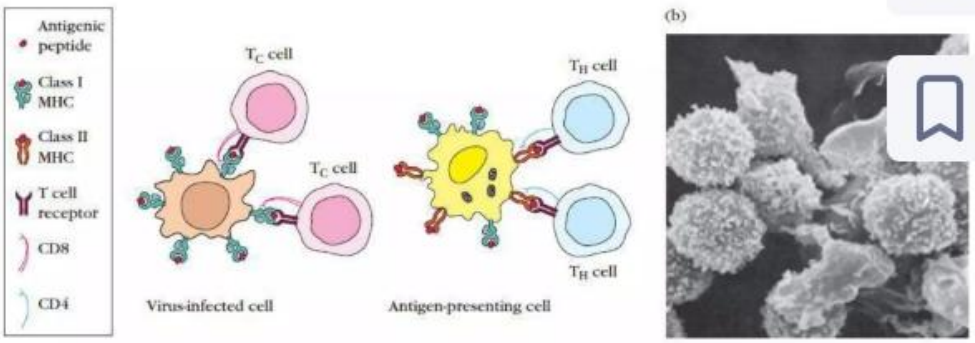
Function of Antigen presenting cells(APCs), DCs, macrophages and B-cells: capture, processing and presentation of Ags to T-cell by MHC molecules.

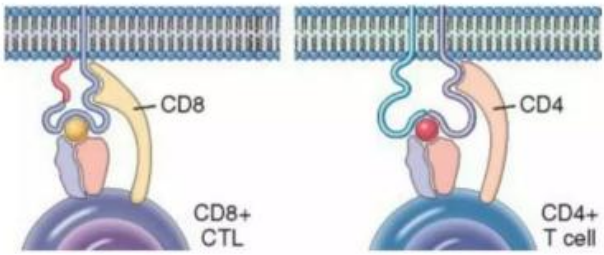


T and B lymphocytes

- *Activation and Differentiation of T-Cells*
- *Activation and Differentiation of B-Cells*
- *Humoral vs Cellular Immunity*
- *The Clonal Selection Theory*

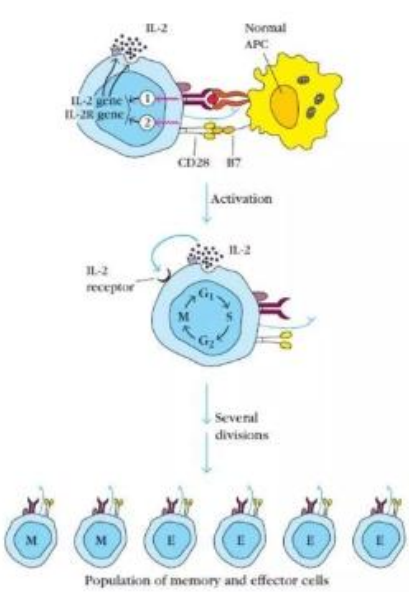


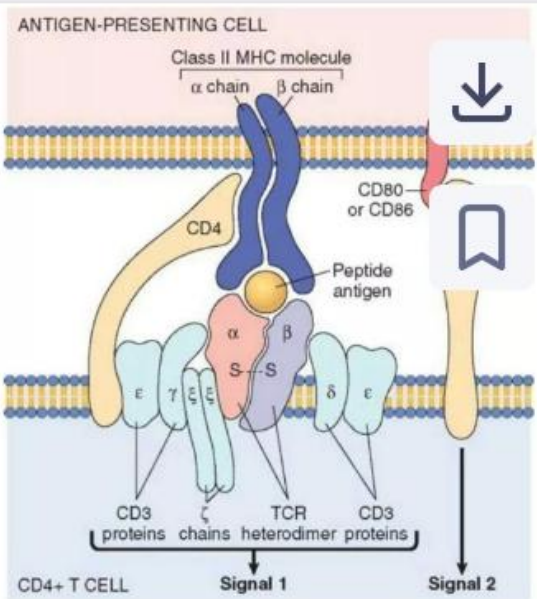


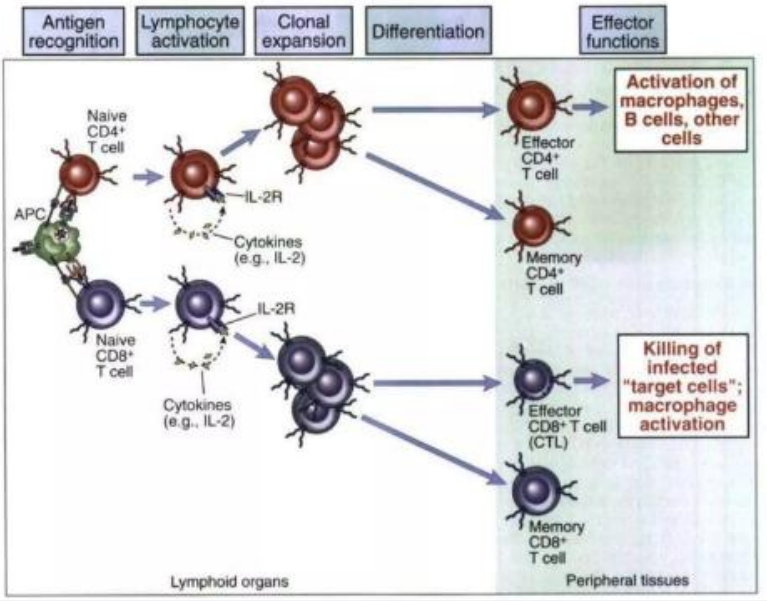


T-Lymphocytes Activation

- *Activation of T-cells require the interaction of TCR-CD3 complex with a processed antigenic peptide bound to self-MHC molecule, this is termed **signal 1**.*
- ***Signal 2** involves interactions between CD28 on the T-cell and members of the B7 f on the APC (**the co-stimulatory signal**).*
- *Activation causes cells to enter the cell cycle, resulting in their proliferation and differentiation into **effector** and **memory** cells.*

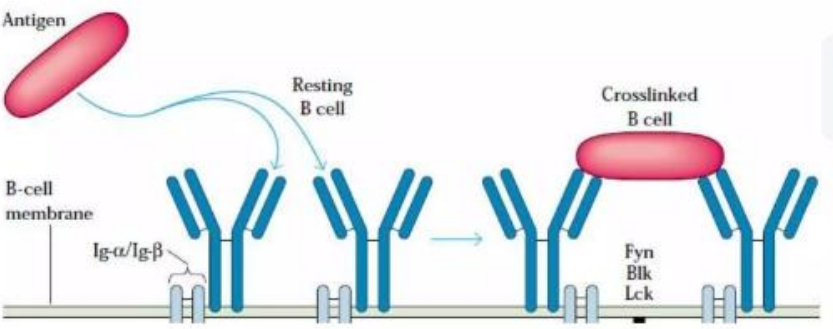


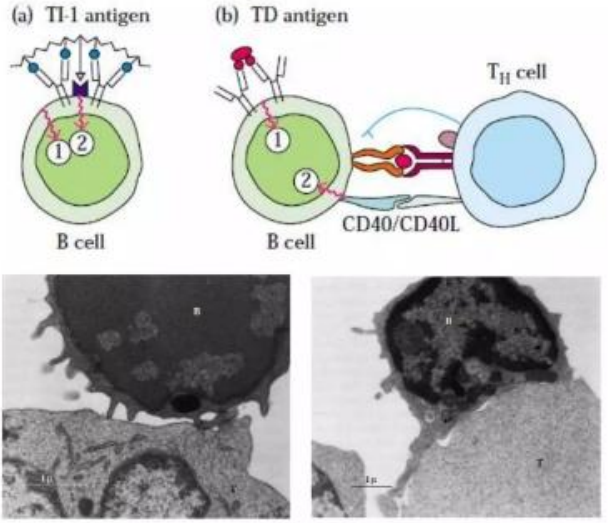


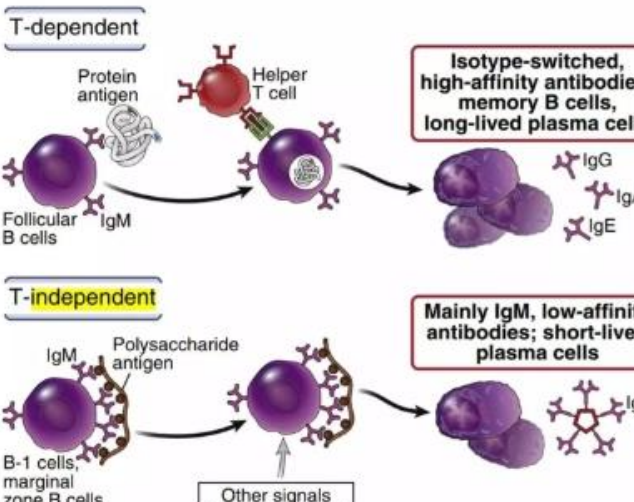


B-Lymphocytes Activation

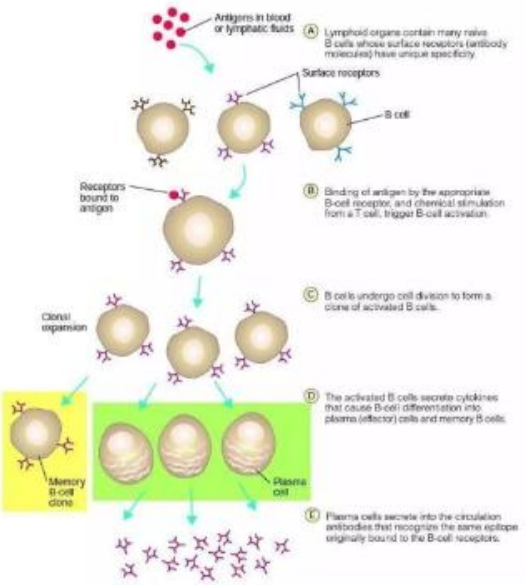
- *In contrast to T-cells, B-cells recognize **intact**, **unprocessed antigens** via their mIgM.*
- *Like T-cells, two signals are required for activation. In addition to antigen binding through BCR, the second signal is delivered differently in TD and TI antigens.*
- *Activation leads to proliferation and differentiation into **plasma** and **memory** cells*




(a) TI-1 antigen
(b) TD antigen
T_H cell
1
2
B cell
B cell
CD40/CD40L

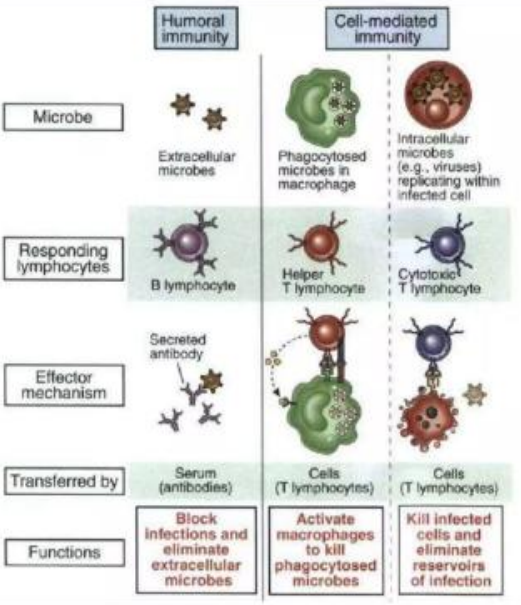


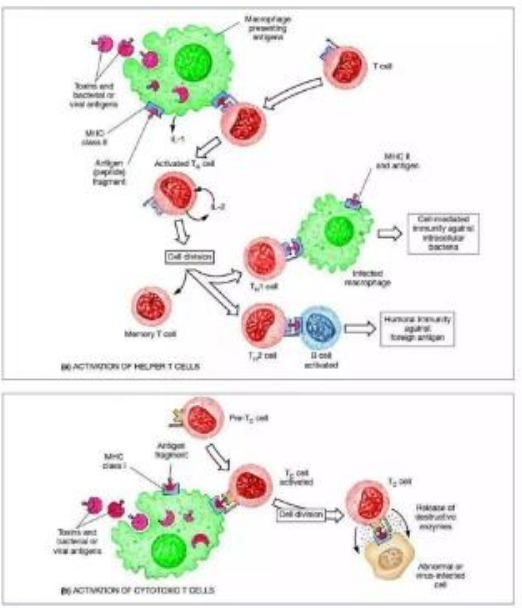
T-dependent
Protein antigen
Helper T cell
Isotype-switched, high-affinity antibodies; memory B cells, long-lived plasma cells
IgG
IgA
IgE
Follicular B cells
IgM
T-independent
IgM
Polysaccharide antigen
Mainly IgM, low-affinity antibodies; short-lived plasma cells
IgM
B-1 cells, marginal zone B cells
Other signals (e.g., complement protein, microbial product)

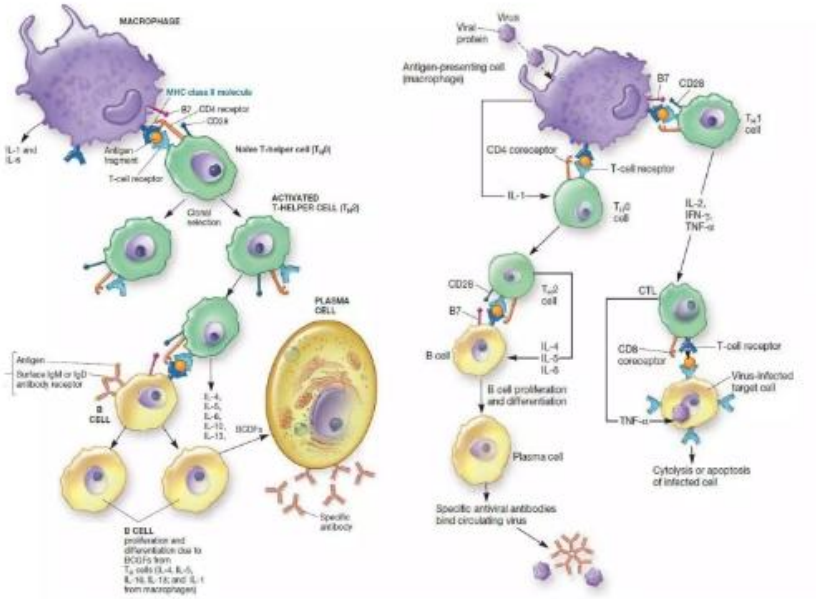

Antigens in blood or lymphatic fluids
A Lymphoid organs contain many naive B cells whose surface receptors (antibody molecules) have unique specificity.
Surface receptors
B cell
Receptors bound to antigen
B Binding of antigen by the appropriate B-cell receptor, and chemical stimulation from a T cell, trigger B-cell activation.
C B cells undergo cell division to form a clone of activated B cells.
Clonal expansion
D The activated B cells secrete cytokines that cause B-cell differentiation into plasma (effector) cells and memory B cells.
Memory B-cell clone
Plasma cell
E Plasma cells secrete into the circulation antibodies that recognize the same epitope originally bound to the B-cell receptors.

Humoral vs Cellular Immunity

- *Activation of **Th cells** is essential in developing the both types of immune response.*
- *Humoral immune response is concerned with extracellular antigens, mediated by antibodies that are produced by plasma cells after the influence of **Th_2** cytokines.*
- *CMI is responsible for eliminating intracellular antigens, either ingested in vesicles **macrophages**, or presented to **CTLs**. This requires the help of **Th_1** cytokines.*

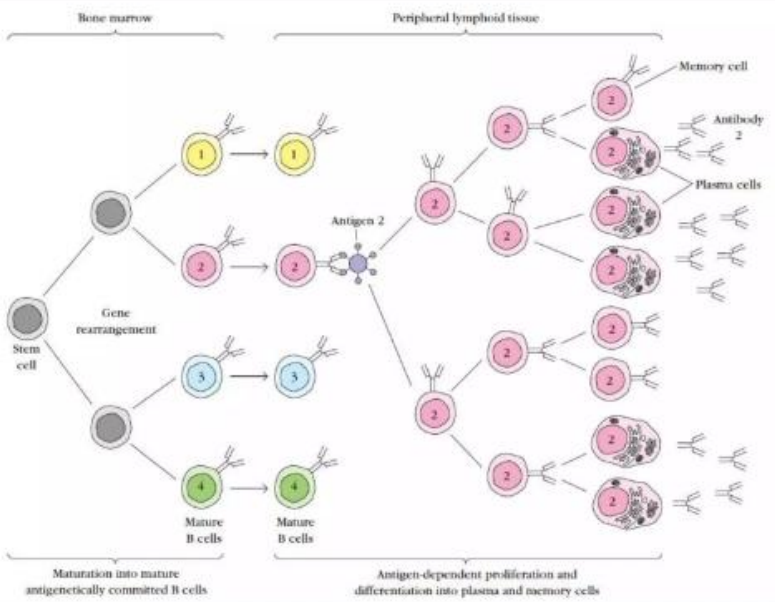






Clonal Selection Theory

- *A mature immunocompetent animal contains a large number of antigen-reactive clones of T and B lymphocytes.*
- *When an **antigen** binds to a clone of cells with the **same antigenic receptor** for th antigen, expansion of that clone occurs, thus, the antigen has "**selected**" the clone.*
- *Clonal selection results in many cells with the same specificity as the parent cell, an production of memory cells.*



Cytokines

- *Soluble protein molecules secreted by one cell type that affect other cells, turn on genes target cells*

TABLE 4-1 IMPORTANT CYTOKINES		
Cytokine	**Cellular Source**	**Primary Target**
IL-1	Macrophages, B cells, fibroblasts, etc.	T cells, B cells, macrophages, endothelium, tissue cells
IL-2	T cells	T cells
IL-3	T cells	Stem cells
IL-4	T cells	B cells, T cells
IL-5	T cells	B cells
IL-6	T cells, B cells, fibroblasts, macrophages	B cells, hepatocytes
IL-7	Bone marrow, stromal cells	Pre-B cells, T cells
IL-8	Monocytes	Fibroblasts
IL-9	T cells	T cells, mast cells
IL-10	T cells	TH 1 cells
TNF	Macrophages, mast cells, lymphocytes	Macrophages, granulocytes, tissue cells
IFN-α	Leukocytes, epithelia, fibroblasts	Tissue cells
IFN-β	Fibroblasts, epithelia	Tissue cells, leukocytes
IFN-γ	T cells, NK cells, epithelia, fibroblasts	Leukocytes, tissue cells, TH 2 cells

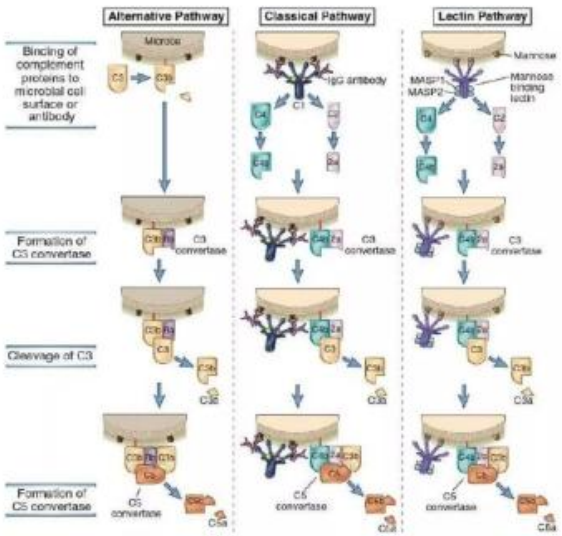
- ***Interferons:***
  - *Interferon-alpha* ***(INF-alpha)*** *and* ***INF-beta*** *are antiviral proteins that inhibit viral replication and activate NK cells. They are produced by viral-infected cells.*
  - ***INF-gamma****, has antiviral effects, activates macrophages and NK cells, stimulates B cells to produce antibodies. It is produced by TH 1 cells.*
- ***Tissue necrosis factors:***
  - ***Tumor necrosis factor-alpha*** *(****TNF-alpha****): Produced by macrophages, lymphocytes, and NK cells when encountering bacteria, viruses, tumor cells, toxins, and complement protein C5a*
  - ***TNF-beta****: Produced by CD4 and CD8 positive cells after exposure to a specific antigen*

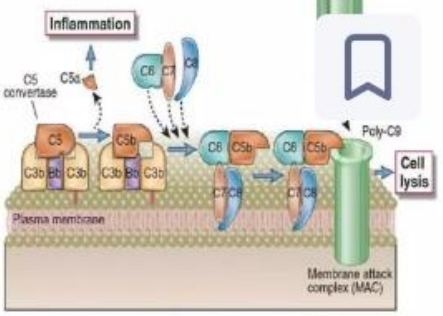
Complement system

- *The complement system is a set of around 35 serum proteins synthesized by the liver that enhance the strength and activity of an innate as well as the adaptive immune response.*
- *Exist as zymogens, once activated, interact in a cascade fashion.*
- *Phagocytic properties of neutrophils and macrophages are significantly enhanced in the presence of complement proteins. Furthermore, chemotaxis by cytokines is upregulated and bacterial killing is stronger with different proteins of the complement system.*
- *Upon cleavage, the resultant smaller fragment is designated a, whereas the larger one designated b (eg; C3b, C4a). C2 is an EXCEPTION!!!!!!*

Complement Is Activated in Three Distinct Pathwa

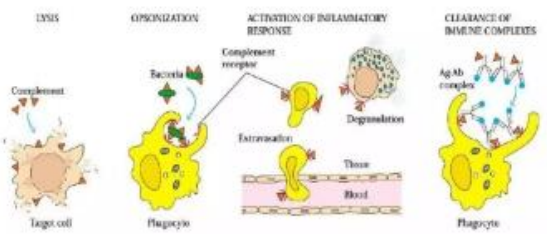
- **The classical pathway**; initiated by **antigen-antibody** complexes.
- **The lectin pathway**; initiated by **CHO** targets on microbes.
- **The alternative pathway**; initiated by **microbial surfaces**.
- Although the pathways are triggered differently, they converge in cleavage central component C3, using C3 convertases.
- Adding C3b to the C3 convertases results in formation of C5 convertases, setting in motion the formation of the membrane attack complex (MAC).
- MAC is formed by the association of the late acting components, C5b, C6, C7, C8, and multiple C9.
- The resulting tube-like structure inserts into the microbial cell, causing osmotic imbalance and cell lysis.





Complement Functions

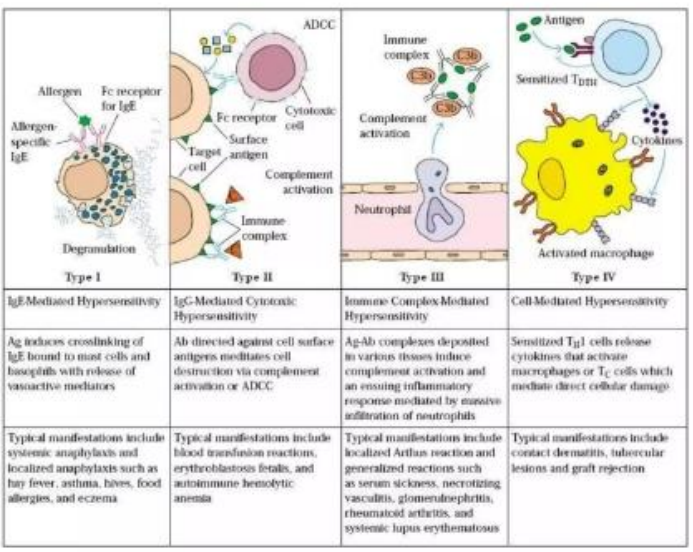
- *Lysis of cells, bacteria, and viruses through formation of MAC.*
- *Opsonization, which promotes phagocytosis, mediated by C3b and C4b.*
- *Promotion of inflammation, through production of smaller fragments "anaphylatoxins", namely, C3a, C4a, and C5a.*
- *Removal of immune complexes from the circulation and depositing them in the spl and the liver.*



- ***Complement system:*** *Enhances phagocytosis, stimulates inflammatory response, and lyses foreign cells.*
- *Most abundant complement protein is C3.*
- *C3b is the best opsonin.*
- *C5a is the best chemotaxis .*
- *Alternative pathway also called properdin pathway, factor P, which stabili the alternative* ***pathway*** *C3 and C5 convertases.*

Hypersensitivity reaction

- *Overreactive immune response to innocuous substances on re-exposure that can result in tissue damage.*
- *Involve humoral- and cell-mediated responses.*
- *Types I through III are humoral mediated and immediate.*
- *Type IV is cell mediated and delayed.*
- ***Allergen:*** *Molecule that triggers a hypersensitivity reaction.*



Type I	Type II	Type III	Type IV
IgE-Mediated Hypersensitivity	IgG-Mediated Cytotoxic Hypersensitivity	Immune Complex-Mediated Hypersensitivity	Cell-Mediated Hypersensitivity
Ag induces crosslinking of IgE bound to mast cells and basophils with release of vasoactive mediators	Ab directed against cell surface antigens mediates cell destruction via complement activation or ADCC	Ag-Ab complexes deposited in various tissues induce complement activation and an ensuing inflammatory response mediated by massive infiltration of neutrophils	Sensitized T_H1 cells release cytokines that activate macrophages or T_C cells which mediate direct cellular damage
Typical manifestations include systemic anaphylaxis and localized anaphylaxis such as hay fever, asthma, hives, food allergies, and eczema	Typical manifestations include blood transfusion reactions, erythroblastosis fetalis, and autoimmune hemolytic anemia	Typical manifestations include localized Arthus reaction and generalized reactions such as serum sickness, necrotizing vasculitis, glomerulonephritis, rheumatoid arthritis, and systemic lupus erythematosus	Typical manifestations include contact dermatitis, tubercular lesions and graft rejection

I = Allergic Anaphylaxis and Atopy
II = antiBody
III = immune Complex
IV = Delayed

Type V (Stimulatory Type) Hypersensitivity

- In this type of hypersensitivity reaction, antibodies combine with antigens on cell surface, which induces cells to proliferate and differentiate and enhances activity of effector cells.
- Type V hypersensitivity reaction plays an important role in pathogenesis of Graves' disease, i which thyroid hormones are produced in excess quantity. It is postulated that long-acting thyro stimulating antibody, which is an autoantibody to thyroid membrane antigen, combines with th stimulating hormone (TSH) receptors on a thyroid cell surface.
- Interaction with TSH receptor produces an effect similar to the TSH, resulting in an excess production and secretion of thyroid hormone, which is responsible for Graves' disease.

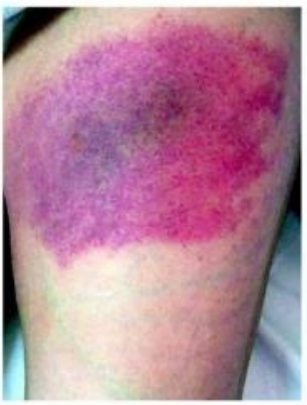
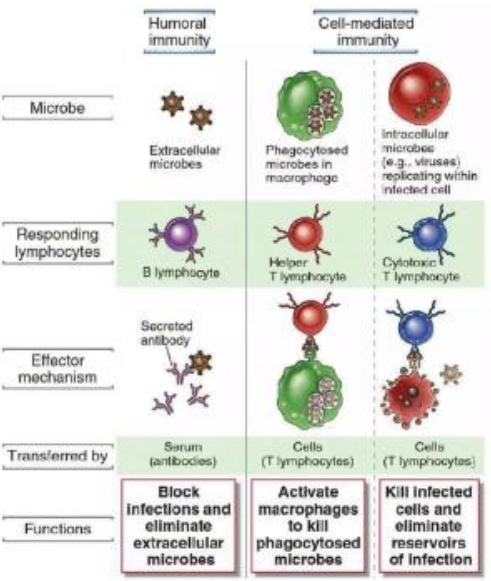


FIGURE 15-13 An Arthus reaction. This photograph shows an Arthus reaction on a thigh of a 72-year-old woman. This occurred at the site of injection of a chemotherapeutic drug, 3 to 4 hours after the patient received a second injection (15 days after the first). This response was accompanied by fever and significant discomfort. *[From P. Boura et al., 2006, Eosinophilic cellulitis (Wells' syndrome) as a cutaneous reaction to the administration of adalimumab, Annals of the Rheumatic Diseases 65:839–840. doi:10.1136/ard.2005.044685.]*



	Innate Immmunity	vs	Adaptive Immunity
Timing	minutes-days		hours-potentially lifelong
Pathogen recognition	limited specificities		highly variable, selective specif.
Response during primary infection	constant		improves with time
Response to second infection	identical to primary infection		more rapid, more efficient (memory)