Immunology

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Lac. 1

Immunity is defined as resistance to disease, specifically infectious disease and cancer. The collection of cells, tissues, and molecules that mediate resistance to infections is called the **immune system,** and the coordinated reaction of these cells and molecules to infectious microbes comprises an **immune response. Immunology** is the study of the immune system, including its responses to microbial pathogens and damaged tissues and its role in disease, The Latin term *immunis,* meaning "exempt," is the source of the English word **immunity***,* a state of protection from infectious disease.

Historical background

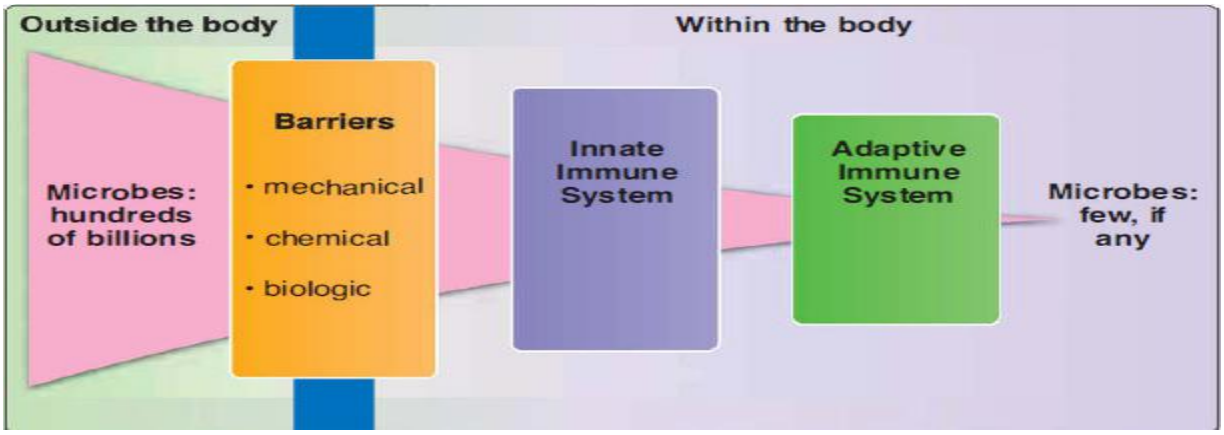
Looking back over the brief history of immunology, the first recorded attempts to deliberately induce immunity were performed by the Chinese and Turks in the fifteenth century. They were attempting to prevent smallpox, a disease that is fatal in about 30% of cases and that leaves survivors disfigured for life. Reports suggest that the dried crusts derived from smallpox pustules were either inhaled or inserted into small cuts in the skin (a technique called *variolation*) in order to prevent this dreaded disease. In 1718,Lady Mary Wortley Montagu, the wife of the British ambassador in Constantinople, observed the positive effects of variolation on the native Turkish population and had the technique performed on her own children. The English physician Edward Jenner later made a giant advance in the deliberate development of immunity, again targeting smallpox. In 1798, intrigued by the fact that milkmaids who had contracted the mild disease cowpox were subsequently immune to the much more severe smallpox, Jenner reasoned that introducing fluid from a cowpox pustule into people (i.e., inoculating them) might protect them from smallpox. To test this idea, he inoculated an eight-year-old boy with fluid from a cowpox pustule and later intentionally infected the child with smallpox. As predicted, the child did not develop smallpox. Louis Pasteur catapulted immunology into universal awareness 100 years later, In 1881, Pasteur first vaccinated one group of sheep with anthrax bacteria (*Bacillus anthracis*) that were attenuated by heat treatment. In 1885, Pasteur administered his first vaccine to a human, a young boy who had been bitten repeatedly by a rabid dog. the immunology has only

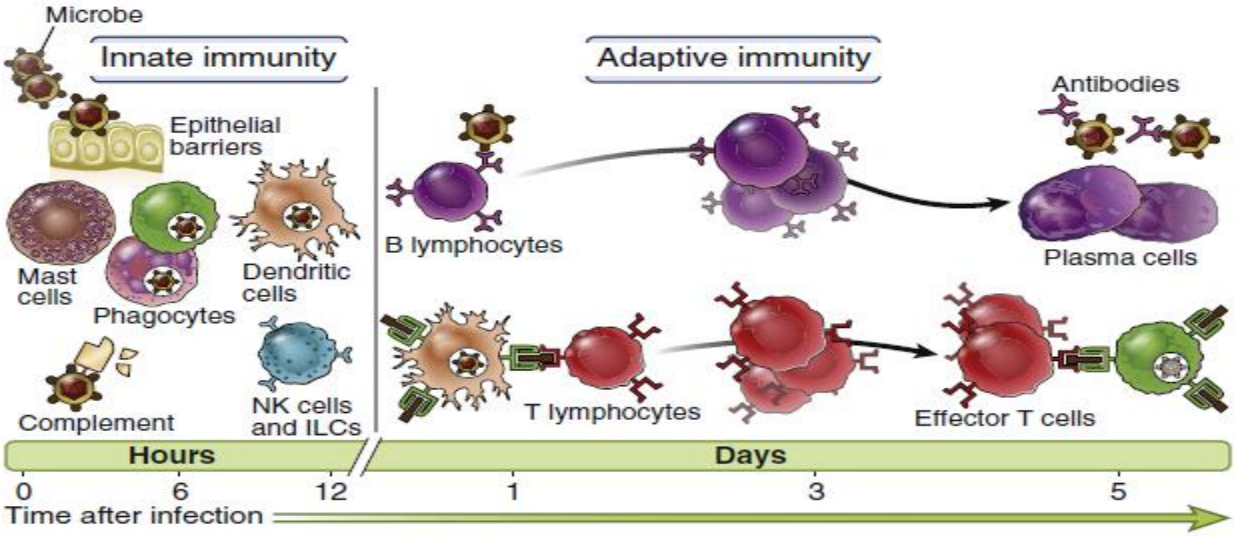
become mature within the past 50 years. For almost 100 years after Pasteur, experimentalists focused on observations of the reactions of whole experimental animals or humans to the administration of putative antigenic substances. For the first time, around 1960, it was appreciated that lymphocytes are the cells that mediate the immune reaction and experimentation moved for the first time from in vivo to in vitro, which allowed one to manipulate and investigate an immune reaction of cell populations During the 1960s, various techniques were improved so that it was possible to discern that several different types of cells cooperated to ultimately generate a measurable immune response, usually monitored by the appearance of antibody-forming cells (AFCs). new and novel experimental methods were introduced in the 1970s that revolutionized all of biological sciences, which enabled a further reduction from cells to molecules, and led to the discipline that now can be recognized as molecular immunology.

1905 Robert Koch (Cellular immunity to tuberculosis)
1908 Elie Metchnikoff (Role of phagocytosis (Metchnikoff)
1919 Jules Bordet Belgium (Complement-mediated bacteriolysis)
1930 Karl Landsteiner (Discovery of human blood groups)
1957 Daniel Bovet (Antihistamines)
1960 F. Macfarlane Burnet (Discovery of acquired immunological)
1972 Rodney R. Porter Gerald M. Edelman United States
(Chemical structure of antibodies)
1980 George Snell (Major histocompatibility complex)
1984 Niels K. Jerne (Immune regulatory theories (Jerne) and
technological advances in the development monoclonal antibodies)
1991 E. Donnall Thomas (Transplantation immunology)
2002 Sydney Brenner (Genetic regulation of organ development
and cell death (apoptosis)
2008 Harald zur Hausen (Role of HPV in causing cervical cancer
(Hausen) and the discovery of HIV)
2011 Jules Hoff man (Discovery of activating principles of innate
immunity (Hoff man and Beutler) and role of dendritic cells in adaptive immunity
(Steinman)

Immune system

the body defense against infections organisms and other invaders, the immune system is made up of a network of cells, tissues and organs that work together to protect the body. The human body possesses many ways to protect itself from harmful substance or pathogenic microorganisms in the environment by the number of very effective mechanisms including non-specific (Innate) and specific (Acquired) immunity. **Innate immunity**, also called **natural immunity** or **non-specific immunity** is always present in healthy individuals, prepared to block the entry of microbes and to rapidly eliminate microbes that do succeed in entering host tissues. Adaptive immunity, also called **specific immunity** or **acquired immunity**, requires expansion and differentiation of lymphocytes in response to microbes before it can provide effective defense; that is, it adapts to the presence of microbial invaders.





Innate immunity

In innate immunity, the first line of defense is not directed to the infection agent, and the response is not affected by prior exposures. is provided by epithelial barriers of the skin and mucosal tissues and by cells, all of which function to block the entry of microbes. If

microbes do breach epithelia and enter the tissues or circulation, they are attacked by phagocytes, specialized lymphocytes, inflammation and several plasma proteins, including the proteins of the complement system.

Barriers to infection

1- Physical barriers

The initial mechanical barriers that protect the body against invasive microbes include the skin ; mucous membranes of the gastrointestinal , respiratory, and the cilia in the respiratory tract.

A- Skin

The skin is the most resistant barrier because of its outer horny layer , Continuously dividing keratinocytes and constant sloughing of the superficial epidermal layer removes microbes attach to cutaneous surfaces.

B-mucous membranes

The epithelium of mucous membranes lines all of the body's cavities, This epithelium mucus that traps bacteria, fungi, and other particles.

C-Respiratory tract

The hair like cilia of the epithelia lining the respiratory tract passages help the tract clean by moving the secretions containing trapped microbes and particles outward for expulsion by coughing and sneezing.

D-Urinary tract

The flushing action of urine helps to inhibit movement of microbes from the environment up into the bladder and kidneys

2- CHEM ICAL BARRIERS

The acidic pH of the skin, stomach, and vagina serves as a chemical barrier against microbes. Most pathogens are very sensitive to an acidic environment where an acid pH inhibits the growth of potential pathogens. lysozyme, which are secreted by various cell types, also provide protective environment barriers.

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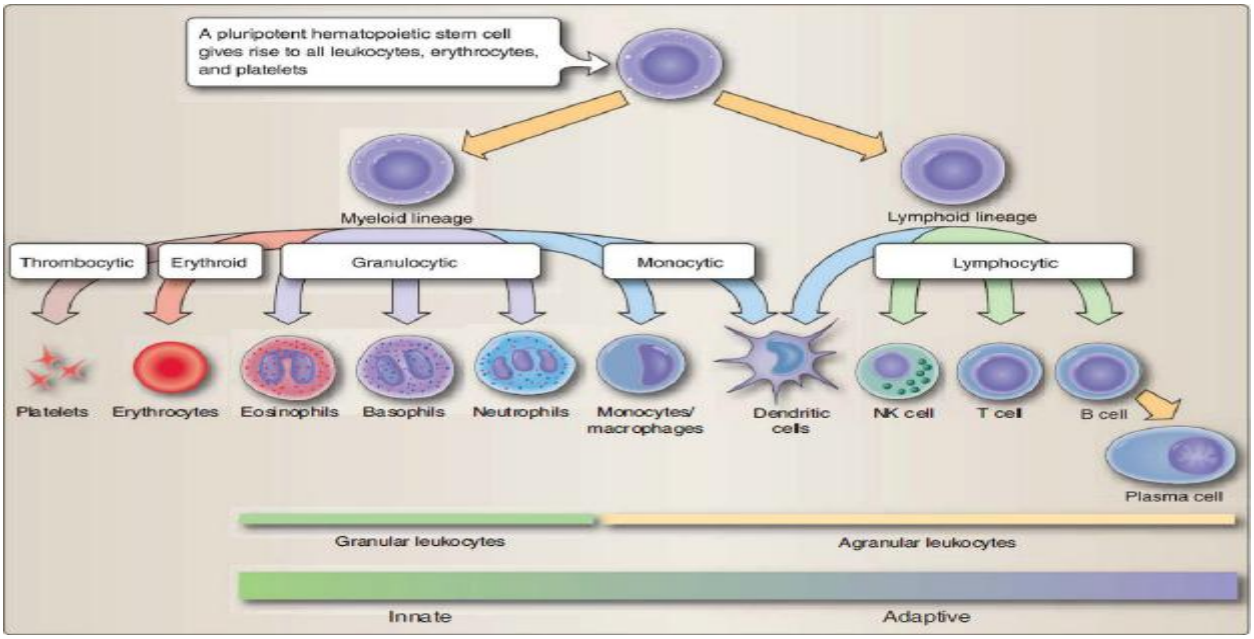
CELLS AND ORGANS OF IMMUNE SYSTEM

All blood cells originate from the same type of cell, the hematopoietic stem cell, found in the bone marrow. Under the influence of colony stimulating factors, specific types of blood cells are produced. Red blood cells **erythrocytes , platelets,** White blood cells **Leukocytes** are important in immunity. Leukocytes are the cells primarily responsible for the defense of the body against microorganisms, there are several subsets of leukocytes, each with special function. They are the granulocytes, including eosinophils, basophils, neutrophils and mononuclear phagocytes, including monocytes, macrophages dendritic cells and lymphocytes.



Phagocytosis

Phagocytosis is the engulfment and degradation of microbes and other particulate matter by cells such as macrophages, neutrophils and tissue macrophage. **First**, the phagocytes must be attracted to the microorganisms, chemical products of microorganisms , complement system (C5a) and same materials from mammalian cell membranes act as chemoattractants to phagocytes, which then move toward the microorganisms by a process called **chemotaxis. Asecond step is attachment** once the phagocytic cell comes inti contact with the microorganisms, the C3b component of complement coats

microorganisms, allowing them to be attached to phagocytes. This process of coating to enhance phagocytosis called **opsonization** . **Third** the microorganisms is engulfed by the phagocyte into a vacuole known as a **phagosome.** In the phagocytes a variety of digestive enzymes (granules in neutrophils and lysosomes in mononuclear). **Fourth,** the granules and lysosomes come and fuse with the phagosome and release their enzymes into the vacuole known as a **phagolysosome** (Lysosomes employ multiple mechanisms for killing and degrading ingested matter. These include,

* lysosomal acid hydrolases, including proteases, nucleases, and lipases;
* several oxygen radicals, including superoxide radicals (0_2 -) , hypochlorite (HOCI -) , hydrogen peroxide (H_20_2) , and hydroxyl radicals (OH') that are highly toxic to microbes.
* nitrous oxide (NO) ;
* decreased pH
* other microcidal molecules.

.**Fifth** within phagolysosome, organisms are killed and **sixth,** they are digested. **seventh,** and finally following of the phagolysosome are eliminated by **exocytosis .**

NOT. *Macrophages are phagocytes are derived from blood to various tissues that undergo further differentiation into macrophages and that named according to their location. kupffer cells in the liver, alveolar cells in the lung, dendritic cells in the spleen and lymph nodes, Langerhans in the skin.*

So phagocytes occurs in several steps 1- chemotaxis ,2- attachment , 3- ingestion , 4- fusion to produce phagolysosomes ,5- killing within phagolysosomes, 6- breakdown of dead materials ,7- exocytosis of the resulting debris.

NOT. *Some organisms resist killing and continue to live within mononuclear phagocytes.*

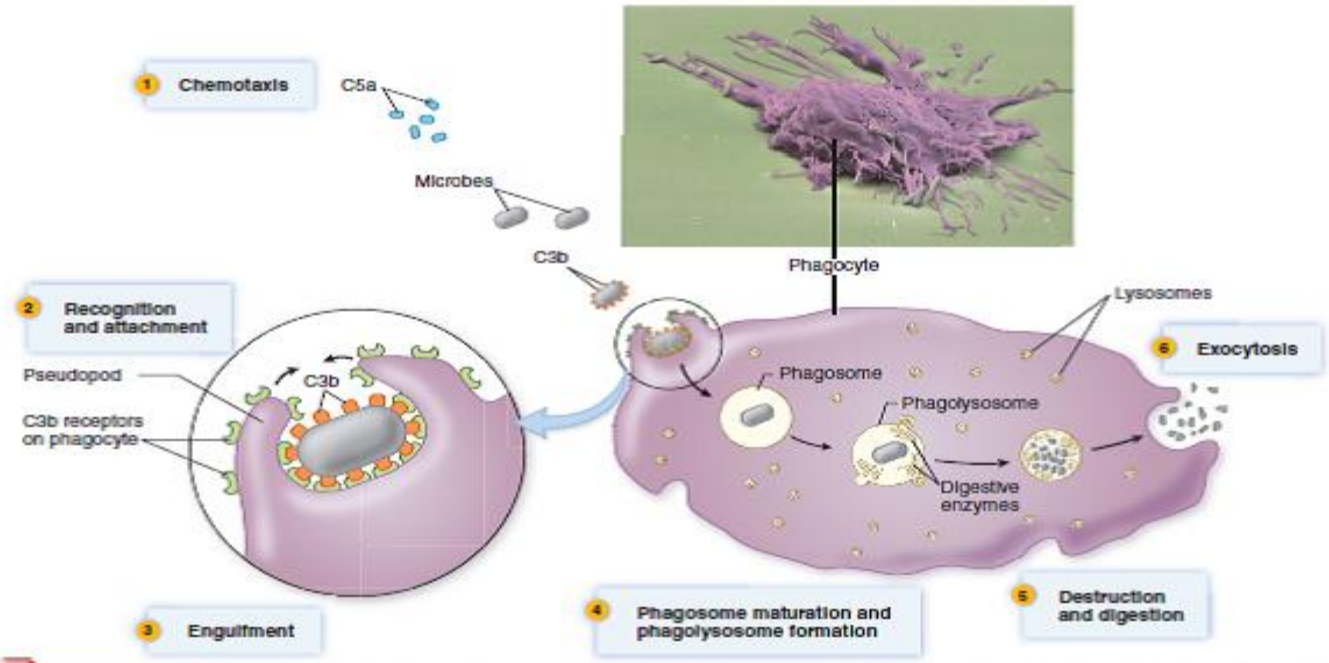


FIGURE 14.13 **Phagocytosis** This diagram shows a microbe that has been opsonized by the complement protein C3b; certain classes of antibodies can also function as opsonins.

Inflammation

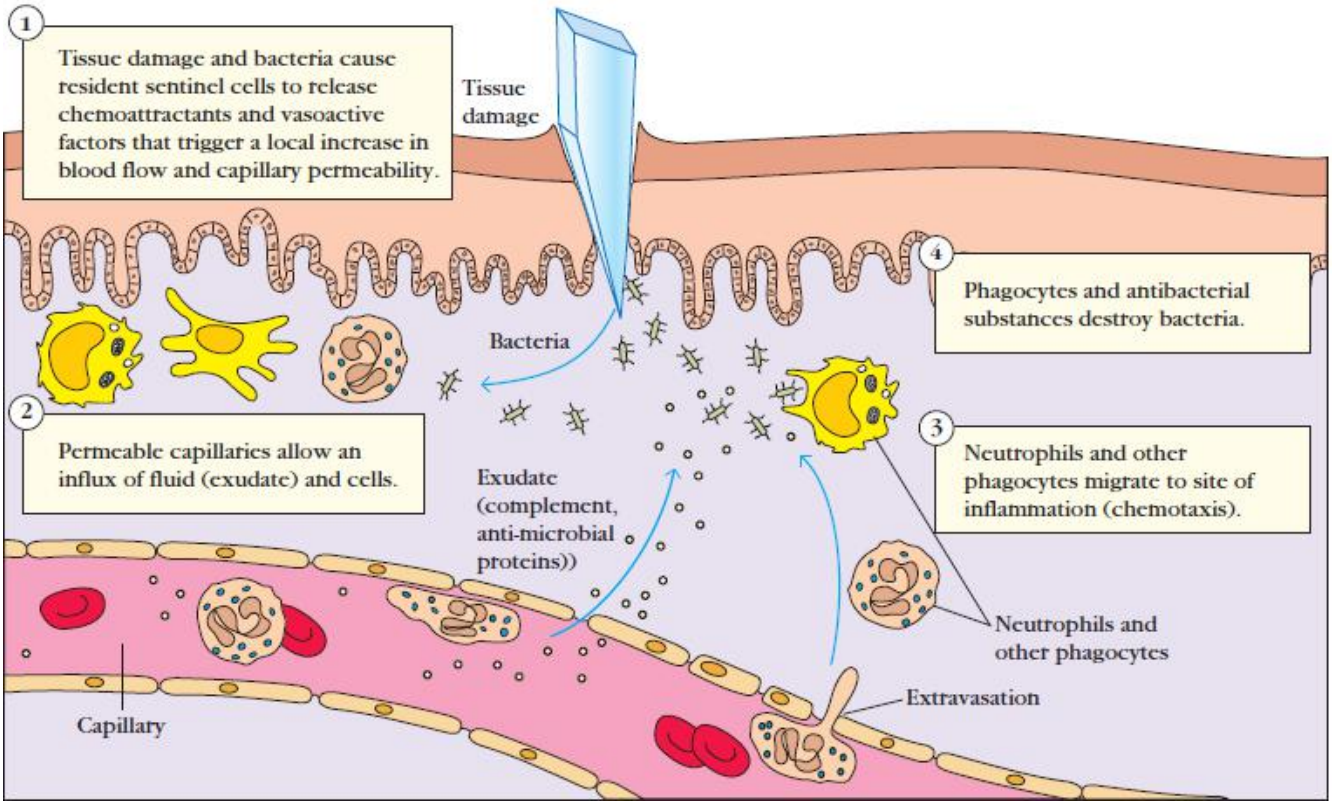
When the infection agent has penetrated external barriers such as skin or mucous membranes and has entered the tissues, the first host response is a nonspecific reaction to injury called the inflammatory response or inflammation. The four cardinal signs were described by the roman physician Celsus, they are **swelling**, **redness**, **heat,** and **pine** in sometimes **loss of function.** The same sequence of events occurs in response to any injury, whether caused by invading bacteria, burns, trauma.

Very early cytokines, C3a, C5a, compound of complements and other substance cause the release of chemical mediators from tissue mast cell granules.

Chemical	Effects
Histamine	Dilation and increase of permeability of small blood vessels; constriction of the bronchi
Chemotactic factors	Eosinophil and neutrophil (PMN) chemotaxis
Interleukins 3, 4, 5, and 6	Many interactions
Tumor necrosis factor alpha	Recruitment of granulocytes to area of inflammation; inducement of fever
Leukotrienes	Dilation of small blood vessels; constriction of bronchi; chemotaxis of leukocytes
Prostaglandins	Increase in vascular permeability; regulation of immune responses

These chemicals, in turn , dilate small blood vessels, making them permeable. Some of the chemicals cause the production of receptors of leukocytes on blood vessels walls in the area of the inflammation. Circulating leukocytes adhere to these receptors on the inner wall of the altered blood vessels and then migrate through the dilated permeable vessels walls by the process called ***diapedesis*** in to the tissues in response to chemical attractant. This response is termed ***chemotaxis*.** Plasma leaks into the tissues accounting for the **swelling**. The **heat** and **redness** in the region result from increased blood flow in the dilated vessels. **Pine** is caused by the increased fluid in the tissues and by direct effects of chemicals on the sensory nerve ending.

The first kind of leukocytes to be lured from the circulation is the neutrophil .



After the influx of the neutrophil, monocytes they mature in to macrophages. Clotting occurs, this helps to prevent bleeding and halt dissemination invading organisms. Large quantities of dead neutrophils accumulate and tissue debris these make up pus. A large amount of pus constitutes **boil** .

NOT. *Inflammation may be acute (short-term effects contributing to combating infection, followed by healing) for example, in response to local tissue damage or it may be chronic (long term, not resolved), contributing to conditions such as arthritis, inflammatory bowel disease, cardiovascular disease.*

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Lac. 3

Complement System

The complement system is a collection of circulating and membrane-associated proteins that are important in defense against microbes. Many complement proteins are proteolytic enzymes, and complement activation involves the sequential activation of these enzymes. complement is also involved in inflammatory response by contributing to vascular permeability stimulating chemotaxis and enhancing phagocytosis.
Complement consists of a group of at least 26 different proteins, The activation of the complement system involves sequential proteolytic cleavage of complement proteins, (the complement cascade) leading to the generation of effector molecules that participate in eliminating microbes in different ways.
The complement cascade may be activated by any of three pathways.

1- classical pathway

antibody that combined with antigen interacts with the inactive enzyme C1making it active, this enzyme then splits C4 and C3 resulting in an enzyme called C3 which cleaves C3 into C3a and C3b . (specific)

2- alternative pathway

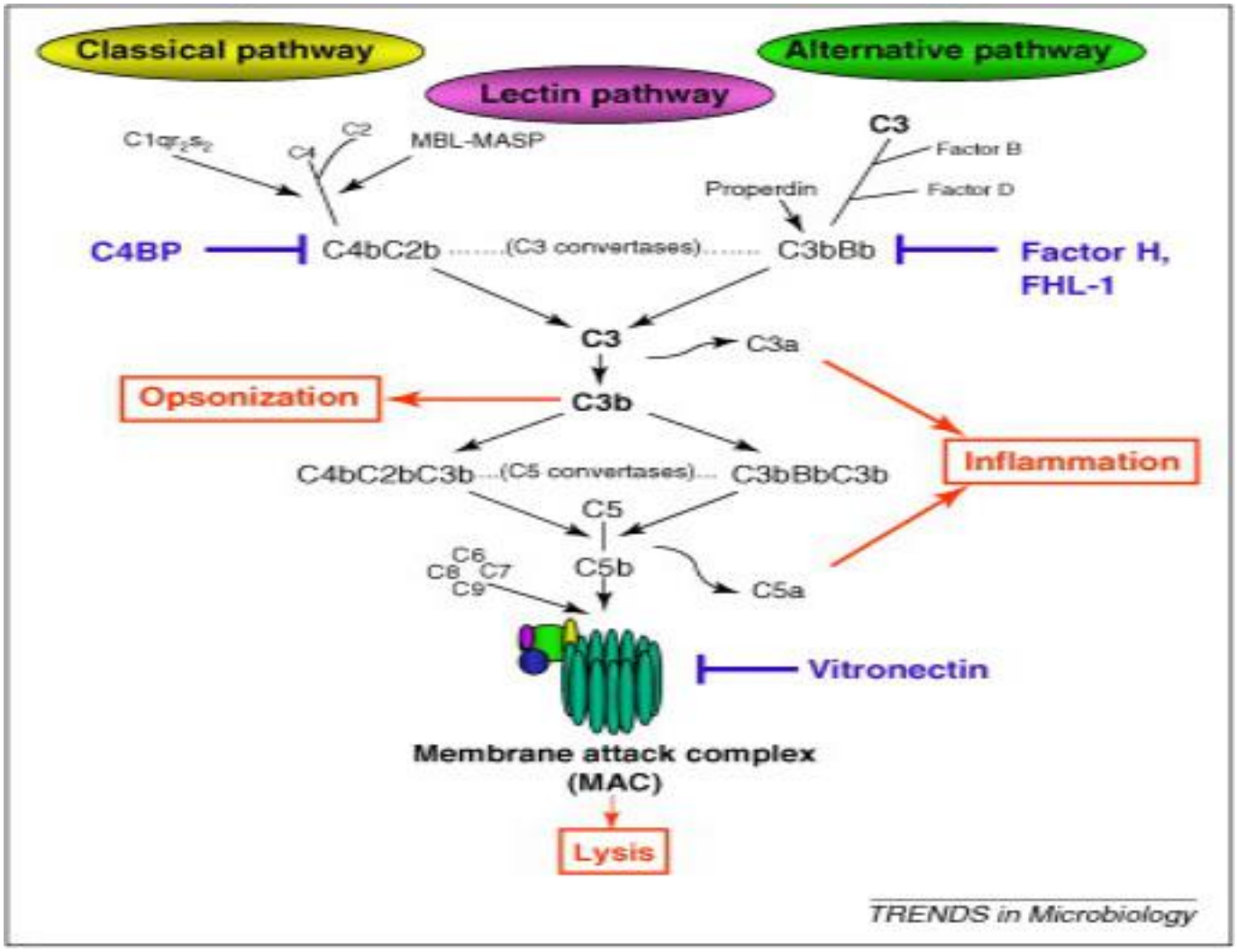
is triggered when some complement proteins are activated on microbial surfaces (cell walls, capsules, polysaccharides) the cascade begins with C3. A small amount of C3b is always found in circulation as a result of spontaneous cleavage of C3.so the microbial surfaces react with a tiny amount of C3b. properdin and factors B and D lead production of C3 convertase which cleaves C3 to C3a and C3b. (nonspecific)

3- lectin pathway

mannose in the pathogen's surface (mannose is present in many bacterial cell walls) binds to the lectin, a protein that binds carbohydrates. This substance called mannan-binding lectin (MBL) is found normally in the blood . the combination of MBL is similar to part of the C1component ,so they activates complement enzymes. (nonspecific)
All pathways of complement activation follow the same sequence after cleavage of C3. These pathways differ in their initiation, but once triggered, their late steps are the same.

Following the cleavage C5 to release C5a and C5b on the surface of bacteria or foreign cells bind together loosely and form complex with C6 and C7. This complex C5b,C6

and C7 causes C7 to insert in to the cell membrane. C8 joins the complex, creating changes in C9 such that it polymerizes and forms a **membrane attack complex (MAC)** That inserts through the membrane of eukaryotic cells, resulting in cell lysis.



***Not**. Major components are C1 through C9. These were numbered in the order in which they were discovered and not in order in which they react.*

***Not.** The classical pathway remains the most efficient because many more C3 molecules are involved in the reaction however the alternative and lectin pathway advantage of response.*

The multilayer of peptidoglycan in gram-positive bacteria may limit complement access to the cell membrane and thus interfere with lysis, but C3b still increases phagocytosis and intracellular distraction of these bacteria. gram-negative bacteria are more susceptible to complement lysis than are gram-positive bacteria.

Cytokines

are low-molecular-weight soluble protein messengers that are involved in all aspects of the innate and adaptive immune response, including cellular growth and differentiation, inflammation, and repair. these substances are produced by a wide variety of leukocytes and nonleukocytes. A large number of cytokines have been identified, although the roles of many of them are not yet fully understood. Many cytokines are crucial in regulating lymphocyte development and in determining the types of immune responses evoked by specific responses.

Cytokine	Principal cell source(s)	Principal cellular targets and biologic effects
Tumor necrosis factor (TNF)	Macrophages, T cells, mast cells	Endothelial cells: activation (inflammation, coagulation) Neutrophils: activation Hypothalamus: fever Liver: synthesis of acute-phase proteins Muscle, fat: catabolism (cachexia) Many cell types: apoptosis
Interleukin-1 (IL-1)	Macrophages, dendritic cells, endothelial cells, some epithelial cells, mast cells	Endothelial cells: activation (inflammation, coagulation) Hypothalamus: fever Liver: synthesis of acute-phase proteins T cells: Th17 differentiation
Chemokines	Macrophages, dendritic cells, endothelial cells, T lymphocytes, fibroblasts, platelets	Leukocytes: increased integrin affinity, chemotaxis, activation
Interleukin-12 (IL-12)	Dendritic cells, macrophages,	Natural killer (NK) cells and T cells: IFN-γ production,increased cytotoxic activity T cells: Th1 differentiation
Interferon-γ (IFN-γ)	NK cells, T lymphocytes	Activation of macrophages Stimulation of some antibody responses
Type I IFNs (IFN-α, IFN-β)	IFN-α: Dendritic cells, macrophages IFN-β: Fibroblasts	All cells: antiviral state, increased class I major histocompatibility complex (MHC) expression NK cells: activation
Interleukin-10 (IL-10)	Macrophages, dendritic cells, T cells	Macrophages, dendritic cells: inhibition of cytokine and chemokine production, reduced expression of costimulators and class II MHC molecules
Interleukin-6 (IL-6)	Macrophages, endothelial cells, T cells	Liver: synthesis of acute-phase proteins B cells: proliferation of antibody-producing cells
Interleukin-15 (IL-15)	Macrophages, others	NK cells: proliferation T cells: proliferation
Interleukin-18 (IL-18)	Macrophages	NK cells and T cells: IFN-γ synthesis
TGF-β	Many cell types	Inhibition of inflammation T cells: differentiation of Th17, regulatory T cells

Natural killer (NK) cell

NK cells make up approximately 10% of the lymphocytes in the blood and peripheral lymphoid organs. named for their ability to kill abnormal (e. g . ,infected or malignant) host cells. NK cells contain abundant cytoplasmic granules and express some unique surface proteins , NK cells they attach to the target cell release some of their granule contents close to the target cell membrane and thereby kill the target.

LYMPHOID TISSUES AND ORGANS

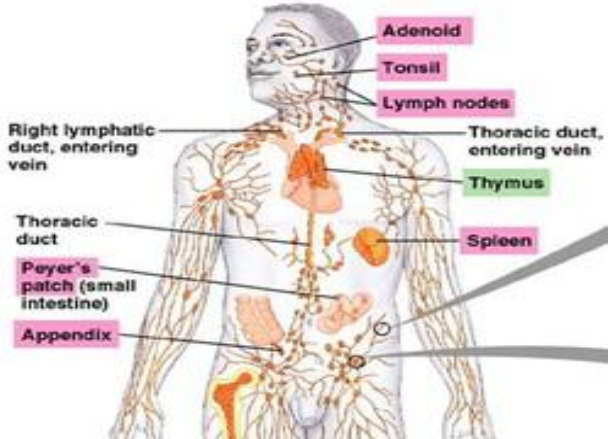
Leukocytes may be found in the body distributed as single cells in the tissues and circulation , as lymphoid accumulations or with in lymphoid organs. Lymphoid organs are classified as primary or secondary. Lymphocytes develop within the primary organs: thymus and bone marrow. The secondary lymphoid organs (e. g . , spleen, lymph nodes, lymphoid accumulations) trap and concentrate immunogens and provide sites where large numbers of circulating immune cells can make contact with each other. Specific immune reactions are initiated with the interactions that occur in secondary lymphoid organs.

A. Primary organs

The primary lymphoid organs, the thymus and bone marrow, serve as lymphocyte educational centers. Although all lymphocytes originate within the bone marrow, those destined to become T cells are sent at an early age to the thymus for "advanced education" in distinguishing self from non self. Other lymphocytic lineage cells are "home schooled" and remain within the bone marrow, destined to become B cells. Stromal cells within the thymus and bone marrow closely regulate the development of T and B lymphocytes.

B. Secondary lymphoid tissues and organs

Cellular interactions are critical for the development of adaptive immune responses. The secondary lymphoid tissues function as filtration devices removing foreign matter, dead cells, and protein aggregates from the circulation . Secondary lymphoid organs are richly supplied with blood vessels and lymphatic vessels that facilitate movement of lymphocytes, monocytes, and dendritic cells into and out of these organs. Specialized regions of the vasculature, called high endothelial venules, permit the movement of cells between the blood and the tissues or organs through which they are passing. The leukocyte-rich nature of the secondary lymphoid tissues facilitates cellular interaction , providing leukocytes an environment in which they can "compare notes," exchange regulatory signals, undergo further development, and proliferate before reentering the circulation .The major secondary lymphoid organs are the spleen and lymph nodes. The tonsils and Peye r's patches also act as secondary lymphoid accumulations.



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Lac. 4

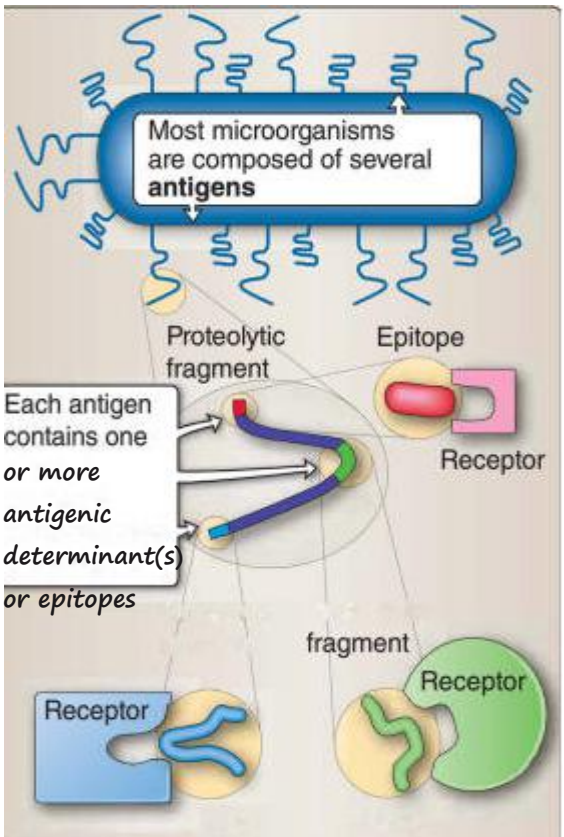
ANTIGENS

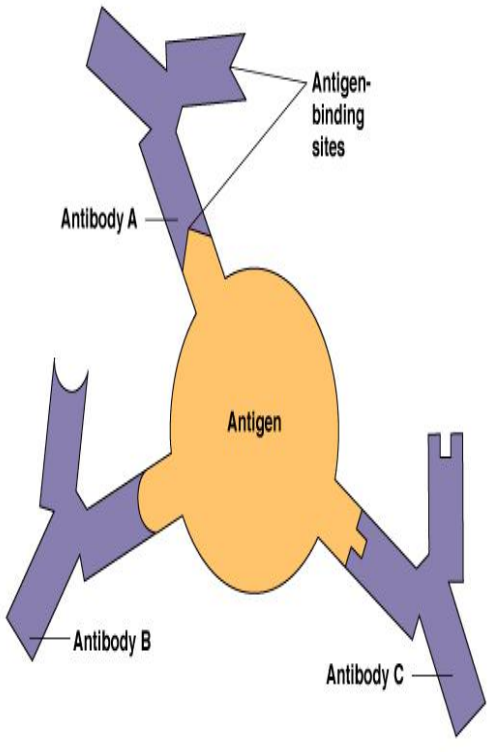
Classically, an antigen is defined as an organism, a molecule, or part of a molecule that is recognized by the immune system . Antigens may be simple or complex, protein, carbohydrate, or synthetic in origin. Often, the term is associated primarily with those molecules recognized by the extremely diverse receptors found on T and B lymphocytes.

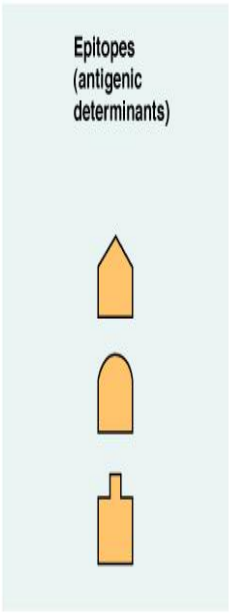
Epitopes.

Antigen receptors recognize discrete regions of molecules called **antigenic determinants or epitopes**,(large protein molecules sequences of 10 to 25 amino acid) the smallest part of an antigen that is "seen" by somatically generated B- and T-cell receptors, Different lymphocytes, each with a unique set of receptors, may recognize different epitopes on the same antigen. A cell will usually have many macromolecules on its surface each with a number of different epitopes.

Depending on the nature of the immune responses they trigger, antigens/epitopes are divided into three broad functional types: immunogens, haptens, and tolerogens.





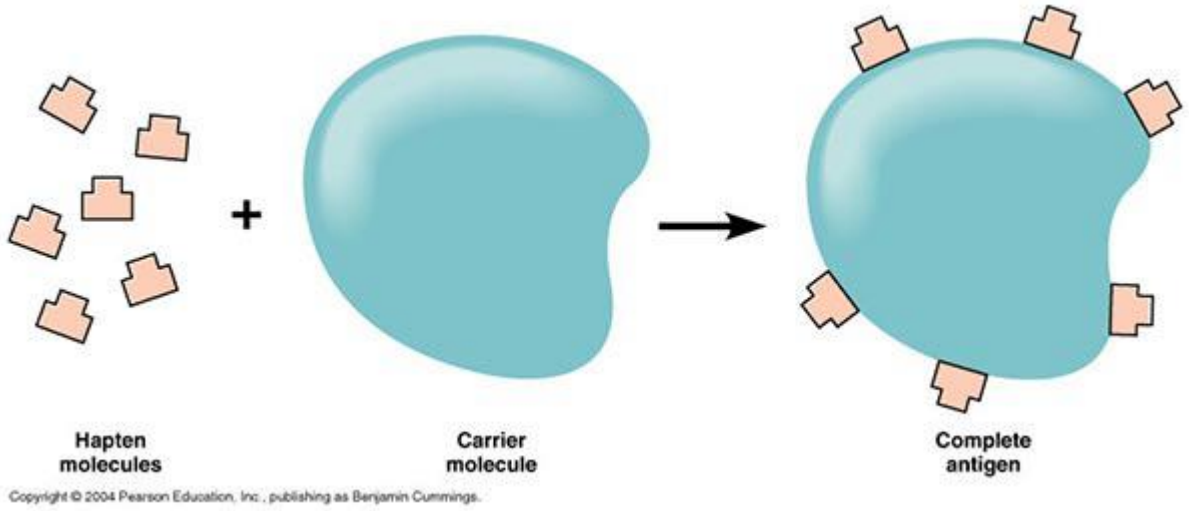


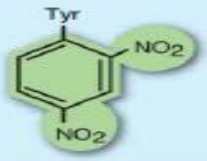
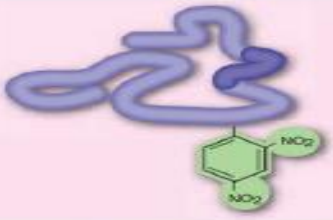
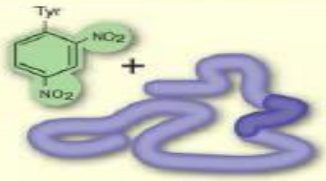
1- lmmunogens

lmmunogens contain epitopes that both induce an immune response and are the targets of that response. lmmunogens contain epitopes that both induce an immune response and are the targets of that response . The amount of the immune response by the innate system is the same, no matter how many times it encounters the same immunogen. In contrast, reexposure of the adaptive immune system to the same immunogen usually increases the intensity of the epitope-specific immune response.Although epitopes on antigens may bind to soluble or cell-surface receptors, not all antigens are immunogens.
***NOT**. the terms "antigen" and "immunogen" are often used interchangeably. we use the term "immunogen" to mean a substance or antigen that evokes a specific, positive immune response and the term "antigen" to mean a molecule or cell recognized by the immune system .*

2- Haptens

Haptens are small , normally nonimmunogenic, molecules, usually of nonbiologic origin, that behave like synthetic epitopes. Haptens are antigens and can bind to immune receptors but cannot by themselves induce a specific immune response and hence are not immunogenic. However, when a hapten is chemically bound to an immunogen (also called a **carrier**) , immune responses may be generated against both the hapten and the epitopes on the immunogen.
NOT. *Penicillin has a molecular weight 350 D and is a hapten that by itself is incapable of causing immune response. In the body the penicillin is changed by enzymes so that can combine with large protein carrier molecules and causing immune response allergic reactions.*



Injection with	Structure	Response to protein epitope	Response to hapten	Comment
Immunogen or carrier		Yes	Not applicable	An injected protein (sometimes called a carrier) that elicits an immune response is called an immunogen
Synthetic epitope or hapten		Not applicable	No	Injection of a synthetic molecule, in this case 2,4-dinitrophenyltyrosine, by itself does not elicit an immune response and is called a hapten
Hapten–Carrier conjugate		Yes	Yes	Injection of a hapten chemically bound to a carrier elicits an immune response to both carrier epitope(s) and to the hapten
Hapten NOT conjugated to carrier		Yes	No	Injection of unconjugated hapten and carrier does not elicit a response

3- Tolerogen

A substance that invokes a specific immune non-responsive due to its molecular form. If its molecular form is changed, a tolerogen can become an immunogen.

Immunogenicity

1- Size: molecules greater than 10 kDa are usually more immunogenic.

2- Complexity: proteins and polysaccharides generally induce a strong response.

NOT*. Complex proteins with numerous, diverse epitopes are more likely to induce an immune response than are simple peptides that contain only one or a few epitopes.*

3-Foreign (not recognizable as self)

NOT. Antigen may be virtually any substance recognized by individual's body such as bacterial cell, fungi, plant pollen, drugs, foods. For example red blood cells from other people may recognized as having foreign epitopes and be destroyed by the recipients immune system in transfusion reaction.

Adaptive immunity, specific immunity or acquired immunity

Adaptive immune responses are especially important for defense against infectious microbes that are pathogenic for humans (i.e., capable of causing disease) and may have evolved to resist innate immunity. Whereas the mechanisms of innate immunity recognize structures shared by classes of microbes, the cells of adaptive immunity

(lymphocytes) express receptors that specifically recognize a much wider variety of molecules produced by microbes as well as noninfectious substances. Any substance that is specifically recognized by lymphocytes or antibodies is called an antigen. Adaptive immune responses often use the cells and molecules of the innate immune system to eliminate microbes, and adaptive immunity functions to greatly enhance these antimicrobial mechanisms of innate immunity. For example, antibodies (a component of adaptive immunity) bind to microbes, and these coated microbes avidly bind to and activate phagocytes (a component of innate immunity), which ingest and destroy the microbes.

***NOT**. The adaptive immune system consists of lymphocytes and their products, such as antibodies.*

TYPES OF ADAPTIVE IMMUNITY

The two types of adaptive immunity, called humoral immunity and cell-mediated immunity, are mediated by different cells and molecules and provide defense against extracellular microbes and intracellular microbes, respectively

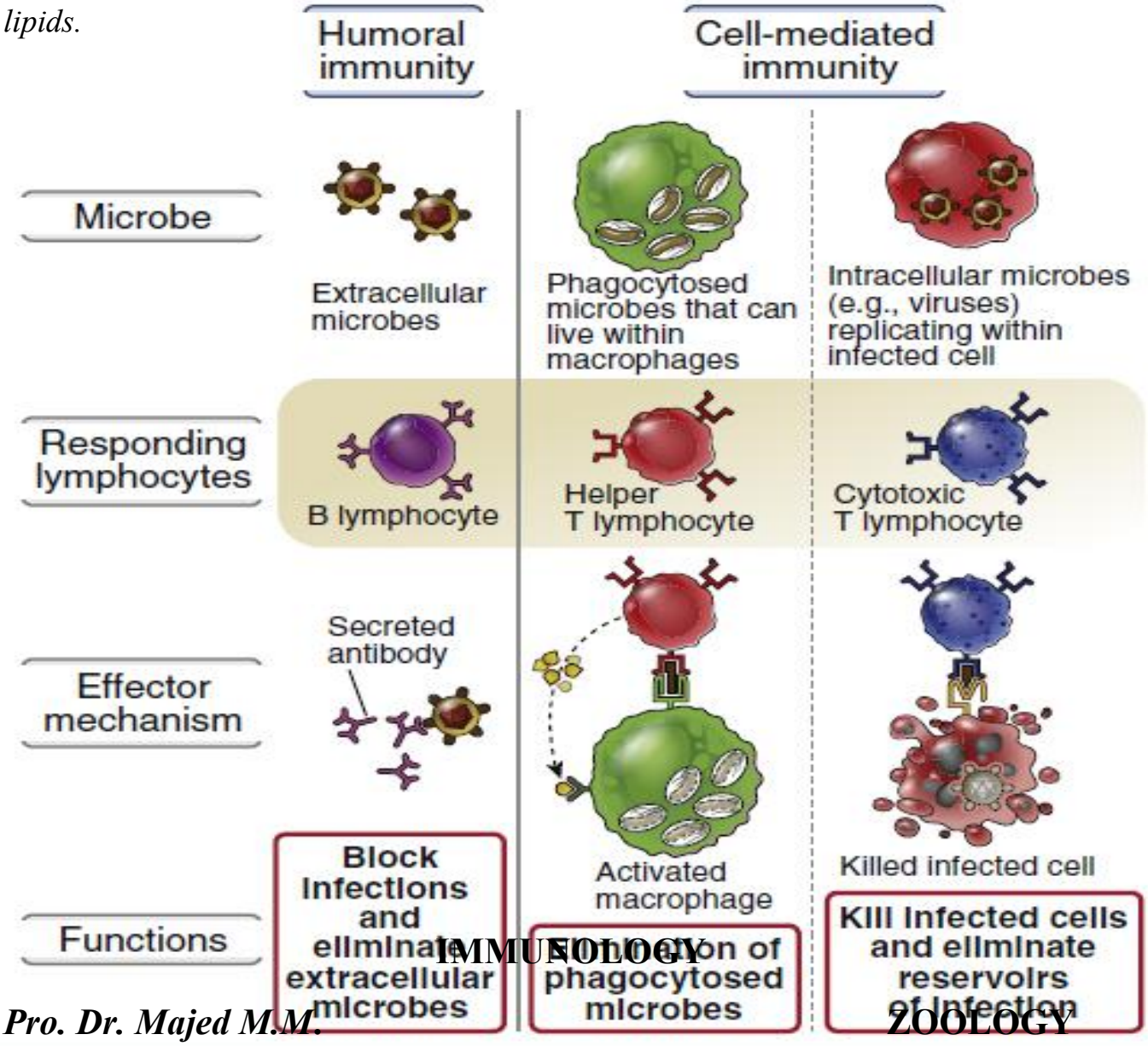
Humoral immunity

is mediated by proteins called antibodies, which are produced by cells called B lymphocytes. Secreted antibodies enter the circulation and mucosal fluids, and they neutralize and eliminate microbes and microbial toxins that are present outside host cells, in the blood, extracellular fluid derived from plasma, and in the lumens of mucosal organs such as the gastrointestinal and respiratory tracts. One of the most important functions of antibodies is to stop microbes that are present at mucosal surfaces and in the blood from gaining access to and colonizing host cells and connective tissues. In this way, antibodies prevent infections from ever being established. Antibodies cannot gain access to microbes that live and divide inside infected cells.

Cell-mediated immunity

Defense against such intracellular microbes is called cell-mediated immunity because it is mediated by cells, which are called T lymphocytes. Some T lymphocytes activate phagocytes to destroy microbes that have been ingested by the phagocytes into intracellular vesicles. Other T lymphocytes kill any type of host cells that are harboring infectious microbes in the cytoplasm. In both cases, the T cells recognize microbial antigens that are displayed on host cell surfaces, which indicates there is a microbe inside the cell.

***NOT**. The specificities of B and T lymphocytes differ in important respects. Most T cells recognize only protein antigens, whereas B cells and antibodies are able to recognize many different types of molecules, including proteins, carbohydrates, nucleic acids, and lipids.*



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Lac. 5

Antibodies

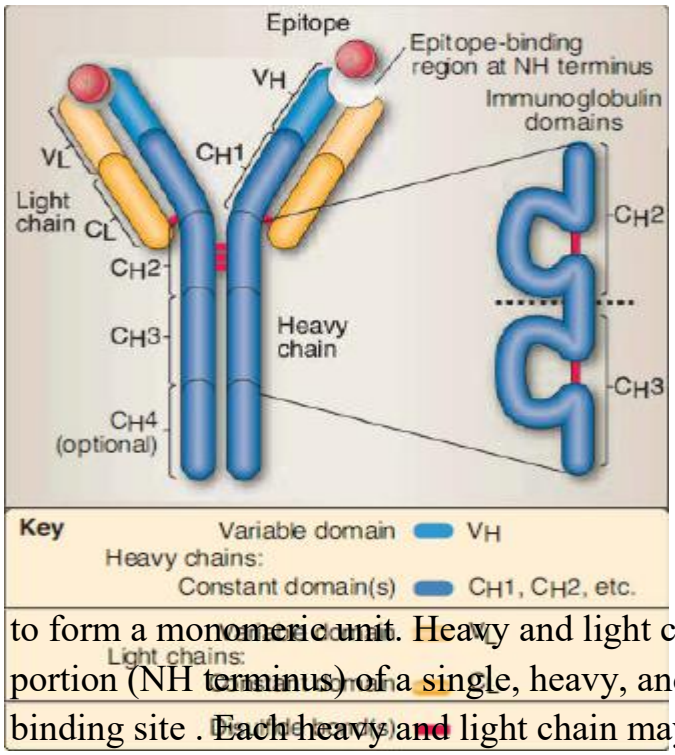
Are the glycoprotein molecules called **immunoglobulins** that react specifically with the antigen that induced their production. Immunoglobulins are synthesized by B lymphocytes (B cells) and are both synthesized and secreted by plasma cells. Plasma cells are terminally differentiated B cells. The term antibody is applied to an

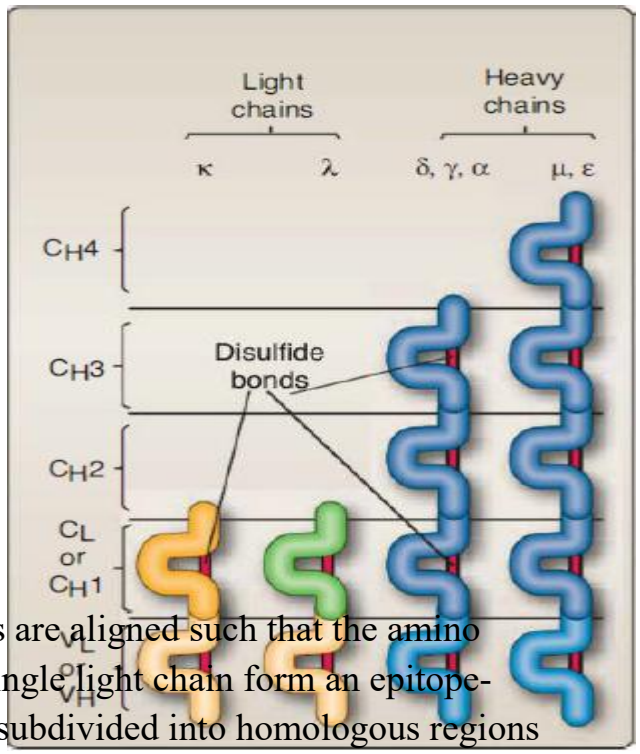
immunoglobulin molecule with specificity for an epitope of the molecules that make up antigens . Ab they protect

- Recognizing and binding to foreign substances and facilitating their removal.
- Increasing phagocytosis
- Neutralizing toxins or viruses
- Activation complement

Basic structure

An antibody molecule is composed of four polypeptide chains two identical heavy (H) chains and two identical light (L) chains with each chain containing a variable region and a constant region . The four chains are assembled to form a Y-shaped molecule. Each light chain is attached to one heavy chain, and the two heavy chains are attached to each other, all by disulfide bonds.





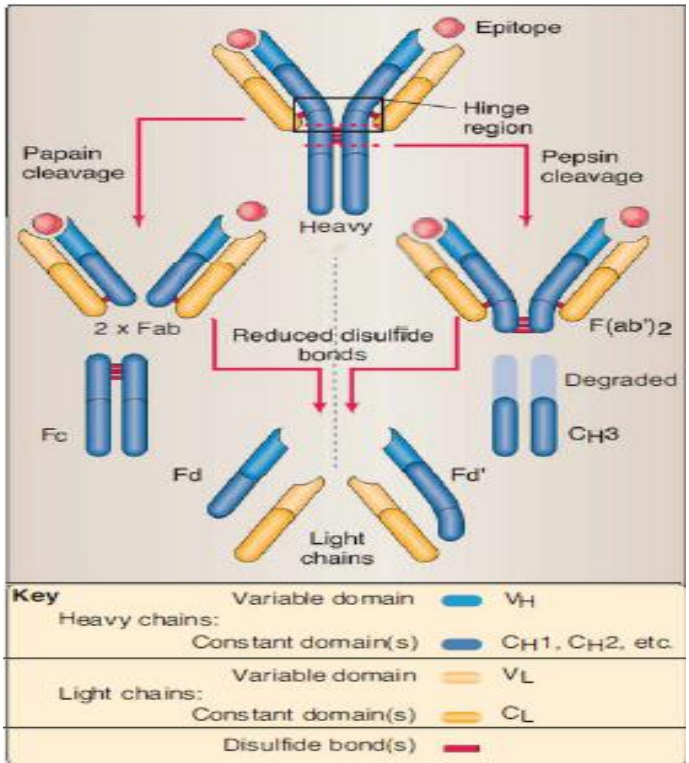
to form a monomeric unit. Heavy and light chains are aligned such that the amino portion (NH terminus) of a single, heavy, and a single light chain form an epitope-binding site . Each heavy and light chain may be subdivided into homologous regions termed domains. Light chains, termed κ (kappa) or λ (lambda), are encoded on chromosomes 2 and 22, respectively. There are five types of heavy chains, all encoded on chromosome 14, termed mu (μ), delta (ð), gamma (γ), epsilon (ϵ), and alpha (α). The genetically different forms of light chains (κ and λ) and of heavy chains (μ, ð, γ, ϵ, and α) are known as isotypes. Immunoglobulin class or subclass is determined by the heavy chain isotype.

1 . Light chains: An immunoglobulin monomer contains two identical κ or two identical λ light chains but never one of each. Light or L chains contain a variable (V_L) domain and a constant (C_L) domain. Each domain contains about 110 amino acids and an intrachain disulfide bond . Variable regions (in both heavy and light chains) are so named for their variation in amino acid sequences between immunoglobulins synthesized by different B cells.

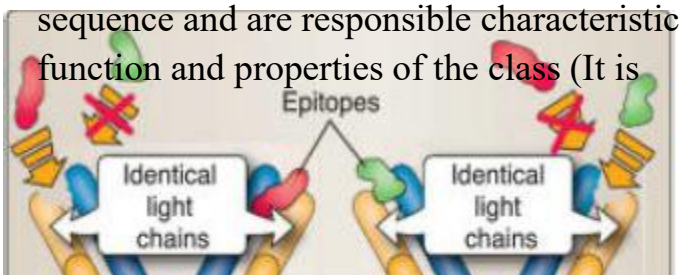
2. Heavy chains: Heavy chains contain one variable (V_H) and three or four constant (C_H) domains . Heavy (H) chain variable domains (V_H) are extremely diverse, and constant domains (C_H) display a relatively limited variability for members of an isotype. The ð, γ, and α heavy chains contain three constant domains (C_H 1 , C_H2, C_H3) , and μ and ϵ heavy chains contain a fourth constant domain (C_H4) , making them both longer and heavier than γ, ð, or α heavy chains.

3. Antigen-binding sites : A light chain variable domain and a heavy chain variable domain together form a cavity that to form the antigen (epitope)-binding region of the immunoglobulin molecule. Because an immunoglobulin monomer contains two identical light chains and two identical heavy chains, the two binding sites found in each monomeric immunoglobulin are also identical . The variability in the amino acid sequences of the V_L and V_H domains, together with the random pairing of light and heavy chain that occurs from one B cell to another, creates a many of binding sites capable of recognizing a very large number of different epitopes.

4- Fragment antigen binding (Fab): the variable regions on the outer end of each arm of Y-shaped on both H and L chins contain the section of the molecule that interaction with epitopes of antigens, and together they are called Fab region. Since each epitope differs from other epitopes, the variable regions of the Ab also differ in the amino acid sequences. This difference accounts for the specificity of Abs.



5- fragment crystallizable (Fc): the constant regions of H chains for all molecules of the same immunoglobulin class have virtually the same amino acid sequence and are responsible characteristic function and properties of the class (It is



responsible for many biologic activities that occur following engagement of an epitope).

lsotypes

Heavy chain isotypes (μ, ð, γ, α, and ϵ) also determine immunoglobulin isotype or class (lgM , lgD, lgG , lgA, and lgE , respectively) Normally, humans produce all five immunoglobulin isotypes. Of the two light chain isotypes, an individual B cell will produce only κ or λ . chains, never both. B cells express surface-bound immunoglobulin monomers as epitope-specific receptors; B cells produce and display only one heavy chain isotype, with the exception that unstimulated B cells express both lgM and lgD. When secreted into the body fluids, soluble lgG and lgE remain monomeric, soluble lgM forms a pentamer, and soluble lgA can be found in either a monomeric or dimeric form.

*** lgG**

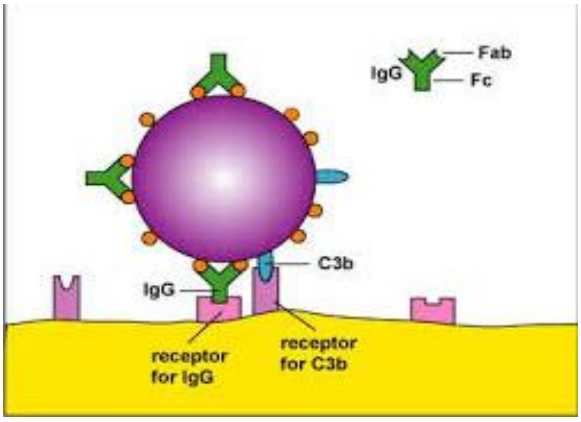
exists as both surface and secreted monomeric molecules(80% - 85%). four human lgG subclasses, lgG1 , lgG2, lgG3, and lgG4. Collectively, lgG subclasses make up the greatest amount of immunoglobulin in the serum . Many lgG antibodies are effective in activating complement, opsonizing and neutralizing microorganisms and viruses, and initiating antibody-dependent cell-mediated cytotoxicity, and they function in a wide variety of hypersensitivity functions.

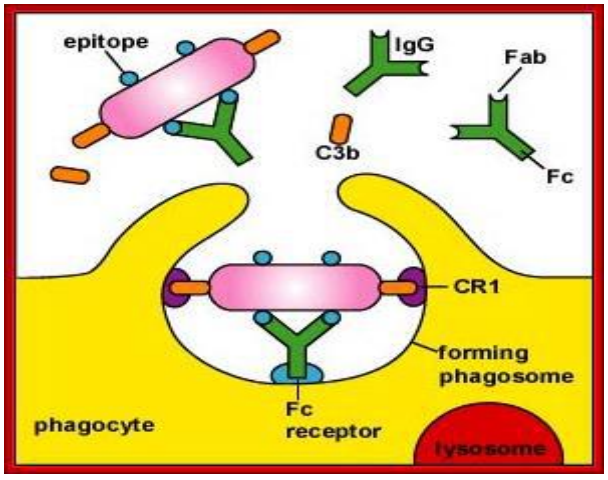
TABLE 18.3

Antibody Classes

CLASS	GENERAL STRUCTURE	LOCATION	FUNCTION
IgG	Monomer	Free in blood plasma; about 80 percent of circulating antibodies	Most abundant antibody in primary and secondary immune responses; crosses placenta and provides passive immunizationto fetus
IgM	Pentamer	Surface of B cell; free in blood plasma	Antigen receptor on B cell membrane; first class of antibodies released by B cells during primary response

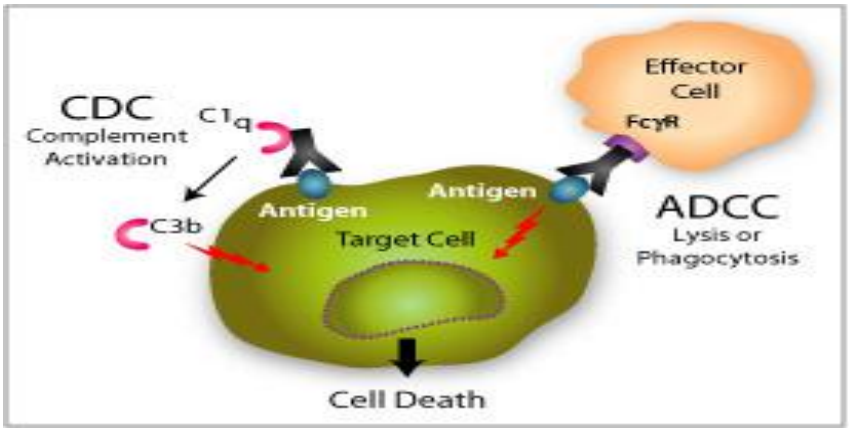
IgG opsonizes, increasing phagocytosis in two ways both of these activities occur through specific sites in the constant Fc region of the IgG , 1- after Ag reacts with specific IgG the Fc portion interacts with complement producing complement components that coat Ag and then attach to the receptors on phagocytes.2- The Fab portion of IgG react with Ag and coat it and the Fc attaches directly to Fc receptors on phagocytosis





IgG also can neutralize toxin and they can prevent infection by blocking adherence of viruses and microorganisms to host cells. IgG act together with neutrophils, eosinophils, macrophages, or NK cells to kill target cells in **antibody-dependend cellular cytotoxicity** (**ADCC**) target cell may be virus or other that cannot phagocytized . antibody attach to specific target cells leaving the Fc portion exposed cells that participated in ADCC have Fc receptors so they attach via the Fc portion and come close

contact with target cells, contents of granules and lysosomes within the attacking cells are released in close to target cell membranes resulting in target cell killing.



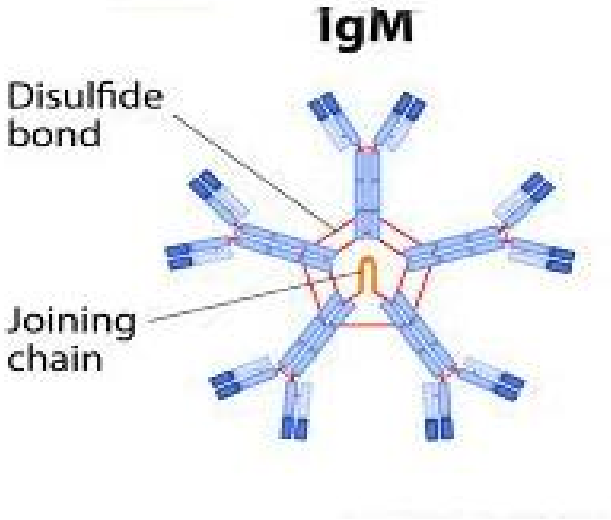
IgG is only class of Abs can cross the placenta from the mothers to the fetus, it does this by means of an amino acid sequence in Fc portion that is recognized by receptors in the placenta.

***lgM**

is found either as a cell surface-bound monomer or as a secreted pentamer (5% - 10%) Most unstimulated B cells display lgM on their cell surfaces. In general , lgM is the first immunoglobulin to be formed following antigenic stimulation. lgM is effective both at immobilizing antigen (agglutination) and in activating the classical pathway of complement. IgM is actually more than five times larger than the IgG

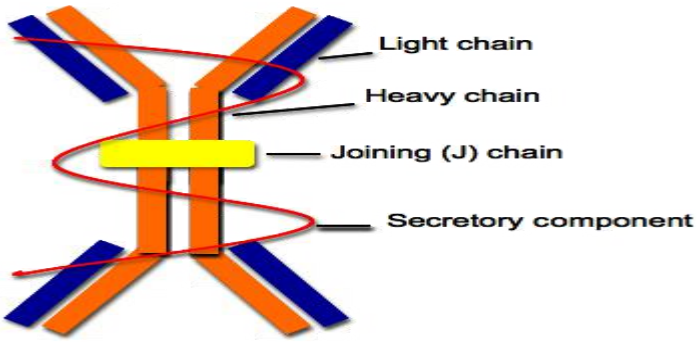
- IgM pentamer contain five unites monomer with J chain
- H chain are longer than IgG

The multiple antigen-binding sites of IgM make it very efficient in many functions like phagocytosis .



***IgA**

is present in both monomeric and dimeric forms(10% -13%). Monomeric lgA is found in the serum .The addition of a J or joining chain to two lgA monomers forms a dimer. Epithelial cells use a specialized receptor to transport the lgA dimer to mucosal surfaces. This specialized receptor becomes an accessory molecule that binds to the lgA dimers is known as secretory component (SC) . Secretory lgA dimers are found in mucus, saliva, tears, breast milk, and gastrointestinal secretions. The SC provides increased resistance to enzymatic degradation . Two isoforms of lgA (a1 and a2) show slightly different functions. lgA1 predominates in the blood plasma and in secretions above the diaphragm . Secretory lgA2 accounts for most lgA found in the lumen of the lower portion of the gastrointestinal tract. Large amounts of lgA are synthesized and secreted daily at the mucosal surfaces of the Gl tract, respiratory tracts, and other secretory epithelia. More lgA is produced daily than all the other isotypes combined.

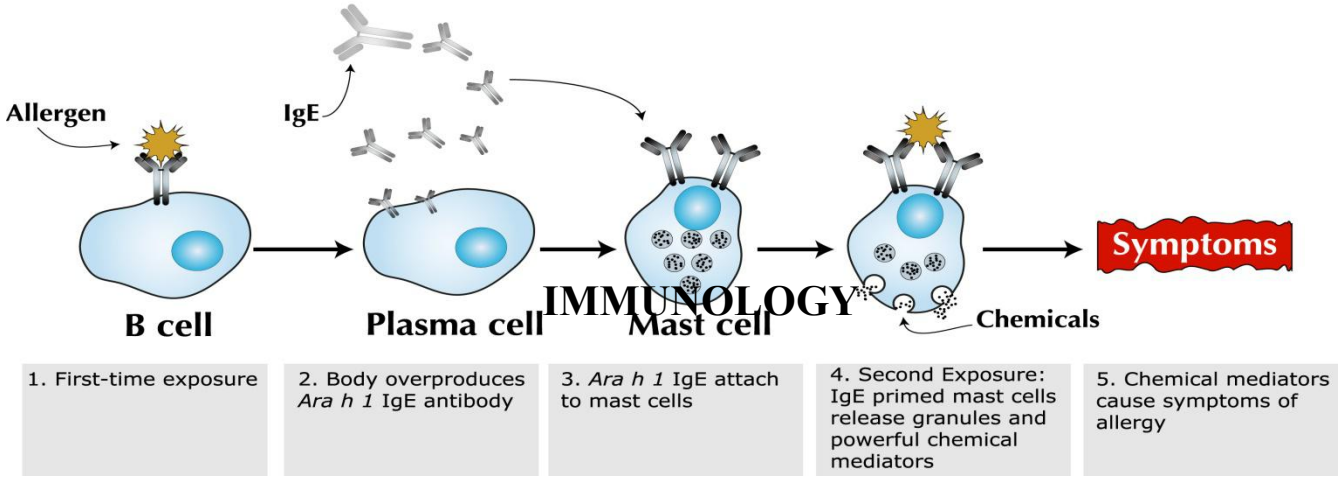


***IgD**

(1%) has a monomeric structure and is almost exclusively displayed on B-cell surfaces. Little is known of its function.

***IgE**

is present in relatively low serum concentration ; most is adsorbed on the surfaces of mast cells and eosinophils. Mast cells and basophils have isotype-specific receptors for the Fc portion of free lgE molecules. Cross-linking of lgE on mast cell surfaces by antigen triggers the release of histamine and other inflammatory mediators, leading to immediate hypersensitivity (allergic) responses.



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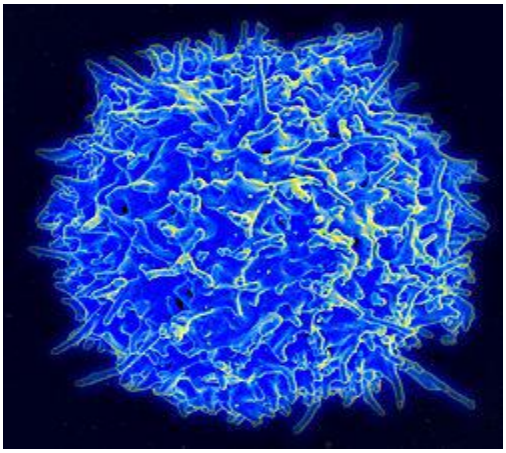
Lac. 6

The role of lymphocytes in specific immunity

Lymphocytes are the cells responsible for specific immune response. Most lymphocytes are either T cells or B cells . T cells (thymus cells) and B cells (bone marrow) are the major cellular components of the adaptive immune response. T cells are involved in cell-mediated immunity the direct distraction of body cells that have been involved by parasites or that undergo degeneration. T cells also play a significant regulatory role in the development and activation of all types of immune responses, whereas B cells are primarily responsible for humoral immunity (relating to antibodies) also can be antigen presenting cells. T cells can be distinguished from other lymphocytes, such as B cells and natural killer cells, by the presence of a T-cell receptor on the cell surface.

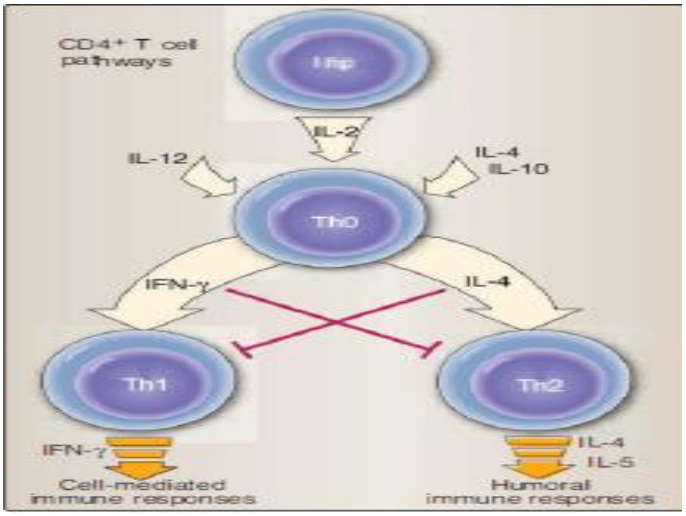


T and B lymphocytes cannot be distinguished by a Appearance . lymphocytes can see by scanning Electron microscopy .
B and T cells recognize antigen in different way.

B and T cells recognize antigen in different ways. All lymphocytes are identified by protein on the surfaces of cells; B cells are identified by presence of immunoglobulin on their surfaces. T cells express unique T-cell receptors for antigen on their surfaces. During maturation a variety of **cluster of differentiation** or **CD** protein molecules (or markers) are expressed on the cell membranes of subpopulations of cells enabling them to be identified. CD molecules are especially useful in identifying lymphocytes . The category of effector T cell is a broad one that includes various T cell types that actively respond to a stimulus, such as co-stimulation. This includes helper, killer, regulatory, and potentially other T cell types. All T cells carry CD3 molecules which are associated with the T-cell receptors for antigen. The subgroups of T cell that can be farther identified by other CD molecules. Most of the mature T cells are either CD4 cells bearing the CD4 protein or CD8 cells with CD8 protein.

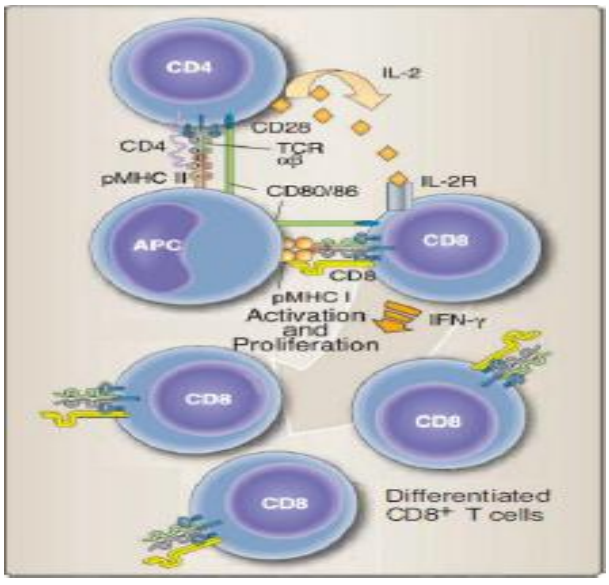
-Helper CD4+ T cells

T helper cells (TH cells) assist other white blood cells in immunologic processes, These cells are also known as CD4+ T cells, there are two functional subsets of CD4 lymphocytes , **Th1 cells** produce cytokines that drive the development of CD8 cytotoxic cells and activate macrophages. **Th2 cells** produce cytokines that stimulate B cells to produce antibodies. (Helper T cells become activated when they are presented with peptide antigens by MHC class II molecules, which are expressed on the surface of antigen-presenting cells (APCs).

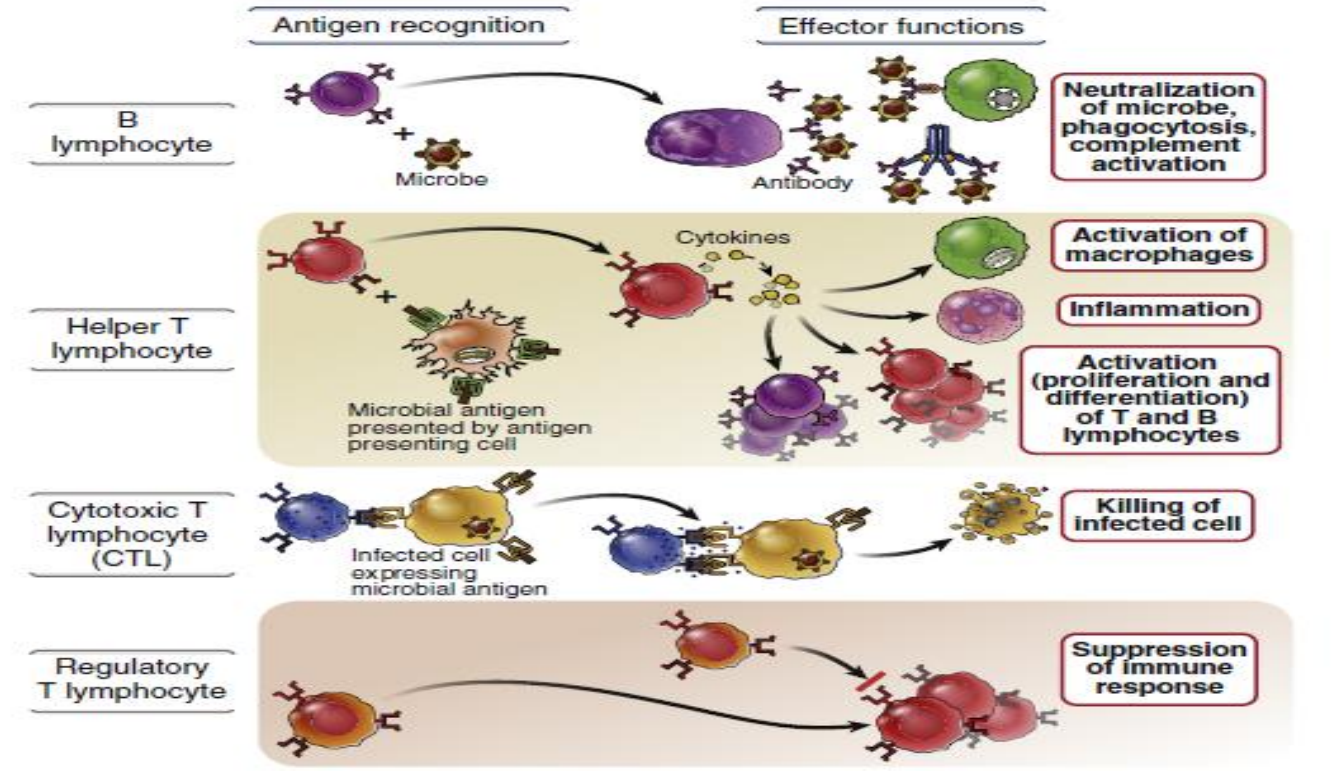


- Cytotoxic (killer) CD8+ T cells

Cytotoxic T cells (TC cells, T-killer cells,) destroy virus-infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as CD8+ T cells since they express the CD8 glycoprotein at their surfaces. These cells recognize their targets by binding to antigen associated with MHC class I molecules, which are present on the surface of all nucleated cells. Through IL-10, adenosine, and other molecules secreted by regulatory T cells, the CD8+ cells can be inactivated to an anergic state, which prevents autoimmune diseases.



Some other lymphocytes act as suppressor (Ts) cells or T-regulatory cells to suppress immune responses, probably by means of secreted factors (Their major role is to shut down T cell-mediated immunity toward the end of an immune reaction and to suppress autoreactive T cells that escaped the process of negative selection in the thymus.) This is an important "self-check" built into the immune system to prevent excessive reactions. Regulatory T cells come in many forms with the most well-understood being those that express CD4, CD25.



Major histocompatibility complex (MHC)

In addition to CD markers and immunoglobulins, many other recognition molecules are found in the cell surfaces. One interesting group is **Major histocompatibility complex (MHC) is** a set of molecules displayed on cell surfaces that are responsible lymphocytes recognition and antigen presentation. The MHC molecules control the immune response through recognition of self and non-self and consequently serves as targets in translation rejection. In humans the major gene complex is composed of closely linked genes located on chromosome 6 Human MHC proteins are called **human leukocyte antigens (HLAs)** because they were discovered as antigens of leukocytes.in individual who are genetically the same, such as identical twins have the same MHC molecules on their

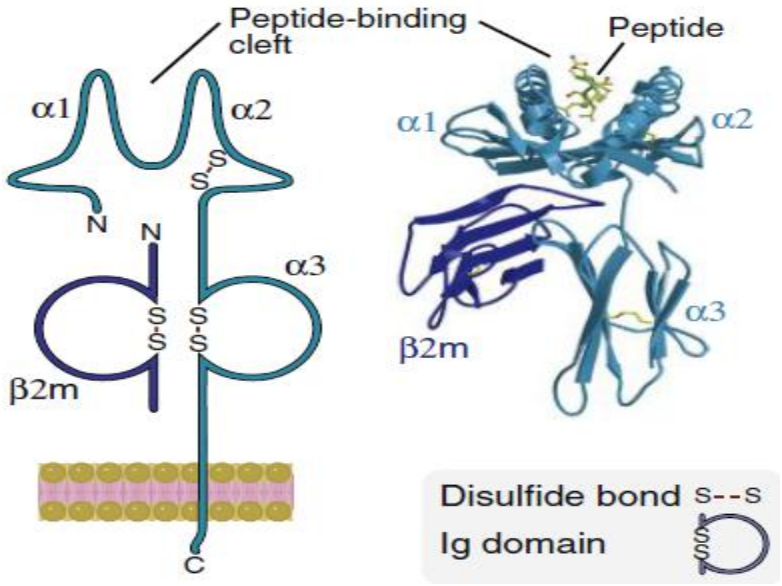
when transplant is made between identical twins the immune system fails to recognize the MHC molecules on the transplanted cells as foreign and the transplant is accepted. When cells are transplanted between nonidentical people the immune system recognizes the MHC molecules on the transplanted cells and makes a vigorous immune response leading to rejection of the tissue. In all mammals, the MHC locus contains two sets of highly polymorphic genes, called the class I and class II MHC genes. Both class I and class II MHC have a peptide-binding groove or cleft where peptide antigen fragment can be inserted.

MHC class I

found on the cell surface of all nucleated cells in the bodies of jawed vertebrates, They also occur on platelets, but not on red blood cells. the CD8(cytotoxic T cells) bind to MHC class I molecules.

Structure

MHC class I molecules are heterodimers that consist of two polypeptide chains, α and β2-microglobulin (b2m). The two chains are linked noncovalently via interaction of b2m and the α3 domain. Only the α chain is polymorphic and encoded by a HLA gene, while the b2m subunit is not polymorphic and encoded by the Beta-2 microglobulin gene. The α3 domain is plasma membrane-spanning and interacts with the CD8 co-receptor of T-cells. The α3-CD8 interaction holds the MHC I molecule in place while the T cell receptor (TCR) on the surface of the cytotoxic T cell binds its α1-α2 heterodimer ligand, and checks the coupled peptide for antigenicity. The α1 and α2 domains fold to make up a groove for peptides to bind. MHC class I molecules bind peptides that are 8-10 amino acid in length.



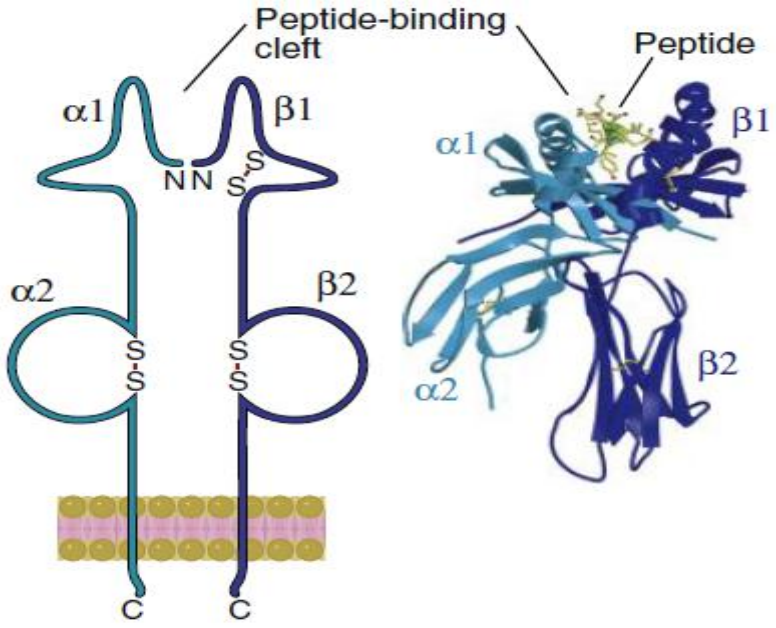
Antigen activate T cytotoxic cells only when they are presented as peptides complexed with MHC class I molecules in this manner and in conjunction with a signal given by antigen presenting cells . if the peptides are nonself such as those produced by intracellular pathogens Tc cells can identify and destroy the infection cell . so class I present endogenous antigen like fragment of viral proteins or tumor proteins.

MHC class II

Are found principally on macrophages and dendritic cells ,antigen presenting cells and B cells with can also presenting antigen. CD4 helper T-lymphocytes bind to MHC class II

Structure

Like MHC class I molecules, class II molecules are also heterodimers, but in this case consist of two homogenous peptides, an α and β chain, both of which are encoded in the MHC. The subdesignation α1, α2, etc. refers to separate domains within the HLA gene; each domain is usually encoded by a different exon within the gene, and some genes have further domains that encode leader sequences, transmembrane sequences, etc. Because the antigen-binding groove of MHC class II molecules is open at both ends while the corresponding groove on class I molecules is closed at each end, the antigens presented by MHC class II molecules are longer, generally between 15 and 24 amino acid residues long.



Because class II MHC is loaded with extracellular proteins, it is mainly concerned with presentation of extracellular pathogens (for example, bacteria that might be infecting a

wound or the blood). Class II molecules interact mainly with immune cells, like the T helper cell (TCD4+) . The helper T cells then help to trigger an appropriate immune response which may include localized inflammation and swelling due to recruitment of phagocytes or may lead to a full-force antibody immune response due to activation of B cells

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Lac. 7

B lymphocytes activation

B lymphocytes recognized an antigen by means of specific antibody molecules (IgM, IgD) on the surface of B cell, there are generally only a few B lymphocytes that recognize one of the foreign epitopes of the antigen. Another small set of B lymphocytes that recognized another epitope.

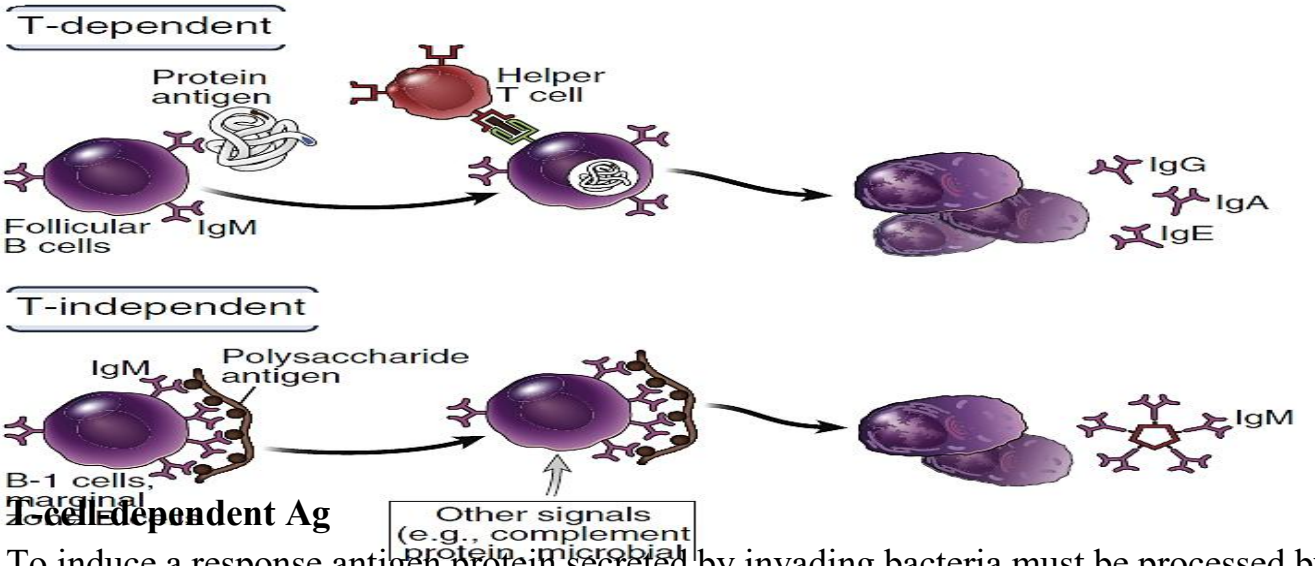
Antibody responses to different antigens are classified as T-dependent or T-independent, based on the requirement for T cell help

B lymphocytes recognize and are activated by a wide variety of chemically distinct antigens, including proteins, polysaccharides, lipids, nucleic acids, and small chemicals. Protein antigens are processed and presented by antigen-presenting cells (APCs) and recognized by helper T lymphocytes, which play an important role in B cell activation and induce immunoglobulins.

(Antigen-presenting cell (APC) *A cell that displays peptide fragments of protein antigens, in association with MHC molecules, on its surface and activates antigen-specific T cells. In addition to displaying peptide-MHC complexes, APCs also express costimulatory molecules to optimally activate T lymphocytes.)*

In the absence of T cell help, protein antigens elicit weak or no antibody responses. Therefore, protein antigens and the antibody responses to these antigens are called T-dependent. Polysaccharides, lipids, and other nonprotein antigens stimulate antibody production without the involvement of helper T cells. Therefore, these nonprotein antigens and the antibody responses to them are called T-independent.

NOT. Thus, the most specialized and effective antibody responses are generated under the influence of helper T cells, whereas T-independent responses are relatively simple.

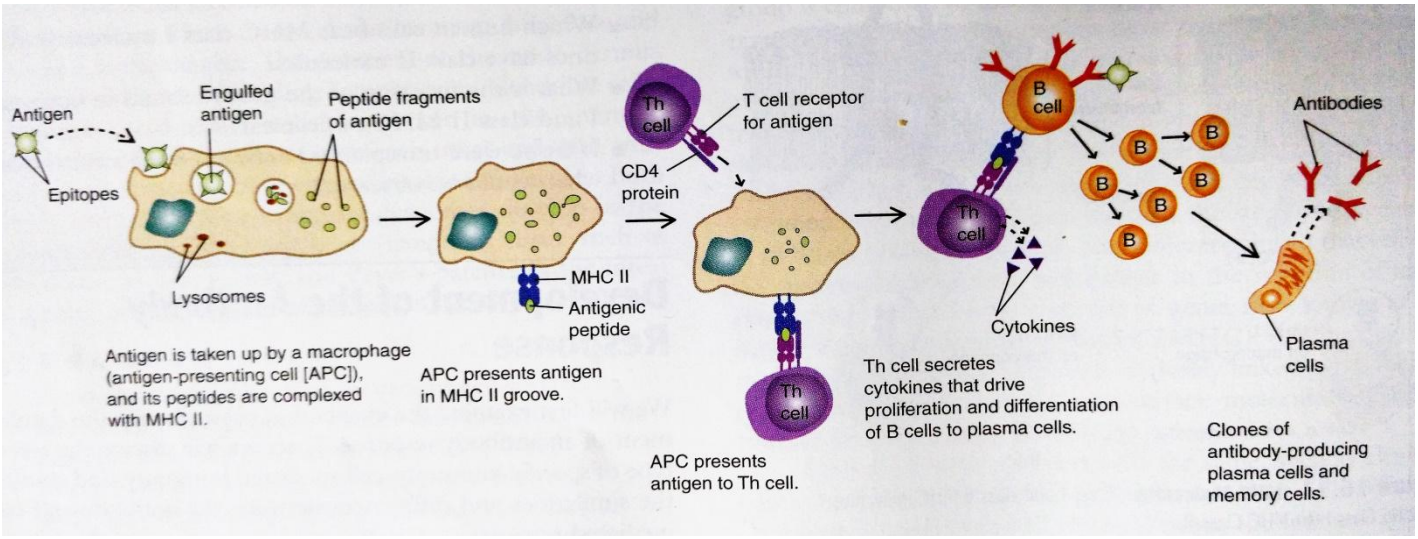


T-cell-dependent Ag

To induce a response antigen protein secreted by invading bacteria must be processed by macrophages (APCs) ,the large Ag molecules are broken down in the cell in to smaller fragments, attached to the groove of MHC II and presented to the cell surface.

When the Th cell recognized and bind to the fragment presented in MHC II , the BCR binds a Th , the antigen is taken up into the B cell through receptor and presented to T cells as peptide pieces in complex with MHC-II molecules on the cell membrane.

Already T helper (TH) cells, that were activated with the same antigen recognize .Th cell secretes cytokines such as IL4 , IL5 and IL10 that activate B cell. Now activated, B cells participate in a two-step differentiation process that yields both short-lived plasmablasts for immediate protection and long-lived plasma cells and memory B cells for persistent protection.



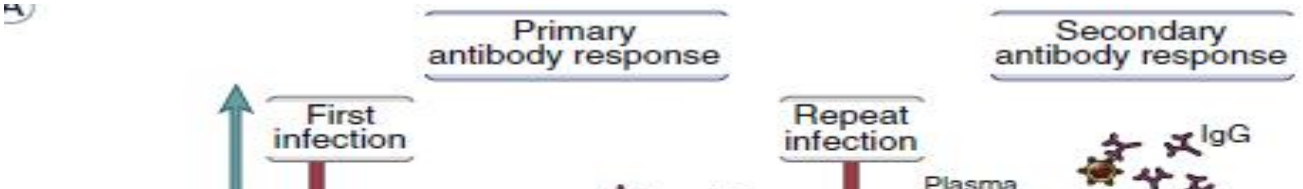
T-cell-independent Ag

Polysaccharides, lipids, and other nonprotein antigens elicit antibody responses without the participation of helper T cells. Recall that these nonprotein antigens cannot bind to MHC molecules, so they cannot be seen by T cells. Many bacteria contain polysaccharide-rich capsules, and defense against such bacteria is mediated primarily by antibodies that bind to capsular polysaccharides and target the bacteria for phagocytosis. Antibody responses to T-independent antigens differ from responses to proteins, and most of these differences are attributable to the roles of helper T cells in antibody responses to proteins. Because polysaccharide and lipid antigens often contain multivalent arrays of the same epitope, these antigens may be able to cross-link many antigen receptors on a specific B cell. This extensive cross-linking may activate the B cells strongly enough to stimulate their proliferation and differentiation without a requirement for T cell help. Polysaccharides also activate the complement system, and many T-independent antigens engage BLRs, thus providing activating signals

to the B cells that also promote B cell activation in the absence of T cell help. Naturally occurring protein antigens usually are not multivalent, possibly explaining why they do not induce full B cell responses themselves but depend on helper T cells to stimulate antibody production.

The primary and secondary responses

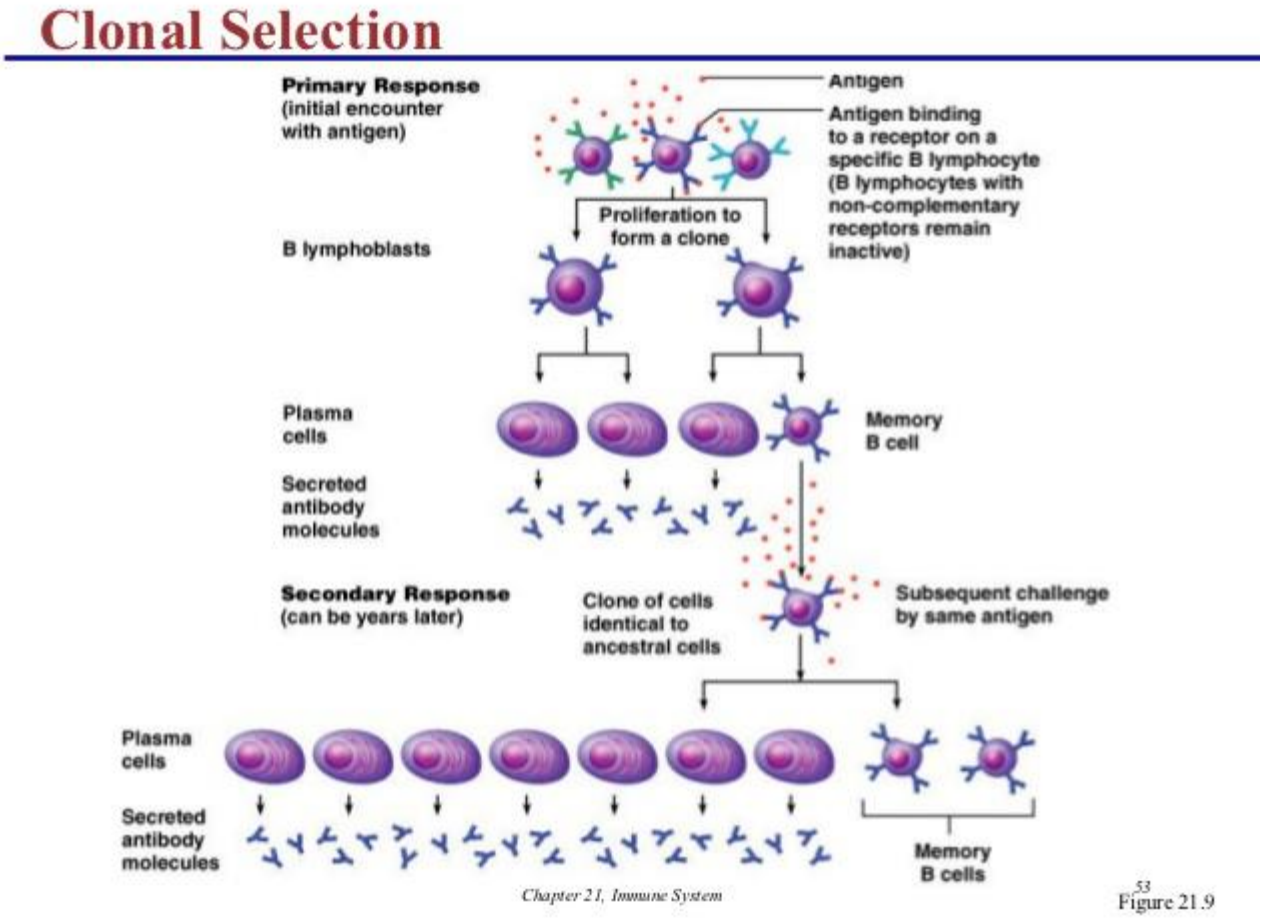
The first time a particular antigen is introduced into the body a primary response occurs about 5 to 10 days is required before a substantial amount of antibody is detected in the blood. The amount of antibody or titer rises with time until the antigen is removed and the response wanes. A slow rise in titer is typical of antibody production during the primary antibody response. If however the same antigen is introduced at a later data, the titer of antibodies rises much faster and is much higher, due to rapid activation of the clones of memory cells present. This is typical of the secondary(memory) antibody response. IgM is the first class of antibody produced during an immune response, and it is the only class produced in response to T cell-independent Ag .With T cell dependent Ag, though, there is a switch to other classes of immunoglobulin as the response develops. In the secondary antibody response, essentially the same sort of IgM response occurs as the primary response but the IgG response is greatly accelerated and enhanced. in other words, memory develops for IgG production but not for IgM. The production of Abs of all classes contributes to the elimination of pathogens because each class can confer beneficial clearance mechanisms.



Clonal selection hypothesis

That acquired specific immunity depends on individual antigen specific lymphocytes that proliferation in response to Ag. The effector cells eliminate the Ag while the memory cells maintain immunity against later exposure to the Ag .during primary antibody response, B lymphocytes recognize the Ag by means of specific antibody on their surfaces. This recognition alone does not initiate antibody production rather it primes the B cells to respond to costimulatory signals given by the Th cells inducing the B cells to proliferate. Each cell divides to give tow cells with the same antibody specificity then four, then eight and so on to form large clones of B cells producing the same antibody. After a period of division some B cell differentiate resulting in the production of plasma cells, these are highly specialized antibody producing cells, capable of producing thousands of molecules of antibody per second. Plasma cells are terminally differentiated cells after they produce quantities of antibody they die, further some cells of the developing clone respond to the cytokine signals to differentiate into memory cells with the same specificity as the B cells from which they arose. These memory cells persist in the body for years and are present in number sufficient to give

prompt and effective protective anamnestic or memory secondary response when the same Ag is encountered again at later time .



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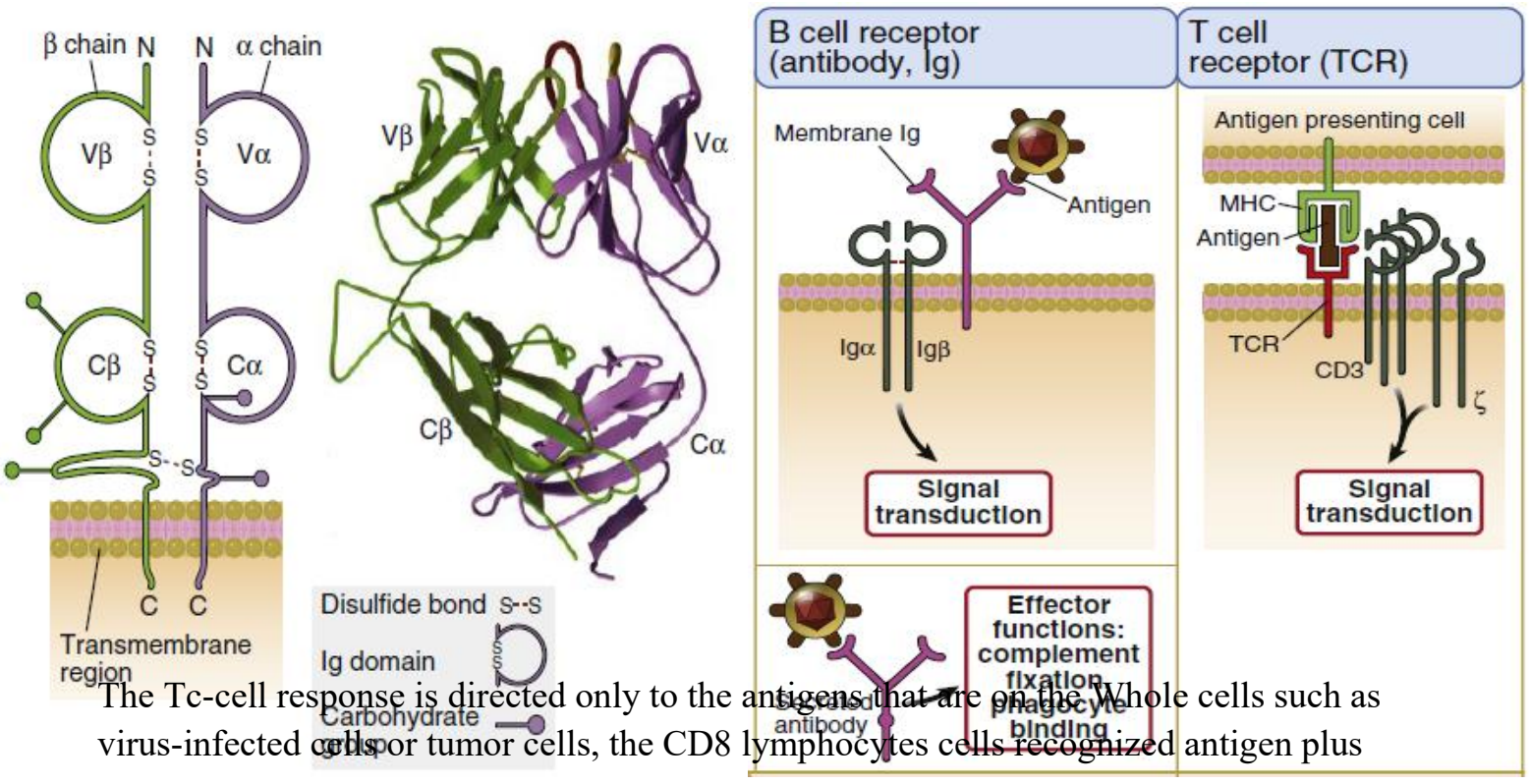
Development of the cell-mediated Immune response

Cell-mediated immunity is directed towered eliminating certain dysfunctional host such as those infected by a pathogen or cancerous cells .T lymphocytes capable to recognized specific antigen and operates in two ways. Either a CD8 T cytotoxic cell (Tc) they can kill Ag bearing target cell, or CD4 (Th1) can activated macrophages.

T lymphocytes and cell-mediated Immune response

In Cell-mediated immunity Ag is recognized by specific molecules called T cell receptors TCRs on the T cell surface, (*The TCR, which recognizes peptide antigens displayed by MHC molecules, is a membranebound heterodimeric protein composed of an polypeptide α chain and a β chain , each chain containing one variable (V) region and one constant (C) region . The V and C regions are homologous to immunoglobulin V and C regions. In the V region of each TCR chain, there are three hypervariable, or complementarity-determining, regions, each corresponding to a loop in the V domain Both the α chain and the β chain of the TCR participate in specific recognition of MHC molecules and bound peptides,)*

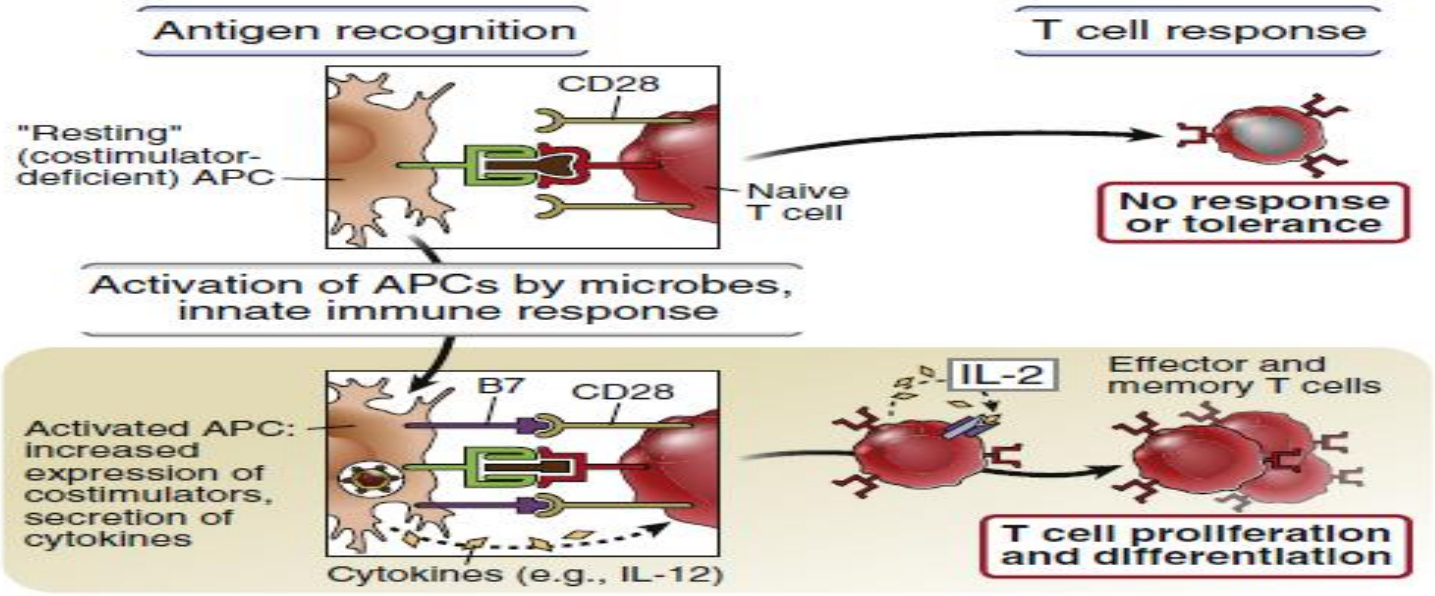


The Tc-cell response is directed only to the antigens that are on the Whole cells such as virus-infected cells or tumor cells, the CD8 lymphocytes cells recognized antigen plus

MHC class I antigen. The Th1 cells that activate macrophages to control intracellular microorganisms are CD4 lymphocytes that only recognized antigen complexed with MHC II molecules. Bothe CD4 and CD8 develop from naïve T cell that have specific TCRs but have not yet encountered Ag.

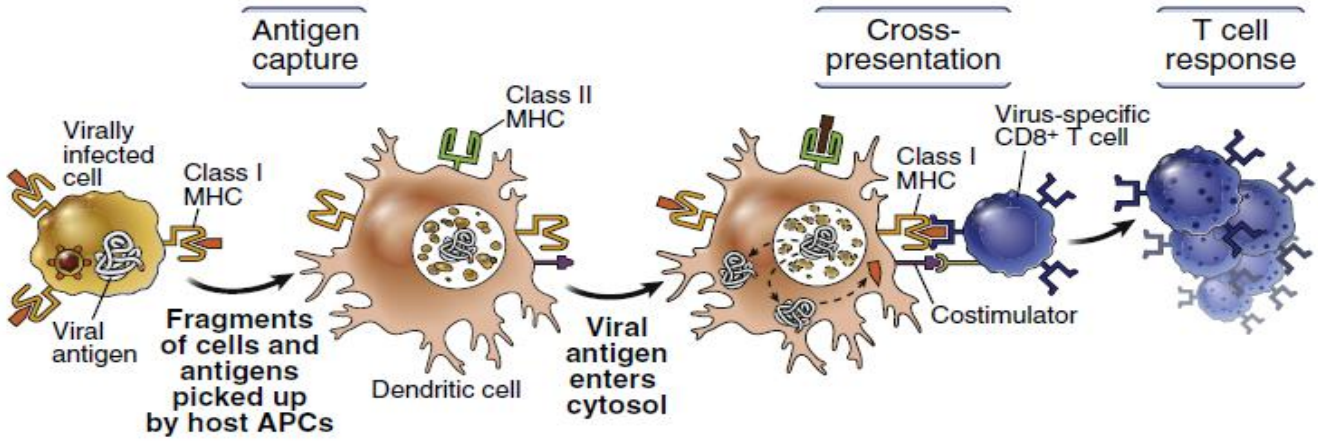
Cytotoxic T cells against cells

During cell-mediated immunity, a cancer cell or a virus- infected cell becomes a target to be destroyed. All nucleated cells routinely sample a small portion of protein synthesized with in the cell. The protein is degraded in the cellular recycling center and the resulting peptide fragment inserted into the grooves of newly synthesized class I MHC for display on the cell surface. Nonself peptides presented with a costimulatory signal(*CD80 and CD86 are known as costimulators for T cell activation. This second signal can be assisted (or replaced) by stimulating the TC cell with cytokines released from helper T cells*). *The best-defined costimulators for T cells are two related proteins called B7-1 (CD80) and B7-2 (CD86), both of which are expressed on APCs and whose expression is increased when the APCs encounter microbes. These B7 proteins are recognized by a receptor called CD28, which is expressed on most T cells.*



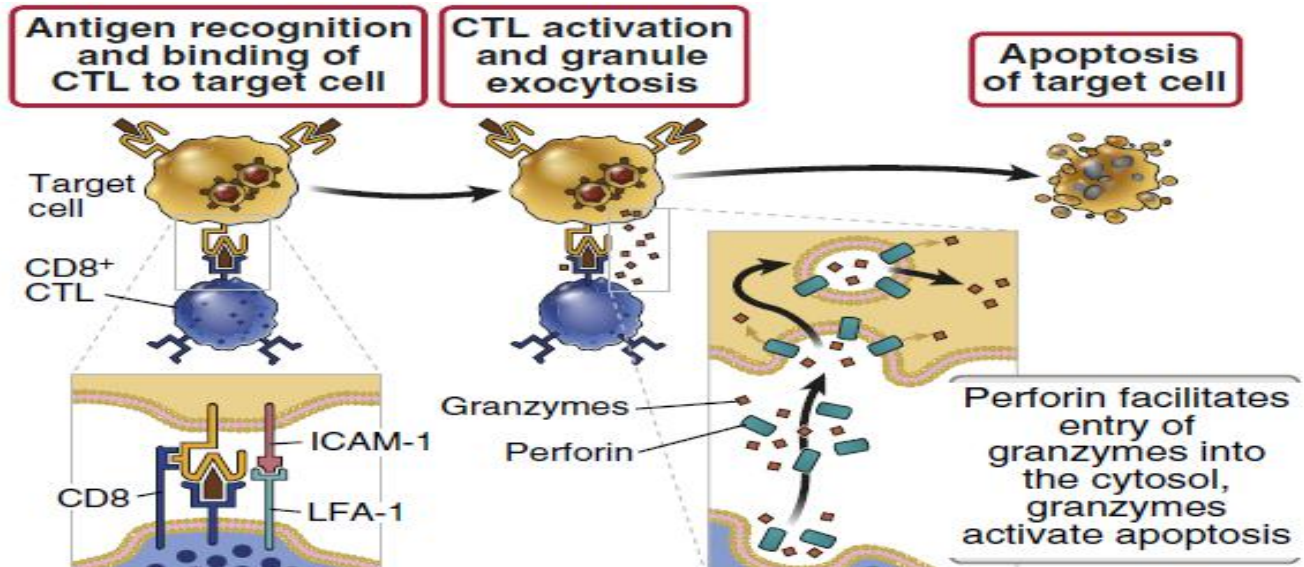
Lead to activation of T cells and induction of their cytotoxic capacity. Subsequent recognition of the same peptides on the body cells leads to their destruction by these activated T cells or their daughters. For example, in the virus infected cell, the virus causes the host cell to synthesize proteins of the viral coat. Just as with normal cell proteins, some of these are enzymatically degraded into short peptide sequences. Then

within the cell, they complex with MHC I molecules begin formed there by the process *known as cross-presentation*. The complex of MHC I with Ag peptide is then moved to the cell surfers, where it they can be presented to specific responding Tc cells. Only protein Ag can induce cell-mediated immunity, and the epitopes recognized are short peptides.



The disastrous if Tc cells destroyed normal cells that were not really infected but only had a molecule of foreign Ag attached to their surface. The fact that the Ag is recognized by the Tc cells only when complexed with MHC I prevents uninfected healthy cells from being perceived as the foreign and destroyed.

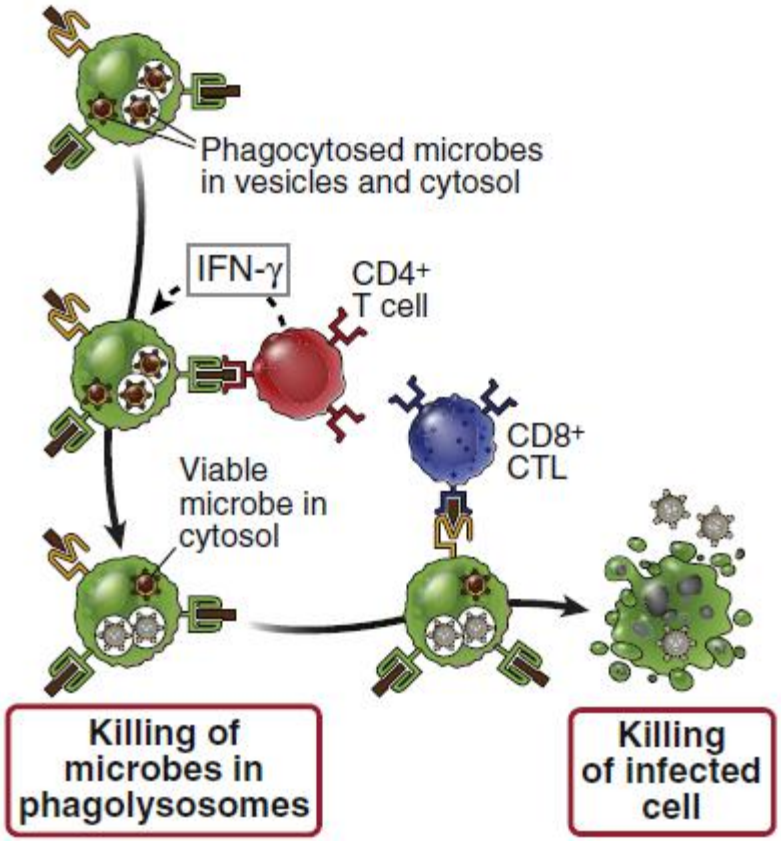
The responding Tc cell not only have Ag receptors they also have CD8 receptors for MHC I. specific reaction of the epitope and the T-cell Ag receptor and interaction between the MHC I and the CD8 that serve as respecters for MHC I help to hold the Tc and the target cells together. Contents of granules in the Tc cell such as perforin and granzymes a molecule produced by Tc cells kills target cells by forming a pore similar to that formed by the membrane attack complex of complement. The Tc cell survives and can go on kill other targets.



Since tumor (cancer) cells arise from host tissue, it might be expected that they would not incite an immune response. It has clearly been shown, however that they produce Ags that differ from normal host tissue and that lead to immune responses. When tumors are induced in animals by certain chemicals each tumor has it is own unique Ags not sherd by other tumors produced in the same way.

Tumor cells are destroyed largely by Tc cells activity, although other mechanisms also act against these immunologically foreign cells.

We have described the effector functions of CD4 T cells and CD8 T cells separately, these types of T lymphocytes may function cooperatively to destroy intracellular microbes . If microbes are phagocytosed and remain sequestered in macrophage vesicles, CD4+ T cells may be adequate to eradicate these infections by secreting IFN-γ and activating the microbicidal mechanisms of the macrophages. If the microbes are able to escape from vesicles into the cytoplasm, however, they become insusceptible to T cell–mediated macrophage activation, and their elimination requires killing of the infected cells by CD8 CTLs.



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Immune tolerance

One of the remarkable properties of the normal immune system is that it can react to an enormous variety of microbes but does not react against the individual's own (self) antigens. This unresponsiveness to self-antigens, also **called immunological tolerance,** when tolerance to self is lost immune responses can damage the body, a condition known as autoimmune diseases, like lupus erythematosus , some forms of diabetes. despite the fact that the molecular mechanisms by which lymphocyte receptor specificities are generated are not biased to exclude receptors for self-antigens. In other words, lymphocytes with the ability to recognize self-antigens are constantly being generated during the normal process of lymphocyte maturation. many self-antigens have ready access to the immune system, so unresponsiveness to these antigens cannot be maintained simply by concealing them from lymphocytes. It follows that there must exist mechanisms that prevent immune responses to self-antigens. These mechanisms are responsible for one of the cardinal features of the immune system namely, its ability to discriminate between self and nonself (usually microbial) antigens.

Immunological tolerance to different self antigens may be induced when developing lymphocytes encounter these antigens in the generative (central) lymphoid organs, a process called central tolerance, or when mature lymphocytes encounter self antigens in peripheral (secondary) lymphoid organs or peripheral tissues, called peripheral tolerance

Central tolerance is a mechanism of tolerance only to self antigens that are present in the generative lymphoid organs namely, the bone marrow and thymus. Tolerance to self antigens that are not present in these organs must be induced and maintained by peripheral mechanisms.

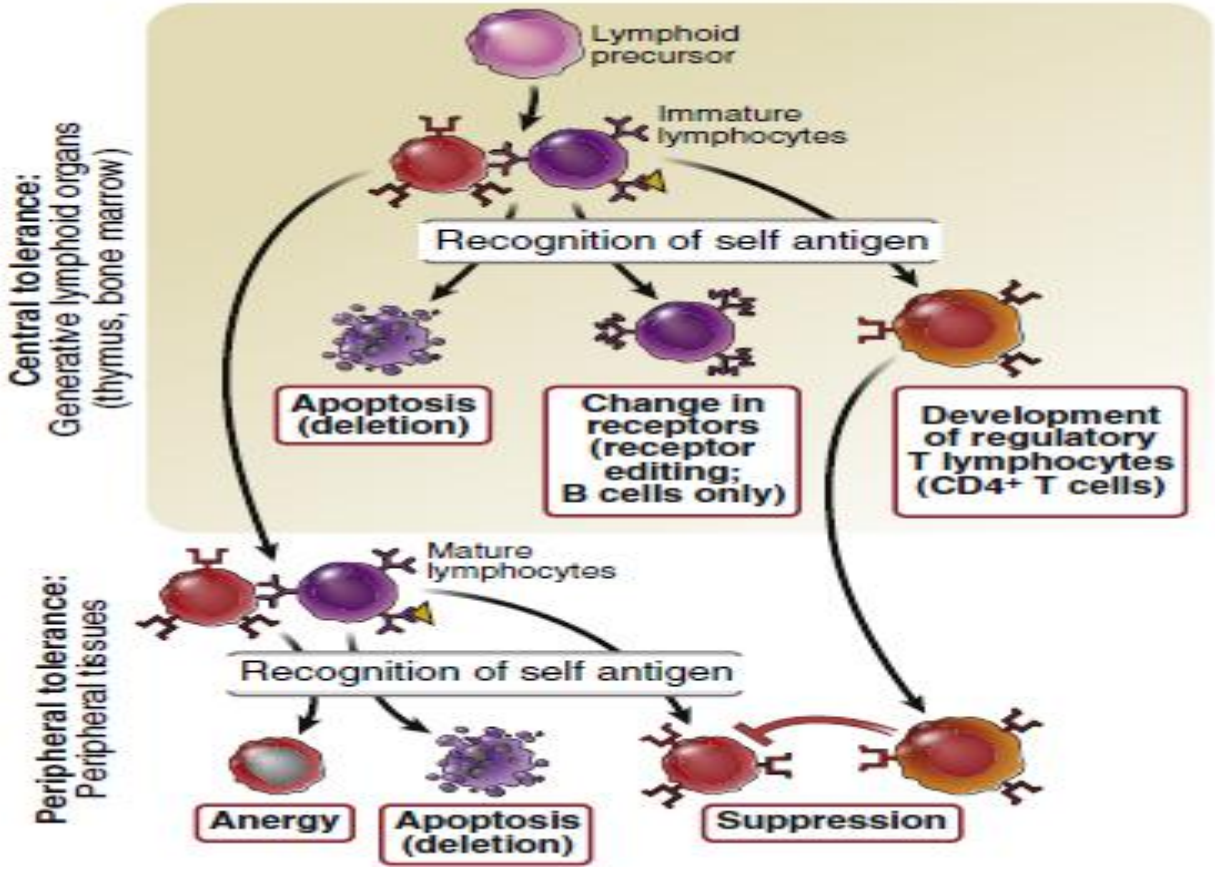
Central tolerance

Central tolerance occurs during the early differentiation of B cells in the bone marrow and T cells in the thymus. Normally, both B and T cells that bind self-epitopes at distinct early stages of development meet an apoptotic death(process of programmed cell death

that occurs in multicellular organisms), thus eliminating large numbers of potentially self-reactive cells before they enter the circulation. B cells express surface lgM as their BCRs. Epitope recognition by BCRs of developing B cells within the bone marrow triggers their apoptotic death , a process known as **negative selection.** Also the binding of peptide-MHC complex (MHC I or MHC II) by TCRs of single positive (CD4,CD8) thymocytes causes them to undergo apoptotic death . This process removes many potentially autoreactive B and T cells before they enter the periphery . A major caveat imposed on central tolerance is that not all self-epitopes are to be found in the primary lymphoid organs, especially those self epitopes that arise after lymphogenesis, such as those that arise during puberty. Other means are needed to prevent the auto reactive cells among them from inflicting damage on the body.

Peripheral tolerance

Several additional mechanisms, collectively called peripheral tolerance, control or eliminate autoreactive B and T cells after they exit the bone marrow or thymus



Hypersensitivity Reactions

Excessive or inappropriate immune responses sometimes lead to host tissue damage resulting from prolonged or repeated antigen exposure. These reactions, called hypersensitivity reactions, cause tissue injury by the release of chemical substances that attract and activate cells and molecules resulting in inflammation. These reactions are classified into four hypersensitivity types depending on the mechanism(s) that underlie the tissue damage . the first three types involve antigen-antibody reactions, whereas the fourth is antibody-independent, involving cell-mediated immune responses only.

TYPES OF HYPERSENSITIVITY REACTIONS

Hypersensitivity reactions are classified on the basis of the principal immunologic mechanism that is responsible for tissue injury and disease.

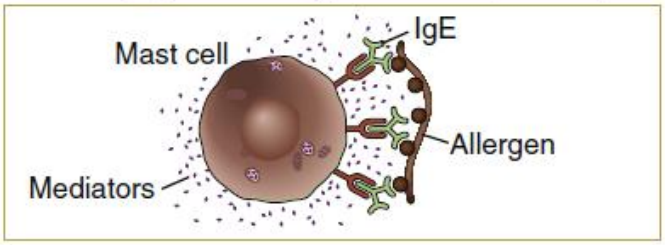
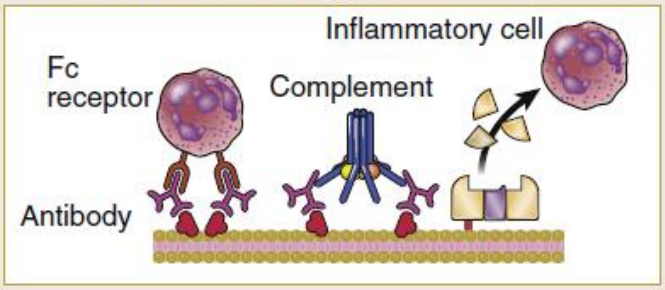
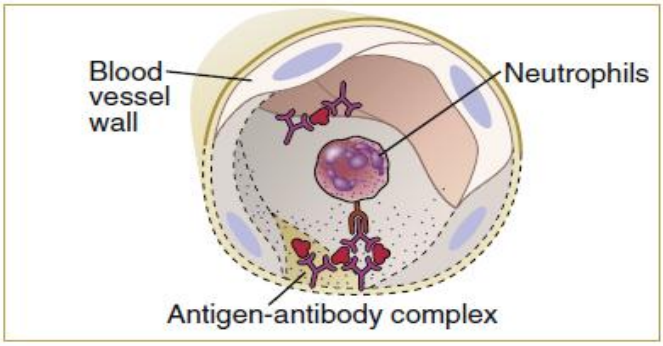
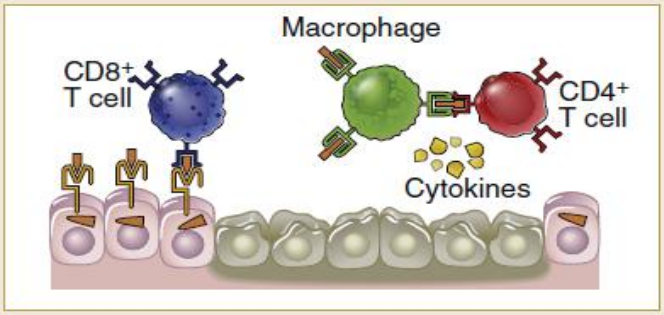
1- Immediate hypersensitivity, or type I hypersensitivity, is a type of pathologic reaction that is caused by the release of mediators from mast cells. This reaction most often depends on the production of immunoglobulin E (IgE) antibody against environmental antigens and the binding of IgE to mast cells in various tissues.

2- Antibodies other than IgE that are directed against cell or tissue antigens can damage these cells or tissues or can impair their function. These diseases are said to be antibody mediated and represent **type II hypersensitivity**.

3- Antibodies against soluble antigens may form complexes with the antigens, and the immune complexes may deposit in blood vessels in various tissues, causing inflammation and tissue injury. Such diseases are called immune complex diseases and represent **type III hypersensitivity**.

4- Some diseases result from the reactions of T lymphocytes, often against self-antigens in tissues. These T cell–mediated diseases represent **type IV hypersensitivity**.

This classification scheme is useful because it distinguishes the mechanisms of immune-mediated tissue injury. In many human immunologic diseases, however, the damage may result from a combination of antibody-mediated and T cell–mediated reactions, so it is often difficult to classify these diseases neatly into one type of hypersensitivity.

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity (Type I)	Th2 cells, IgE antibody, mast cells, eosinophils 	Mast cell-derived mediators (vasoactive amines, lipid mediators, cytokines) Cytokine-mediated inflammation (eosinophils, neutrophils, lymphocytes)
Antibody-mediated (Type II)	IgM, IgG antibodies against cell surface or extracellular matrix antigens 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Opsonization and phagocytosis of cells Abnormalities in cellular function (e.g., hormone or neurotransmitter receptor signaling)
Immune complex-mediated (Type III)	Immune complexes of circulating antigens and IgM or IgG antibodies deposited in vascular basement membrane 	Complement- and Fc receptor-mediated recruitment and activation of leukocytes, and tissue damage secondary to impaired blood flow
T cell-mediated (Type IV)	1. $CD4^+$ T cells (cytokine-mediated inflammation) 2. $CD8^+$ CTLs (T cell-mediated cytolysis) 	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell lysis, cytokine-mediated inflammation