General Introduction

Immunology is a branch of medical science that study of structure and function of the immune system in all organisms.

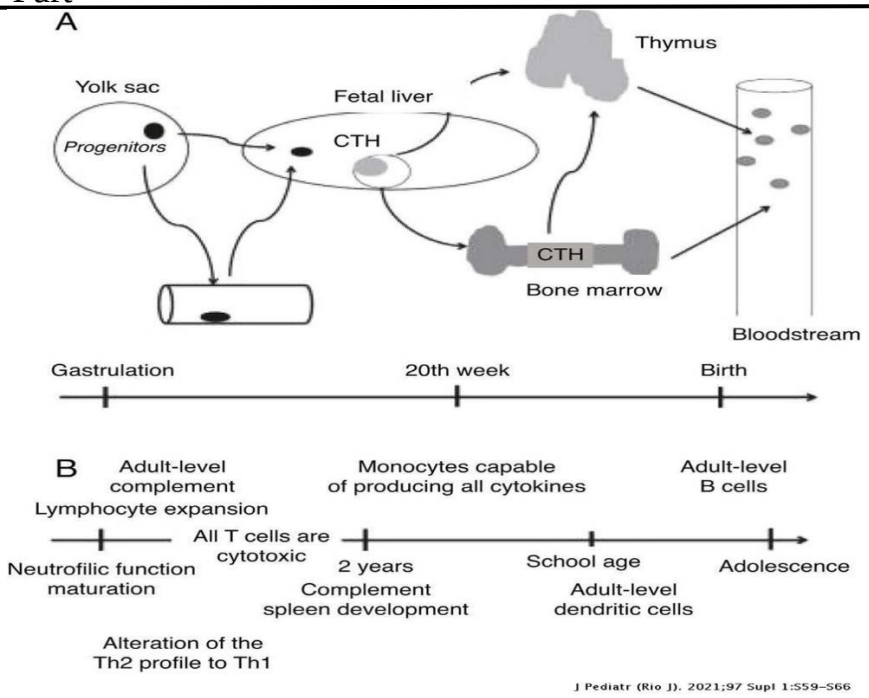
Immunity : is the ability of an organism to resist a particular disease especially through preventing development of a pathogenic microorganism or by counteracting the effects of its products by the action of specific antibodies or sensitized cells.

Immunology branches :

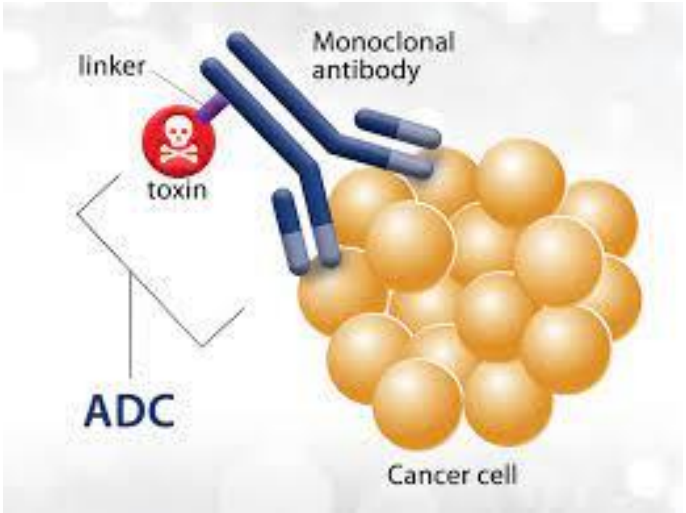
- Classical immunology: is the study the relationship between the body systems, pathogens and immunity.

-Clinical immunology is the study of diseases caused by disorders of the immune system (failure, aberrant action, and malignant growth of the cellular elements of the system). It also involves diseases of other systems, where immune reactions play a part in the pathology and clinical features.

-Developmental immunology The field of developmental immunology is devoted to exploring and gaining an understanding of the multitude of factors that are responsible for the development of the human immune system. It looks at how immune cells are established and how they interact with foreign cells and antigens. This branch of science is vital to furthering our knowledge of how allergies and autoimmune disorders develop and offer an approach to creating new preventative, diagnostic, and therapeutic methods.



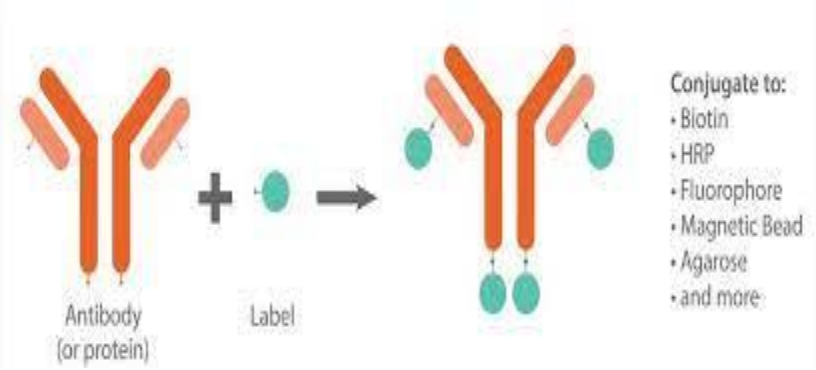
-Immunotherapy :the use of immune system components to treat a disease or disorder is known as immunotherapy. Immunotherapy is most commonly used in the context of the treatment of cancers together with chemotherapy (drugs) and radiotherapy (radiation). However, immunotherapy is also often used in the immunosuppressed (such as HIV patients) and people suffering from other immune deficiencies or autoimmune diseases.



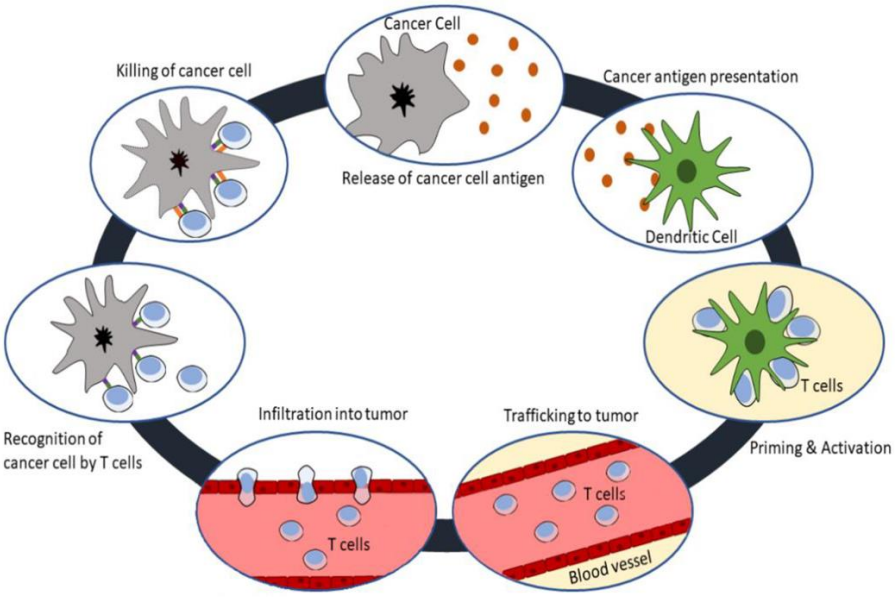
-Diagnostic immunology:

is the study of diagnostic methods that relies on antigen-antibody reaction for detection of the disease.

The specificity of the bond between antibody and antigen has made it an excellent tool in the detection of substances in a variety of diagnostic techniques. Antibodies specific for a desired antigen can be conjugated with an isotopic (radio) or fluorescent label or with a color-forming enzyme in order to detect it. However, the similarity between some antigens can lead to false positives and other errors in such tests by antibodies cross-reacting with antigens that aren't exact matches.



-Cancer immunology:the study of the interaction of the immune system with cancer cells can lead to diagnostic tests and therapies with which to find and fight cancer.

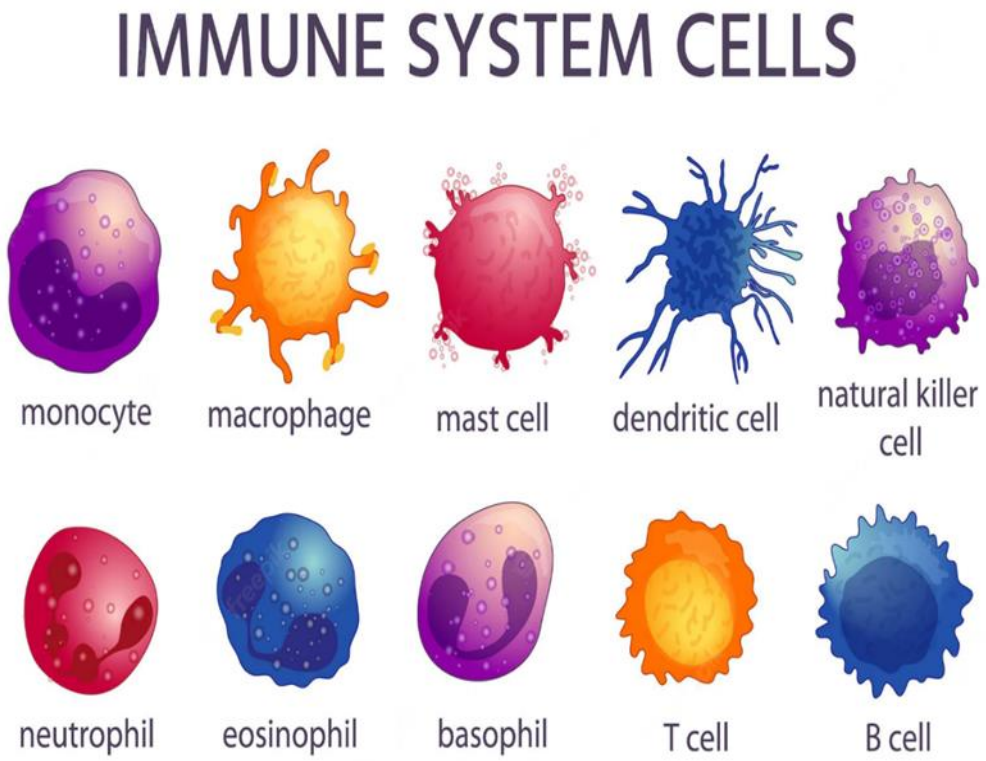


-Immunotoxicology

This is the branch of immunology that deals with the effect or impact of toxins on the immune system. This branch looks at how cells are affected by chemicals (toxins), and how the immune system responds to these invasive chemicals.

General aspects :

- Immunity refers to protection against infection.
- The immune system is the collection of cells, tissues and molecules that functions to defend us against infectious microbes.
- The coordinated reaction of the immune system against infections (and other foreign substances) is known as the **immune response**.
- Abnormalities of the immune system that result in defective immune responses make individuals susceptible to infections by viruses, bacteria, fungi and parasites.
- However, immune responses are also capable of causing damage. Many common diseases are caused by uncontrolled or excessive immune responses (examples include rheumatic fever, asthma and glomerulonephritis; inflammatory bowel disease and autoimmune thyroiditis and multiple sclerosis).



Aquired immunity cells

Types of Immune Response

Immunity is divided into two subdivisions which include:
(A) Innate immune Response (Natural or non-specific immunity).
(B) Adaptive immune Response (Specific immunity).

Innate immunity

Innate immunity, or nonspecific immunity, is the natural resistances with which a person is born. It provides resistances through several physical, chemical , biological and cellular approaches.

Main features:
1. It's present from the moment of birth.
2. It can react with variety of organisms.
3. It's rapidly and immediately in response.
4. It does not have any immunological memory.

Innate Immunity Barriers to Infection

1- Physical/anatomic barriers

- Skin: effective if intact
- Mucus traps pathogens. Respiratory, gastrointestinal, and genitourinary tracts:
- mucosal cell layer continuous with skin.
- Blood clotting - post injury

2- Physiological/chemical

defenses present in body cavities and fluids.

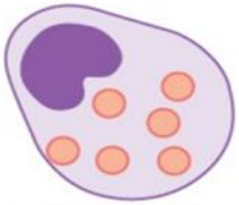
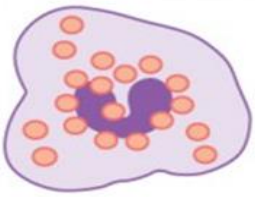
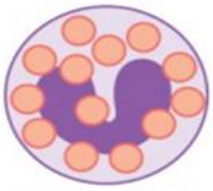
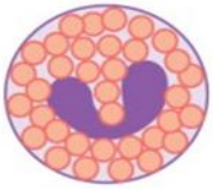
- tearing, coughing, sneezing, vomiting
- low pH in skin , fatty acids, hydrolytic enzymes,anti-microbial peptides
- acidic secretions, degradative enzymes,
- plasma soluble proteins such as (1)the complement system, (2)cytokines, (3)acute phase proteins and (4)coagulation system.

3-Biological barriers such as normal flora .

4- Cellular barriers (Killing of pathogens & infected cells)

Cellular components of innate immunity system :

- polymorphonuclear granulocytes (PMN)
- mast cells
- platelets (thrombocytes)
- endothelial cells
- macrophages and dendritic cells
- natural killer cells

Cell type	Characteristics	Location	Image
Mast cell	Dilates blood vessels and induces inflammation through release of histamines and heparin. Recruits macrophages and neutrophils. Involved in wound healing and defense against pathogens but can also be responsible for allergic reactions.	Connective tissues, mucous membranes	
Macrophage	Phagocytic cell that consumes foreign pathogens and cancer cells. Stimulates response of other immune cells.	Migrates from blood vessels into tissues.	
Natural killer cell	Kills tumor cells and virus-infected cells.	Circulates in blood and migrates into tissues.	
Dendritic cell	Presents antigens on its surface, thereby triggering adaptive immunity.	Present in epithelial tissue, including skin, lung and tissues of the digestive tract. Migrates to lymph nodes upon activation.	
Monocyte	Differentiates into macrophages and dendritic cells in response to inflammation.	Stored in spleen, moves through blood vessels to infected tissues.	
Neutrophil	First responders at the site of infection or trauma, this abundant phagocytic cell represents 50-60 percent of all leukocytes. Releases toxins that kill or inhibit bacteria and fungi and recruits other immune cells to the site of infection.	Migrates from blood vessels into tissues.	
Basophil	Responsible for defense against parasites. Releases histamines that cause inflammation and may be responsible for allergic reactions.	Circulates in blood and migrates to tissues.	
Eosinophil	Releases toxins that kill bacteria and parasites but also causes tissue damage.	Circulates in blood and migrates to tissues.	

Inflammatory Response

The inflammatory response (Inflammation) is a series of local cellular and vascular responses which are triggered when the body is injured, or invaded by antigen. For instance, when you nick your skin, get a foreign object in your eye, or are stung by a bee, reactions occur in order to protect you.

The purpose of inflammation

1. Eliminate the initial cause of cell injury
2. Clear out necrotic cells and tissues damaged
3. Initiate tissue repair.

The classical signs of acute inflammation

1-pain, 2-heat, 3-redness, 4-swelling, and 4-loss of function.

Inflammation is a generic response, and therefore it is considered as a mechanism of innate immunity, as compared to adaptive immunity which is specific for each pathogen.

Inflammatory Response steps:

1. Bacteria enter tissue/damage

2. Release of histamine which lead to:

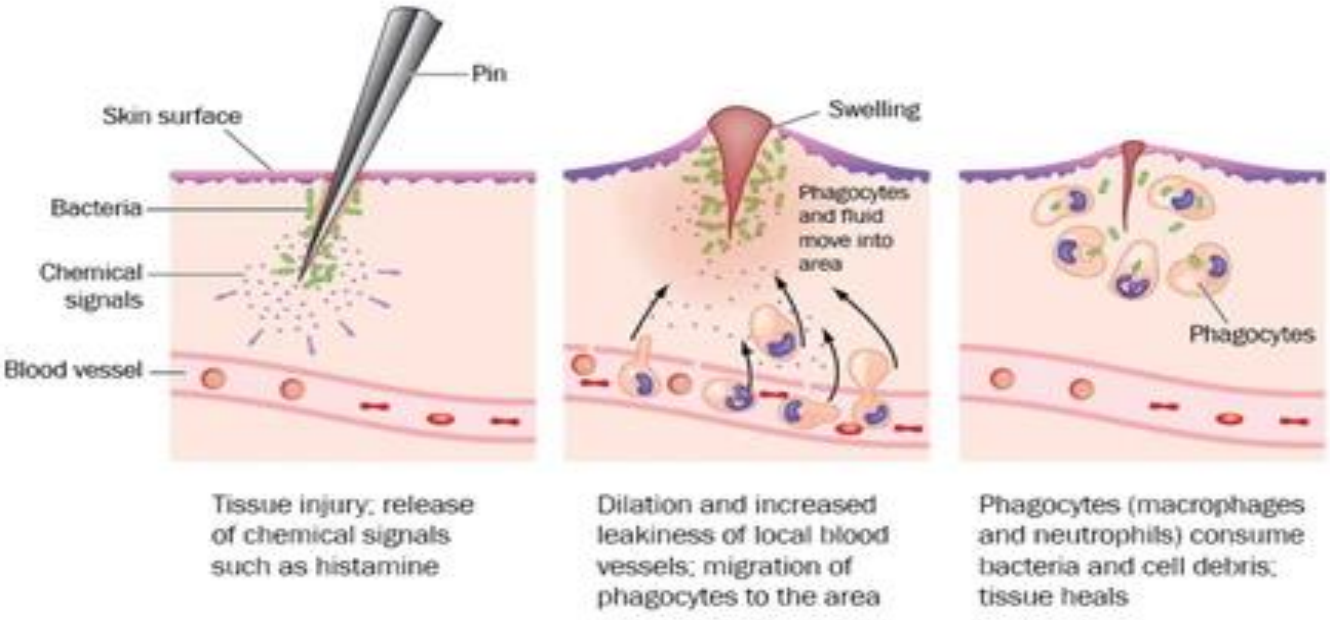
a- Increased blood flow b-Increased vascular permeability

3. Increased leucocytes at site

4. Destroy or inactivate invaders

5. Remove debris

6. Prepare for healing & repair.


Pin
Skin surface
Bacteria
Chemical signals
Blood vessel
Swelling
Phagocytes and fluid move into area
Phagocytes
Tissue injury; release of chemical signals such as histamine
Dilation and increased leakiness of local blood vessels; migration of phagocytes to the area
Phagocytes (macrophages and neutrophils) consume bacteria and cell debris; tissue heals
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Acquired immunity (Adaptive immunity)

Acquired immunity is immune response created after an interaction of lymphocytes with particular foreign substances which are recognized specifically by those lymphocytes.

This recognition process triggers proliferation and maturation of the lymphocytes which in the case of B lymphocyte results in the secretion of antibodies and the "memorizing" of that particular agent in a process called the **primary immune response**. On the second contact with the same agent the magnitude of the response is increased as a result of the more rapid and more abundant production of specific antibodies: a process called **secondary immune response.**

The acquired immune response is a more highly developed system than the innate immune system. It includes not only **humoral immunity** but also **cellular immunity**.

Features of adaptive immunity

The adaptive immune response is characterized by:

1- Specificity: The ability to discriminate between different antigenic epitopes, and respond only to those that necessitate a response rather than making a random response.

2- Memory: The ability to recall (remember) previous contact with a particular antigen, such that subsequent exposure leads to a more rapid and larger immune response.

3- Adaptiveness: The ability to respond to previously unseen antigens, which may never have existed before on earth.

4- Discrimination between "self" and "nonself": The ability to respond to those antigens that are not "self" and to avoid making responses to those antigens that are part of "self".

Types of acquired immunity :

1- **Active immunity** results from the development of antibodies inresponse to an antigen, as from exposure to an infectious disease or through vaccination.

i. Naturally acquired active immunity: is immunity that comes from infections encountered in daily life.

ii. Artificially acquired active immunity: It is stimulated by initial exposure to specific foreign macromolecules through the use of vaccines to artificially establish a
state of immunity.

2- **Passive immunity** results from the transmission ofantibodies, as from mother to fetus through the placenta or by the injection of antiserum

i. Naturally acquired passive immunity: refers to antibodies that transferred from mother to fetus across the placenta and to newborn in colostrum and breast milk during the first few months of life.
ii. Artificially acquired passive immunity: is transferred of antibodies that are formed by an animal or a human to an individual to prevent or treat infection.

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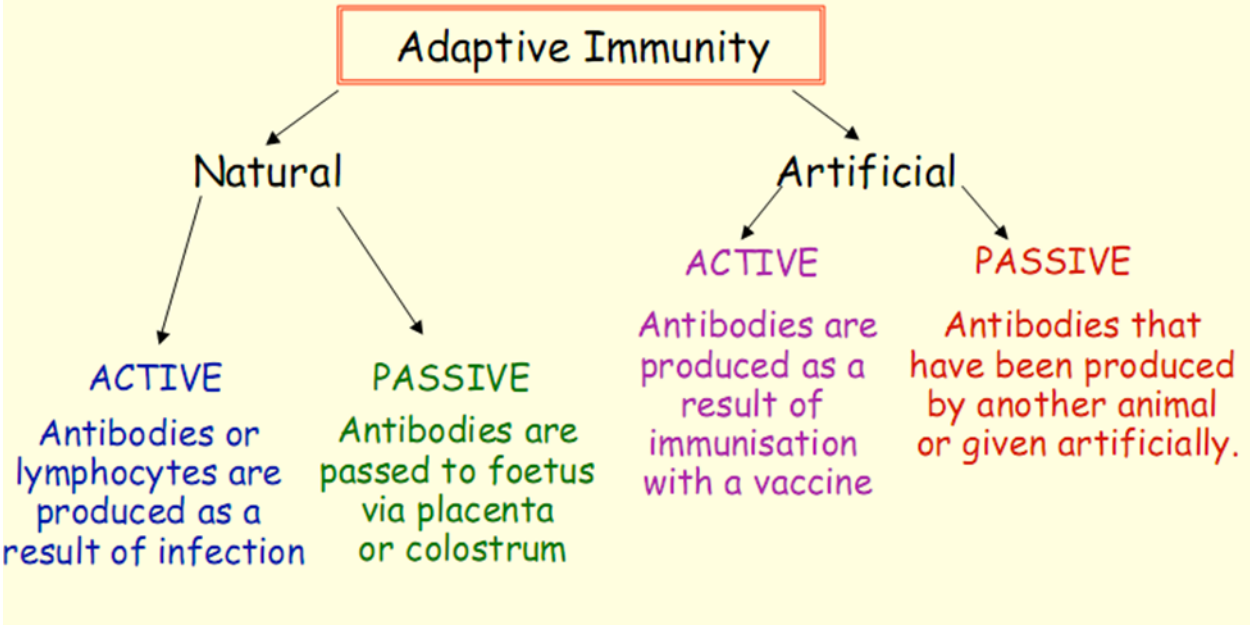
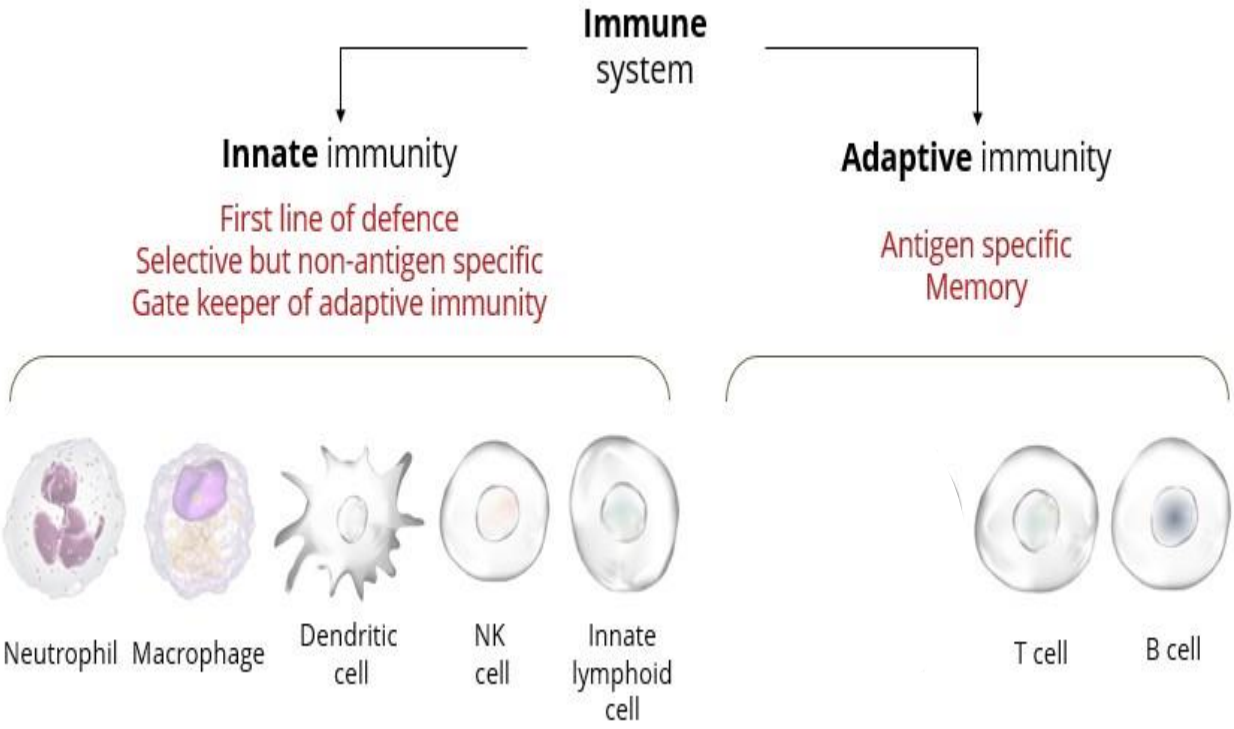
Adaptive Immunity can be NATURAL or ARTIFICIAL





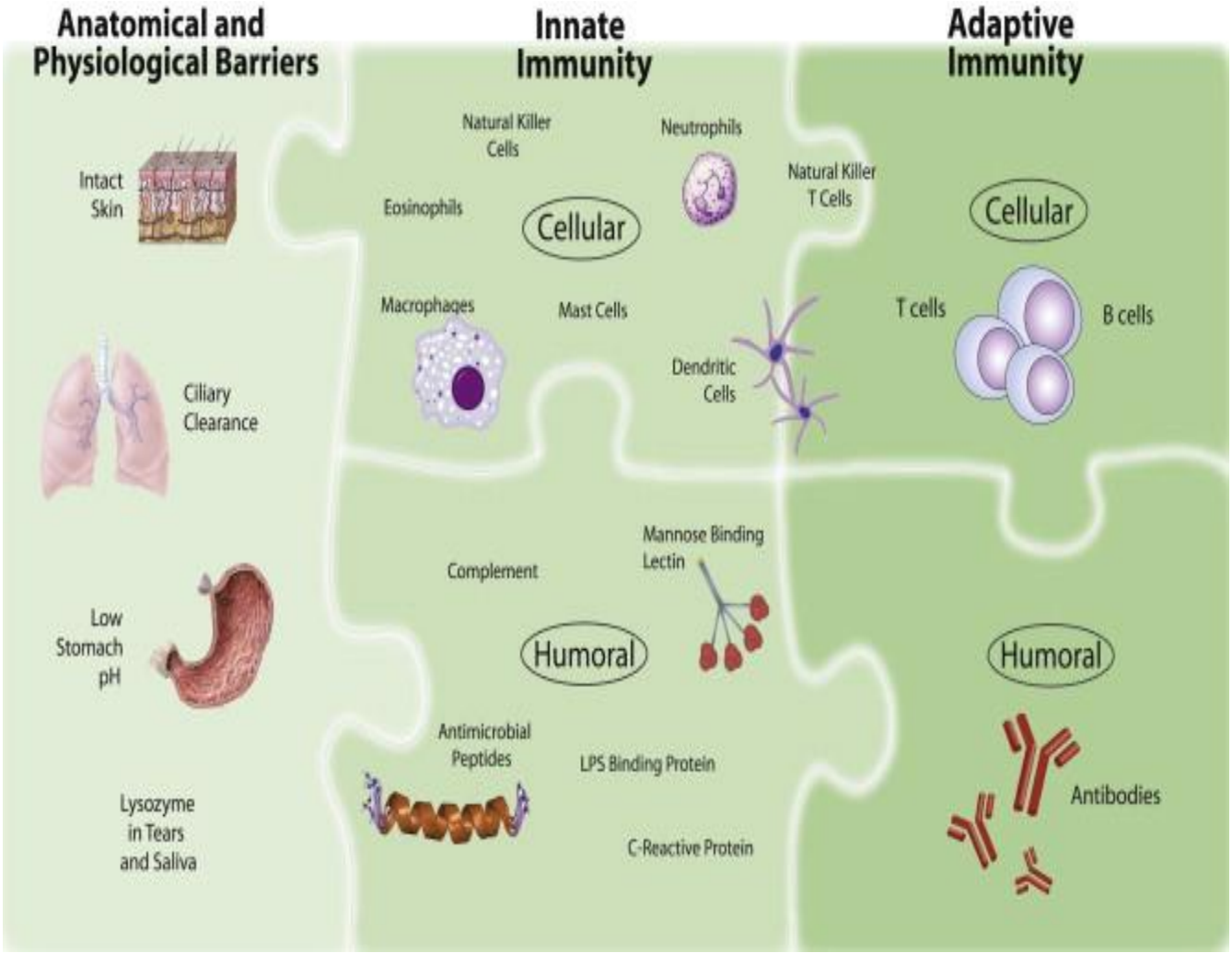
Comparison between actively and passive acquired immunity

Attribute	Active acquired immunity	Passive acquired immunity
Source	Self (Defense mechanism of the host)	other human or animal (Borrowed from outside)
Method	• Pathogens infection • Immunization by vaccine	• Material transplantation • Antibodies injuction
Time to develop	5-14 days	Immediate on injection
Duration of effectiveness	Long (may be years)	Short (few days to several weeks)
Result of use	Prophylactic	Prophylactic and therapeutic
Effect of reactivation	Boost immunity	Danger , may cause anaphylaxis

Comparison between innate and adaptive immunity

Attribute	Innate immunity	Adaptive immunity
Response time	Minutes/hours	Days
Specificity	Absence specific response	Highly specific response
Memory	Absence	Present
Self/non-self discrimination	Perfect when no microbe specific patterns in host	-Very good -Occasional failures of self/non-self-discriminations result in autoimmune diseases.
Soluble component of	Many antimicrobial	Antibodies and cytokines

blood (humeral response)	Peptides, proteins and other mediators.	
Major cell types	-Phagocyte: • Monocyte cell • macrophage cell • neutrophil cell • dendritic cell -Natural killer	Lymphocyte • T cell • B cell



Antigen Characteristics

Definitions

- **Immunogen** - a substance that induces a specific immune response.
- **Antigen (Ag)** - a substance that reacts with the products of a specific immune response.
- **Epitope or Antigenic Determinant** - the portion of an antigen that combines with the specific immune response (B- cell receptor or T- cell receptor).
- **Haptens** are small molecules which could never induce an immune response when administered by themselves but which can when coupled to a carrier molecule. Free haptens, however, can react with products of the immune response after such products have been elicited. Haptens have the property of antigenicity but not immunogenicity.
- **Superantigens**: are a class of antigens that result in excessive activation of the immune system. Specifically it causes non-specific activation of T-cells resulting in polyclonal T cell activation and massive cytokine release.

The foreign substances that induce an immune response possess two properties:

- **Immunogenicity** is defined as the property of a substance (immunogen) that endows it with the capacity to provoke a specific immune response.
- **Antigenicity** is defined as the property of a substance (antigen) that allows it to react with the products of a specific immune response (antibody or T-cell receptor).

Factors influencing immunogenicity

The following characteristics have an important influence in the ability that a substance has to behave as an immunogen:

1-Contribution of the immunogen

A. Foreignness. only substances which are recognized as "non-self" will trigger the immune response.
B. Molecular Size. The most potent immunogens are macromolecular proteins [molecular weight (M.W.) > 100,000]. Molecules smaller than 10,000 daltons are weakly immunogenic.
C. Chemical Structure: the more chemical complexity of substance is more immunogenic it will be.
D. Degradability**:** Antigens that are easily phagocytized are generally more immunogenic.

So can be divide the antigens based on Immunogenicity:

i. Complete antigen: substances which possess both of immunogenicity and immunoreactivity (antigenicity).
ii. Incomplete antigen (hapten): substances which possess only immunoreactivity.

2-Contribution of the Biological System

A. Genetic Factors: Some substances are immunogenic in one species/individual but not in another.
B. Age: It can also influence immunogenicity; because very young and very old have a diminished ability in immune response to an immunogen.

3-Method of Antigen Administration.

A. The dose of administration of an immunogen can influence its immunogenicity.
B. Route of administration: which include subcutaneous ,intradermal ,intravenous, intramuscular , intraperitoneal, intranodal and intrasplenic .
C. Use of Adjuvants : an agent that mixed with an immunogen to enhance the immune response .

Chemical nature of immunogens:

A. Proteins: proteins usually are major immunogens.

B. Polysaccharides: they are good immunogens.

C. Nucleic Acids: they are usually poorly immunogenic.

D. Lipids: lipids are non-immunogenic, although they may be haptens.

Types of antigens:

Antigens can be dividing into:

I. **According to origin: which includes:**

1. Exogenous antigens: are antigens can entry the body from outside by inhalation,ingestion, or injection.
2. Endogenous antigens: are antigens can be generated within cell either a result of normal cell metabolism, or because of viral or intracellular bacterial infection.
3. Auto-antigens: is usually a normal protein or complex of proteins (sometimes DNA or RNA) that is recognized by immune system of patients.

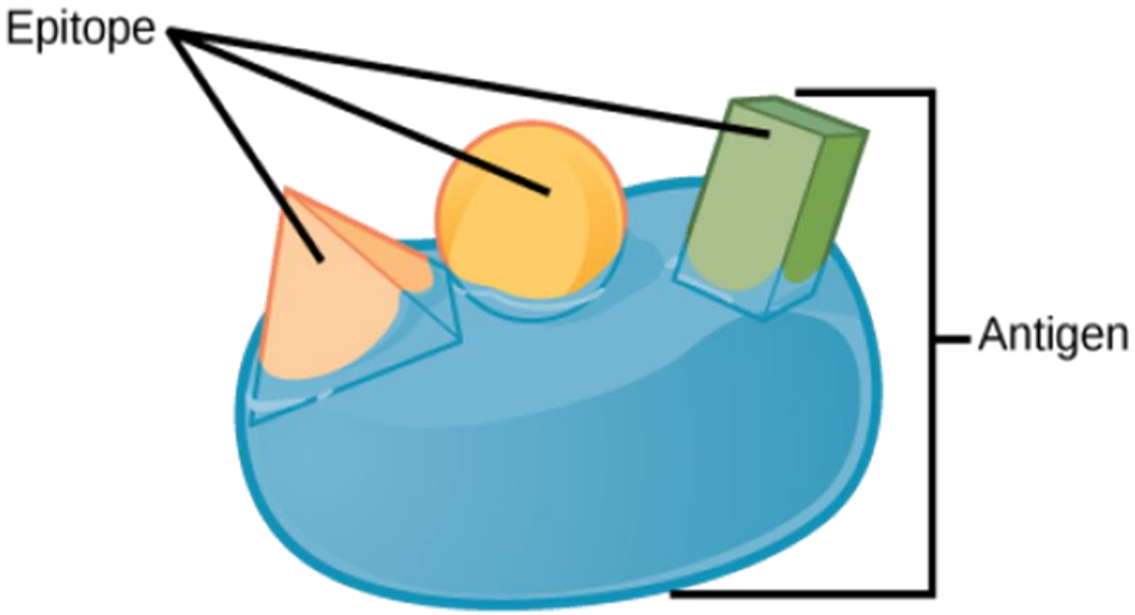
II. According to the cellular response generated:

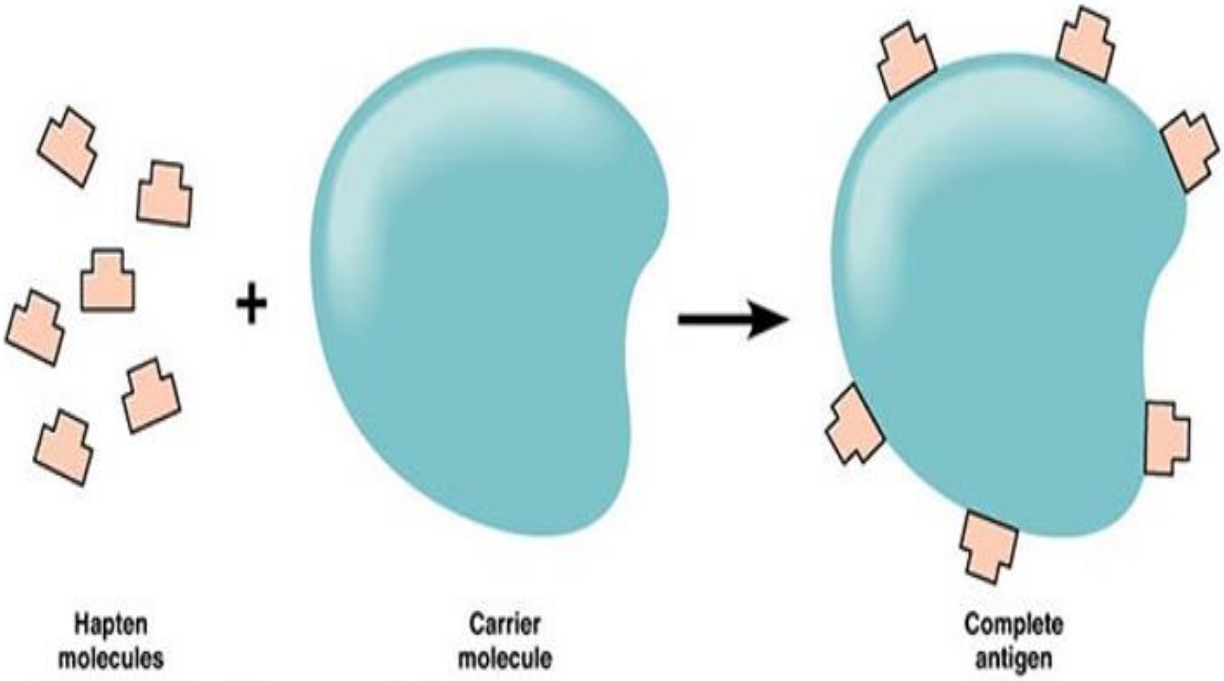
A. T-independent Antigens: antigens which can directly stimulate B cells to produce antibody without requirement for T cells help such as polysaccharides antigens.

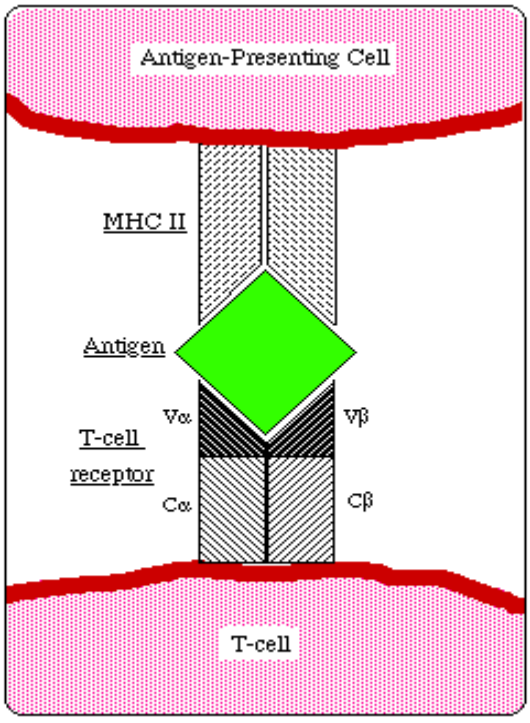
B. T-dependent Antigens: are an antigen doesn't directly stimulate the production of antibody without helps of T cells and contain a few copies of many different antigenic determinants such as proteins.

Comparison between T cell-dependent antigens and T cell-independent antigens

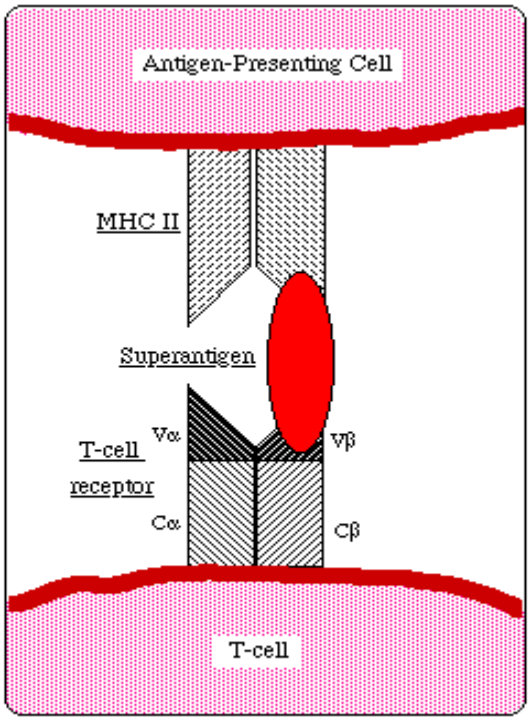
Properties	**T cell-dependent antigens**	**T cell-independent antigens**
Activation of B	Can only activate B cells in the presence of Th cells.	Can only activate B cells in the absence of Th cells.
Structural properties	Complex	Simple
Antibody class-induced	IgG, IgM, IgA, IgD, IgE	IgM
Immunological memory	yes	No
Presence in most pathogenic microbes	yes	No







Normal Antigen Presentation



Superantigen

The Lymphocytes

Lymphocytes are one of white blood cells classes; derived from stems cells and maturate either in the bone marrow or thymus; comprise 20-40% of all leukocytes, distributed into blood, lymph and lymphoid organs.
Typically, it is a small, round cell with diameter of 5-10μm, spherical nucleus, densely compacted nuclear chromatin and scanty cytoplasm, divide in three major types of lymphocyte:

1-T lymphocyte 2- B lymphocyte 3-NK cells.

Different lymphocytes are identified by protein markers on their surface called "cluster of differentiation" or "CD" system like CD45 which is found in all leukocytes.

T- Lymphocyte:

- "T-cell" is an abbreviation of "thymus dependent lymphocyte".
- It arise in the bone marrow as T-cell precursors, then migrate and passage through the thymus as prethymocytes to complete their maturation which includes rearrangements and coding of the variable part of the TCR (T Cell Receptor) by enzymes and hormones activity (e.g. thymulin, thymosin, and thymopoietin). TCRs are dividing into CD8 or CD4 surface molecules. It require to react with many receptors include antigens receptors, Fc fragment of antibodies, RBCs receptors, and Virus receptor.
- T cell found in peripheral blood, bone marrow, lymph node and spleen.
- Surface markers (TCR): they are two kinds of TCR, TCR 1 and 2 with other markers/receptors present on their surface.
- Subsets of T Cells:

A. Helper T cells (TH):

1. Are identified by the presence of CD4 marker.
2. They recognize antigen when presented along with Class II MHC molecules.

3. They are subdivided into the TH1 and TH2 subsets on the basis of the kinds of cytokines they produce. TH1 cells produce interleukin-2 (IL-2), interferon-gamma IFNγ), and tumor necrosis factor-beta (TNF-β) while TH2 cells produce IL-4, IL-5, IL-6, IL-10 and TGF-β.
4. They are promotes differentiation of B-cells and cytotoxic T-cells, Activates macrophages, and secrete cytokines.

B. Cytotoxic T cells (TC):

1. Are identified by the presence of CD8 marker.
2. They recognize antigen when presented along with Class I MHC molecules.
3. They have a role of killing infected cells by attachment to antigens on cells infected with viruses or abnormal cells (for example, cancerous) . **TC** cells then kill these cells by making holes in their cell membrane and injecting enzymes into the cells.

C. Regulatory T cells (T reg):

1. Tregs are able to inhibit T cell proliferation and cytokine production and play a critical role in preventing autoimmunity.
2. T reg is identifying by the presence of CD4 and CD25.

The ratio of CD4: CD8 is approximately 2:1 in normal peripheral blood . A change in this ratio is often an indicator of immunodeficiency ,autoimmune diseases and other disorders.

B - Lymphocyte:

- They are called B cells; because they are developed and mature occurs in bone marrow .
- The stages in B cell development in the bone marrow are: Stem cell → pro-B cell → pre-B cell → immature B cell → mature B cell.

- They found in circulation , bone marrow, lymph node and spleen.
- Surface markers: The most important surface markers on the surface of mature B cellare: CD32 (receptor of Immunoglobulin), CD35 (Receptor for complement component), and markers that distinguish B cells such as CD20, CD21 and CD22.

- **Functions of B-cells**:

1. Direct recognition and presentation of antigen.
2. Secrete large amounts of antibodies after differentiation into plasma cells.
3. It has memory can survive 20 years or more (Memory B cells).

B lymphocyte types :

A. Mature B Cells

1. mature B cell is exposed to the antigen-presenting cells specific to its B cell receptor. Upon activation, B cell can become a plasma B cell or a memory B cell.
2. Surface marker : CD19

B. Plasma B Cells

1. Plasma B cells, also called effector B cells, are large cells with a very large endoplasmic reticulum .
2. Plasma cells produce large quantities of antibodies.
3. Surface marker : $CD38^{+}$.

C. Memory B Cells

1. A type of B lymphocyte that is necessary for building long-term immunities within the body. These cells remain in the bloodstream after an infection subsides. If the host is re-exposed to that same antigen in the future, memory B cells can quickly activate with the help of T cells.
2. Memory B cells have a $CD19^{+}$, a $CD27^{+}$, and a $CD38^{-}$ marker.

Complement system

Complement system can be defined as a major effector of humoral immune system, it is a complex series of more than 30 soluble and cell-bound proteins that interact in a very specific way to enhance host defense mechanisms against foreign body.

Complement system functions:

After initial activation, the various complement components interact to carry out a number of basic functions including:

1. Destruction of foreign target cells by lysis (cytotoxicity, hemolysis, and bacteriolysis) of cell membrane to WBCs, tumor cells, RBCs, and bacteria.
2. Opsonize of bacteria that facilitate and enhanced phagocytosis.
3. Recruit and activate various cells as polymorphonuclears PMNs and macrophages by Chemotaxis.
4. Regulate of antibody responses that aid in clearance of immune complexes.
5. It contributes in inflammation and tissue damage; because it trigger of anaphylatoxins that stimulate mast cells to release histamine, which enhances vascular permeability and smooth muscle contraction .

The components of complement system:

- Numerous soluble proteins and glycoproteins that constitute the complement systemare synthesized mainly by liver hepatocytes, although significant amounts are also produced by blood monocytes, tissue macrophage including(C1, C2, C3, and C4 components), epithelial cells of the gastrointestinal andgenitourinary tracts including (C1 component) and factor D, which is made in adiposetissue.
- Complement components constitute 5% of serum globulin fraction. Most of them are circulating in serum with inactive functions to forms as pro-enzymes (zymogens) until proteolytic cleavage removes an inhibitory fragment and exposes the active site of the molecule.

Pathways of complement system:

The complement system can be activated in three different ways. The early steps of all these pathways are form of C5b and the final steps of all these pathways lead to formation of the membrane –attack complex (MAC).

I. Classical Pathway:

It is the first pathway, which involves nine proteins that are triggered by antigen–antibody combination.

The first stage involves C1, which is known as the **recognition unit**. Once C1 is fixed to immune complex, the next components activated are C4, C2, and C3, known collectively as the activation unit. C5 through C9 comprise the membrane attack complex(MAC), which is the last unit that completes lysis of foreign particle. Each stage of this pathway was detail in the following:

The activation of classical pathway requires interacting between nine of complement components with Ca^{++} and Mg^{++}cations .

- The binding of C1 to antibody via C1q which may linkage with at least two antibody molecules which is lead to activate of C1r which in turn activates C1s.
- This occurs when C1q binds to IgM or IgG complexed with antigens. (A single pentameric IgM can initiate the pathway, while several IgGs are needed). This also occurs when C1q binds directly to the surface of the pathogen. Such binding leads to conformational changes in the C1q molecule, which leads to the activation of two C1r molecules. C1r is a serine protease. They then cleave C1s(another serine protease).
- The $C1r^2s^2$ component now splits C4 and then C2, producing C4a, C4b, C2a, and C2b. C4b and C2a bind to form the classical pathway C3-convertase (C4b2a complex), which promotes cleavage of C3 into C3a and C3b. C3b later joins with C4b2a to make C5 convertase (C4b2a3b complex) to form the final proteolytic complex of the complement cascade which cleavage C5 to C5a and C5b .

- The C5bC6C7C8 complex polymerizes C9 to form a tubule (pore), which spans the membrane of the cell being attacked, allowing ions to flow freely between the cellular interior and exterior. By complexing with C9, the osmotic cytolytic reaction is accelerated. This tubule is a hollow cylinder with one end inserted into the lipid bilayer and the other projecting from the membrane.
- A structure of this form can be assumed to disturb the lipid bilayer sufficiently to allow the free exchange of ions and water molecules across the membrane. Ions flow out, but large molecules stay in, causing water to flood into the cell. The consequence in a living cell is that the influx of sodium (Na+) ions and H2O leads to disruption of osmotic balance, which produces cell lysis.

II.Alternative pathway

- Microbial and mammalian cell surfaces can activate the alternative pathway in the absence of specific antigen-antibody complexes.
- Factors capable of activating the alternative pathway include inulin, zymosan (polysaccharide complex from surface of yeast cells), bacterial polysaccharides and endotoxins .
- C3b that is generated from C3 by a C3 convertase enzyme complex in the fluid phase is rapidly inactivated by factor H and factor I.
- The alternative complement pathway can be activated as a by-product of the classic pathway when the C4–C2 dimer facilitates direct binding of the activated C3 to the pathogen surface or when circulating C3 is spontaneously hydrolyzed and acted on by two proteins **(factors B and D)** to form a free C3 convertase molecule.
- The surface-bound C3b may now bind factor B to form C3bB. This complex in the presence of factor D will be cleaved into Ba and Bb. Bb will remain associated with C3b to form C3bBb, which is the alternative pathway C3 convertase.
- The C3bBb complex is stabilized by binding oligomers of **factor P (Properdin)**. The stabilized C3 convertase (C3bBbP) then acts enzymatically to cleave much more C3, some of which becomes covalently

attached to the same surface as C3b. This newly bound C3b recruits more B, D and P activity and greatly amplifies the complement activation.

- The association of numerous C3b units, factor Bb, and properdin on the surface of an aggregate of protein or the surface of a microorganism has potent activity as a C5 convertase. With the cleavage of C5, the remainder of the complement cascade continues as in the classic pathway.

III.Mannose – binding lectin Pathway

Mannose – binding lectin Pathway is homologous to the classical pathway but with mannose-binding lectin (MBL) and ficolins, instead of C1q. This pathway is activated by binding of MBL to mannose residues on the pathogen surface, which activates the MBL-associated serine proteases, MASP-1, and MASP-2 (very similar to C1r and C1s, respectively), which can then split C4 into C4a and C4b and C2 into C2a and C2b. C4b and C2b then bind together to form the classical C3-convertase, as in the classical pathway. Ficolins are homologous to MBL and function via MASP in a similar way.

Role of Complement in Disease

The complement system plays a critical role in inflammation and defense against some bacterial infections. Complement may also be activated during reactions against incompatible blood transfusions, and during the damaging immune responses that accompany autoimmune disease. Deficiencies of individual complement components or inhibitors of the system can lead to a variety of diseases which gives some indication of their role in protection against disease.

Complement triggers the following immune functions:

1. Opsonization promote Phagocytosis
2. Chemotaxis
3. Inflammation by attracting macrophages and neutrophils
4. lysis, apoptosis by rupturing membranes of foreign cells

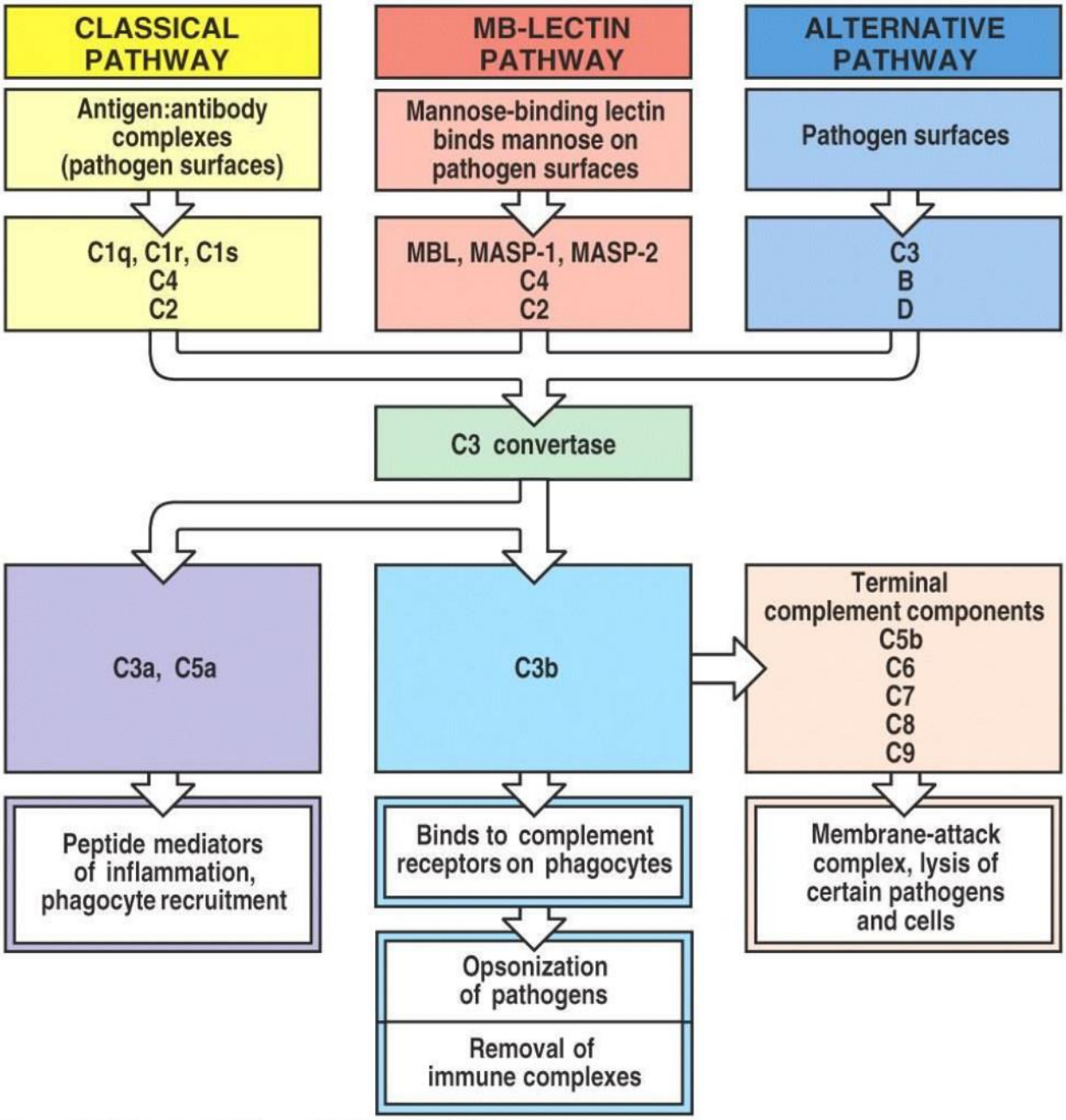


Figure 2-19 Immunobiology, 6/e. (© Garland Science 2005)

Comparision between pathways of complement system

	Classical pathway	Alternative pathway	Lectin pathway
Activated by	Binding of antibody molecules (specifically IgM and IgG1, IgG2, IgG3) to a foreign particle	Invading microorganisms	Binding of MBP to the mannose groups of carbohydrates on microorganisms
Activation mechanism	Antibody-dependent	Antibody-independent	Antibody-independent
Limb of immunity	Adaptive immune response	Innate immune response	Innate immune response
Components	C1 (C1q, C1r, C1s) to C9	Factors B, D, P, H, I	C1 (C1r, C1s) to C9
Components that initiate enzyme cascade	C1 (q, r, s), C4, C2	C3, B, D	Lectin, MASP1, MASP2, C4, C2
C3 convertase	C4bC2a, C2b	C3bBb	C2b, C4bC2a
C5 convertase	C4bC2aC3b	C3bBbC3b	C4bC2aC3b
Terminal components	C5-C9, MAC	C5-C9, MAC	C5-C9, MAC (

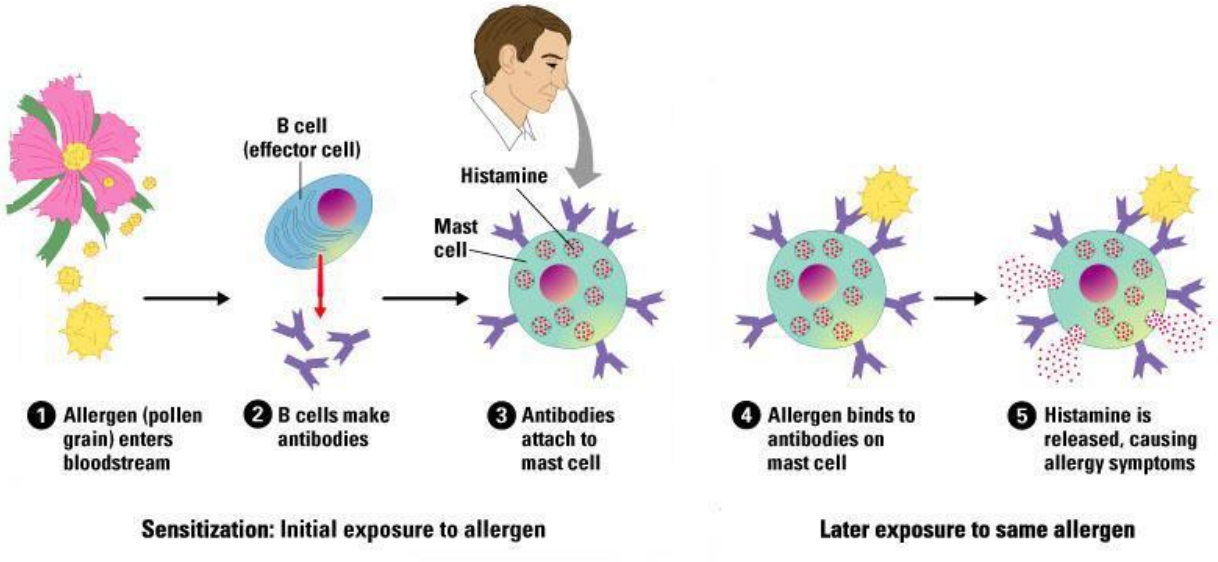
Hypersensitivity

Hypersensitivity is a set of undesirable reactions produced by the normal immune system, including allergies and autoimmunity. They are usually referred to as an over- reaction of the immune system and these reactions may be damaging, uncomfortable, or occasionally fatal. Hypersensitivity reactions require a pre-sensitized (immune) state of the host.

They are classified in four groups based on the mechanisms involved and time taken for the reaction.

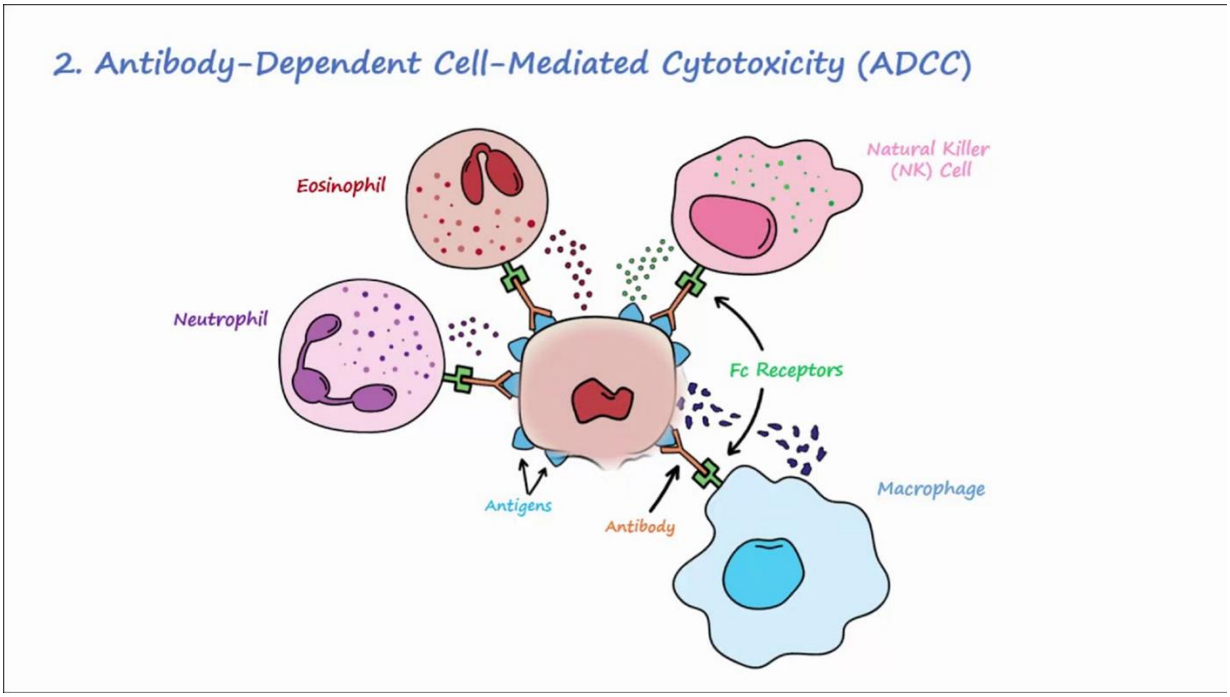
Type I hypersensitivity

- It is also known as **immediate or anaphylactic** hypersensitivity. The reaction may involve skin (urticaria and eczema), eyes (conjunctivitis), nasopharynx (rhinorrhea, rhinitis), bronchopulmonary tissues (asthma) and gastrointestinal tract (gastroenteritis).
- The reaction may cause a range of symptoms from minor inconvenience to death.
- The reaction usually takes 15 - 30 minutes from the time of exposure to the antigen, although sometimes it may have a delayed onset (10 - 12 hours).
- Immediate hypersensitivity is mediated by IgE.
- The primary cellular component in this hypersensitivity is the mast cell or basophil. The reaction is amplified and/or modified by platelets, neutrophils and eosinophils.
- Diagnostic tests for immediate hypersensitivity include skin (prick and intradermal) tests, measurement of total IgE and specific IgE antibodies against the suspected allergens. Total IgE and specific IgE antibodies are measured by a modification of enzyme immunoassay (ELISA). Increased IgE levels are indicative of an atopic condition, although IgE may be elevated in some non-atopic diseases (*e.g.*, myelomas, helminthic infection, *etc.*).
- There appears to be a genetic predisposition for atopic diseases and there is evidence for HLA association.



Type II hypersensitivity

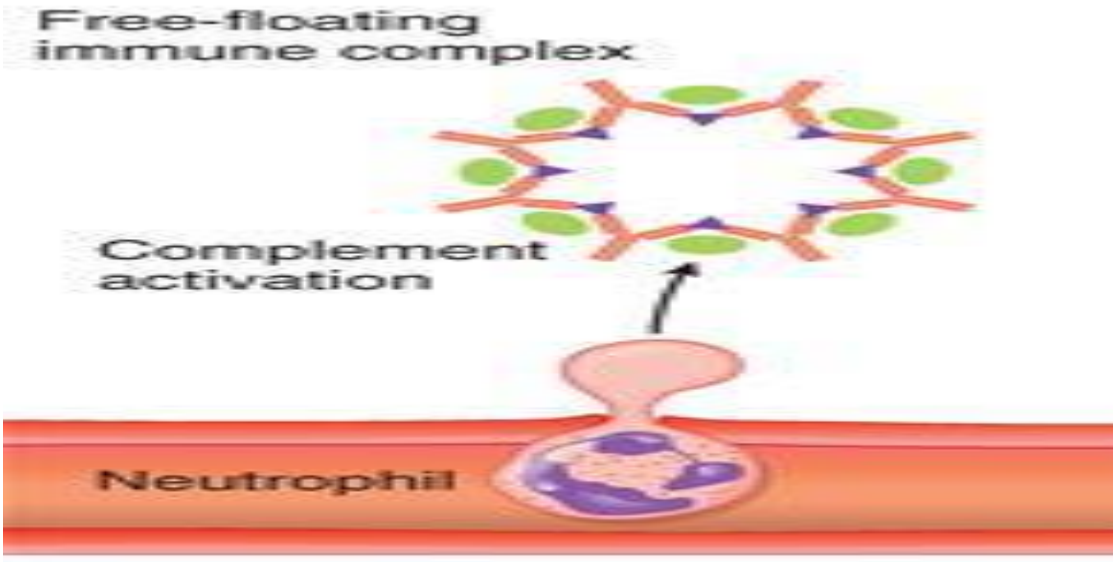
- It is also known as **cytotoxic hypersensitivity** and may affect a variety of organs and tissues.
- The antigens are normally endogenous, although exogenous chemicals which can attach to cell membranes can also lead to type II hypersensitivity. Drug induced hemolytic anemia, granulocytopenia and thrombocytopenia are such examples.
- The reaction time is minutes to hours.
- Type II hypersensitivity is primarily mediated by antibodies of the IgM or IgG classes and complement .
- Phagocytes may also play a role. The lesion contains antibody, complement and neutrophils.
- Diagnostic tests include detection of circulating antibody against the tissues involved and the presence of antibody and complement in the lesion (biopsy) by immunofluorescence.
- Treatment involves anti-inflammatory and immunosuppressive agents.



Type III hypersensitivity

- It is also known as immune complex hypersensitivity. The reaction may be general (e.g., serum sickness) or may involve individual organs including skin (e.g., systemic lupus erythematosus, Arthus reaction), kidneys (e.g., lupus nephritis), lungs (e.g., aspergillosis), blood vessels (e.g., polyarteritis), joints (e.g., rheumatoid arthritis) or other organs.
- This reaction may be the pathogenic mechanism of diseases caused by many microorganisms.
- The reaction may take 3 - 10 hours after exposure to the antigen (as in Arthus reaction).
- It is mediated by soluble immune complexes.
- They are mostly of the IgG class, although IgM may also be involved.
- The antigen may be exogenous (chronic bacterial, viral or parasitic infections), or endogenous (non-organ specific autoimmunity :e.g., systemic lupus erythematosus, SLE).

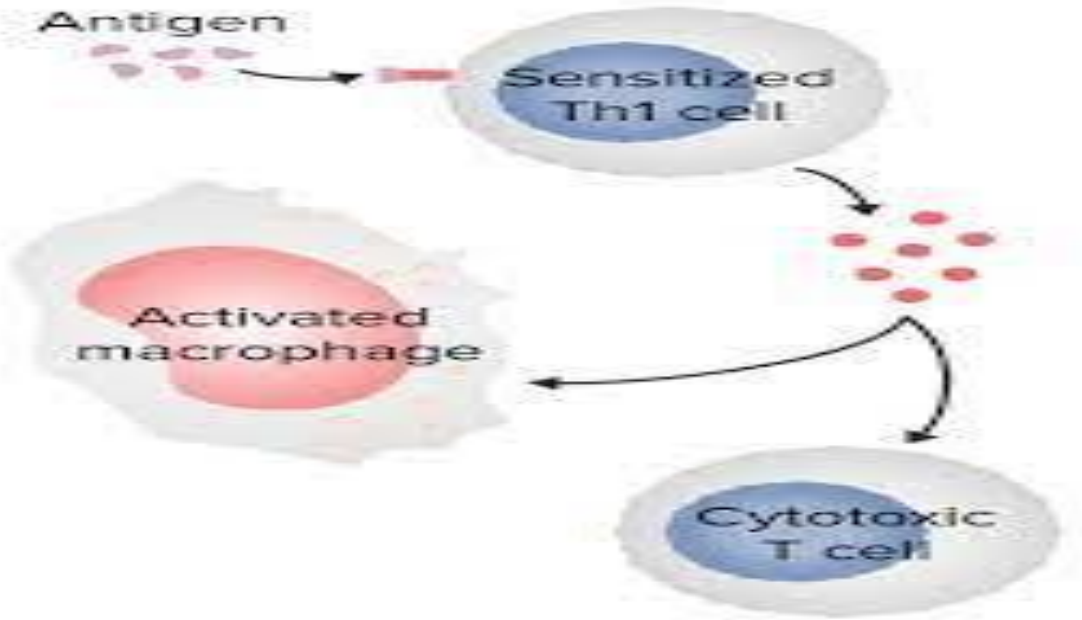
- Primary components are soluble immune complexes and complement (C3a, 4a and 5a).
- The damage is caused by neutrophils and complement. The lesion contains primarily neutrophils and deposits of immune complexes and complement.
- Macrophages infiltrating in later stages may be involved in the healing process.
- The affinity of antibody and size of immune complexes are important in production of disease and determining the tissue involved.
- Diagnosis involves examination of tissue biopsies for deposits of immunoglobulin and complement by immunofluorescence microscopy. The presence of immune complexes in serum and depletion in the level of complement are also diagnostic.



Type III

Type IV hypersensitivity

- It is also known as **cell mediated or delayed type hypersensitivity**.
- The lesion is characterized by induration and erythema.
- Type IV hypersensitivity is involved in the pathogenesis of many autoimmune and infectious diseases (tuberculosis, leprosy, blastomycosis, histoplasmosis, toxoplasmosis, leishmaniasis, etc.) and granulomas due to infections and foreign antigens. Another form of delayed hypersensitivity is contact dermatitis, chemicals, heavy metals, etc.) .
- Mechanisms of damage in delayed hypersensitivity include T lymphocytes and monocytes and/or macrophages. Cytotoxic T cells (Tc) cause direct damage whereas helper T (TH1) cells secrete cytokines which activate cytotoxic T cells and recruit and activate monocytes and macrophages, which cause the bulk of the damage . The delayed hypersensitivity lesions mainly contain monocytes and a few T cells. Major lymphokines involved in delayed hypersensitivity reaction include monocyte chemotactic factor, interleukin-2, interferon gamma, TNF alpha/beta, etc.
- Diagnostic tests in vivo include delayed cutaneous reaction.



characteristics	**type-I (immediate)**	**type-II (cytotoxic)**	**type-III (immune complex**	**type-IV (delayed type)**
Mediated by	IgE	IgG, IgM	IgG, IgM	T cell
Antigen	Exogenous	Cell surface	Soluble	Tissue & organ
Response time	15-30 min.	Minutes-hours	3-8 h.	48-72h.
Damage causes	Mast cell Basophil	Complement	Neutrophils Complement	Monocyte T cell

Oncogenic Immunity

Cancer immunology is the study of interactions between the immune system and cancer cells, which is a rapid growing field of research that aims to identify biomarkers in cancer immunodiagnosis and to develop innovative cancer immunotherapeutic strategies.

Causes of tumor

1. Environmental factors

(A) Physical factors such radiate (e.g. UV, X-ray).

(B) Chemical factors such toxic and carcinogen agents.

2. Biological factors such preservative and genetic engineering foods.

3. Behavioral factors such smoking, alcohol, and drug may enhance tumors.

4. Some microorganisms can induce tumor such virus and bacteria.

5. Genetics factors, as high expression oncogenes genes which stimulator to cell

proliferation, or defective expression of tumor suppressor genes which normally control proliferation, genetic alternations (mutation, gene amplification, chromosomal deletion or translocation) and genetics of family history.

Common immune properties of tumor cells:

1. Failure response to regulatory mechanisms.

2. Almost variably of origin, because mutation in chromosomes leads to generate heterogeneity within tumor populations.

3. Variance in appearance e.g. shape and size, also in antigenic properties.

Types of tumor

A tumor (also called *neoplasm*) is an abnormal mass of cells in the body. It is caused by cells dividing more than normal or not dying when they should. **Tumors can be classified as benign or malignant.**

1. **Benign tumors** are those that stay in their primary location without invading other sites of the body. They do not spread to local structures or to distant parts of the body. Benign tumors tend to grow slowly and have distinct borders.

2. **Malignant tumors** have cells that grow uncontrollably and spread locally and/or to distant sites. Malignant tumors are cancerous (they invade other sites). They spread to distant sites via the bloodstream or the lymphatic system. This spread is called *metastasis*. Malignant tumors can spread rapidly and require treatment to avoid spread. A malignant tumor has irregular borders and grows faster than a benign tumor.

Tumor markers

They are biomarkers found in blood, urine, or body tissues that are produced by the cancer tissue itself or sometimes by the body in response to cancer . Tumor markers will be elevated by the presence of one or more types of cancer and can be used for diagnosis and therapy of tumor.

Tumor markers types :

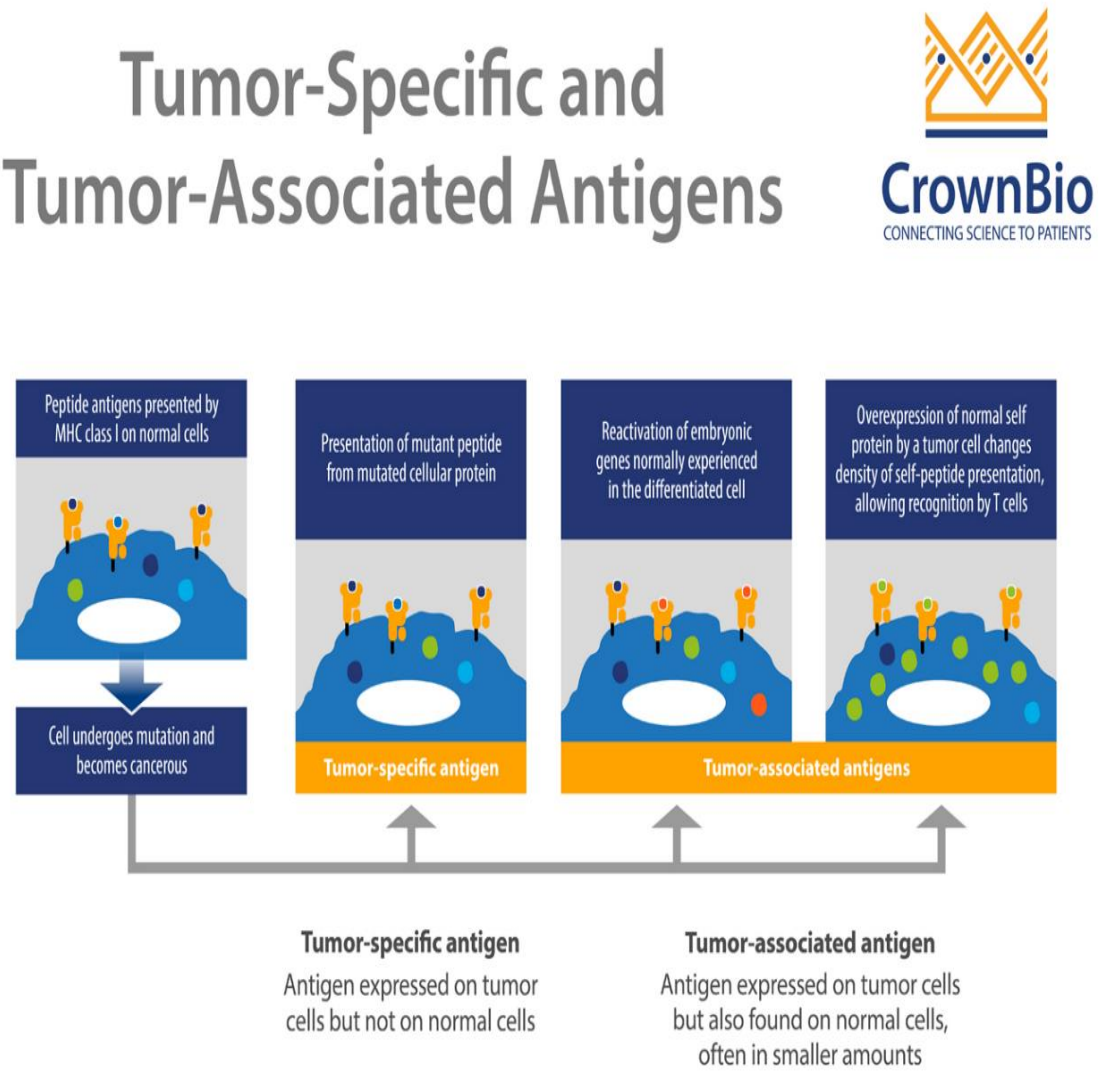
1. Hormones such beta HCG secreted in choriocarcinoma, Thyroxin (T3 & T4) in thyroid gland cancer.
2. Enzymes such: - Alkaline phosphatase, lipase and amylase in pancreas cancer and acid phosphatase in prostate cancer.
3. Tumor antigens (neoantigen): produced by tumor cells which may remained in surface or released in the blood stream.

Generally there are 2 main types of tumor antigens:

A. **Tumor-specific antigens (TSTA)** which are unique to tumor cells and not expressed on normal cells.
B. **Tumor associated antigens (TATA)** which are expressed by tumor cells in high levels then normal cells, they include:

I. **Tumor-associated developmental antigens** are expressed only during cell maturation and lost in adult stage but re-expressed in tumors e.g. alpha-fetoprotein (AFP) produced from normal fetal liver, also present in patient sera with hepatocellular cancer, and carcino-embryonic antigen (CEA).

II. **Tumor associated viral antigens** are express on the cell surface results by virus induced tumors e.g. hepatitis-B virus in hepatic carcinoma, and papilloma virus in cervical cancer.



Effector immune mechanisms against tumor:

Immune effector mechanisms that are capable to destroy tumors include:

I. Humoral effector mechanisms result from activate of B cell response:

- Lysis of tumor cells by Abs. serves as targets to T cytotoxic cell- killing mechanism(ADCC).
- Destruction of tumor cells by binds to phagocytose in the presence of complement by complement dependent cytotoxicity (CDC).
- Antibody mediated block or loss adhesive properties of tumor cells that prevent metastatic activity (antagonist activity of antibody).
- Antibody mediated to blockage of growth factor receptor to tumor cells.

II. Cellular mediated effectors mechanisms:

A. Mediated by TH cells: T helper cells recognized tumor antigens when presented with class II MHC on APCs, produce cytokines e.g. IFN-γ, and activate macrophages.

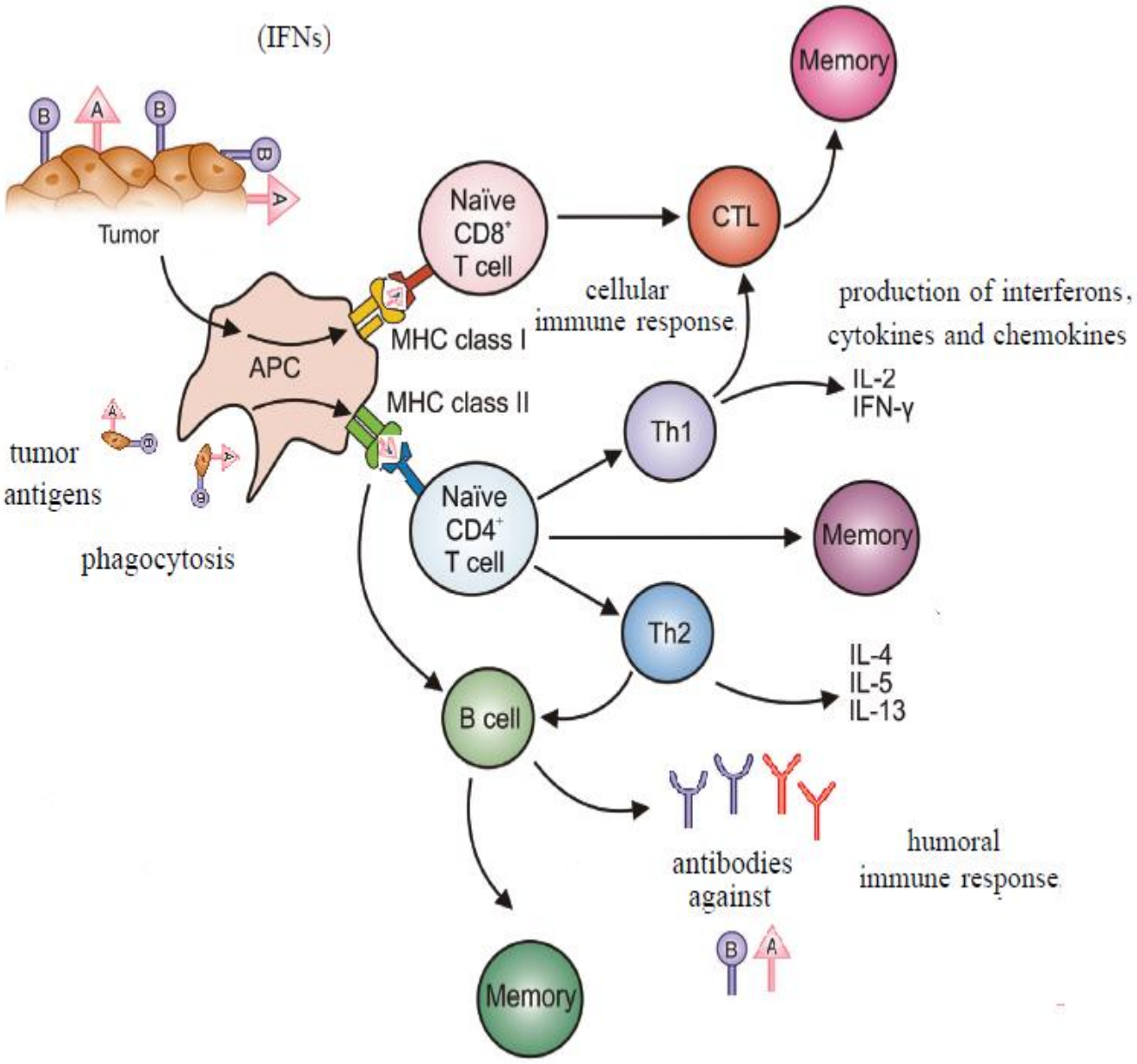
B. Antibody dependent cellular cytotoxicity (ADCC): It depend onto binds of antitumor antibodies and Complement to tumor cells; then interact with various immune cells e.g. macrophages and granulocytes; that lead to destruction tumor cells by released substanceas toxin and enzyme have tumoricidal activity .

C. Mediated by cytotoxic lymphocyte cells (CTL): The CTLs recognize tumor antigens by class I MHC and mediate tumor cell lysis.

D. Mediated by natural killer cells (NK): By have receptors to Fc region of Abs attached to tumor cells, and enable to secrete of TNF, granzyme and perforins lead to tumor cell lysis.

E. Mediated by Macrophage and neutrophil cells: It can kill tumor cells when activated by combination factors e.g. lymphokines and cytokines, also it can present tumor antigens to T cells and stimulate tumor specific immune response.

F. Mediated by dendritic cells: It responsible of initiate tumor specific immune response by present tumor antigens to T cells and to stimulate of CTL response.


(IFNs)
Memory
Tumor
Naïve CD8+ T cell
CTL
cellular immune response
production of interferons, cytokines and chemokines
MHC class I
APC
MHC class II
IL-2
IFN-γ
Th1
tumor antigens
Naïve CD4+ T cell
Memory
phagocytosis
Th2
IL-4
IL-5
IL-13
B cell
antibodies against
humoral immune response
Memory

Escape mechanisms of tumor from immune response:
Tumors evade immune recognition by several mechanisms:
1. Doesn't express neo-antigens that failed to express co-stimulatory molecules used into
activation of T cells.
2. Too smallest amount of Ag produced (low dose, tolerance).
3. Rapid proliferation of malignant cells (high dose tolerance).
. Secreting immune-suppressive molecules e.g. TGF-β and may induce regulatory T cells
which are inhibitors antitumor immune response.
5. Shed their Ag by another normal Ag that block antibodies and inhibit T cells reacting
with tumor cells.

Immunodiagnosis:
* Used of monoclonal antibodies labeled with radioisotope for *in vivo* detection of relatively small tumor foci.
** Antibodies have also been used *in vitro* to identify of tumor cells.
*** Immune-histological staining is used to confirm suspected metastatic foci, especially
in bone marrow.
Tumor immunotherapy:
Is one of the most approaches to cancer therapy by establish an effective antitumor response through the immune system based on the agents used and type of caner treated.
Immunotherapy can be classified into:
I. **Active immunotherapy**: Based onto generate specific antitumor responses through
stimulation of the host immune system and/or tend to have more significant effects than
other immunotherapies modalities.
II. **Passive immunotherapy**: Based on transfer of effector molecules or cells, such as
antibodies, cytotoxic T lymphocytes (CTL), LAK cells and combined to patients.

There are three common types of immunotherapeutic bispecific antibodies:

1. **Cytotoxic Effector Cell Redirectors:** These redirect T cell cytotoxicity to tumor cells by using bispecific compounds to engage a TAA/TSA and the T cell receptor/CD3 complex.

2. **Tumor-targeted Immunomodulators:** These are designed to bind to a TAA/TSA and an immunomodulating receptor (e.g. CD40). These compounds are typically intended to be inactive until they bind the tumor antigen, so that the immune stimulation is hyper-localized to the tumor environment, effectively reducing the risk of immune-related side effects.

3. **Dual immunomodulators:** These bind two different immunomodulating targets resulting in blockade of inhibitory targets, depletion of suppressive cells or activation of effector cells (e.g. PD-1xLAG-3, PD-1xTIM-3, PD-1xCTLA-4, CTLA4xOX40).