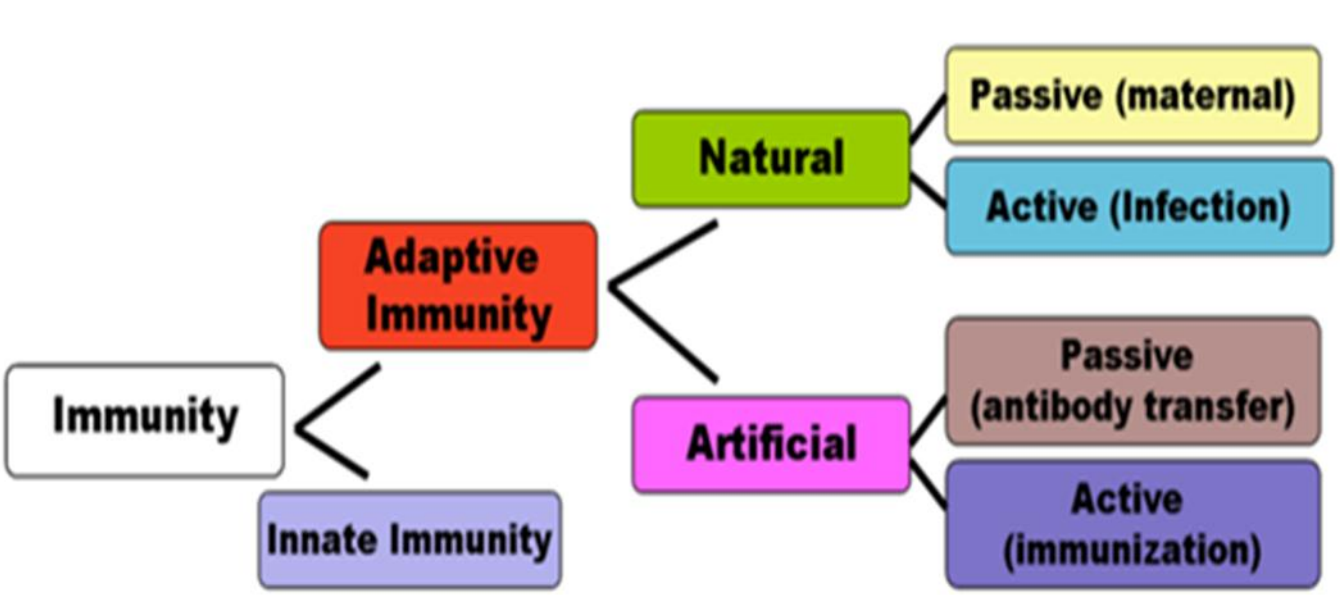
Introduction

- Immunity (immunis- Latin-name, state of protection from infectious diseases)
- Immunity is body's ability to resist or eliminate potentially harmful foreign materials or abnormal cells
- Immunity consists of following activities:

a. Defense against invading pathogens (viruses & bacteria)
b. Removal of 'worn-out' cells (e.g., old RBCs) & tissue debris (e.g., from injury or disease)
c. Identification & destruction of abnormal or mutant cells (primary defense against cancer)
d. Rejection of 'foreign' cells (e.g., organ transplant)
e. Inappropriate responses:
f. Allergies - response to normally harmless substances
g. Autoimmune diseases


Immunity
Innate Immunity
Adaptive Immunity
Natural
Passive (maternal)
Active (Infection)
Artificial
Passive (antibody transfer)
Active (immunization)

Immunity is classified into 2 divisions

- **Innate immunity**
- Innate immunity refers to nonspecific defense mechanisms that come into play immediately or within hours of an antigen's appearance in the body.
- These mechanisms include physical barriers such as skin, chemicals in the blood, and immune system cells that attack foreign cells in the body.
- The innate immune response is activated by chemical properties of the antigen.

Adaptive immunity

- Adaptive immunity refers to antigen-specific immune response.
- The adaptive immune response is more complex than the innate.
- The antigen first must be processed and recognized.
- Once an antigen has been recognized, the adaptive immune system creates an army of immune cells specifically designed to attack that antigen.
- Adaptive immunity also includes a "memory" that makes future responses against a specific antigen more efficient.

INNATE (NON-SPECIFIC) IMMUNITY

- It is non-specific natural inborn and can act against any microorganism or foreign invador.
- It includes natural barriers to infection that are part of normal body function.
- A single defense barrier will afford protection against many different potential pathogens.

Components or determinants of innate immunity or natural resistance:

- The innate immune system recognizes and plays a role in blocking and in eliminating microbes that enter the tissue of the host through:

- **(1) Anatomical barriers**
- - Skin as a mechanical barrier- keeps out 95% of household germs while intact.
- - Mucus membrane in respiratory and GI tract traps microbes
- - Cilial propulsion on epithelia cleans lungs of invading microorganisms .

- **(2) Chemical Barriers** at the portal of entry. These include:
- Sweat and sebaceous secretions have antimicrobial actions by acidic pH and high fatty acids content.
- Hydrolytic enzymes in the saliva, HCl of the stomach, proteolytic enzymes in the small intestine are bactericidal.
- Lysozyme, an enzyme that dissolves bacterial cell walls (by breaking down peptidoglycan). It is present on the skin, in tears and cervical secretions.
- Acidic pH in the adult vagina is protective.
- .

- **(3) Normal bacterial flora** present at the portal of entry suppresses the growth of many pathogenic bacteria and fungi by competition for essential nutrients or by production of inhibitory substances such as colicins or acids

II- Second Line of Natural Defense:

- If the invading organism gets through the first line of defense and enters the tissues, These include:

- **1. Circulating effector proteins** They include:
- **a. Lysozyme** which is present in all body fluids.
- **b. Complement:**
- c. Acute phase proteins: These are substances that increase in response; to inflammation and include:
- C-reactive protein (CRP).
- * Acute phase proteins are synthesized in the liver in response to certain cytokines namely, IL-1, IL-6 and TNF- α which are produced by macrophages when stimulated by microbial products.

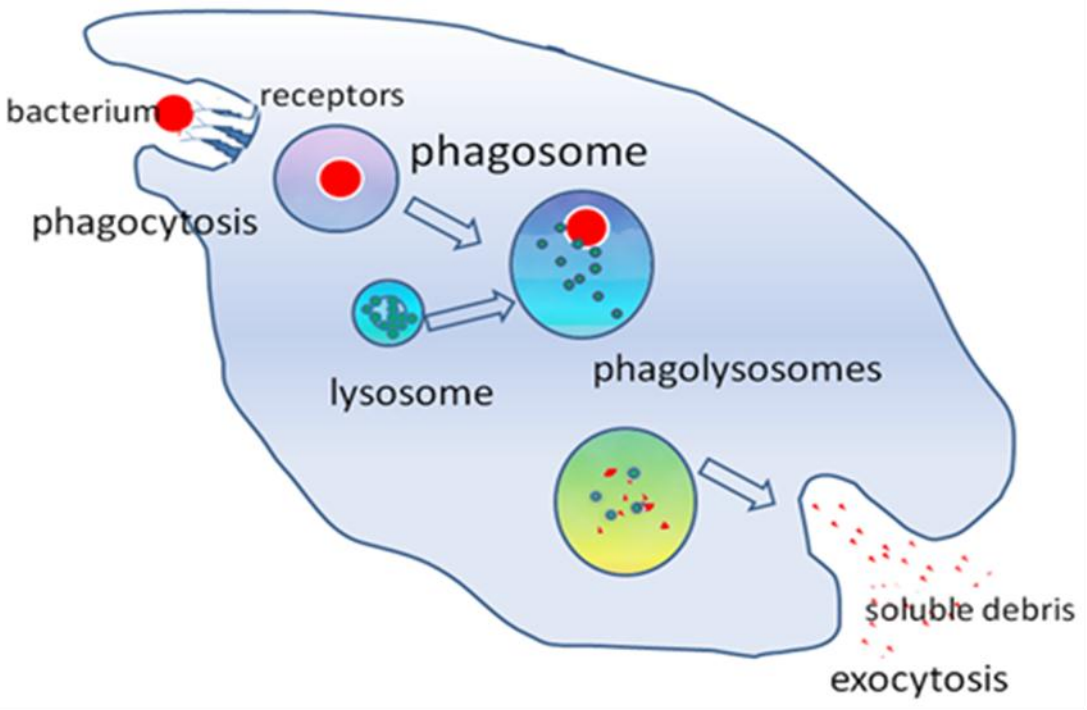
d. Interferons (IFNs):

- defense against viral infections. They are released from virus-infected cells and,
- when taken up by other cells, protect them from infection not only by the same virus but also by other types of viruses
- 1-Type I IFNs comprise IFN-α and IFN-β. Virus infection itself triggers the production of type I IFNs,.
-
- 2-Type II IFN consists of IFN-γ. IFN-γ is produced by activated NK cells in innate immune responses and by specifically sensitized T cells in adaptive immune responses. Moreover, the cytokines IL-12 can trigger T cells to produce IFN-γ.
-

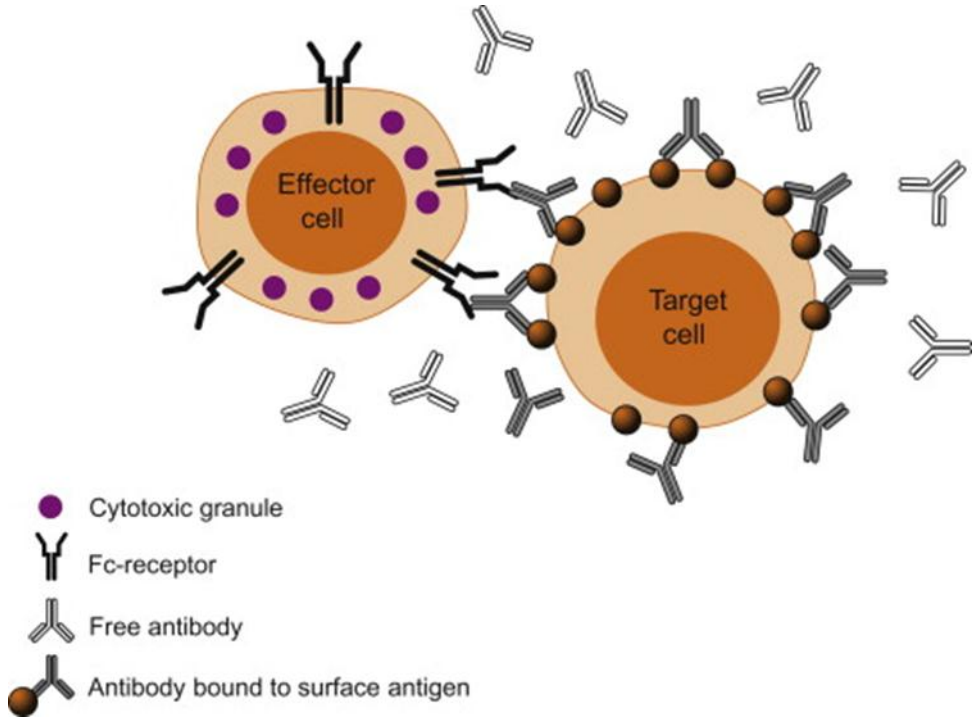
Cells of the innate immune system

- **1-Macrophages:**
- Macrophages that have phagocytized microbes and protein antigens process the antigens and present peptide fragments to T cells.
- Thus, macrophages function as APCs in T-cell activation.
- Macrophages are key effector cells in cell-mediated immunity, the reaction that serves to eliminate intracellular microbes. In this type of response, T cells activate macrophages and enhance their ability to kill ingested microbes.

- Macrophages can be activated by cytokines such as interferon-gamma (IFN-gamma) and bacterial endotoxins, such as lipopolysaccharide (LPS).


bacterium
receptors
phagosome
phagocytosis
lysosome
phagolysosomes
soluble debris
exocytosis

ADCC

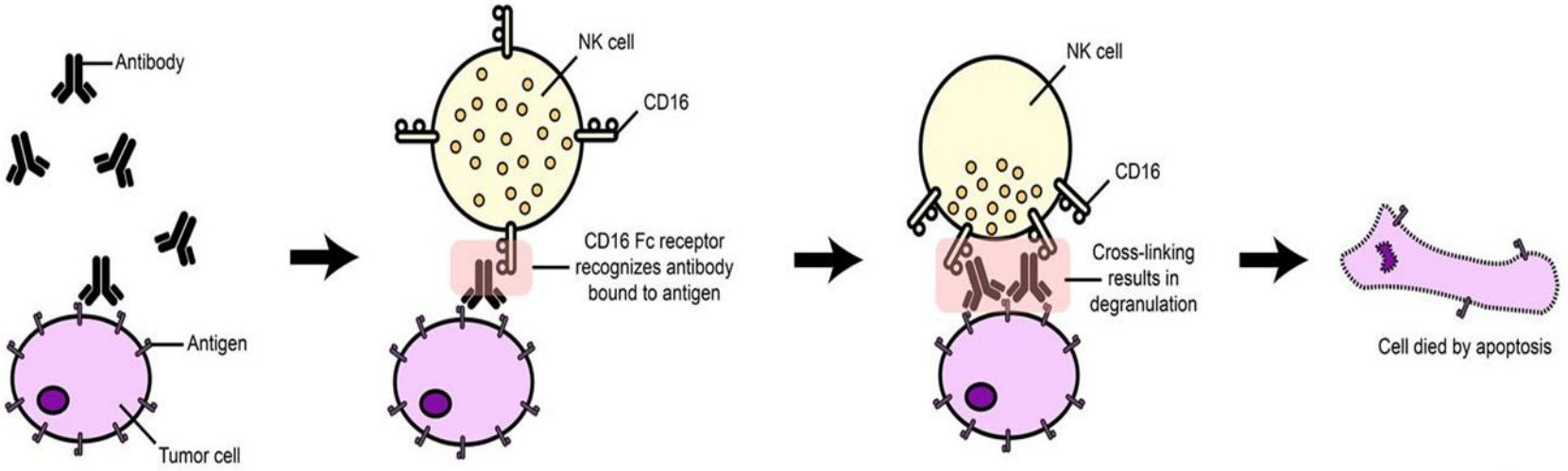

Effector cell
Target cell
Cytotoxic granule
Fc-receptor
Free antibody
Antibody bound to surface antigen

2-Granulocytes

a-Natural Killer (NK) cells

- it has the ability to kill a variety of infected and tumor cells, without prior exposure to or activation by these microbes or tumors. This ability makes NK cells an early line of defense against viral infections and, perhaps, some tumors. CD16 is an Fc receptor for IgG, and it confers on NK cells the ability to lyse IgG-coated target cells. This phenomenon is known as antibodydependent cell-mediated cytotoxicity (ADCC).

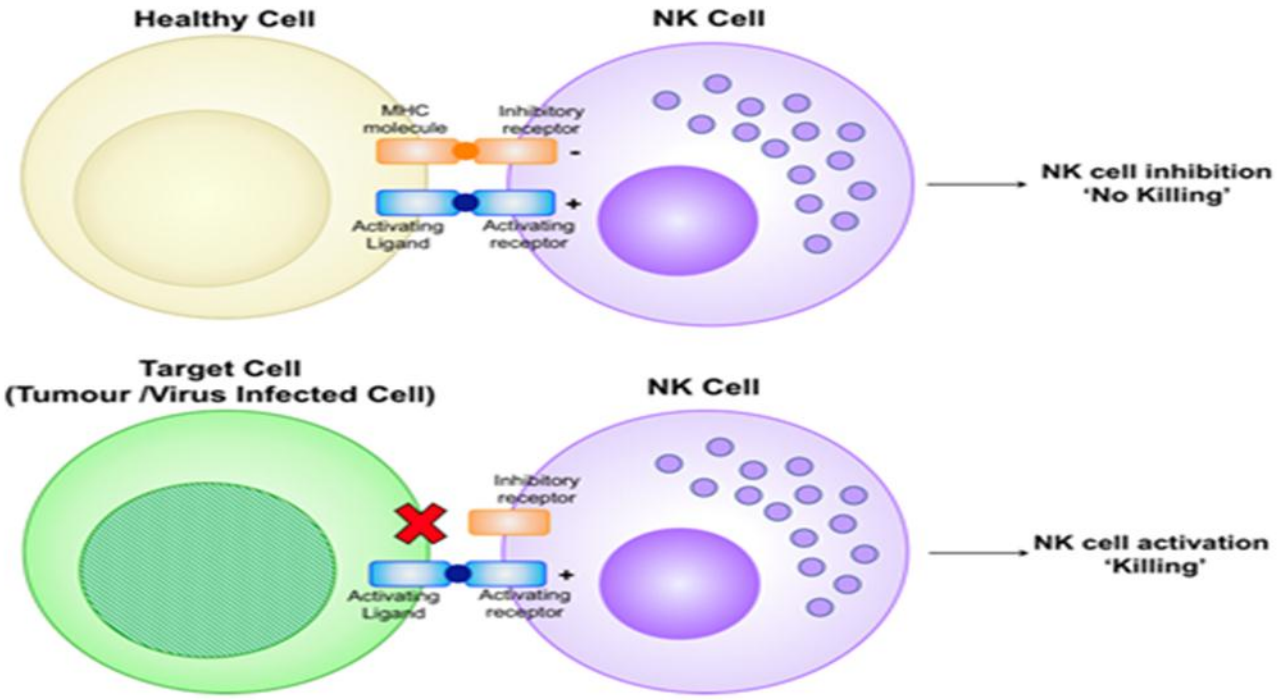
Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC)



Moises Dominguez

Mechanism of NK cell response in normal and target cells

- NK cells recognise _self‘ MHC on normal cells, when activating receptors bind, an inhibitory interaction will suppress NK cell activation and no killing will take place .
- If NK cells encounter tumour cells or virally infected cells that lack the _self‘ MHC molecule it will promote NK cell activation, leading to cytotoxicity, and results in the killing of the unwanted cell .


Healthy Cell
NK Cell
MHC molecule
Inhibitory receptor
-
+
Activating Ligand
Activating receptor
NK cell inhibition
'No Killing'
Target Cell
(Tumour /Virus Infected Cell)
NK Cell
Inhibitory receptor
+
Activating Ligand
Activating receptor
NK cell activation
'Killing'

NK cells mediated cytolysis differs from CTLs in the following:

- 1- They are non-specific i.e. one NK cell can kill many different foreign cells.
- 2- They act spontaneously without prior recognition or activation.
- 3- They do not require antigen presentation by MHC i.e. not MHC restricted.
- 4- They destroy cells coated with antibodies i.e. antibody dependent cellular cytotoxicity (ADCC).

LAK cells:

- IL-2 activated NK cells are called lymphokine activated killer (LAK) cells. These cells have been used in cancer immunotherapy; however, they have shown variable results in clinical trials to treat metastatic cancer.

b- Neutrophils Eosinophils and Basophils

- Neutrophils are the first responders of the body's defense system. Neutrophils rapidly localize to areas of acute infection and phagocytize bacteria. Their cytoplasmic granules contain proteases to kill the invading organism. Neutrophils are the most abundant white blood cell in circulation .

- Eosinophils can ingest bacteria, but they also target foreign cells that are too large to ingest. Eosinophils contain granules that release enzymes and other toxic substances when foreign cells are encountered. These substances make holes in the target cell's membranes.

- Eosinophils circulate in the bloodstream. However, they are less active against bacteria than are neutrophils and macrophages. One of their main functions is to attach to and thus help immobilize and kill parasites

- Basophils do not ingest foreign cells. They contain granules filled with histamine; a substance involved in allergic reactions.
- When basophils encounter allergens (antigens that cause allergic reactions), they release histamine. Histamine increases blood flow to damaged tissues, resulting in swelling and inflammation.

3-Denderitic cells

- **Dendritic cells** are phagocytic and can degrade pathogens; however, their main role is to activate T cells in the adaptive immune response by acting as antigen-presenting cells (APCs) and by producing regulatory cytokines.
-
- They are primarily located under the skin and mucosa of most organs where they capture foreign antigens and transport these antigens to local lymph nodes, where they present antigen to naive helper T cells.

Cytokines of Innate Immunity:

Pro-inflammatory cytokines:

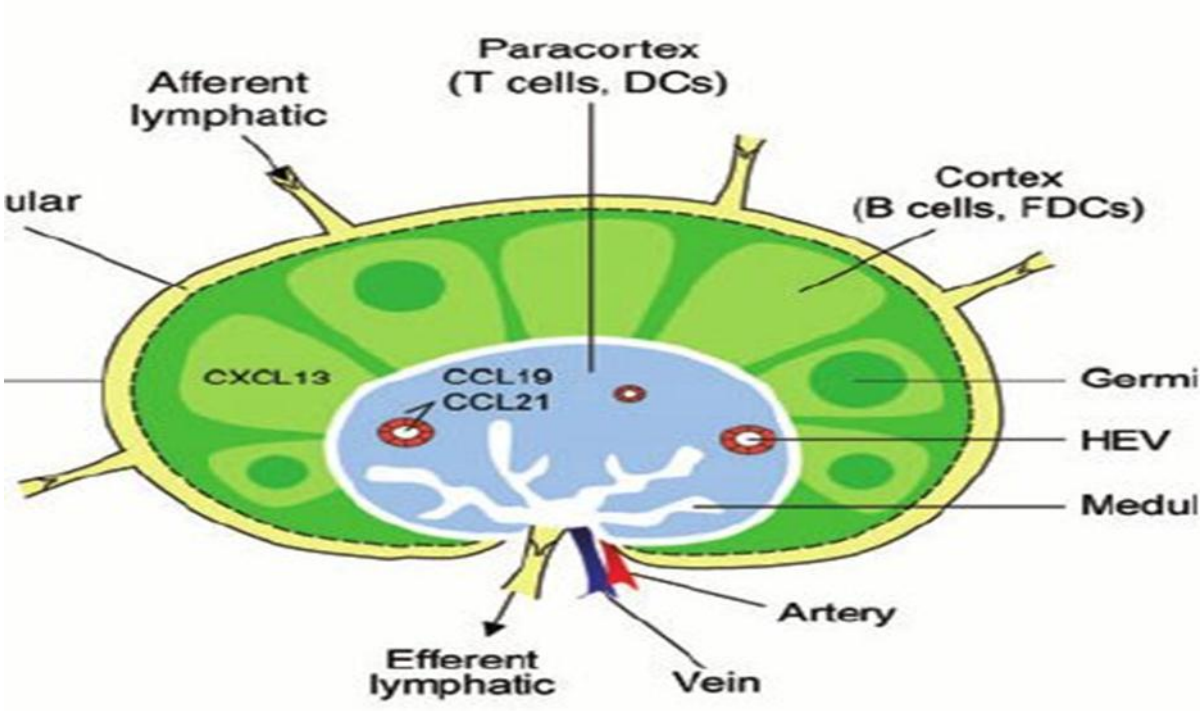
- Play a key role in inflammation.
- They include IL-1, IL-6, IL-8 and TNF-α.
- They are released from activated macrophages.
- They function to increase extravasation of neutrophils to the site of inflammation, induce coagulation and increase vascular permeability.
- **b. IL-12:** also released from activated macrophages and it activates NK cells and T cells.
- **c. IFN-γ** produced by NK cells activates macrophages and T cells .
- **d. IFN-α** produced by viral infected cells inhibits viral replication and prevents spread of infection to uninfected cells.

THE COMPONENTS OF IMMUNE SYSTEM

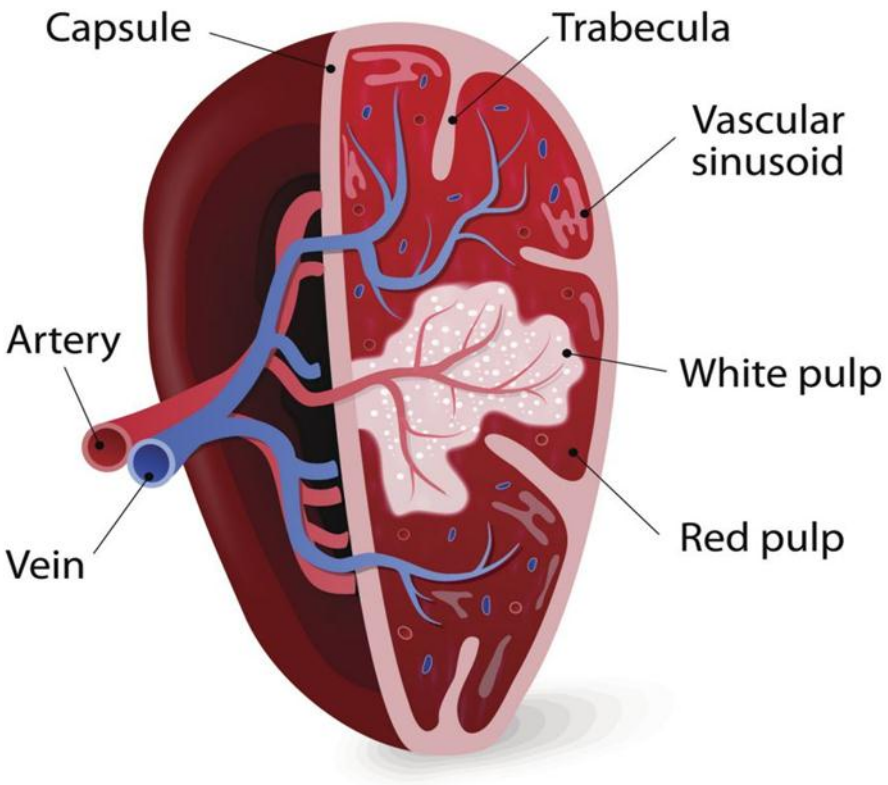
- **The immune system consists of many organs and cells**
- ***1- Primary (central) lymphoid organs:***
- ***a) Bone marrow:*** It is located inside the cavity of long and large bones. it is the site of haematopoiesis of B-cells and T cells). It is also the site of maturation of B-cells in mammals.
- ***b) Thymus:*** It is the site of maturation of T-cells (Thymus dependent lympthocyte).

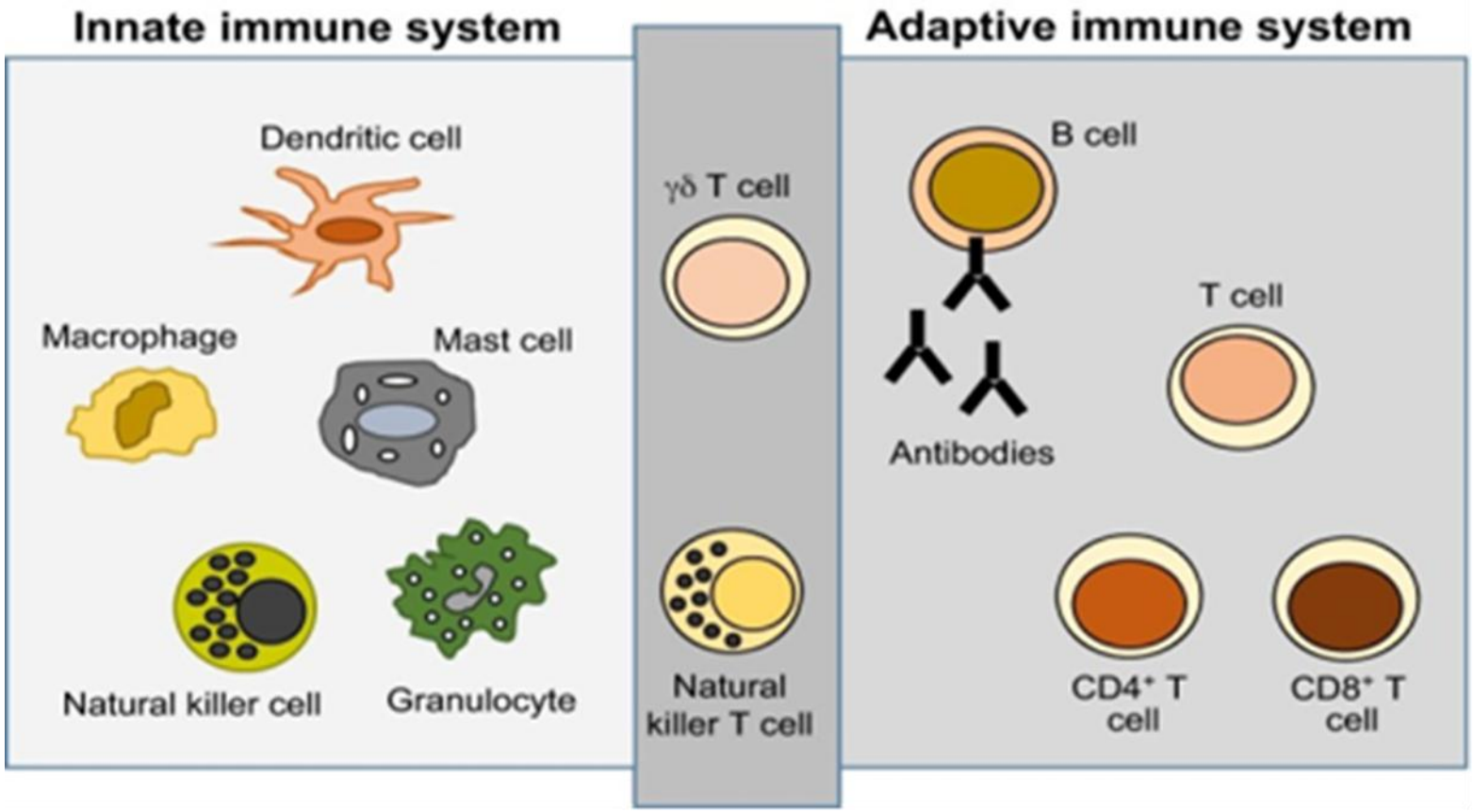
2- Secondary (peripheral) lymphoid organs:

- ***a) Lymph nodes:***
- ***b) Spleen:***
- ***c) Mucosa-associated lymphoid tissue (MALT):*** e.g., Gut associated lymphoid tissue (GALT) as Payer's patches, appendix and tonsils.


Paracortex
(T cells, DCs)
Afferent
lymphatic
ular
Cortex
(B cells, FDCs)
CXCL13
CCL19
CCL21
Germi
HEV
Medul
Artery
Efferent
lymphatic
Vein

SPLEEN ANATOMY




Innate immune system
Adaptive immune system
Dendritic cell
γδ T cell
B cell
Macrophage
Mast cell
T cell
Antibodies
Natural killer cell
Granulocyte
Natural killer T cell
CD4⁺ T cell
CD8⁺ T cell

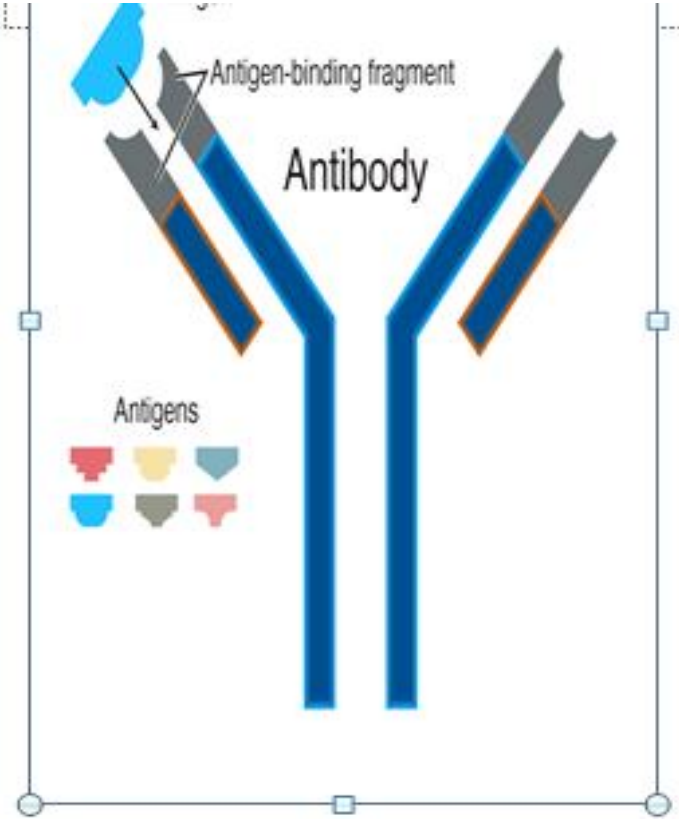
Cells of the immune system

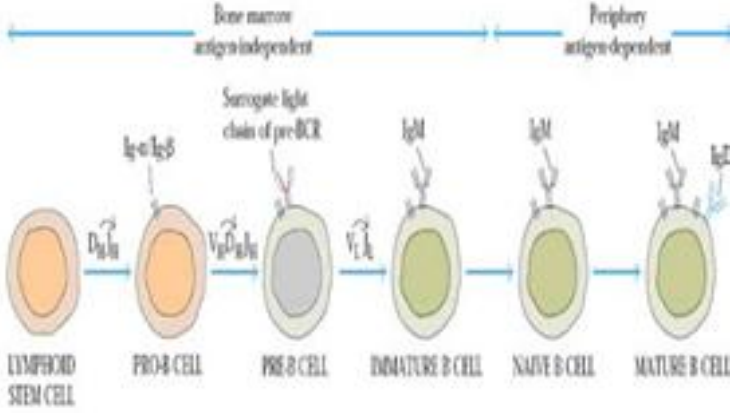
I. Lymphocytes:

- They include B-lymphocytes, T- lymphocytes and NK cells .

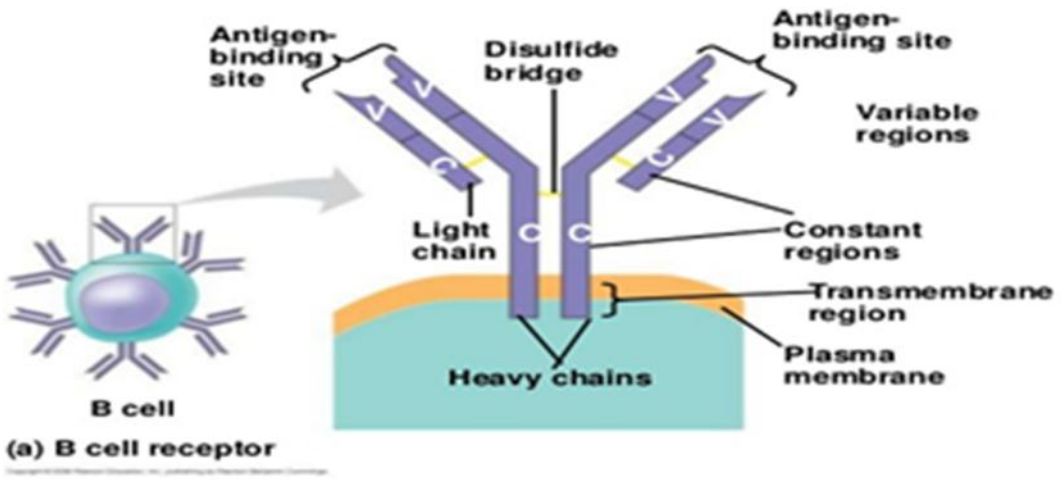
1) B-lymphocytes (B-cells):

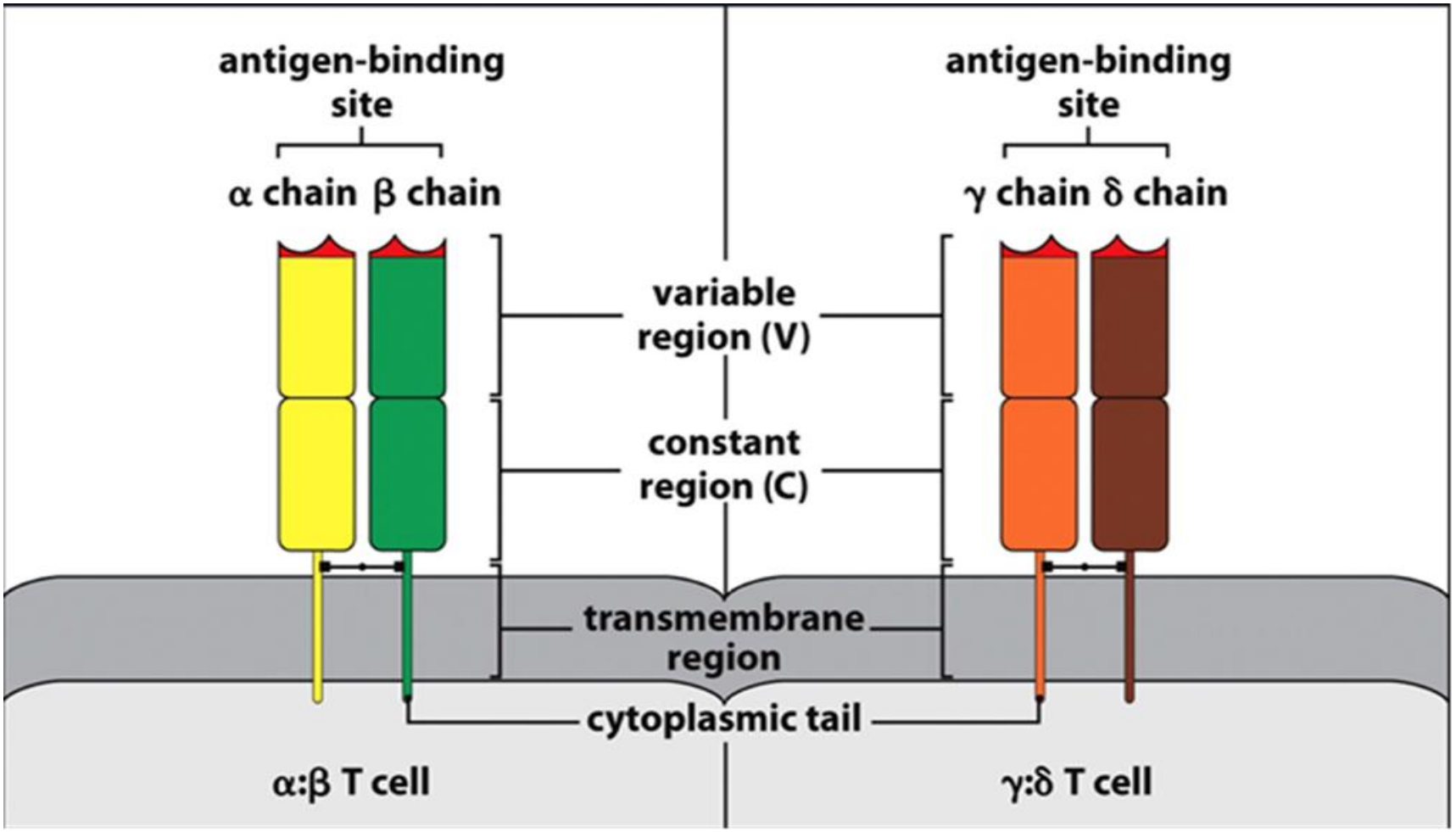
- B-cells constitute about 30% of circulating blood lymphocytes. They originate and mature in the bone marrow (hence the name) and responsible for humoral immunity. Activated B-cells recognize antigens and differentiated into plasma cells that secrete antibodies.


Antigen-binding fragment
Antibody
Antigens


Bone marrow
antigen-independent
Periphery
antigen-dependent
Surrogate light
chain of pre-BCR
IgM
IgM
IgM
LYMPHOID
STEM CELL
PRO-B CELL
PRE-B CELL
IMMATURE B CELL
NAIVE B CELL
MATURE B CELL

B CELL RECEPTOR




antigen-binding site
α chain β chain
antigen-binding site
γ chain δ chain
variable region (V)
constant region (C)
transmembrane region
cytoplasmic tail
α:β T cell
γ:δ T cell

- **B-cells function:**

1. They are the only cells capable of producing antibodies (Humoral immunity).
2. Recognize antigen in soluble form by the BCR.
3. They act as an antigen presenting cells (APCs).

2- T-lymphocytes (T-cells):

- They constitute about 70 % of circulating blood lymphocytes. They originate from a stem cell in the bone marrow but mature in the thymus (hence the name T lymphocytes) and responsible for CMI.

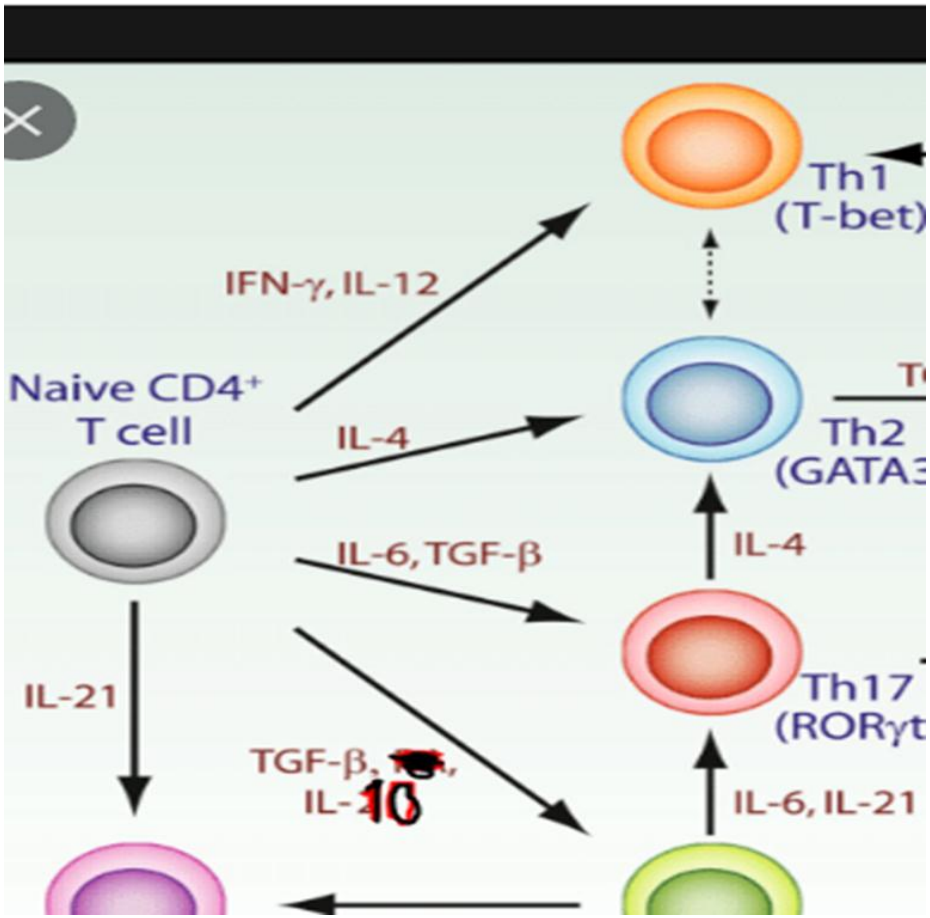
T Lymphocytes

- **T- cell subsets (T- cell subpopulations)**

- **I- Effectors $CD4^+$ T-cells (T-helper) TH cells:**

- Constitute 65% of peripheral T-cells.
- They recognize the antigen on the surface of APCs in association with class II MHC proteins (present on macrophages, dendritic cells and B cells).
- Help B cells to become antibody producing plasma cells.
- Help CD8 T cells to become activated Cytotoxic T-cells.

- **T-helper cells subsets:**
- Naïve CD4 (TH0) can be induced to differentiate into Th1, Th2, Th17 and regulatory (Treg) according to cytokine stimulus.
-
- **a) TH0:**
- - Produce IL-2, 4, 5 and 10 and γ-INF.
- - Precursers of Th1 and Th2.


Th1
(T-bet)
IFN-γ, IL-12
Naive CD4+
T cell
IL-4
Th2
(GATA3
IL-6, TGF-β
IL-4
IL-21
Th17
(RORγt
TGF-β,
IL-
10
IL-6, IL-21

b) TH_1 cells and TH_2:

- **TH1 cells**:- develop in the presence of :-
- 1-**IL-12** which synthesized by activated macrophages and dendritic cells
- 2- IFN-γ secreted by NK cells.
-
- TH1 cells synthesize IFN-γ and IL-2. These cytokines activate macrophages, CD8+ T cells, and NK cells. Once activated, these effector cells kill host cells that have been infected with intracellular pathogens, in particular with viruses and bacteria.

- **TH2 cells** develop in the presence of IL-4, early in the response to parasitic worms such as helminths and to allergens.
-
- -TH2 cells synthesize IL-4, IL-5, IL-6, IL-10 and IL-13.
-
- **-IL-4 and IL-13** influence the B-cell class switch to IgE in humans, and IL-5 activates eosinophils.

c) TH17:

- They secrete IL17 that: Recruit leukocytes mainly neutrophils to sites of infection.
- Thy play an important role in defense against extra cellular bacteria and fungi.
- TH17 cells differentiate from naïve CD4+ T cells in response to **IL-6 and TGF-β**.

c) Regulatory T- cells (Teg):

- They regulate the activation of other T-cells and maintain tolerance to self antigens. Most Treg cells express CD4, CD25 and FOXP3.
- When activated they secrete IL-10 and TGF-β and function as immunosuppressant inhibiting Th1, Th2 and possibly Tc.
- They form 5-10% of the CD4 positive cells.

Thymic education

Negative selection (clonal deletion) is an important mechanism of self tolerance is the elimination of self reactive T cells during their development in the thymus

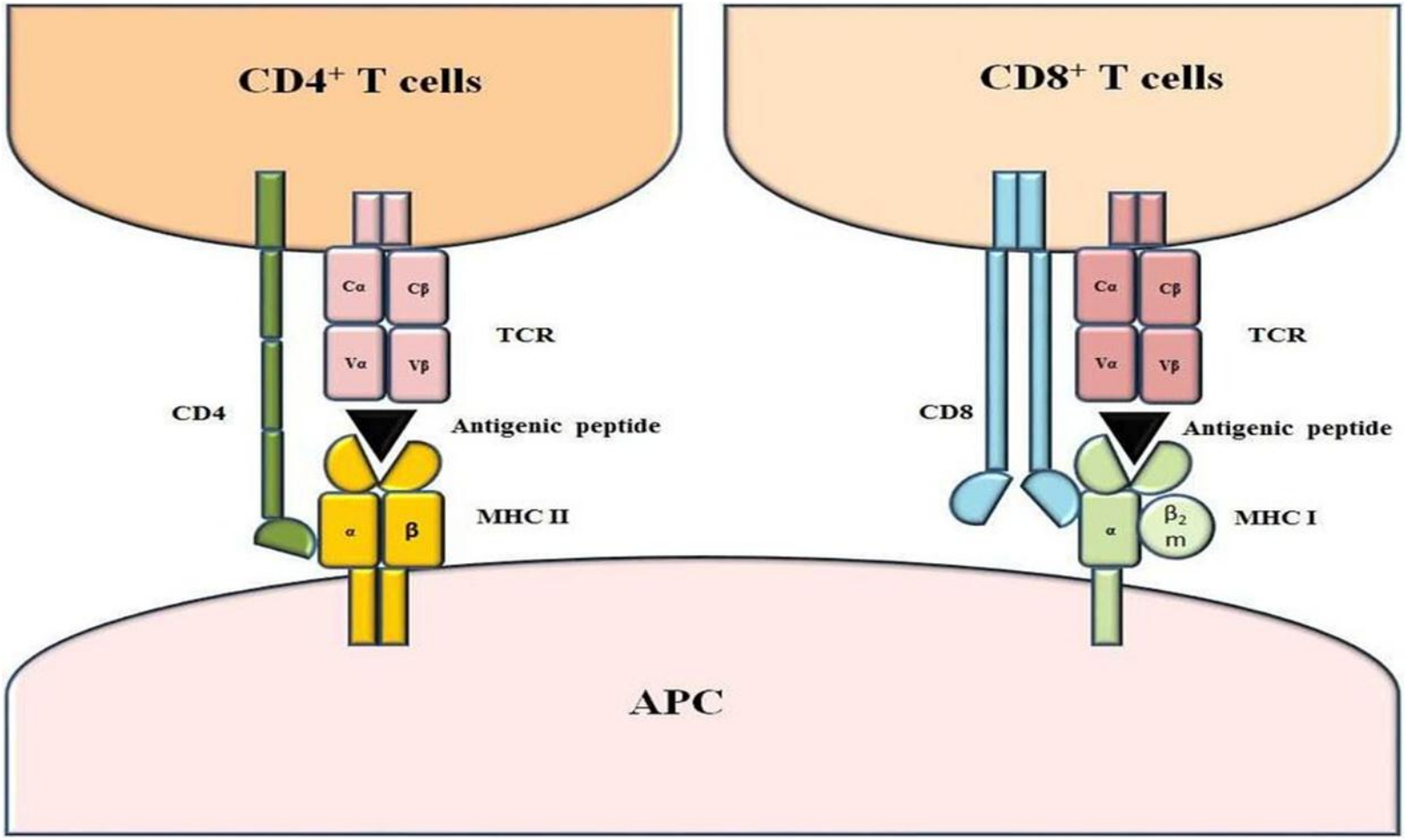
- **A-Positive Selection**
- Results in MHC restriction
- **Mechanism:**
  - Immature thymocytes cluster with MHC molecules on the cortical cells of the thymus
- If TCR interacts with MHC → *protective signal* results that prevents apoptosis.
- If TCR does not interact with MHC → apoptosis occurs.
- **Only reactive thymocytes (with low affinity to MHC) survive**

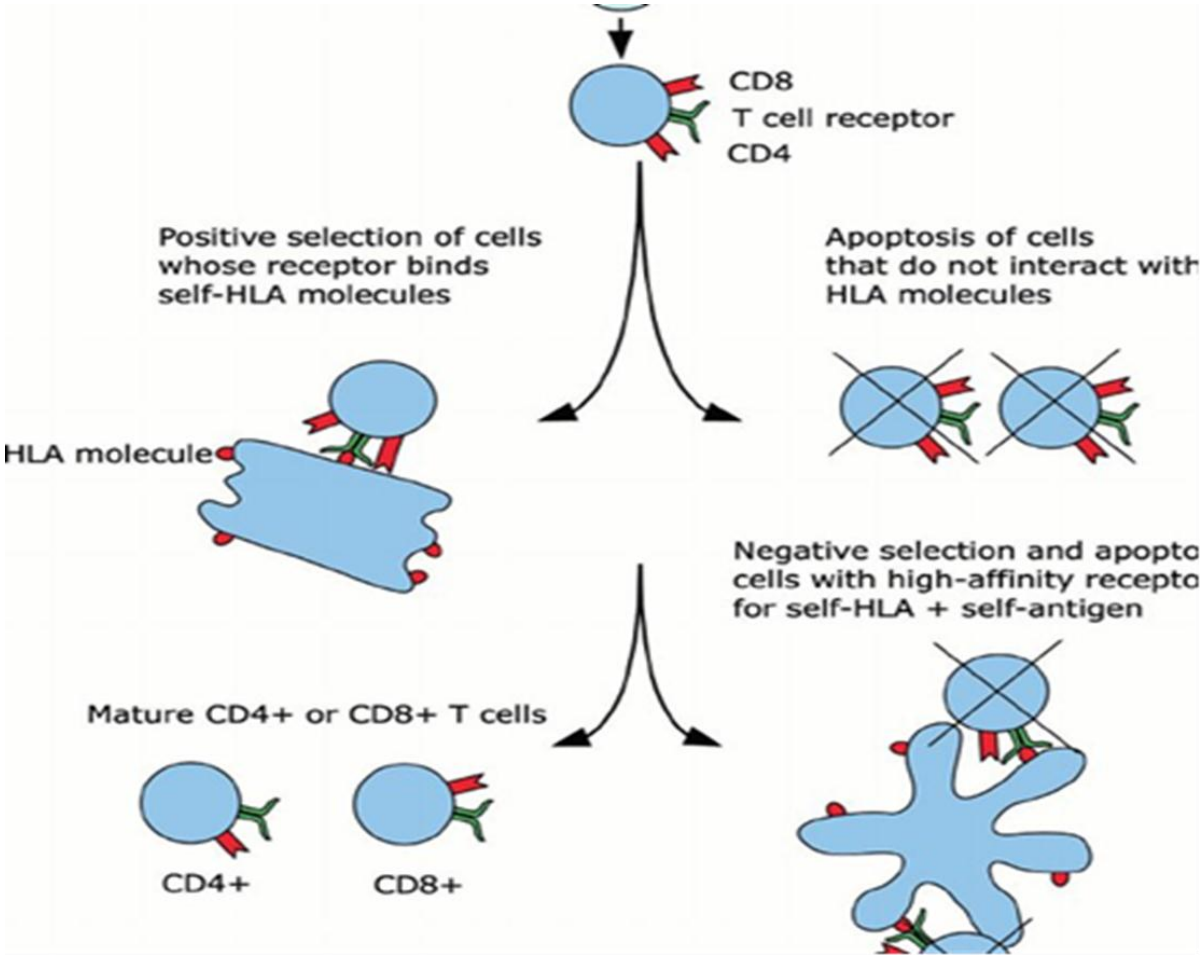
B-Negative selection

Negative Selection Ensures ***self-tolerance***

- Mechanism:
  - APC's bearing MHC's (HLA) interact with thymocytes

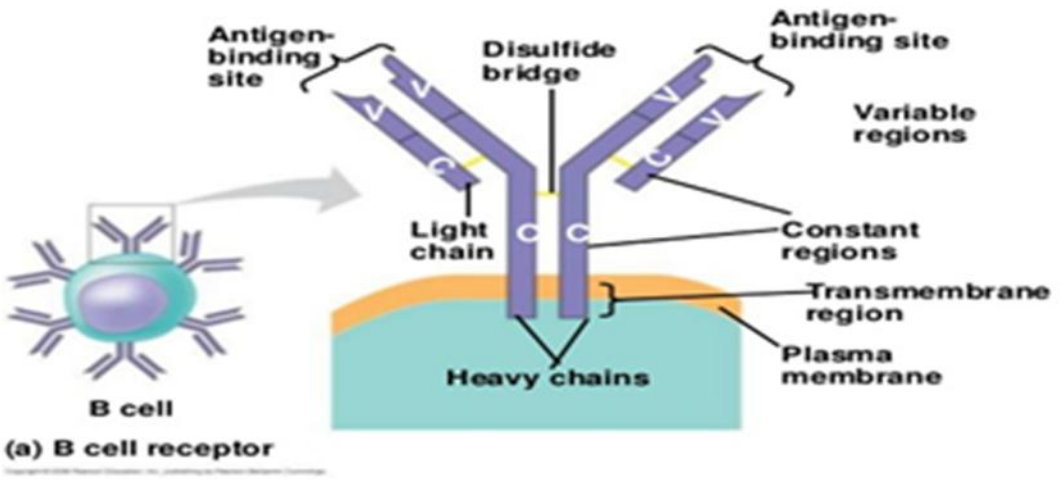
- If avidity is too strong → thymocyte undergoes apoptosis.


CD4+ T cells
CD8+ T cells
Cα
Cβ
Vα
Vβ
TCR
CD4
CD8
Antigenic peptide
α
β
MHC II
β2 m
MHC I
APC


CD8
T cell receptor
CD4
Positive selection of cells
whose receptor binds
self-HLA molecules
Apoptosis of cells
that do not interact with
HLA molecules
HLA molecule
Negative selection and apopto
cells with high-affinity recepto
for self-HLA + self-antigen
Mature CD4+ or CD8+ T cells
CD4+
CD8+

- To summarize the selection process, we can say that thymocytes with affinity that is either *too low* or *too high* for self-MHC do not survive thymic selection (negative selection). Only thymocytes with some *intermediate* affinity for self-MHC survive thymic selection (positive selection).

B CELL RECEPTOR



Properties	Natural killer cells (NK)	T cytotoxic (Tc) cells
Specificity	Non specific	Specific
MHC restricted	No	Yes
Required activation	No	Yes
Immunity	Innate	Acquired

APCs

- APCs that express MHC class II molecules are often called **professional antigen-presenting cells**. There are three main types of professional antigen-presenting cell:

1. **Dendritic cells (DCs)**, which have the broadest range of antigen presentation, and are probably the most important APC..
2. **Macrophages**.
3. **B-cells**, which express (as B cell receptor) and secrete a specific antibody,

THE COMPLEMENT SYSTEM

- The complement system is a group of proteins normally present in serum and body fluids, except urine and CSF.
- The complement system is composed nearly of 30 proteins components designated as C_1, C_2… C9.

Complement Nomenclature

- 1- Designated by numerals **(C1-C9)**, letter
- 2- Symbols **(factor D)**,
- 3-Two Peptide fragments made by activation of a component are denoted:
- For example, activation of C4 results in
- • "a" for smaller fragment – C4a
- • "b" for larger fragment – C4b
- • Exception: C2a fragment is larger than C2b
- Larger fragments bind to the target near the site of activation, while smaller fragments diffuse from the site of activation and can initiate localized inflammatory response

Activation of the Complement System

- There are three ways to activate the complement system, involving different molecules initially but converging to produce the same effector molecules. Each involves activation of enzymes that cleave their substrates to form a cascade, so that the complement response is amplified.
-

1. The Classical Pathway

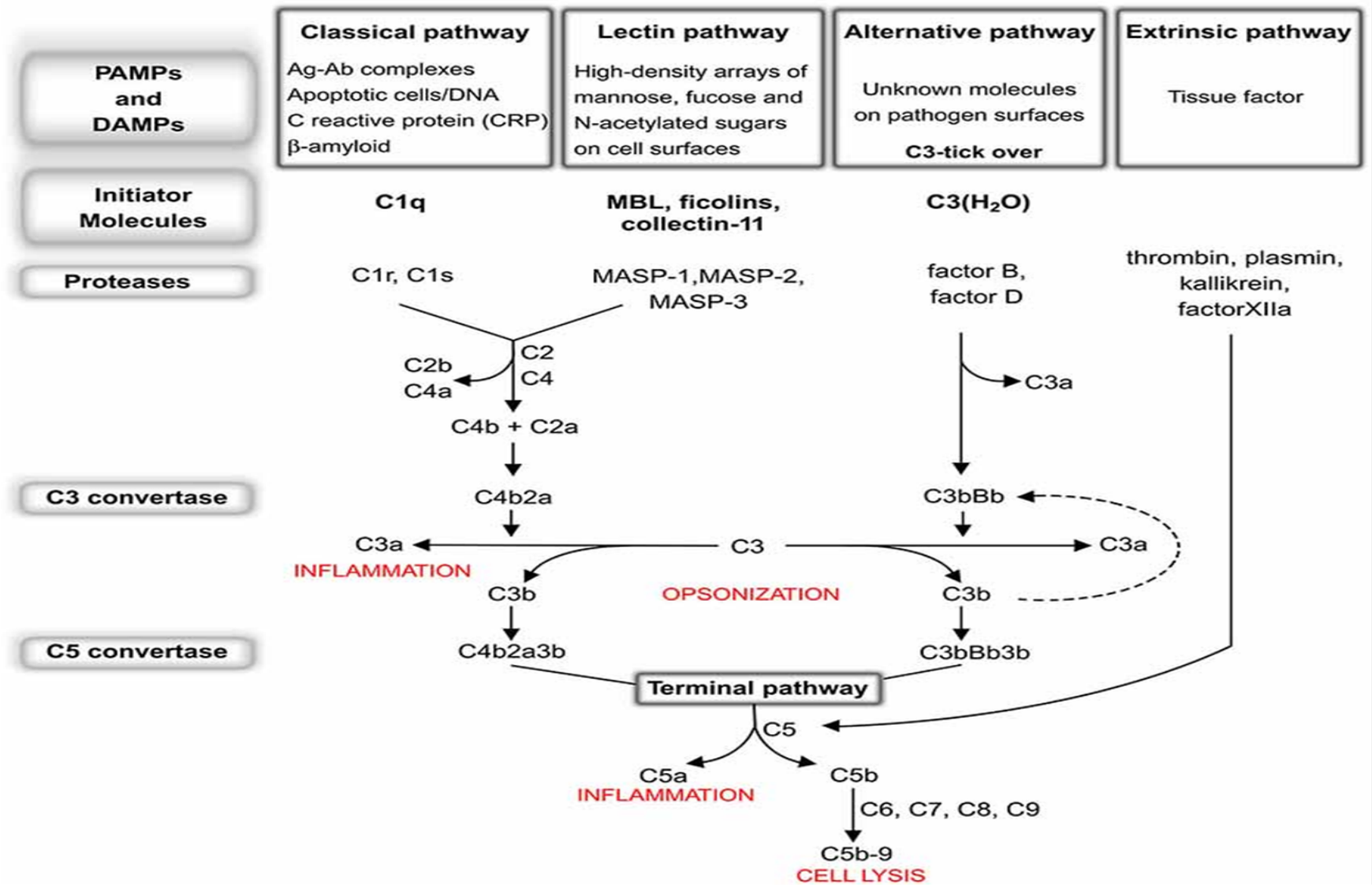
2. The Mannose-Binding Lectin Pathway

3. The Alternative Pathway

- All three pathways produce **C3 convertase**, an enzyme which triggers further effects downstream. The effects of C3 convertase are discussed below.

1-The Classical Pathway

- The classical pathway is activated when a complement protein called **C1q (in association with C1r,C1s)** binds onto an antigen-antibody (IgM or IgG) complex . (Compement bind to Fc portion in Ig)
- This will then trigger cleavage of the subsequent complement proteins in the cascade, resulting in production of C3 convertase and it's downstream to C9 to form membrane attacking complexes (MAC) leading to cell lysis.
- Its involvement in **antigen-antibody complexes** means it has a role in the adaptive immune response.


Classical pathway
Ag-Ab complexes
Apoptotic cells/DNA
C reactive protein (CRP)
β-amyloid
Lectin pathway
High-density arrays of mannose, fucose and N-acetylated sugars on cell surfaces
Alternative pathway
Unknown molecules on pathogen surfaces
C3-tick over
Extrinsic pathway
Tissue factor
PAMPs and DAMPs
Initiator Molecules
C1q
MBL, ficolins, collectin-11
C3(H2O)
Proteases
C1r, C1s
MASP-1,MASP-2, MASP-3
factor B, factor D
thrombin, plasmin, kallikrein, factorXIIa
C2
C4
C2b
C4a
C3a
C4b + C2a
C3 convertase
C4b2a
C3bBb
C3a
C3
C3a
INFLAMMATION
OPSONIZATION
C3b
C3b
C5 convertase
C4b2a3b
C3bBb3b
Terminal pathway
C5
C5a
INFLAMMATION
C5b
C6, C7, C8, C9
C5b-9
CELL LYSIS

- **2-The Mannose-Binding Lectin (MBL) Pathway**

  - The lectin pathway is initiated when mannose-binding lectin (MBL) binds to terminal mannose residues on the surface glycoproteins or glycolipids of microbes. MBL is structurally homologous to C1q in the classical pathway. *Early Steps in the Lectin Pathway That Lead to C3 Cleavage.* However, after initiation, the lectin pathway proceeds through C4 and C2 in a manner identical with the classic pathway, and the subsequent steps are essentially the same.

  - Like the alternative pathway, it does not depend on antibody for its activation(component of innate immunity starts in absence of antibody). (Only bypass C1qrs)

3-The Alternative Pathway

- The alternative pathway is usually activated by **bacterial endotoxin,** (a lipopolysaccharide present on the outer membrane of gram negative bacteria); the cell walls of some yeasts; and cobra venom factor(a protein present in some snakes). This results in spontaneous hydrolysis of C3 into small amounts of factor C3b, which combines with other factors to produce C3 convertase.

- **Steps Shared by All Pathways: Activation of** C3 cleavage is the first step that is common to all three complement pathways .
-
- In the classical and lectin pathways , the C3 convertase C4b2a cleaves C3 into two fragments, C3a and C3b. In the alternative pathway , the C3 convertase C3bBb cleaves C3 into the same two fragments ;C3a, and C3b.
-
- Consequently, under normal conditions, the alternative pathway is not continually activated.
-
- Which ever way C3 is activated it will then activate C5, which in turn activates C6, C7, C8 and C9 in a cascade. As such even a small signal can lead to the rapid activation of many thousands of complement molecules – this is important in the immune response as pathogens are also able to replicate very quickly within the body.

Immune Effects of the Complement System

Once activated the complement system has several effects, including:

Opsonisation

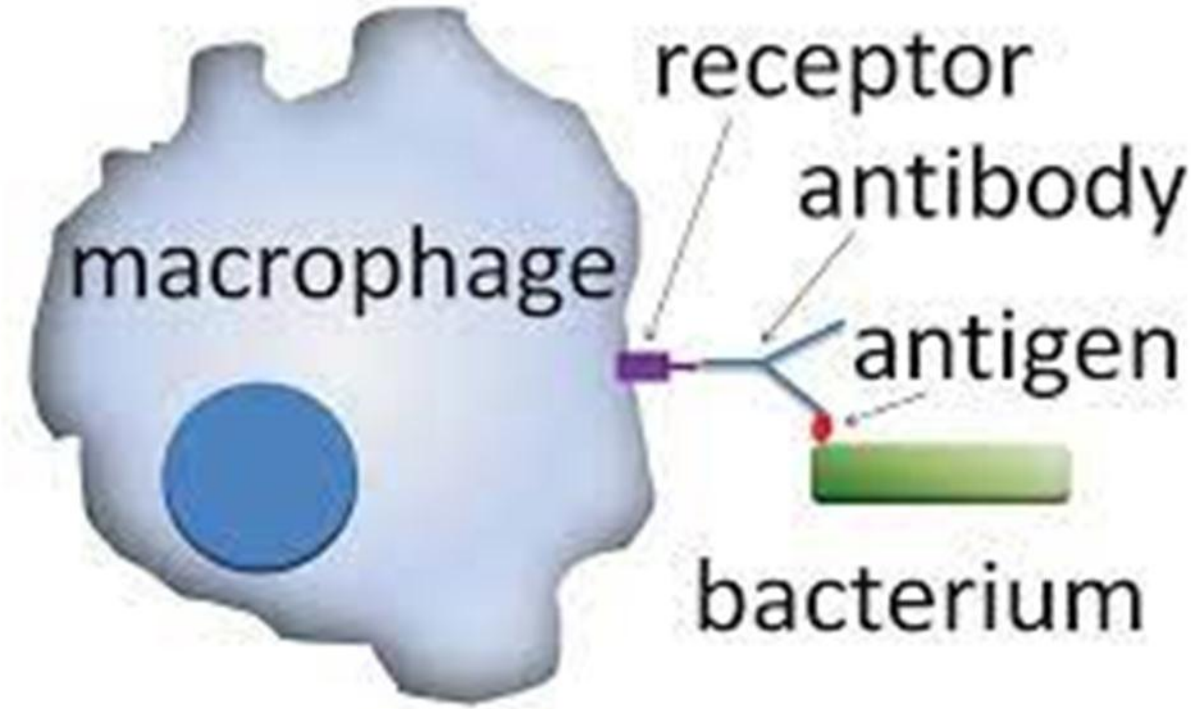
Lysis of pathogens

Chemotaxis

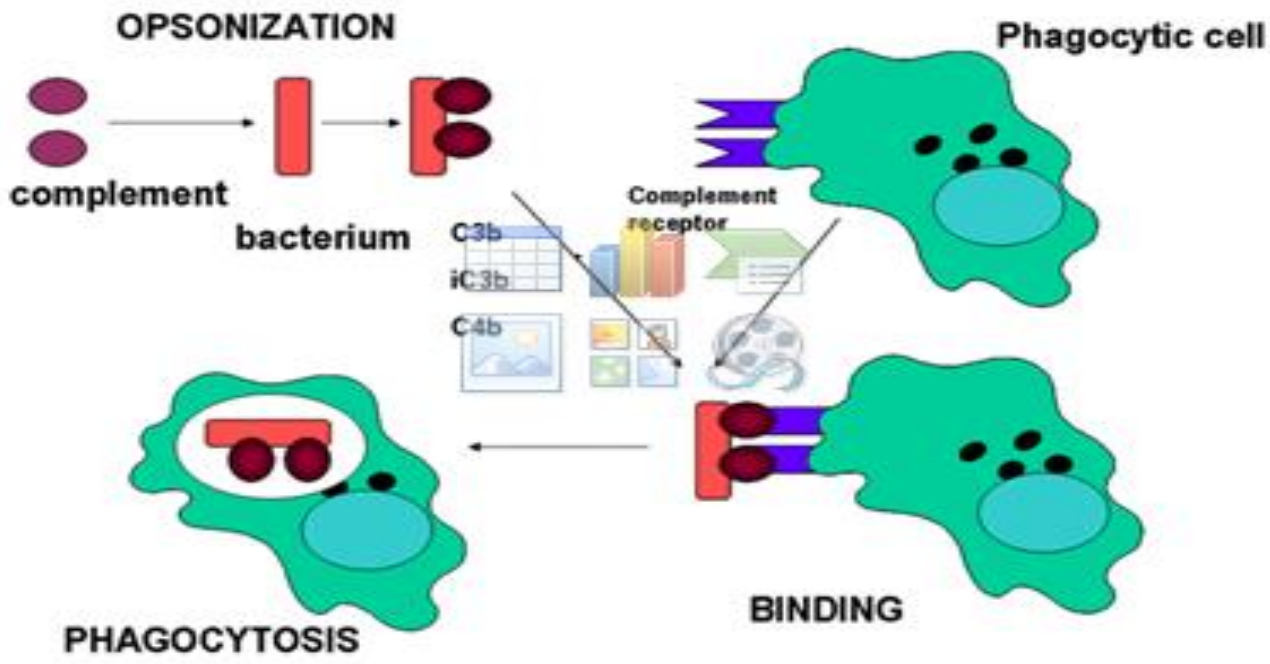
Inflammation

1-Opsonisation

- C3 convertase is a product of all the pathways triggering the complement cascade and is responsible for converting factor C3 into C3a and C3b. **C3b** binds to antigens on the pathogen, which stimulates neutrophils and macrophages to phagocytose pathogens – this is called opsonisation .This is due to the presence of C3b receptors on the surface of phagocytes.


receptor
antibody
macrophage
antigen
bacterium

Opsonization and phagocytosis



2-Lysis of Pathogens

- Lysis of pathogens is facilitated by the formation of the **membrane attack complex** (MAC). C3 convertase is vital to the production of the MAC because it generates C3a and C3b. C3b combines with other factors to produce C5 convertase, an enzyme which converts factor C5 to C5a and C5b.C5b combines with several factors to produce the MAC (C5b6789) into the cell membrane, results in its disruption and the entry of water and electrolytes into the cell leading to its lysis.

- **3-Chemotaxis**
- The production of C5a by **C5 convertase** attracts neutrophils and macrophages to the site of infection and causes extravasation of leucocytes from capillaries to tissues. C3a is another complement component that acts as a chemotaxin.

- **4-Inflammation**
- C3a, C4a and C5a (are anaphylatoxins) are the complement components responsible for causing inflammation. They bind to mast cells and basophils to cause degranulation. The histamine and serotonin released increase vascular permeability. C3a, C4a and C5a also promote synthesis of pro-inflammatory cytokines.

HYPERSENSITIVITY

HYPERSENSITIVITY

It is a term used to describe a state in which the immune response takes place in a way that cell damage of the host and harmful pathological lesions may occur; the immune response results in exaggerated reactions harmful to the host. It may be auto-immune responses directed against self-antigens or due to exogenous foreign antigens.

Types:

- Hypersensitivity reactions can be subdivided into 5 types (type I, II, III, and IV). Types I, II, and III are antibody-mediated, whereas type IV is cell–mediated.
- Type I: (Immediate, anaphylactic): IgE antibody on basophiles and mast cells.
- Type II: (Cytotoxic or cytolytic): IgM or IgG against cellular antigens.
- Type III: (immune complex): IgM or IgG against soluble antigens.
- Type IV: (Cell-mediated or DTH): sensitized T- cells (TH_1) activate macrophages causing inflammation.
- Type V: IgG class against cellular antigens.

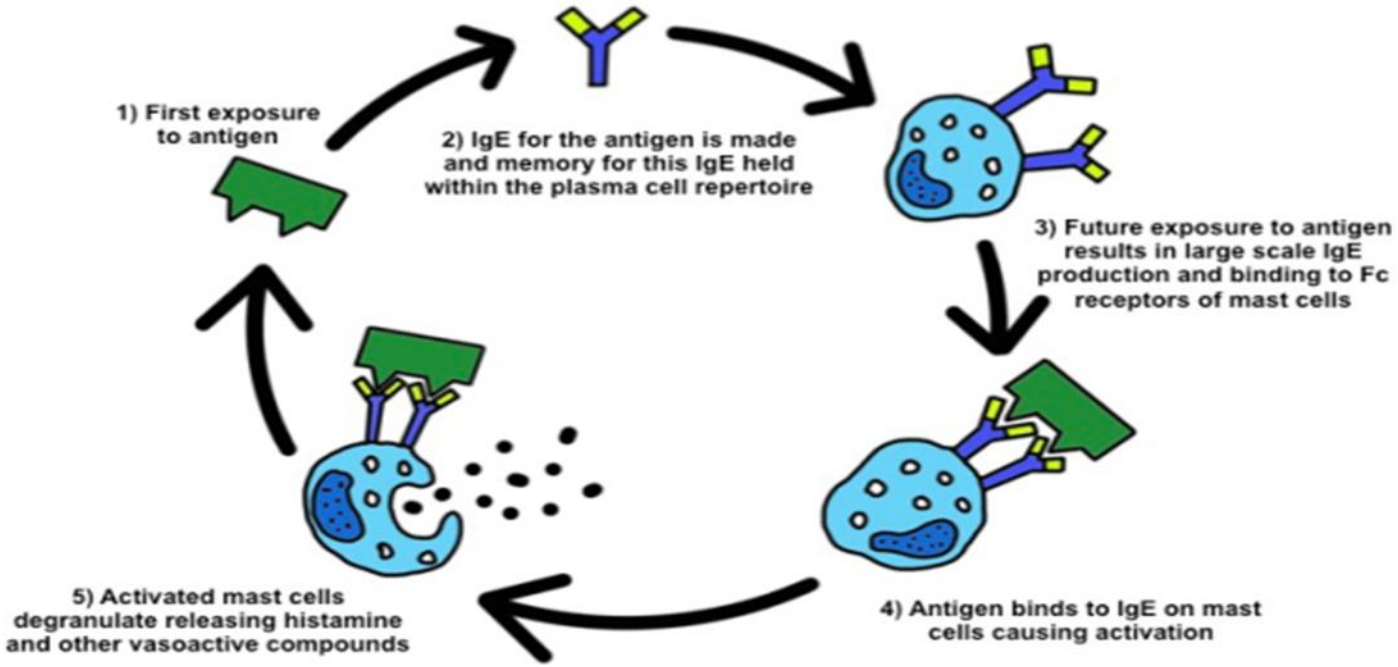
1- Type I- hypersensitivity (Anaphylactic reaction)

(Immediate type, IgE- mediated)

- **Mechanism (Pathogenesis) of type I :**
- Type 1 hypersensitivity reaction is an allergic reaction provoked by re-exposure to a specific type of antigen referred to as an allergen. The reaction may be either local or systemic. Symptoms vary from mild irritation to sudden death from anaphylactic shock.

- Exposure (first exposure) may be by ingestion, inhalation, injection, or direct contact. The b lymphocytes differentiate into an plasma cell which secrete IgE .
- The difference between a normal immune response and a type I hypersensitivity response is that plasma cells secrete IgE.
- This class of antibodies binds to Fc receptors on the surface of tissue mast cells and blood basophils. Mast cells and basophils coated by IgE are "sensitized."

- Second or later exposure to the same allergen, cross-links the bound IgE on sensitized cells resulting in degranulation and the secretion of histamine, leukotriene, and prostaglandins that act on the surrounding tissues.
- The principal effects of these products are vasodilation and smooth-muscle contraction


1) First exposure to antigen
2) IgE for the antigen is made and memory for this IgE held within the plasma cell repertoire
3) Future exposure to antigen results in large scale IgE production and binding to Fc receptors of mast cells
4) Antigen binds to IgE on mast cells causing activation
5) Activated mast cells degranulate releasing histamine and other vasoactive compounds

Clinical types:

- ***1- Systemic (Anaphylaxis) reaction- Anaphylactic shock:***
- It occurs within few minutes on exposure to an allergen.
- The condition usually develops after administration of penicillin, and anti-toxic serum.

2-Localized (Atopy):

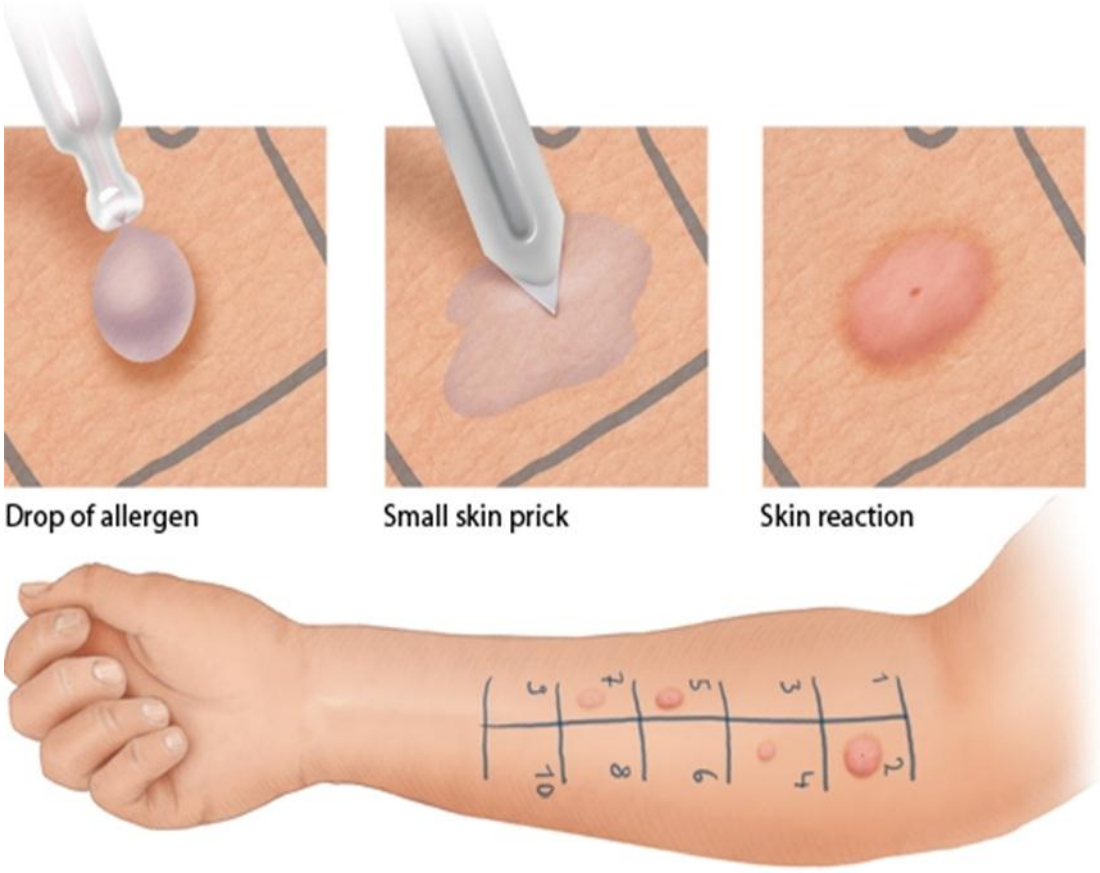
- In this type the symptoms are localized in one organ or system. It occurs as a result of exposure to certain allergens e.g.:
- i) Inhalants: House dust, pollens and mould spores which are widely distributed in nature.
- ii) Ingestants: Milk, fish, egg and chocolate.
- iii) Contactants: Wool and nylon.

Diagnosis of type 1 hypersensitivity:

Allergic test

Skin prick tests using various allergens from animal, plants, food, pathogens and environmental pollutants

Radioallergosorbent test (RAST): Use to determine specific IgE antibodies


Drop of allergen
Small skin prick
Skin reaction
1
2
3
4
5
6
7
8
9
10

Management of type 1 hypersensitivity (Control and treatment)

- 1- Avoidance of exposure to allergens to which the individual is sensitive.
- 2- Desensitization: By repeated subcutaneous injections of the allergen extract to which the patient is sensitive in gradually increasing doses. This results in production of IgG antibodies (Blocking antibodies), that block the allergen and prevent its binding to the IgE.
- 3- Administration of drugs: As antihistaminics, corticosteroids, epinephrine.

Type II hypersensitivity (Cytotoxic or Cytolytic)

Mechanism and Pathogenesis:

In type II hypersensitivity reactions, the antibodies produced by the immune response bind to antigens on the patient's own cell surfaces.

The antigens recognized in this way may either be intrinsic ("self" antigen, innately part of the patient's cells) or extrinsic (absorbed onto the cells during exposure to some foreign antigen, possibly as part of infection with a pathogen). IgG and IgM antibodies bind to these antigens to form complexes that activate the classical pathway of complement activation, for eliminating cells presenting foreign antigens.

That is, mediators of acute inflammation are generated at the site and membrane attack complexes cause cell lysis and death.

The reaction takes hours to a day).

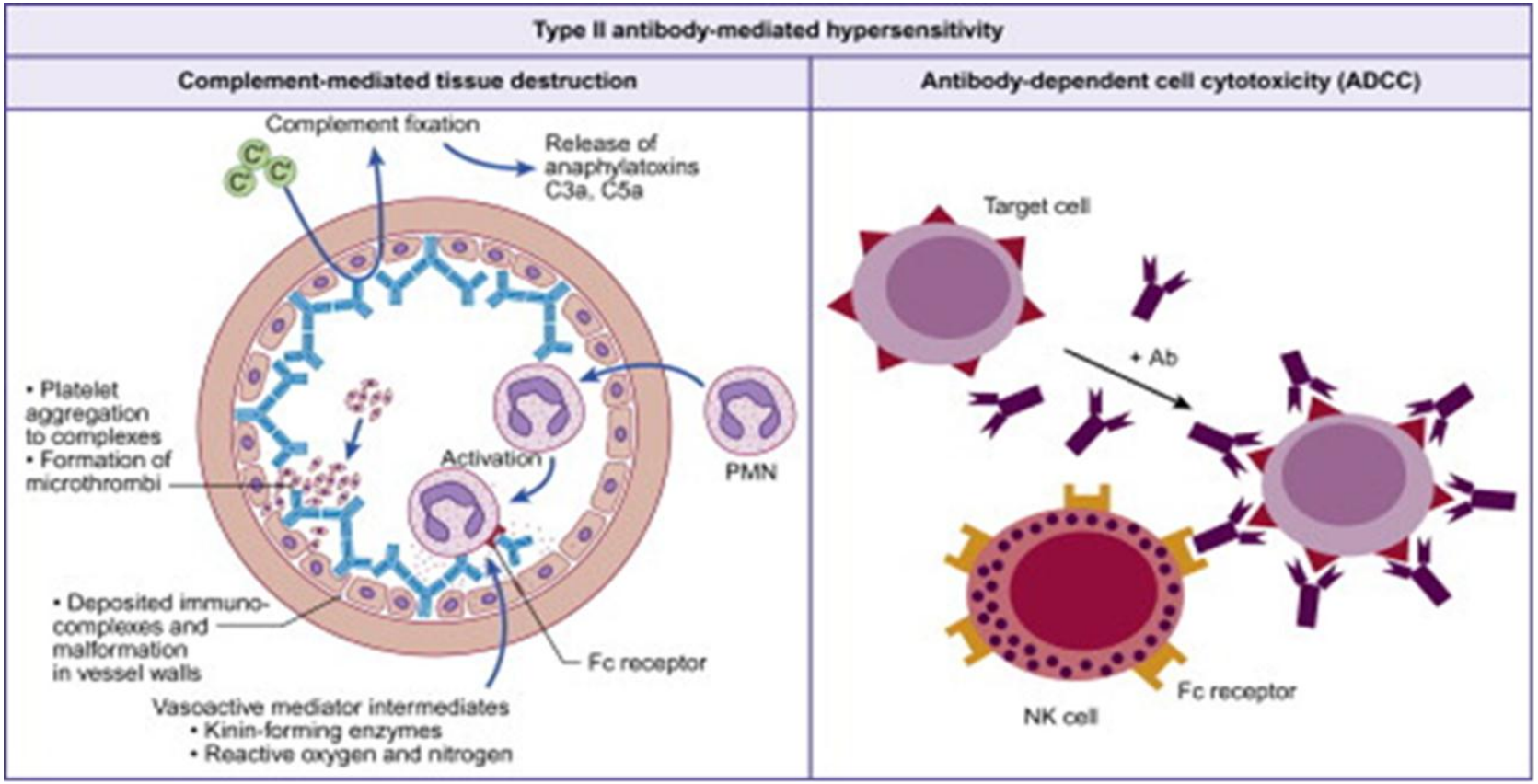
1-Phagocytosis of the cell can be mediated by phagocytes expressing Fc receptors (opsonization).

Click to add title

2-Another form of type II hypersensitivity is called Antibody Dependent Cell Mediated Cytotoxicity (ADCC). Here, cells exhibiting the foreign antigen are tagged with antibodies (IgG). These tagged cells are then recognised by Natural Killer (NK) cells and macrophages (recognised via IgG bound to the cell surface receptor, CD16), which in turn kill these tagged cells.

Clinical examples:

1. Autoimmune hemolytic anemia
2. Erythroblastosis Fetalis
3. Hemolytic disease of the newborn.
4. Immune thrombocytopenia
5. Transfusion reactions
6. Many autoimmune diseases as SLE, Myasthenia gravis
7. Graft rejection , as the receipient already has preformed antibodies against the graft
8. Drugs as penicillin attach as hapten on the surface of RBC--→Haemolysis


Type II antibody-mediated hypersensitivity
Complement-mediated tissue destruction
Antibody-dependent cell cytotoxicity (ADCC)
Complement fixation
Release of anaphylatoxins C3a, C5a
C'
C'
C'
• Platelet aggregation to complexes
• Formation of microthrombi
Activation
PMN
• Deposited immuno-complexes and malformation in vessel walls
Fc receptor
Vasoactive mediator intermediates
• Kinin-forming enzymes
• Reactive oxygen and nitrogen
Target cell
+ Ab
Fc receptor
NK cell

Type III hypersensitivity (Immune or toxic complex syndrome)

- Binding of antibodies with their specific antigen results in formation of immune complex which is normally removed by RES (Macrophages). Sometimes very small soluble immune complex are formed and become deposited in tissues leading to this condition.
- **Mechanism of tissue damage :**

1. The reaction is initiated by antigen-antibody complex that penetrates the endothelium of blood vessel walls and is deposited on the vascular basement membrane leading to tissue damage through:

- a) Activation of complement with the release of anaphylatoxins, C_3a, C_5a.
- b) Release lysosomal enzymes that destroy the basement membrane.
- c) Platelets are aggregated and release vasoactive amine and form microthrombi which cause tissue damage.

Clinical types:

1- Arthus reaction: It is a localized reaction of immune complex disease, which occurs due to repeated injections of the same antigen subcutaneously or intradermaly, e.g. caw insulin injections.

2- Serum sickness: it is a systematic reaction. It follows the injection of foreign serum of relatively large dose or drugs (e.g. anti-tetanic e.g. penicillin).

3-Autoimmune disease e.g. SLE (Anti-nuclear antibodies (ANAs); these antibodies are produced against cellular nuclei) and rheumatoid arthritis (antibodies against normal IgM and IgG).

Management:

1) Anti-histaminics and corticosteroids and immunosuppressive drugs.
2) Removing the immune complex by exchanging the patient's plasma with normal plasma.

(Delayed type hypersensitivity–cell-mediated hypersensitivity)

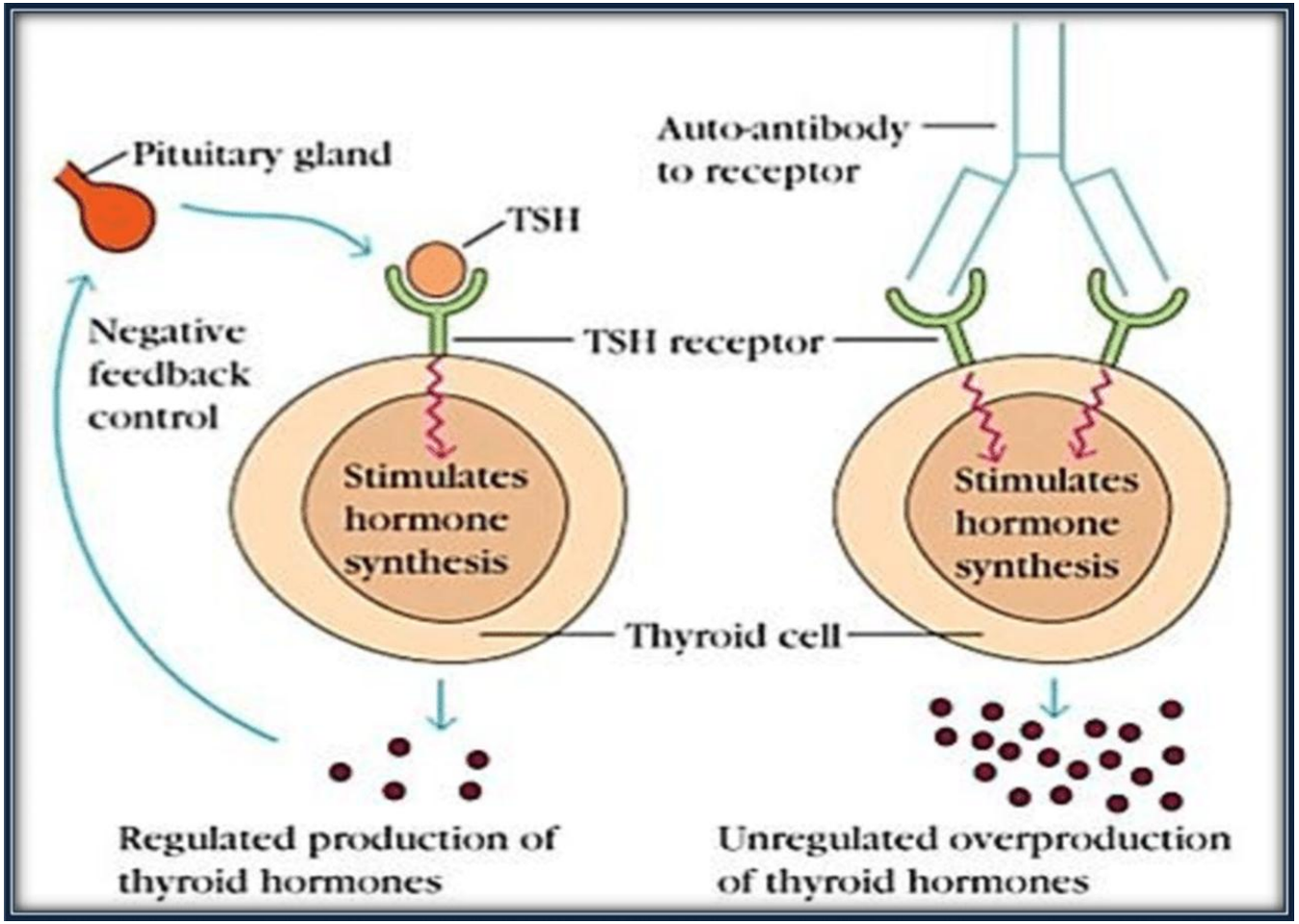
- It is a cell mediated, not antibody mediated. It is initiated by interaction of sensitized T- cells (memory T- cells) with the specific antigen. The response is delayed; the reaction takes 2-3 days to develop.
-
- **Mechanism:**
- On 1st exposure, T-cells react with its specific antigen and become sensitized (memory). On second exposure to the same antigen the sensitized T-cells (TH1) are activated and stimulated to release cytokines. The cytokines will attract and activate monocytes, macrophages and lymphocytes leading to inflammatory reactions that lead to local tissue damage.

Clinical types:

1. Tuberculin reaction: Intradermal injection of PPD into the forearm of a sensitized individual (by exposure to infection or BCG vaccine) results in erythema and induration at the site of injection 2-3 days ≥10 mm in diameter. The induration is due to accumulation of macrophages and lymphocytes.
2. Graft rejection.
3. Autoimmune diseases: e.g. Type 1 insulin dependent diabetes mellitus.

Type V– Stimulatory type

- This is an additional type that is sometimes used as a distinction from Type II reaction.
- These reactions occur when IgG class antibodies directed towards cell surface antigens have a stimulating effect on their target. Instead of binding to cell surface components, the antibodies recognise and bind to the cell surface receptors, which either prevents the intended ligand binding with the receptor or mimics the effects of the ligand, thus impairing cell signalling.
- Some examples: Graves' disease


Pituitary gland
TSH
Auto-antibody to receptor
Negative feedback control
TSH receptor
Stimulates hormone synthesis
Stimulates hormone synthesis
Thyroid cell
Regulated production of thyroid hormones
Unregulated overproduction of thyroid hormones

Rheumatic fever

Prepared by

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Assis Prof. of Microbiology &Immunology

MD Turku University , Finland

STREPTOCOCCI

- **General characters of streptococci:**
- Gram positive cocci
- Arranged in chains or pairs.
- **All are catalase negative.**

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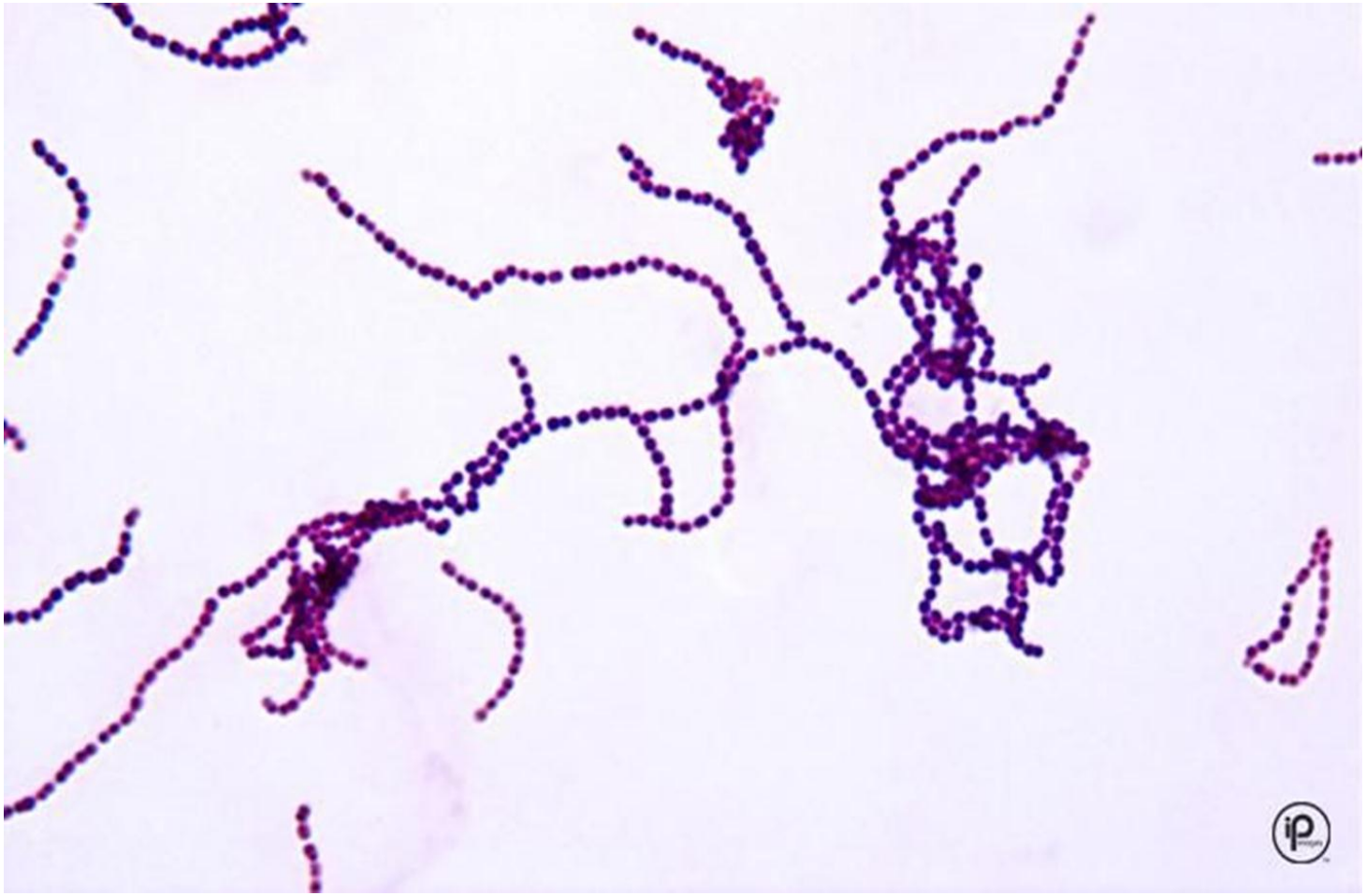
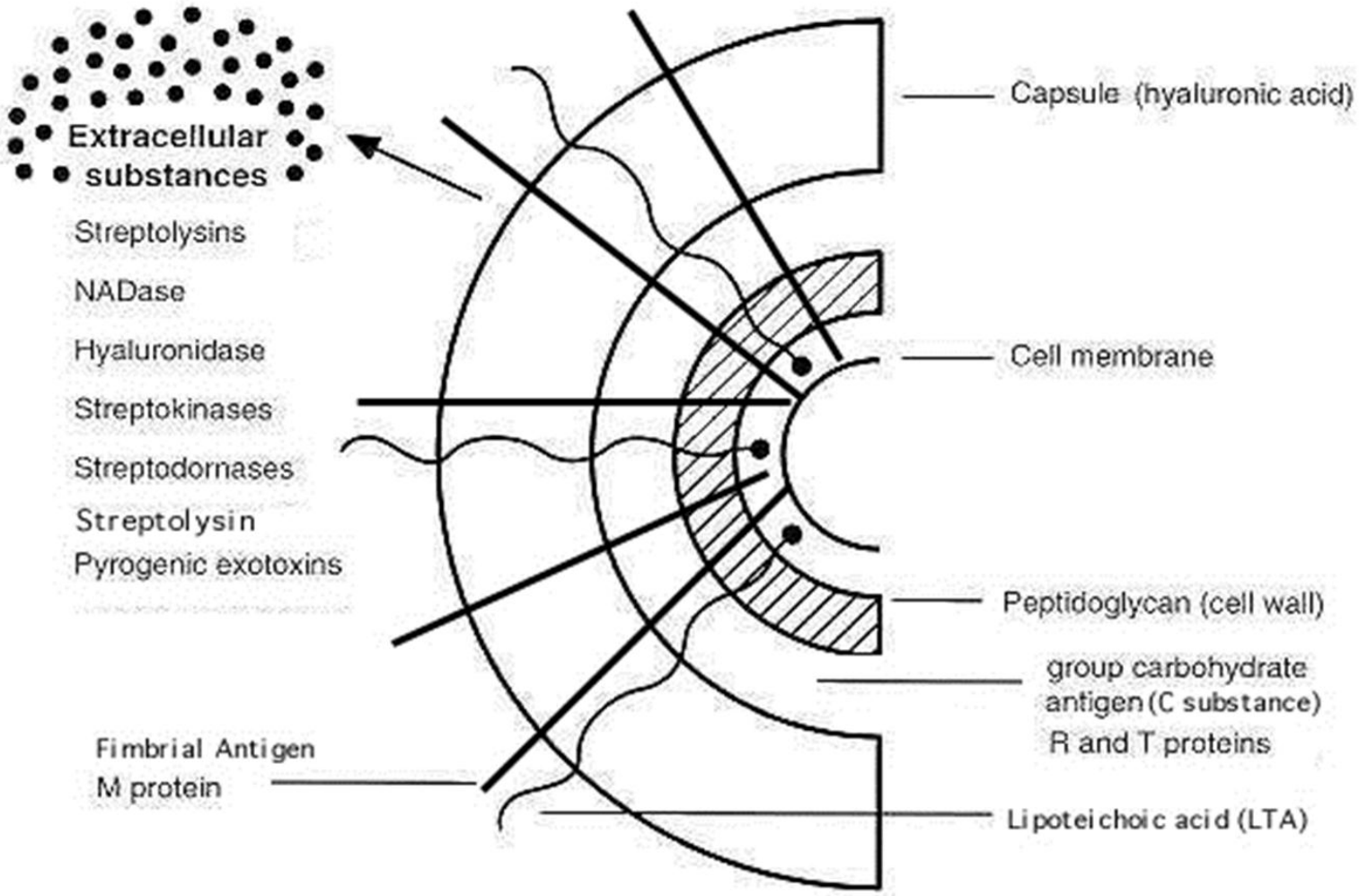
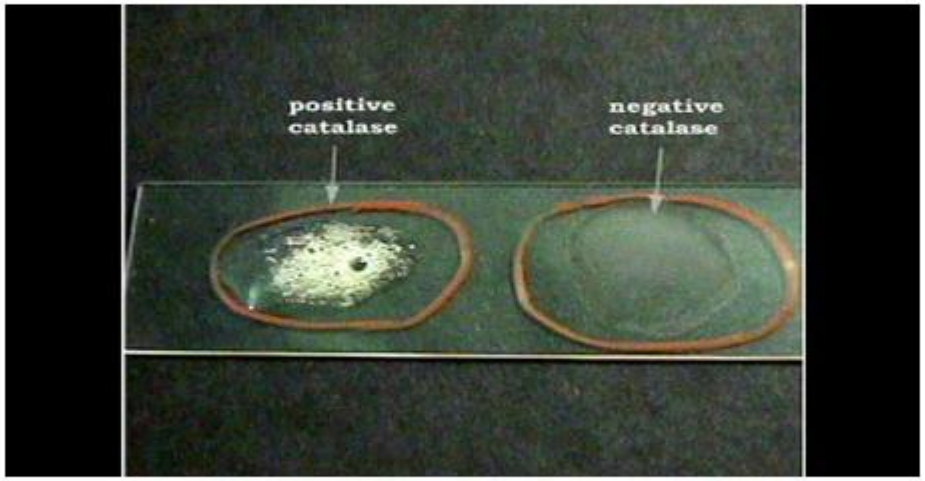



Extracellular substances
Streptolysins
NADase
Hyaluronidase
Streptokinases
Streptodornases
Streptolysin
Pyrogenic exotoxins
Capsule (hyaluronic acid)
Cell membrane
Peptidoglycan (cell wall)
group carbohydrate antigen (C substance)
R and T proteins
Fimbrial Antigen
M protein
Lipoteichoic acid (LTA)

Catalase test

$$H_2O_2 \xrightarrow{\text{------}} H_2O + O_2$$



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Streptococcus pyogenes

- These are group A beta haemolytic streptococci and are the most important human pathogens in the genus Streptococci.

- **Morphology:**
  - Gram positive cocci arranged in chains. Some strains are capsulated.
- They are catalase negative.

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Rheumatic fever

- *Streptococcus pyogenes is the causative agent of Rheumatic fever*
- *Not due to direct effect of organism but through cross reactivity*
- *Rheumatic fever is considered as post-streptococcal disease*

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Virulence factors

- It is the factors which determine the degree of pathogenicity of this organism
- Without theses factors the organism cannot cause disease

Virulence Factors:

- **I) Endogenous (structural) virulence factors:**
- These are cell wall structures that protect the organism. These include:
- **1- M protein;** the most important virulence factor. Streptococci lacking M protein are avirulent. It acts as: Antiphagocytic ,Anticomplementary.

M protein mostly plays an important role in the pathogenesis of rheumatic fever because antibodies to these components react with cardiac muscle tissue. Some M types are rheumatogenic

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- Antibodies that develop against M protein are related to immunity to infection with *str. pyogens*. However; there are over 150 M types of *str. pyogens* this explains why a person can get the infection several times.

2- Toxins:

- **a- Streptolysins (haemolysins):**
- There are 2 types:
- Streptolysin "O" (oxygen labile i.e. inactivated with oxygen); is immunogenic, and antibodies to it (ASO) develop in *Str. pyogenes* infections.
- Streptolysin "S" (oxygen stable) is not immunogenic (i.e. no antibodies develop against it) and is responsible for the haemolysis produced on blood agar.

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Diseases Caused by *Str. pyogenes*:

- **I- Streptococcal sore throat** or **follicular tonsillitis.**
- II- Toxigenic diseases: **AS Scarlet fever:**
- **III Post streptococcal disease as Rheumatic fever**
-

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Acute rheumatic fever (ARF):

- This is the most serious complication of streptococcal throat infection since it may result in damage of the heart valves and muscle. The onset follows 3-4 weeks after throat infection with group A streptococci M types 1, 3, 5, 6, 18 and others.
- Rheumatic fever is a **common complication.**

- The most accepted theory for the pathogenesis of ARF is **an autoimmune disease**. Streptococci have M proteins immunologically similar to proteins present in the heart tissues (myosin and sarcolemmal membrane proteins), so antibodies produced against certain streptococcal M proteins can react with the heart (i.e. cross reactivity) causing damage to the heart valves.

- ARF is characterized by fever, migrating polyarthritis and carditis. Recurrence of rheumatic activity occurs due to repeated streptococcal infections and every attack adds to the cardiac damage.

Clinical diagnosis of rheumatic fever

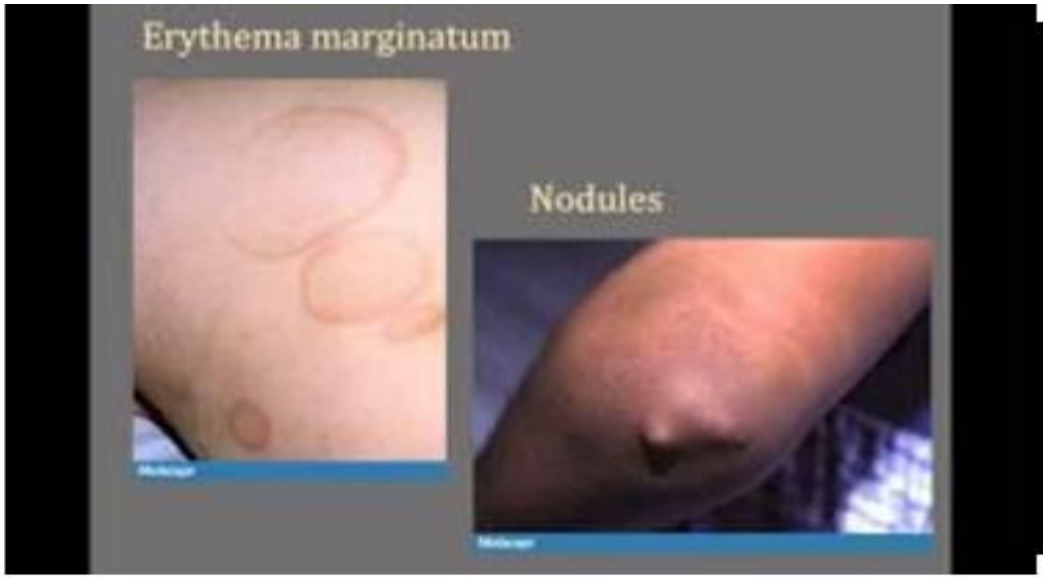
- **Major criteria for diagnosis of rheumatic fever(JONES Criteria)**
- J-----Arthritis in large joint

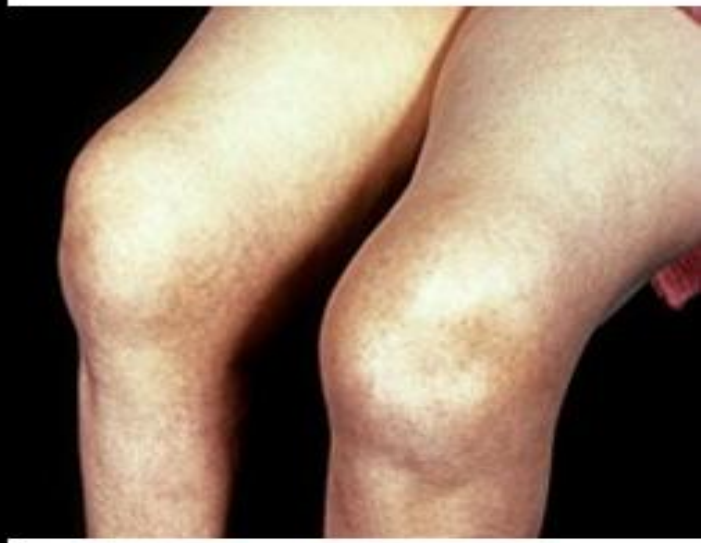
Carditis

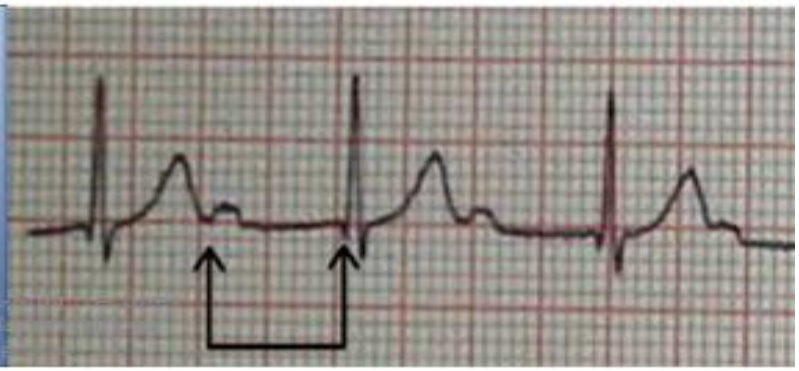
- N-------Subcutenous nodules
- E-------Erythema migrnatum

Minor criteria for diagnosis of rheumatic fever (

- 1-Arthralgia
- 2-Fever
- 3-Raised ESR/CRP
- 4-Prolonged PR interval in ECG
- 5-Leucocytosis







- The presence of 2 major manifestations

or 1 major and 2 minor manifestations

---→ indicates a high probability of an initial acute rheumatic fever illness in any risk population.

Diagnosis of post-streptococcal diseases:

- **I- Rheumatic fever:**

Evidence of preceding group A streptococcal infection:

- **Antistreptolysin O:**

ASO antibody titres are high soon after group A streptococcal infections. In patients suspected of having ARF, an elevated ASO titre (≥200 units) is an evidence of recent streptococcal infection.

- **C-reactive protein (CRP):**

It appears in the serum and is elevated in cases of active RF as well as in other degenerative and inflammatory conditions.

- **ESR**

Treatment and Chemoprophylaxis:

- Penicillin G is the drug of choice for treatment of streptococcal diseases.
- In penicillin allergic patient, erythromycin or azithromycin are used.
- Prompt treatment protects against ARF. Long acting penicillin (Benzathine Penicillin G) 1,200,000 U (Every 3-4 weeks injection until age 25) should be given as a chemoprophylaxis to children who had an attack of ARF to prevent recurrence.

Prevention

- Diagnosis and adequate antibiotic treatment of group A streptococcus Pyogenus is the primary means of preventing acute rheumatic fever.

- Secondary prevention of rheumatic fever requires antibiotic prophylaxis to reduce the likelihood of recurrent attacks in persons with a history of acute rheumatic fever.

Prevention

- -oral macrolides can be taken by individuals who are allergic to penicillin.
- -The spread of group A strep infection can be reduced by good hand hygiene, especially after coughing and sneezing and before preparing foods or eating, and respiratory etiquette (e.g., covering your cough or sneeze).

Addison disease

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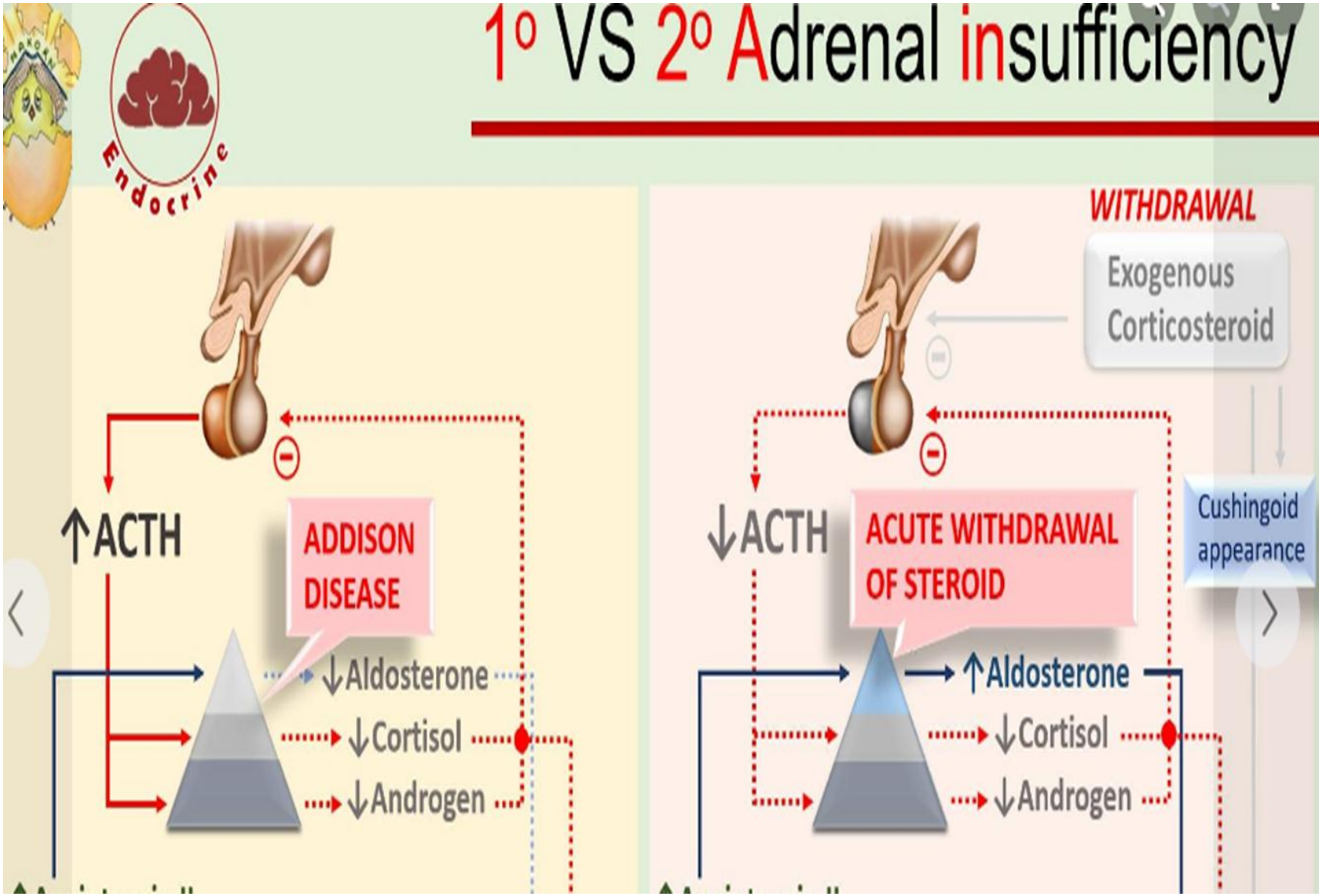
Etiology

This is caused by an inability of the adrenal cortices to produce adequate adrenocortical hormones. Adrenal insufficiency is classified as primary or secondary.

1º VS 2º Adrenal insufficiency



Addison disease

- Addison disease is an acquired primary adrenal insufficiency.
- A primary adrenal insufficiency is termed Addison disease when an autoimmune process causes the condition.
- It is a rare but potentially life-threatening emergency condition.
- It results from bilateral adrenal cortex destruction leading to decreased adrenocortical hormones, which may include cortisol, aldosterone, and androgens.

Click to add title

- Addison disease's insidious course, However, it can also present acutely.
- The most common cause of primary adrenal insufficiency is autoimmune adrenalitis (Addison disease), associated with increased levels of 21-hydroxylase antibodies

Primary Adrenal Insufficiency

- Any disease process which causes direct injury to the adrenal cortex can result in primary adrenal insufficiency (Addison disease).
- Autoimmune: Autoimmune destruction of the adrenal glands is the most common cause of Addison disease.
- Autoimmune destruction can be an isolated finding or autoimmune polyglandular endocrinopathies.

- Infections: This includes sepsis, tuberculosis, cytomegalovirus, HIV, disseminated fungal infections, and syphilis.
- HIV has emerged as the most important cause of adrenal insufficiency associated with adrenal necrosis.
- Adrenal Hemorrhage: Bilateral adrenal hemorrhages can be precipitated by trauma, meningococcemia, neoplastic processes.
- An Adrenal crisis due to meningococcemia is known as the Waterhouse-Friderichsen syndrome. This is more common in children and patients with asplenia.

- Infiltration: Adrenal infiltration occurs in hemochromatosis, amyloidosis, and metastases.
- Drugs: Certain drugs can cause adrenal insufficiency by blocking cortisol synthesis as Ketoconazole and Etomidate (short-acting intravenous anaesthetic agent).

Secondary Adrenal Insufficiency

- Secondary insufficiency occurs most commonly due to exogenous steroid administration resulting in the suppression of ACTH synthesis.
- It is a pituitary-dependent loss of ACTH secretion, which results in a reduction of glucocorticoid production. However, mineralocorticoid secretion, including aldosterone, remains at a relatively normal level.
- It is more common than primary insufficiency. Symptoms usually occur after discontinuation of the steroid.

- Primary = autoimmune-mediated intrinsic adrenal gland dysfunction (both cortisol and aldosterone deficiency).
- Secondary = chronic glucocorticoid administration resulting in hypothalamic-pituitary dysfunction (only cortisol deficiency).

Glucocorticoid deficiency contributes to

1-hypotension

2-severe insulin sensitivity

3-disturbances in carbohydrate, fat, and protein metabolism.

4-insufficient carbohydrate is formed from protein; hypoglycemia and decreased liver glycogen.

mineralocorticoids

- mineralocorticoids stimulate sodium reabsorption and potassium excretion, deficiency results in increased excretion of sodium and decreased excretion of potassium. A low serum concentration of sodium (hyponatremia) and a high concentration of potassium (hyperkalemia) result.
- severe dehydration, plasma hypertonicity, acidosis, decreased circulatory volume, hypotension, and, eventually, circulatory collapse.

- However, when adrenal insufficiency is caused by inadequate adrenocorticotropic hormone (ACTH) production (secondary adrenal insufficiency), electrolyte levels are often normal or only mildly deranged, and the circulatory problems are less severe.

Pathophysiology

- Adrenal failure in Addison disease results in decreased cortisol production initially followed by that of aldosterone, both of which will eventually result in an elevation of adrenocorticotropic (ACTH) and melanocyte-stimulating hormone (MSH) hormones due to the loss of negative feedback inhibition

- Addison disease usually manifests as an insidious and gradual onset of non-specific symptoms, often resulting in a delayed diagnosis.
- In many cases, the diagnosis is made only after the patient presents with an acute adrenal crisis (hypotension, hyponatremia, hyperkalemia, and hypoglycemia). This may be precipitated by a stressful illness or such triggering factors such as infection, trauma, surgery, vomiting, or diarrhea. Significant stress or illness can unmask cortisol and mineralocorticoid deficiency.

- Addison disease can occur at any age but most often presents during the second or third decades of life.
- The initial presentation includes fatigue, generalized weakness, weight loss, nausea, vomiting, abdominal pain, dizziness, tachycardia, and/or postural hypotension.

- Hyperpigmentation is characteristic and occurs in almost all patients. It is usually generalized and most prominent in sun-exposed and pressure areas.
- Hyperpigmentation is more pronounced over palmar creases, gingival mucosa, lips, elbows, posterior neck, breast areola, nipples, and nail beds.
- Hyperpigmentation is not seen in secondary insufficiency because ACTH and MSH levels are low. Multiple new nevi may develop.

Diagnosis of primary adrenal insufficiency

- Elevated ACTH (≥ 50 pg/mL [≥ 11 pmol/L])
- low cortisol (< 5 mcg/dL [< 138 nmol/L]) is diagnostic, particularly in patients who are severely stressed or in shock.

Diagnosis of secondary adrenal insufficiency

- Low ACTH (< 5 pg/mL [< 1.1 pmol/L]) and cortisol suggest secondary adrenal insufficiency.
- If ACTH and cortisol levels are borderline and adrenal insufficiency is clinically suspected—particularly in a patient who is about to undergo major surgery—ACTH stimulation test must be done.
- If time is too short (eg, emergency surgery), the patient should be given hydrocortisone empirically (eg, 100 mg IV or IM), and provocative testing is done subsequently