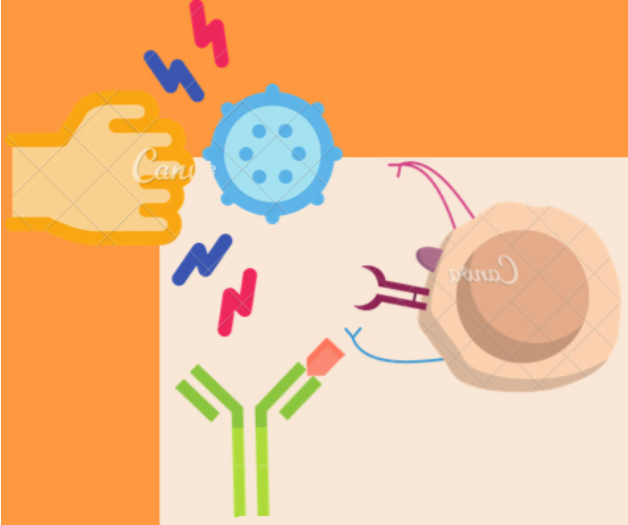

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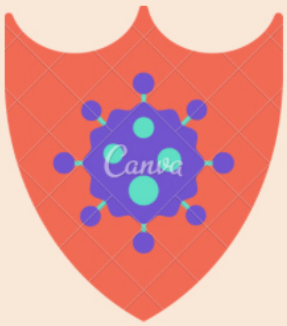
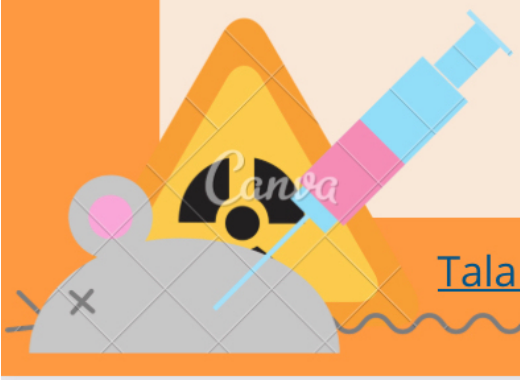


Immunology notes

First and second lectures

- Immune system in general
- self vs non-self
- Antegin & PAMPS & receptors
- Barriers of infection
- innat Immune system
- adaptive immune system



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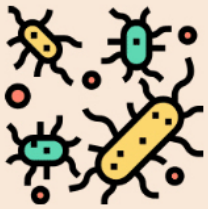
Immune system in general

Immune system: Cells in our bone marrow, thymus, and the lymphatic system of ducts and nodes, spleen, and blood that function to protect us either by isolation, disruption or ingestion of threats or combination of these actions
to maintain normal physiological state of the body .

threats either:

- Enter the body from outside like infectious organisms and toxic agents
- arise From potentially harmful changes occur within the body like malignant transformation



Immune system consist of three layers of defense

Barriers of infection

first line of defence

- mechanical like skin and mucus membrane
- chemical like acidic environment in stomach and microcidal molecules
- biologic like commensal microbes

innate immune system_

pluripotent stem cell

myeloid lineage

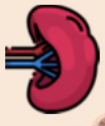
eosinophils
basophils
Neutrophils
monocyte / macrophage
dendritic cell
complement system

adaptive immune system_

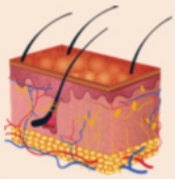
pluripotent stem cell

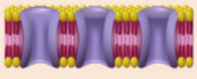
lymphoid lineage

B cell ➡️ Plasma cells
T cell
NK
dendritic cell



organs : primary organs thymus Bone marrow
secondary organs : spleen ,lymph node,mucosa-associated lymphoid tissues





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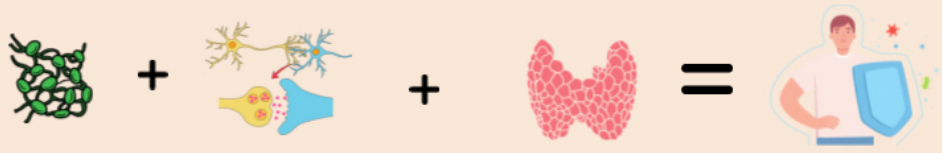
Defense mechanism

Immune system along with along the nervous system and the endocrine system one of the great communication systems of the body



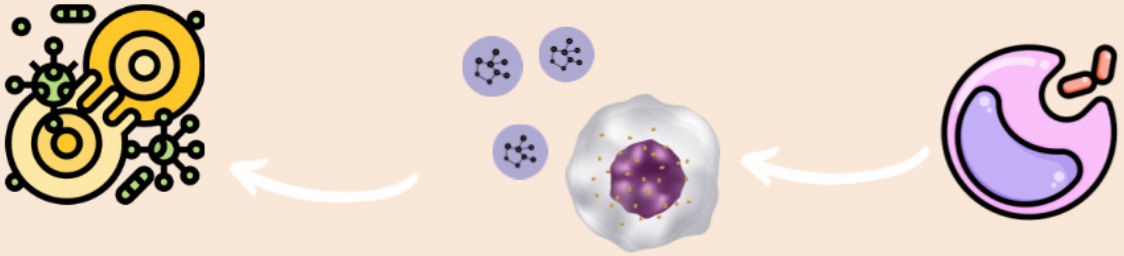
The immune system can eliminate the threats by isolationdisruption or ingestion or combination of these actions land these actions are done by several mechanisms :

Barrier of the body resist the initial entery of microbes to the body like skin ,mucus,acid in stomach,commensal microbes and peptide,enzymes

Invasive microbes may be walled off within structures like (granuloma) to restrict their ability to spread to other parts of the body

Phagocytise cells digest and capture cellular debris

Disruption of non self cells may occur through physical damage inflicted on their membranes or by inducing them to undergo apoptosis



Also some cells become abnormal in our body abandoned are eliminated by Natural killer cells . adaptive mech Include the antibodies secretion by plasma cell and Tcell can directly or indirectly attack microbes

Note : the complement system is a part of both adaptive and innate immune system

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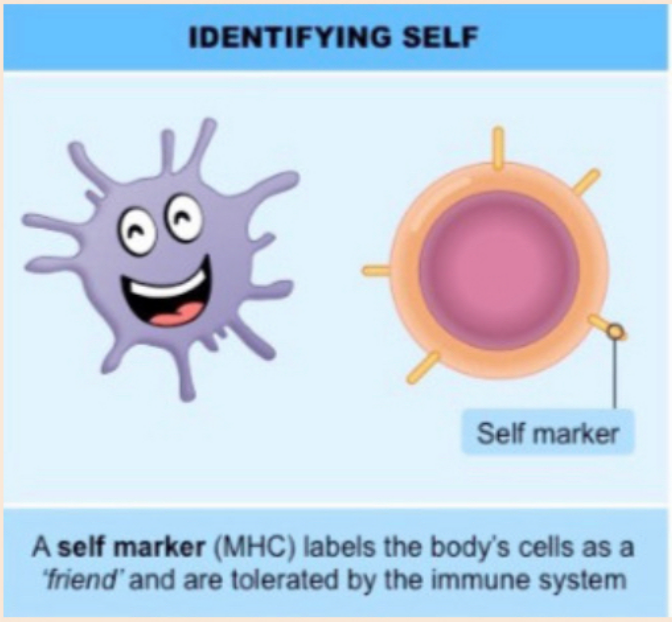
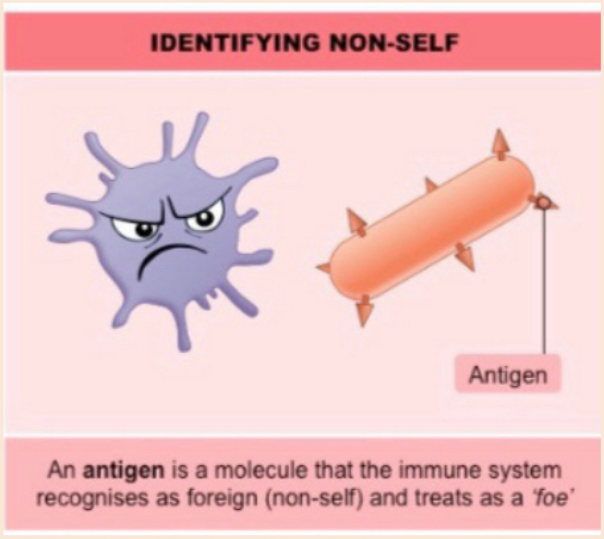
Self vs non-self concept

Recognition of Self:

Any molecules or cells that are related to my body and don't induce the immune response land the recognition of self is used by cells to determine wether an encountered molecules or cells has th appropriate structures to show that it's a part of the body MHC 1 molecules which is a glycoprotein present on the surface of all nucleated cells

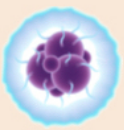


Recognition of Non-self :



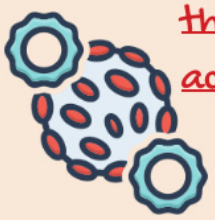
Foreign materials that tend to cause disturbance to my body Normal function and can induce the immune response in the body these are recognised by a specific receptor of cells of the immune system

absence of Self :



expression of MHC 1 molecules become less or may be lost altogether in some cells as a result of viral infection or becoming cancerous

NK cells can detect this reduced expression and kill those cells



Note: the MHC1 molecule is similar between family members and identical between twins .

so take into consideration in case of transplanted tissue may fail to express the appropriate MHC 1 and this leads to activate the immune response

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Antigen & PAMPS &Receptors

Antigen :

Any particle (organism , molecule or part of molecule) that is recognised By immune system , it may be simple or complex , proteins,CHO or synthetic in origin

Antigen :

self Antigen
any molecule or chemical group of an organism which acts as an antigen in inducing antibody formation in another organism

Non-self Antigen
that do not originate in your body are called non-self antigens which invade your body and make you sick.

each antigen has one or more specific epitope:

Epitope :thesmallest individually identifiable part of an antigen that is bound By a receptor.

mainly recognised by adaptive immune cells receptor

Antigen/epitope is Classified into 3 functional types :

immunogen

Whereas any antigen capable of* inducing immune response called immunogen

heptens

Very low molecular weight antigen need to conjugate to a carrier protein*
to induce the immune response, then the immune response (or immunogen) will direct against both the carrier and the hapten
Food additives, lipids, nucleic acids, small peptides and carbohydrates

Tolerogens

Antigen that induce tolerance*
Tolerance (antigen- insensitive) can develop later in life to antigens present frequently as cat fur or antigens that administered orally or exposed to in early life(immunetherapy to house dust mite)
.Tolerogens induce negative or diminished immune response

Each antigen contain one or more antigenic determinant that are* specific for binding to immune components; called epitopes
Epitopes are the smallest part of an antigen that is seen by antigen* .receptors on immune cells, or antibodies

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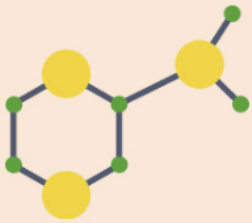
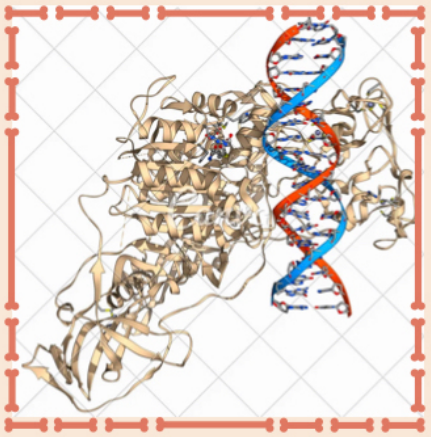
Factors increase the antigenicity (immunogenicity)

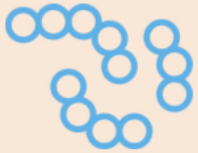
- More Foreignness more response:the molecule should be non self
- More Chemical complexity

complex proteins with numerous diverse epitopes are more likely to induce an immune response than are simple peptides that contain only one or few epitope

Proteins are most potent, polysaccarides are both antigenic or non antigenic whereas nucleic acids and lipids are non antigenic but can be antigenic when bind protein carriers



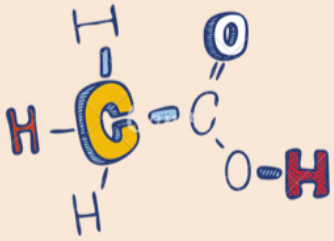


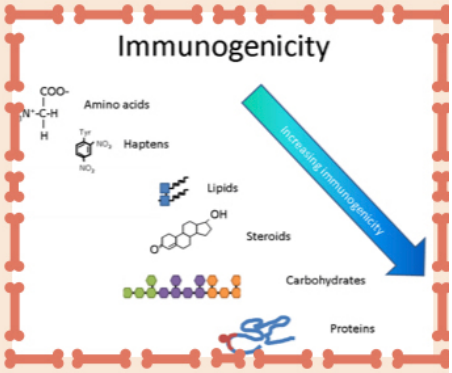


- High molecular weight antigen, whereas hapten have very low molecular weight

- Higher Biodegradable :

A protein immunogen to be enzymatic cleavable are generally good immunogen for example: L amino acid containing polypeptides are good immunogen while D amino acid containing polypeptide are poor immunogen because proteolytic enzymes aren't only able to cleavage L form of amino acid





- Mode of contact more response in Intra venous than subcutaneous or -S .Intramuscular injections

strongest response intravenous and fastest

- More different Host genetics like HLA type in organ transplant

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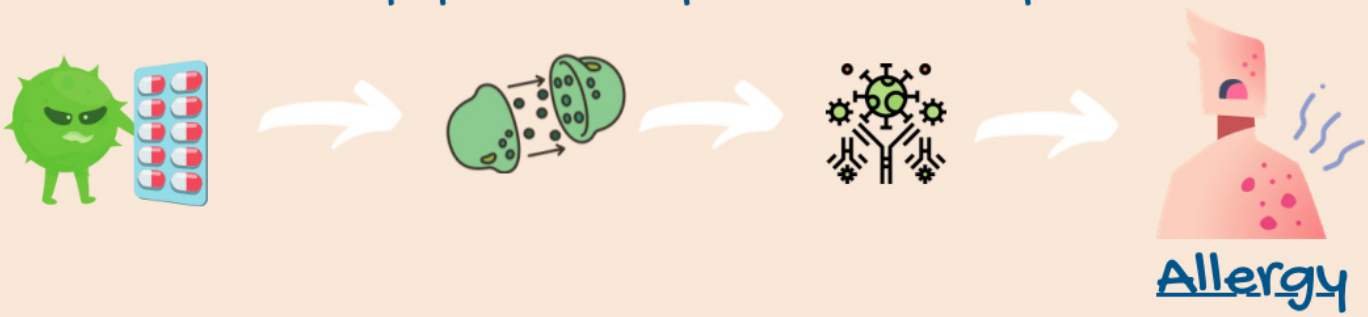
For example :Drugs as penicillin : has very low molecular weight so it considered as hepten, some cases the penicillin can bind to proteins in the body and become immunogen , and cause an allergic reaction in the body (penicillin hapten carrier complex)



Notes :

- A1) carbohydrates are only immunogenic. When : relatively complex polysaccharides structure
- or when associated with proteins carriers
- example :blood group antigen
- 2) lipids and nucleic acids mainly immunogenic when attach to protein carriers

Types of antigens

Auto-antigen * (self antigen)

Iso-antigen; found in genetically identical twins, like HLA antigens *

Allo-antigens; found in members of the same species; blood groups in * human

induce immune response in case lack it

Xeno-antigen; found in different species like animals and human

and is capable of induce immune response *

PAMPS :

Are molecular structures like sugar, proteins, lipids,nucleic acid or combination of these, which differs from one class of microbes to another (classes :bacteria viruses,arches ,fungi,protist) and these structures found only in microbes and not on hos cells , a Are recognised by innate immune receptor

Examples :

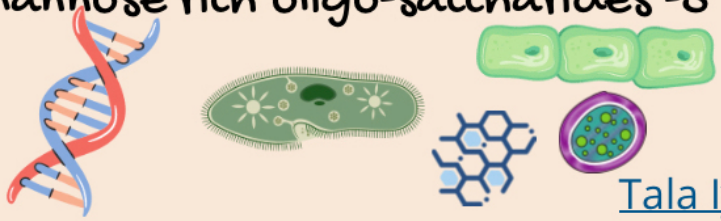
douple stranded RNA in viruses -1

DNA in bacteria -2

Lipo-polysaccharides or endotoxins in G- bacteria -3

Teichoic acid in g+ bacteria -4

Mannose rich oligo-saccharides -5



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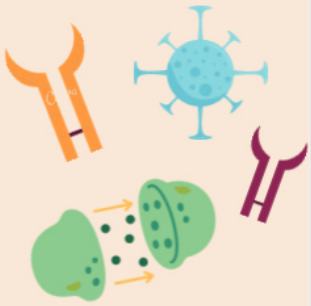
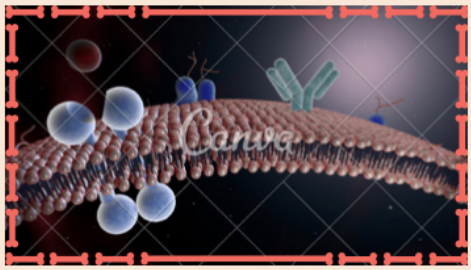
Notes :

The innate immune system also recognizes endogenous molecules that are-produced by or released from damaged and dying cells like damage in cell membrane .These substances are called damage-associated molecular patterns (DAMPS) , are as With cell components released during cell damage like intracellular proteins (heat shock proteins) and non proteins molecules like ATP acids

Receptors :



- Immune responses are initiated by the interaction between a ligand and receptor
- the complementary shapes of the ligand and its receptor are critical



Innate immune receptors :

patterns recognition receptor (PRRS):
The receptors of the innate immune system are fixed and encoded by inherited * (germline) genes present from early life
In Innate cells the receptors are present in nature, and are less in number (103) * and less variety than adaptive cells receptors
binds and recognise PAMPS only non selfmolecules

Types of PRRS:

bind to the target - directly through cell surface receptors binding to the antigen

- Toll-like receptor
- Scavenger receptor

Indirectly by binding to soluble molecules that engage the microbe (opsonins as complements) opsonin receptor:

- Fc receptor
- complement receptor

preformed Rceptors : include PRRS and Receptors of natural killer cells (killer inhibition receptor and killer activation receptor

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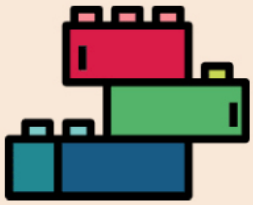
Adaptive immune receptors :

Somatically generated receptor whereas the genes encoding receptors of adaptive immunity are variable and * generated by somatic recombination of gene segments in the precursors of mature lymphocytes throughout the life
recognise and bind to epitope and are specific for each one
each cell produces only a single type of receptor able to recognise only a single structures

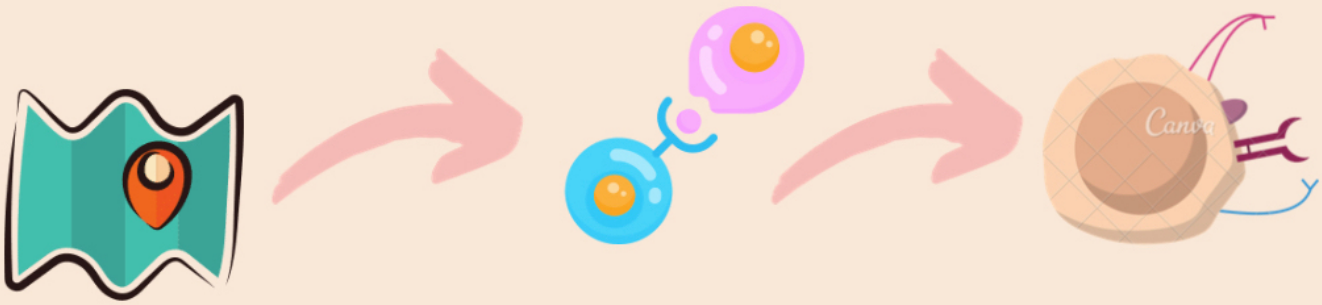
Types :

- T cell receptor
- B cell receptor



Notes :

Because each cell generates its receptor in such a random manner, some cells develop structures capable of recognise self molecules (attack self) other develope receptor capable of recognise non self , as a result T and B lymphocyte undergo a process of education to remove these bearing receptors that could potentially recognise and attack norm structures in the body



Expressed on B and T (BCR and TCR) cells of the adaptive immune system, each cell do random DNA rearrangement to develop

- unique receptor able to recognize single structure.
- Each human has its won receptors depending on what antigens invade his body
- Formed continuously through out life
- The total pool of receptors are capable of recognizing more than 1010 different structures.
- Some cells may develop receptors recognize self as a result T and B cells undergo a process of education to remove those expressing receptors against self.

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Innate immune receptors : directly binding

1. Toll-like receptor:

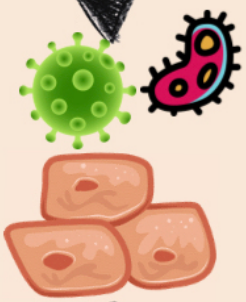
WHEN Triggered by binding to a PAMP ON an infectious organisms
TLRs mediate the generation of defensive responses that include :

- Transcriptional activation ,synthesis and secretion of cytokines from immune cells
- promote inflammation
- attraction of macrophages neutrophils,natural killer cells and dendritic cells

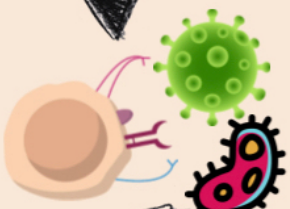
2) scavenger receptor:

WHEN Triggered by binding to a PAMP ON an infectious organisms :
1) internalisation of bacteria i.e engulfment
-
of bacteria
Also has another important function that it binds to LDL
LDL transport cholesterol from liver to the body tissues which cause the formation of fatty adipose and then cause heart disease , it also recognise the DAMPS

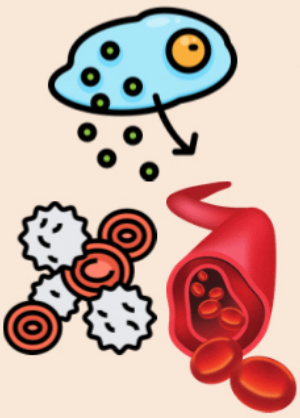
1) tissue Damaged due to cut in the skin



2) infectious organisms may inter the body through the wound



3)PAMPS on invaders are recognised by TLRs



4) TLRS induce the cell to secret cytokines which will recruit the other immune cells from blood vessels and surrounding tissue And all of this promotes the inflammation

Cytokines are immune chemical or immune mediators that :

- Helps in attraction of cells to site of infection
- induce signs of inflammation as high temperature

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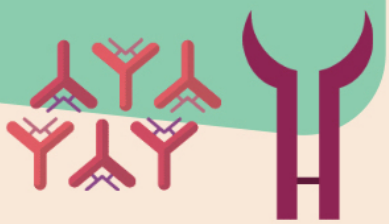
Innate immune receptors : indirectly binding

Opsonin receptors :

definition:

Opsonization of microbe (coating to make it obvious) an immune process which uses opsonins to tag foreign pathogens for elimination by phagocytes

Act indirectly by binding to soluble molecules that engage the microbe(* opsonins as complements or antibodies). the receptors are called depending on opsonin that bind as; antibody receptor or complement .receptors.



Note : opsonisation either by binding of Receptor with :

- antibody antigen complex
- antibody antigen complement complex
- complement antigen complex

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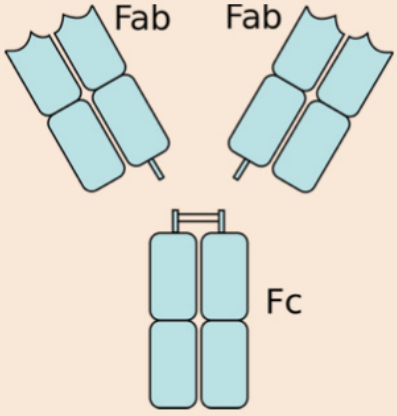
1) FC receptor (antibody receptor):

Immunoglobulins are classified as IgA ,IgD ,IgE,IgG,IgM. epitopes binds immunoglobulin on paratopes (antigen binding site)



Tail portion of the antibody is called Fc prtion where it binds to the Receptor and the receptor is named according to this portion

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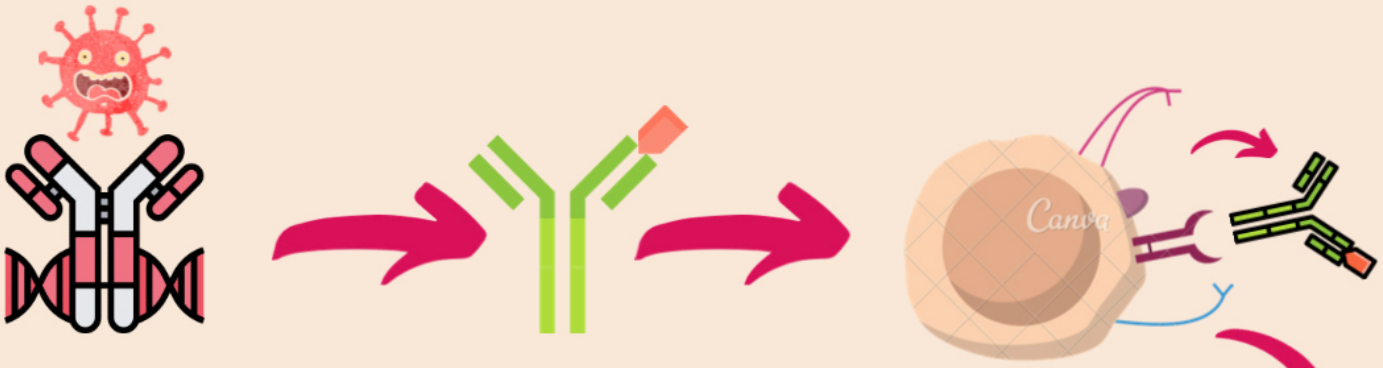
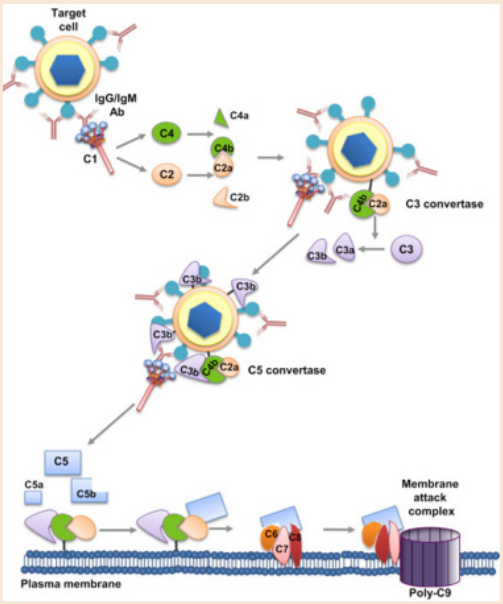
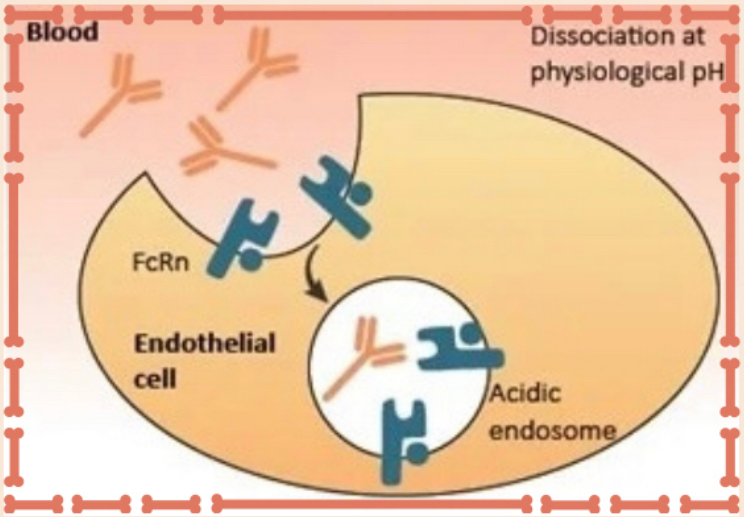
• Mechanism:



1. Epitope binds the antibody and triggers a conformational change in the tail (fc portion)

2. Fc receptor expressed on the surface of phagocytise cells phagocytes recognise and bind the antibody which lead to phagocytosis to the epitope-antibody-FCR complex





• exceptions For FC receptor

• IgM :

IgM binds to antigen then a complement molecule with FC receptor bind the Fc portion of IgM then the complex stimulates complement cascade

• IgE :

- the antigen close to the antibody :

antibody bind the antigen then bind the receptor like worm infection

- the antigen far away from the antibody
- the antibodybind the receptor then wait for the epitope then to start intracellular signaling like allergy reaction

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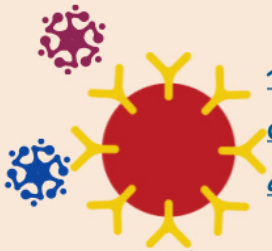
2) complement receptor :

Complex system: is a complex set of soluble that generates various reaction and attct immune cells to site o infection

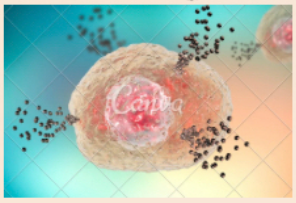
Examples: c4b, c3b, c3bi also has a role in causing sever allergy

- Mechanism: allergy



1)immune cells secret complement molecul as immune response

2) complement binds granular cells receptor



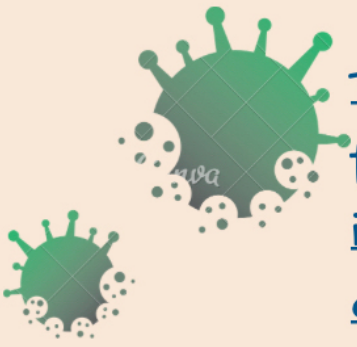
3) granular cells secret excessive histamine and heparin which inDuce the allergy

- Mechanism: phagocytosis

1)immune cells secret complement molecul as immune response

2) complement molecules bind to the microbial surface (tagging)

3) complement receptor in phagocytic cells recognise and bind the complex



Then the receptor facilitate The ingestion and internal degredation of the tagged microbes

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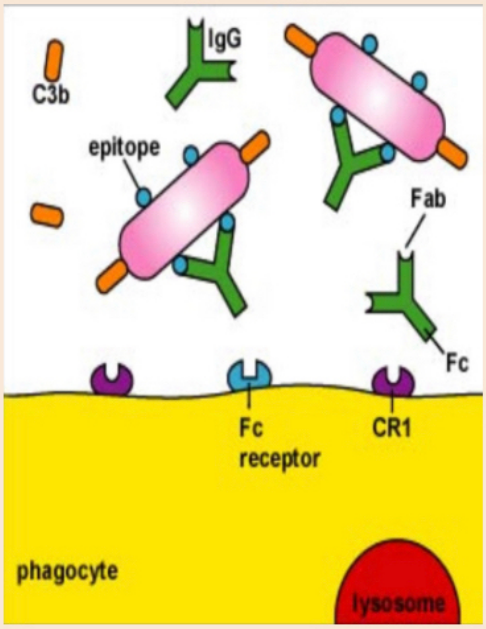
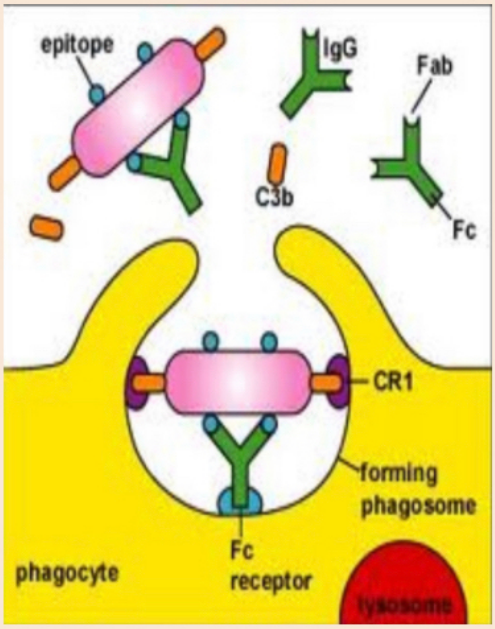
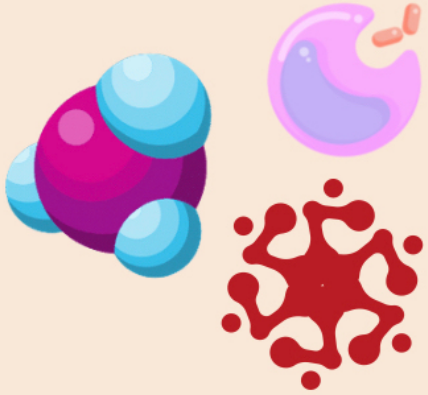
opsonin :





Notes :

- opsonisation by fibronectin and C-reactive proteins or by Cytokine



Some PAMPS and PRRS interactions :

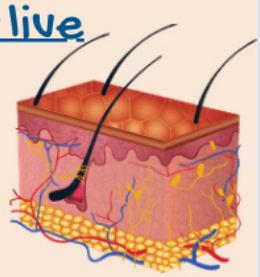
PAMP	PRR	Biological Consequence of Interaction
Microbial cell wall components	Complement	Opsonization; Complement activation
Mannose-containing carbohydrates	Mannose-binding protein	Opsonization; Complement activation
Polyanions	Scavenger receptors	Phagocytosis
Lipoproteins of Gram + bacteria Yeast cell wall components	TLR-2 (Toll-like receptor 2)	Macrophage activation; Secretion of inflammatory cytokines

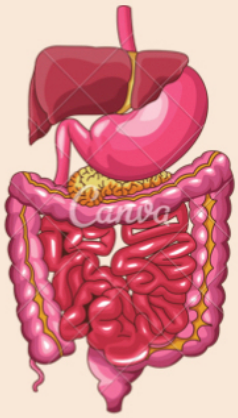
Barrier of infection:first line of defense

first line of defence

- mechanical like skin and mucus membrane
- chemical like acidic environment in stomach and microcidal molecules
- biologic like commensal microbes

1) skin :in the epidermis in stratum corneum contain many keratin proteins which is a hydrophobic proteins thus it maintains water molecules inside and keep the oute surface dry so the microbes can't live there



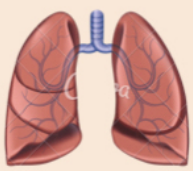


2) stomach acid :stomach has very few bacteria because of its acidic enviroment , while colon and intestin have more basic environment .. thus the
acidic environment of the stomach prevents
the colonization of the intestine .

3)microcidal molecule: act to inhibitor kill mirobe that are attempting to colonise like peptide and enzymes

1) defensins: peptides secreted by various cells types found in the skin , able to inhibit the microbial growth by direct action on the microbes like damaging their membrane and causing lysis

2) surfactants: complex array of proteins and lipids has a role in the innate immune system



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Classifications of immune cells :

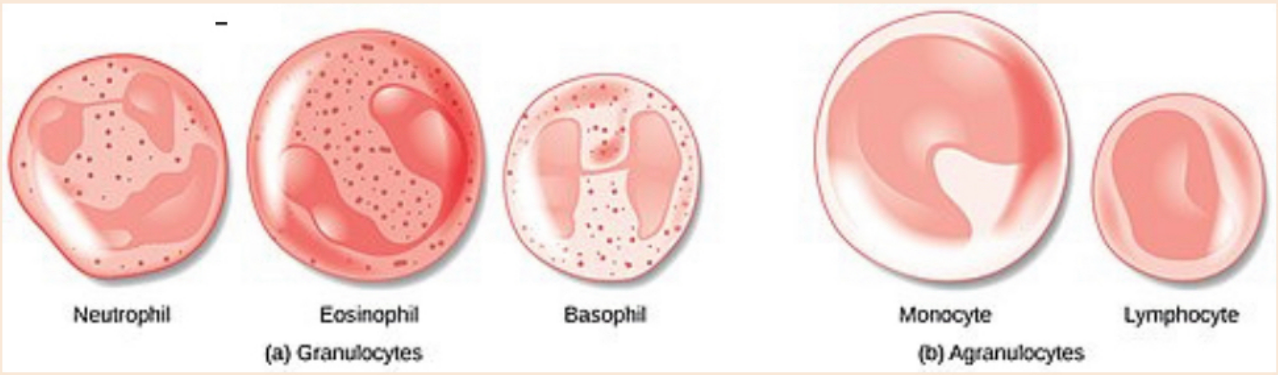
multi-potent /hematopoietic stem cells

myeloid lineage

- eosinophils (granular)
- basophils (granular)
- neutrophils (granular)
- monocytes (macrophages and dendritic cells) (a granular)

lymphoid lineage

- T&B lymphocytes (a granular)
- Nk cells (granular)



GRANULOCYTES VERSUS AGRANULOCYTES

GRANULOCYTES	AGRANULOCYTES
Large cytoplasmic granules	Small indistinct granules, or none
Many lobed nucleus	Nucleus with an indentation or one lobe
Eosinophils, basophils, neutrophils	Monocytes, lymphocytes
Innate general immunity	Specific and humeral immunity
All derived from myeloid stem cells	Some derived from lymphoid stem cells
No memory cells can be formed	Memory cells can be formed
Produce histamine	Doesn't produce histamine

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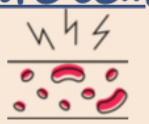
Innate immune system:

- Innate immunity

Innate immunity is the initial response to microbes that prevents, controls, or * eliminates infection, eliminate damaged cells and initiate the process of tissue .repair

Innate immunity stimulates adaptive immune responses *

the major types of responses of the innate immune system that protect against * .microbes are inflammation, innate cells, complements and cytokines



Innate immune cells:

Acording to the site of killing

- Phagocytic cells
  - neutrophils
  - mononuclear phagocytes (like monocytes and macrophages)
  - dendritic cells
- Non-Phagocytic cells extracellular killing
  - Eosinophils
  - basophils
  - NK cells

Notes :

Cells of the innate immune system some are in the blood and some are in the tissues

Phases of innate immune cells response

Antigen enter tissue cause inflammation which activate the local - innate cells (neutrophils, macrophages)

Movement of the cells from all body toward the site of infection - called chemotaxis, and mediated by molecules secreted from .local innate cells

Functional activities of the immune cells -

Recognition of the foreign antigen through cell receptors* Response*

Effector or activated cells-

Memory (only in adaptive response)

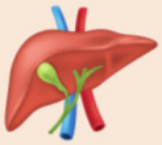
Tala Iyad

1) phagocytic cells:

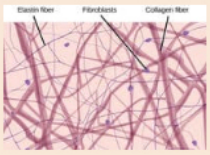
- Mononuclear phagocytes:

- • have rounded or kidney-shaped nuclei with finely granular cytoplasm
- • Mononuclear phagocyte's primary function is phagocytosis
- Originate in BM, and first to leave. When monocyte becomes settled in tissue they are called macrophages.
- Some mononuclear cells may differentiate to dentritic cells.
- some joint to form multi-nucleated giant cells, also help in acquired immune response

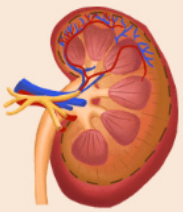
Names of mononuclear phagocytes:



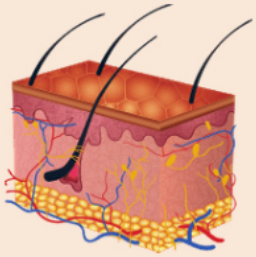
Kupffer cells



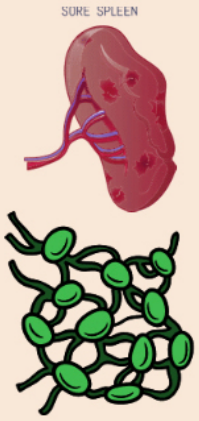
Histiocytes



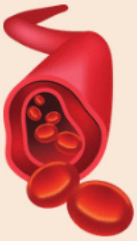
mesangial cells



Langerhans

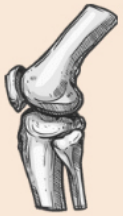


Macrophages



monocytes cells

microglial cells



easteoblast

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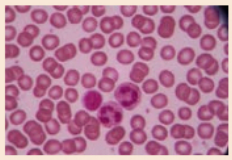
Neutrophils (polymorphs)

- Granulocytes contain nucleus segmented into 3-5 connected lobes, hence the name polymorphonuclear leukocyte and cytoplasmic granules.
- • Neutrophils (95% of granulocytes)
- respond early (the earliest).
- have 20 times as many receptors as macrophages. They have Fc receptor to IG6 and IGA as well as complement receptors.



Activation and function of macrophages & neutrophils

macrophages
• Functions in Natural and adaptive Immunity
1. Phagocytosis of foreign particles the same as neutrophils
— Scavenger receptors
— opsonin dependant phagocytosis; engulf antigen antibody complex as in viruses via receptor for opsonizing IgG and complement C3b, No receptors for IGM
2. Secretion of enzymes and oxidative metabolites if antigen is big, cause tissue damage (respiratory burst- oxygen radicals, NO, prostaglandins)
3. Cytokine production which recruit other inflammatory cells, 4. Antigen-Presentation to T cells,

Neutrophils
Intracellular killing by azurophil lysosomal granules and specific granules.
-Cytokine production which recruit other inflammatory cells

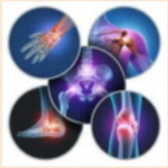
Ingestion in macrophages and neutrophils-1
Intracellular killing, mechanisms of lysosomal killing*
O2 dependent; the process called respiratory burst. O2 metabolites are; - hydrogen peroxide, singlet oxygen, hydroxyl radica, hypohalite (OCl or OI) and nitric oxide
O2 independent; using granules contents as proteases, hydrolases and - nucleases

activation of the adaptive immune sys
Mediated by mainly Macrophages* By either*
1. Indirect way; secretion of molecules that attract adaptive cells to site of - infection
2. .Direct way; present antigen to T cells -

Tala Iyad

Inflammation & phagocytosis & chemotaxis

1) inflammation:



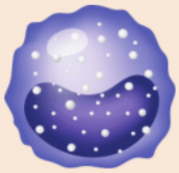
definition:

Inflammation is the process by which circulating leukocytes and plasma proteins* are brought into sites of infection in the tissues and are activated to destroy
and eliminate the offending agents.
Inflammation is also the major reaction to damaged or dead cells and to accumulations of abnormal substances in cells
.and tissues

1. It is the major way by which the innate immune system deals with infections and* tissue injury

Changes in inflammation

A- Increased blood supply to the area
B- expression of endothelial adhesion molecules on blood vessel lining C- Increase capillary permeability
D- Activation of local innate cells to secret chemotactic factors that recruit ,leukocytes

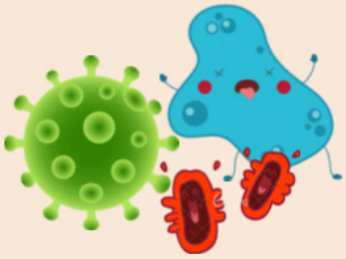


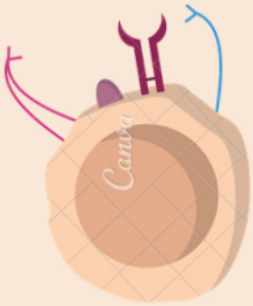
Cells of inflammation (innate immune system cells)*
Local macrophages and Mast cells that secret mediators help in- chemotaxis and vascular permeability

Cell chemotaxis:

Recruitment of phagocytes to site of infection*
Follow chemotactic factors gradient(complements and cytokines) produced by- resident macrophages and phospholipids and peptides of bacteria, they migrate by
Capture and rolling; enhance adhesion molecules on both endothelial* and innate immune cells
enhance the strength of binding of interacting molecules on both* endothelium and leucocytes that make the leukocyte flatten
Extravasation to site of infection. First neutrophils then macrophages.* activated T cells migrate in the same way

Tala Iyad





1) tissue Damaged due to cut in the skin

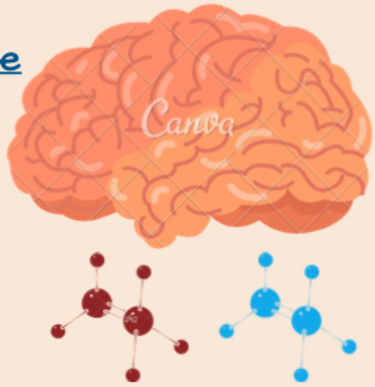
2) infectious organisms may inter the body through the wound

1) damaged cells release DAPs

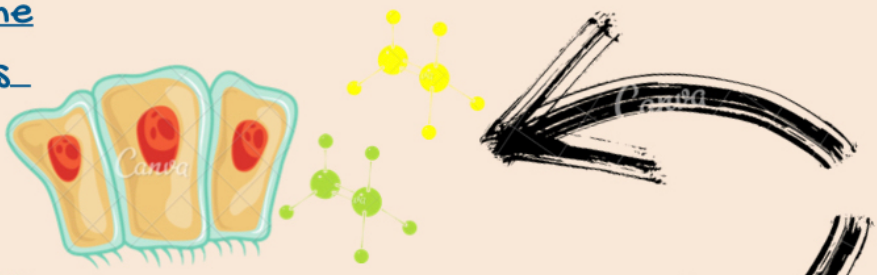
2) scavenger receptor of macrophage recognise and bind the DAMPS

3) toll like receptor recognise and bind the PAMPS of the microbes

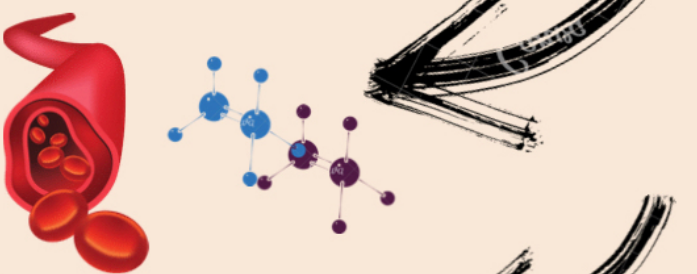
some travels to the brain and cause fever and heat increase



Some spread to the surrounding tissue to recruit the immune cells



Some go to the blood vessel to atract the immune cells



4)the phagocytes ingest the microbes and the toll like receptor cause the synthesis and secretion of cytokines and the cytokines spread into :

Macrophage trevel through the lymph vessel (during exchange with blood vessel) to the lymph node to present the antigen for the T cell and then T cell either become cytotoxic cell or activate B cells

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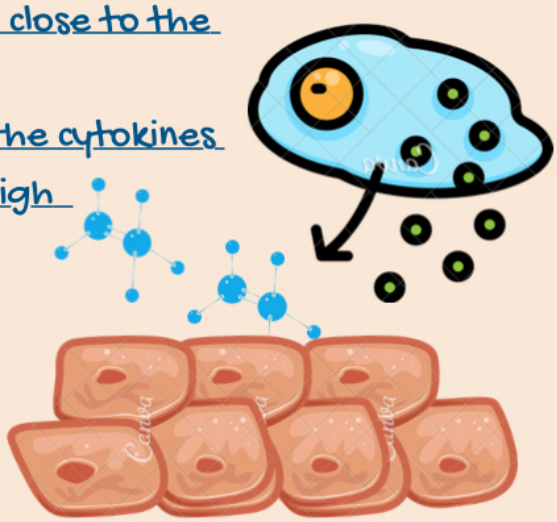
In the blood vessel:

A highly concentration of cytokines close to the blood vessel and a law concentration close to the blood vessel

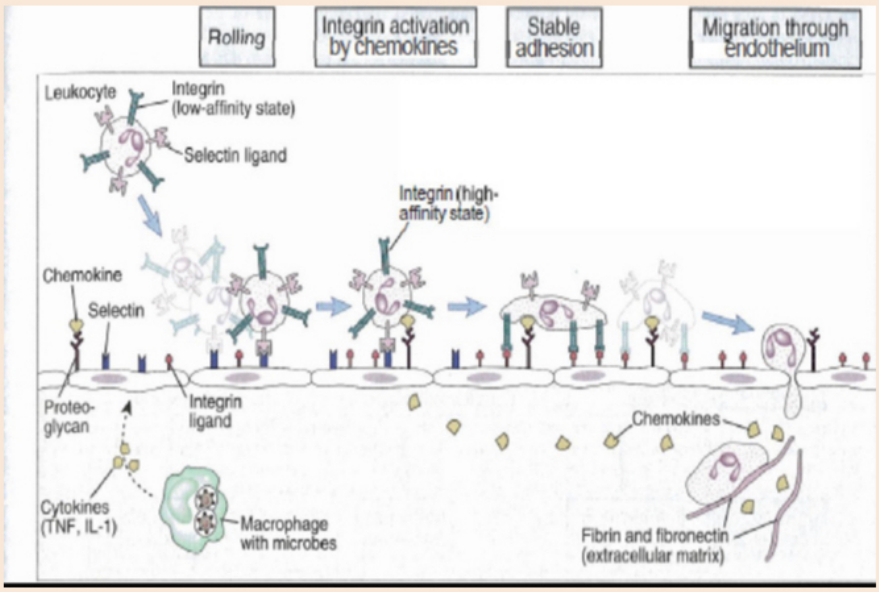
WBCs follow the cytokines from low to high

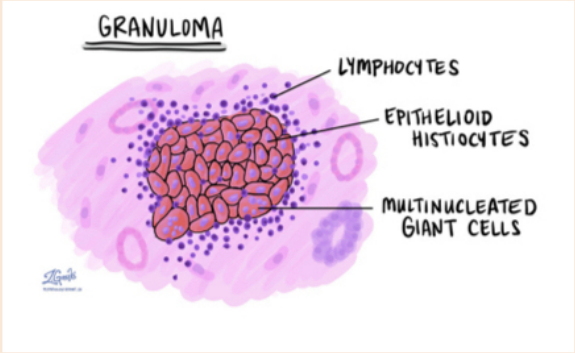


1) vasodilation to increase blood supply for the infected area, to recruit more immune cells

2) increase the permeability between endothelial cells so the WBCS can pass through it

3) expression of endothelial adhesion molecules on blood vessel lining (cell- cell junction proteins like cadherin & selectins)





some macrophages joint to form multi-nucleated giant cells in case of large antigen

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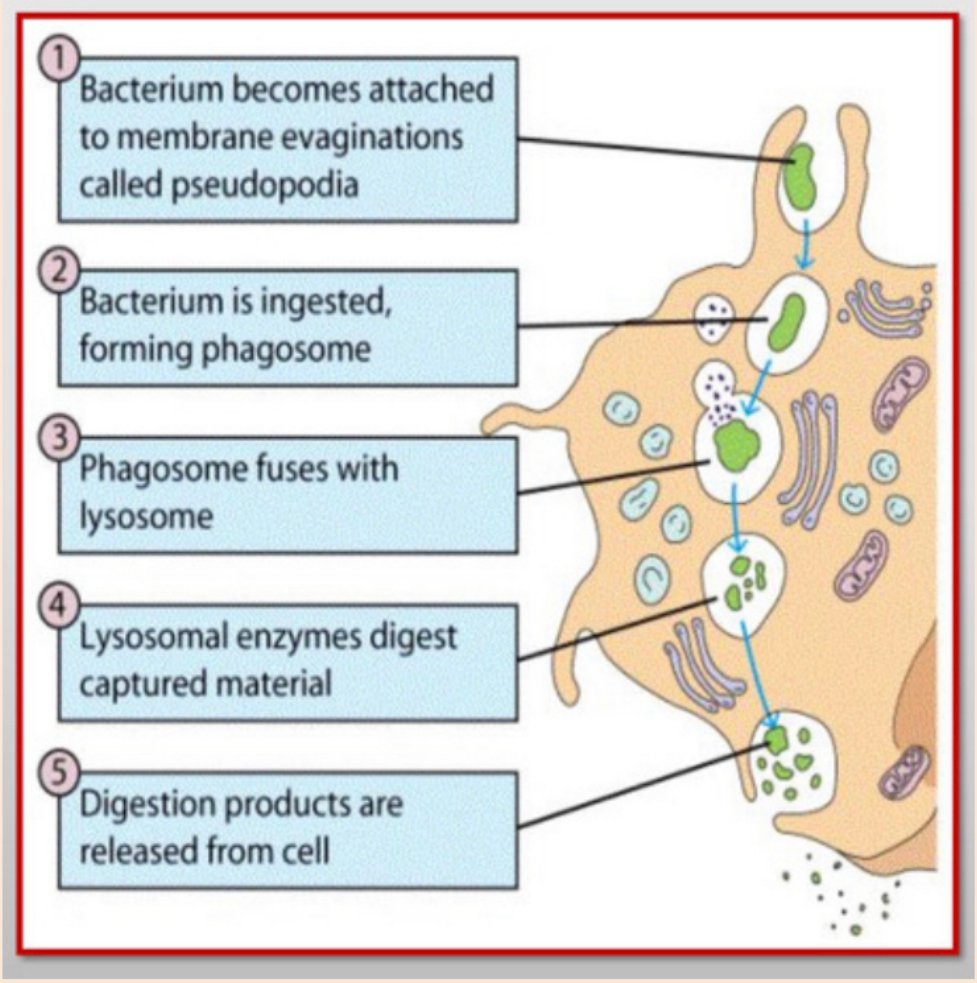
phagocytosis :

Phagocytosis is mediated by scavenger receptors, Fc Receptors (FcRs), and Complement Receptors (CRs). while toll like receptor induce the secretion of cytokines and promotes the inflammation and intracellular signalling to be prepared for phagocytosis



Signs of inflammation*

Swelling : as a result of fluid accumulation

Pain : cytokines induce nerve endings

Redness : increase blood supply

Loss of function result from pain that inhibits mobility or from severe swelling that prevents movement in the area.

Heat : brain and blood supply

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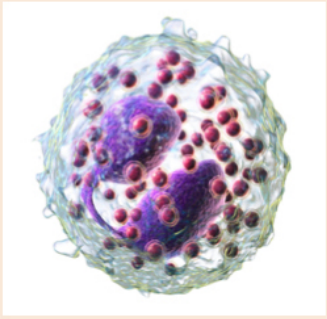
2) non phagocytise cells



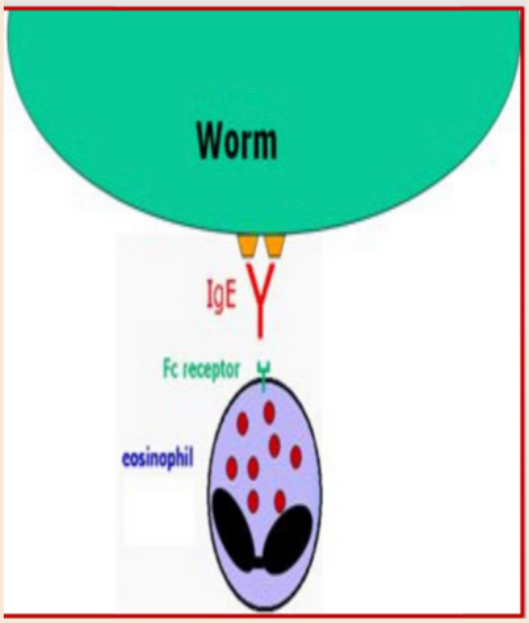
- **Eosinphils :**

1. granul cell
2. These cells are eosinophilic or "acid-loving" as shown by their affinity to coal tar dyes: Normally transparent, it is this affinity that causes them to appear brick-red after staining with eosin, a red dye,
3. non phagocytosis (extracellular killing)

Function and mechanisms of eosinophil

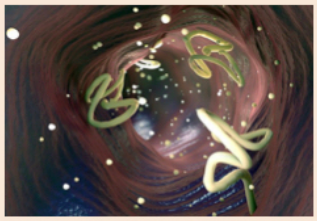
functions

1. • When eosinophils bind to IgE on the surface of a worm, the cell is triggered to degranulate. The contents of the granules cause damage to the worm.
2. • Other function is in allergy.
3. • There are many hydrolytic enzymes present in the granules responsible for the anti-helminthic activity. One component which is unique to the eosinophils - and highly toxic to worms - is a substance known as Major Basic Protein (MBP).

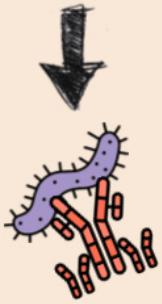


- **anti-helaminthic activity**

1) a worm infect the body and the body start t secret IgE

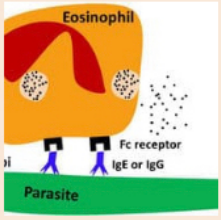


2) because the parasite worms are close to IgE , the IgE will bind to the worm (antigen) first



3) then the antibody binds to the FCR of IgE on eosinophils

4) the binding triggers the degranulation of cytoplasmic granules to secret contents that cause damage to the worm (extracellular killing)
and one of the component is major basic proteins



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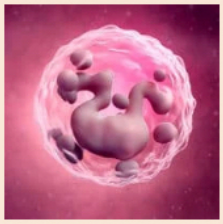
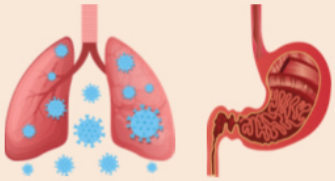
Basophils (mast cell)



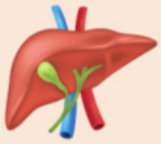
1. Granulocytes, have acidic proteoglycan, Lobed nucleus--more variable, large coarse granules stain blue with basic dye methylene blue.
2. • Mast cells is the cessile form whereas basophils is the circulating form I.e mast cell in tissue and basophils in blood

mast Cell (resident in tissue)

mucosal mast cell : present in the mucosa of the hollow organs like respiratory tract , stomach,intestine



ct Mast cells present in the connective tissue through out the body like liver connective tissue

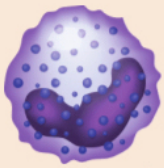


function of the mast cell / basophils

1. Mucosal mast cells, act in allergy and is T cell dependent to degranulate.
2. • Mast cells degranulation and release of the mediators the acidic granules, which help in Inflammatory cell response, allergy.

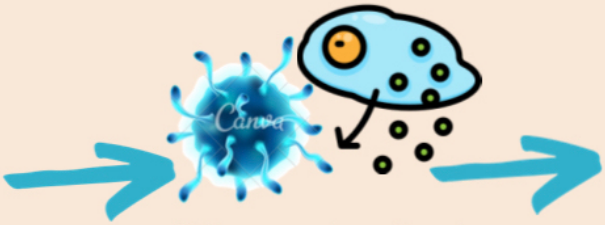
• 2 receptors on mast cells that mediate degranulation
• High affinity IGE receptor. IGE dependent;
• Receptors for anaphylatoxins. C3a and C5a. IGE in-dependent.

Allergy reaction :



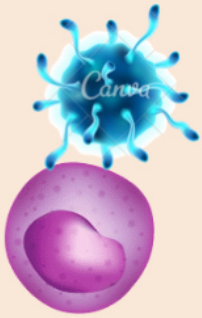
mucosal mast cell

macrophages



1) An antigen enters yourairways

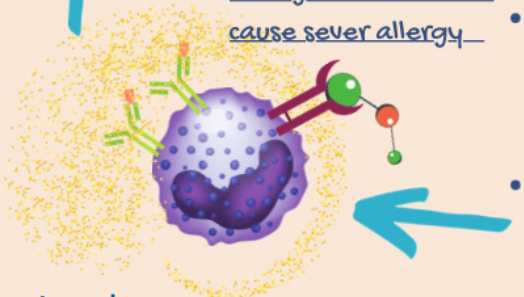
2) the macrophage ingest the antigen andgo through lymphatic vessels to preseNot the antigen to the Tcell in secondary organ



T cell activate B cells then B cells deffrentiate into plasma cells that secrete IgE

IgE independent Anaphylaxis reaction

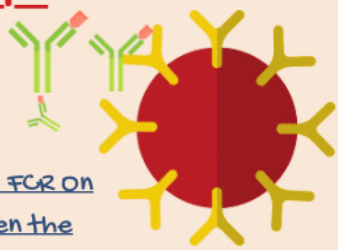
- Some complement called anaphylatoxins (c3a & c5a) binds with their receptor on mast cell thus cause increase in degranulation thus cause sever allergy



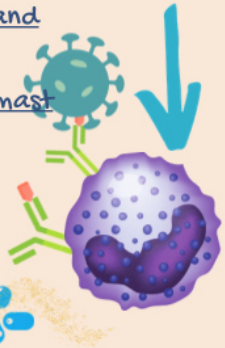
- Degranulation of granule produce histamine which induce the allergy reaction
- and the heparin increase the Permeability of the blood vessel

Allergy

IgE dependent



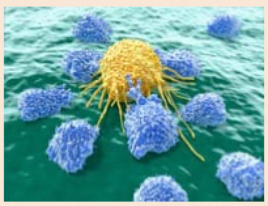
- IgE binds to FCR on mast cell then the antigen bind IgE and this induce the degranulation of mast cell



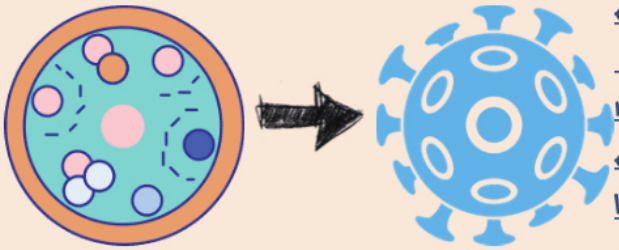
Tala Iyad

- **Natural killer cells:**

1. They are a type of lymphocyte critical to the innate immune system are defined as large granular lymphocytes (LGL) and constitute the third kind of cells differentiated from the common lymphoid progenitor-generating B and T lymphocytes.
2. 10 % of mononuclear (small nucleius) cells in blood and spleen and rare in lymphoid organs



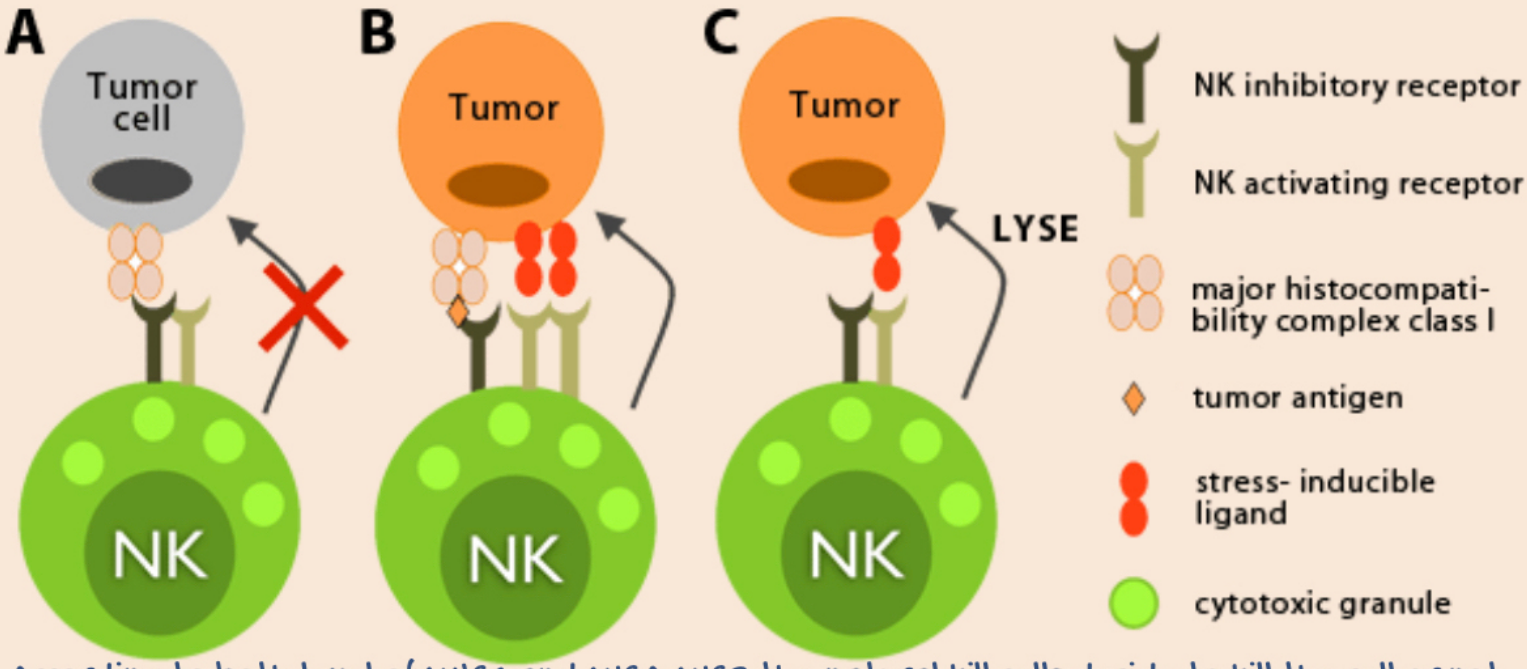
- **Natural killer cells receptors and functions :**



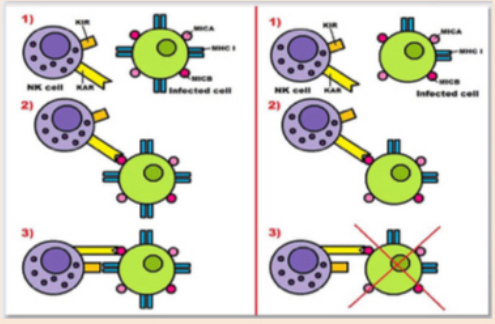
changes occur to the cancerous cells :
expression of antigen and thus antibodies bind to the cell
Secretion of cytokines (IF alpha andIF Beta) which recruit the natural killer cells
expression of stress molecules (MICA & MICB)
less expression of MHC 1 OR LACK IT
expression of FAS ligand

1) killer inhibition receptor And killer activation receptor :

- KARs :Receptors that recognise stress signals that expressed by infected or cancerous cells (MICA MICB)
- KIRs : examine the stressed cell whether they possess sufficient levels of MHC1 molecules



According to both level of MHC1 and MICA MICB the natural kill cells decide to kill the cell or not

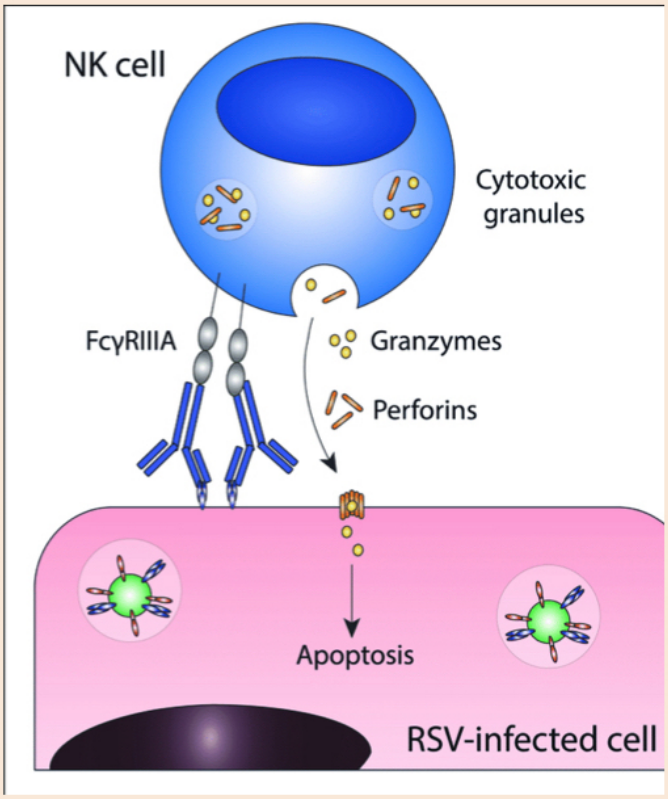


When a KAR binds to MICA and MICB molecules on the surface of an infected cell (or a tumor cell), a KIR examines the levels of MHC class I of this target cell. If the MHC class I levels are enough, killing of the cell doesn't proceed (left), but if they aren't, the killing signal proceeds and the cell is eliminated

Tala Iyad

- Killing action depends on the second type of receptor :

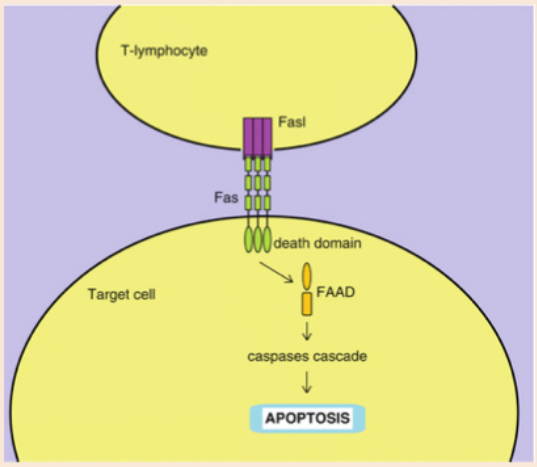
1) killing directly (FASL RECEPTOR) // (FC receptor)



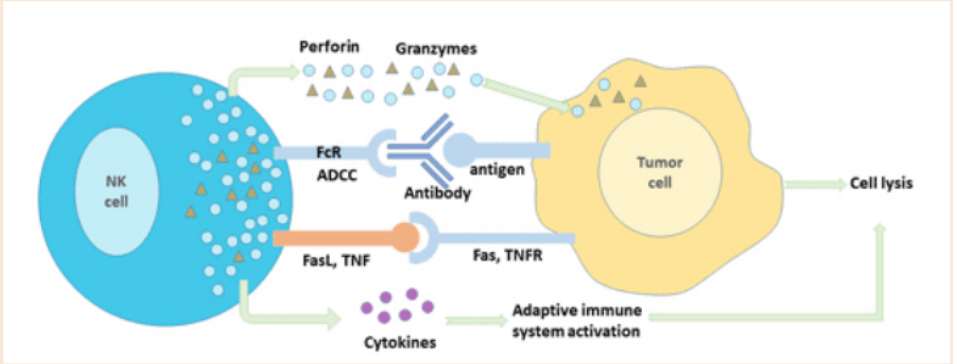
Opsonin receptors for antibodies; low affinity IG6 receptors (IG61 and IG63) (Called low affinity FCγR111 or CD16) and kill these coated cells, this is called antibody dependent cell mediated cyto-toxicity (ADCC)

Direct extracellular killing by secretion

- Perforins; making pores then osmotic lysis
- Granzymes, enzymes enter through perforin pores and activate caspases leading to cell death

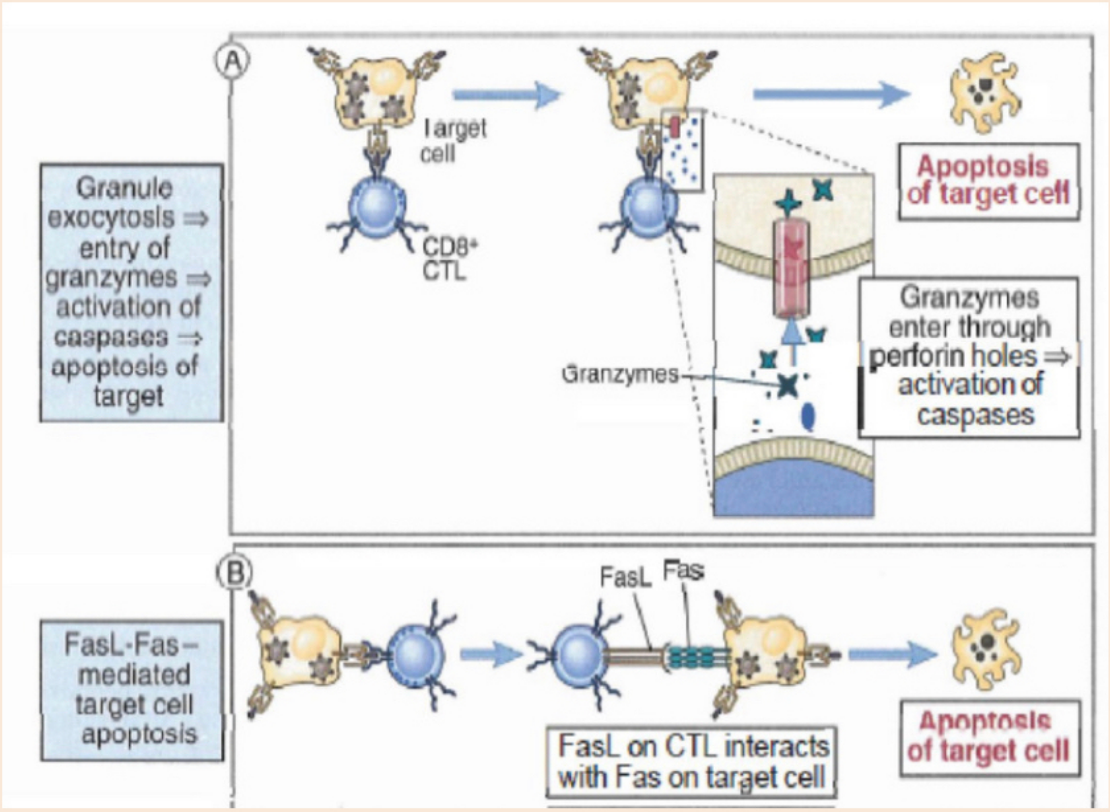


Expression fas ligands that bind fas on target cells and activation of caspases, this is a way in killing activated T cell (activation induced cell death)

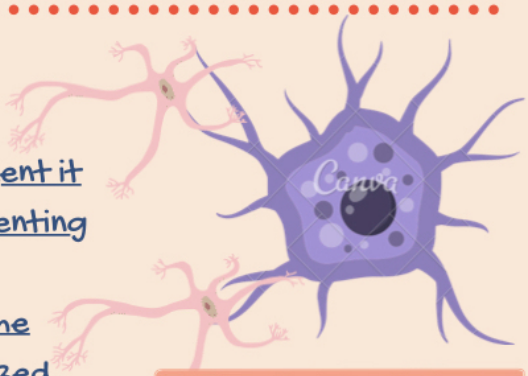


- Indirect killing . increase macrophage killing of phagocytic microbe by secreting IFN gamma Act very early against viruses and intracellular microbes and tumor cells or altered expression of surface MHC 1 molecule until T cells become activated.
- There activity increase by IFN alpha and beta (secreted by virally infected cells).
- activated cells secrete IFN gamma

Tala Iyad

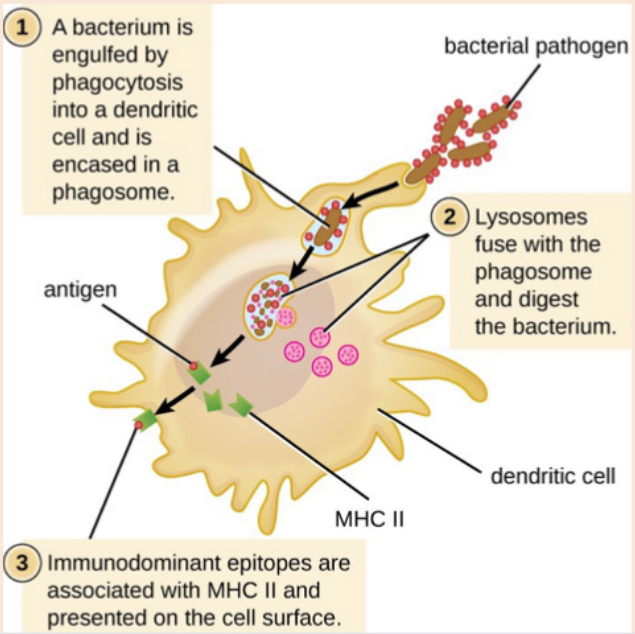


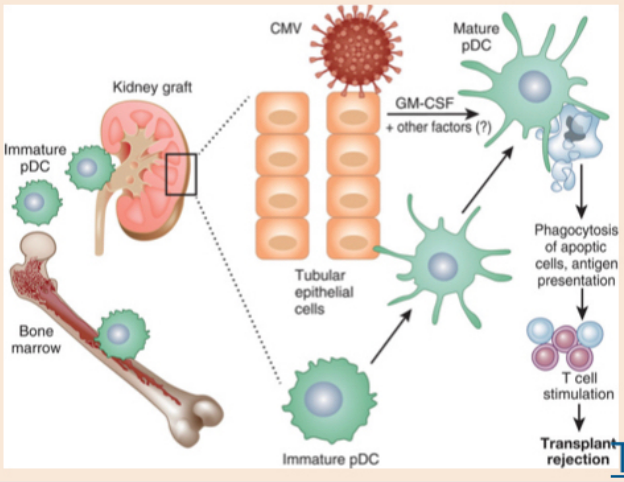
- **dendritic cells :**



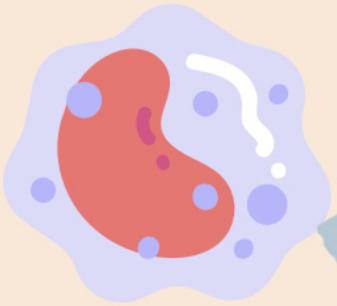
- Their main function is to phagocytose antigen material and present it on the surface to lymphocytes, thus functioning as antigen-presenting cells.
- • Dendritic cells are present in tissues that are in contact with the external environment, mainly the skin (where there is a specialized dendritic cell type called Langerhans cells) and the inner lining of the nose, lungs, stomach and intestines. They can also be found in an immature state in the blood.
- • Once activated, they migrate to the lymphoid tissues where they interact with T cells and B cells to initiate and shape the adaptive immune response. they grow branched projections for that they are called DC,

Myeloid DC, macrophage origin, common, diffuse localization, phagocytose antigen and activate T cells
• Lymphoid DC, lymphocyte origin, recruit cells to site of infection
• Follicular DC, mesenchymal origin, present in peripheral lymph nodes, do B cell activation.
• plasmacytoid DC, are early cellular responders to viral infection. They have potent antiviral activities.

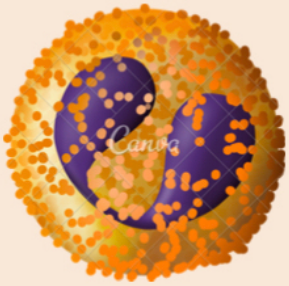




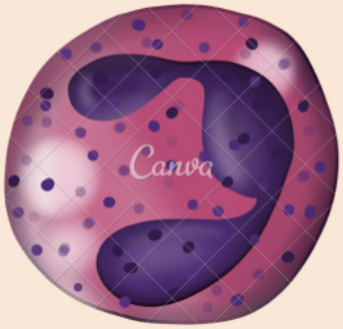
Cellular components of all immune system in ratio :

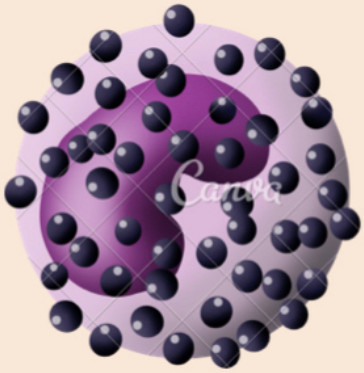


Lymphocytes: 30%
1) T cell : 60 %
2) B cell : 30%
3) NK cell : 10 % (large granular)
high N:C ratio for T and B cells
low N:C ratio for NK cell



innate immune cells: 70%
1)mono nuclear phagocytes
macrophages (5.3%)
2) granulocytes :
neutrophil : 62%
eosinophil : 2.3 %
basophils 0.4%





Tala Iyad

Adaptive immune system:

Organs of immune response :

primary organs :

1) Bone marrow

2) thymus

1) Bone Marrow:

functions :

- Where the immune cells originate
- leukocytes production
- B cell maturation
- hematopoiesis the formation of blood cellular components

Bone marrow components :

- Red marrow :

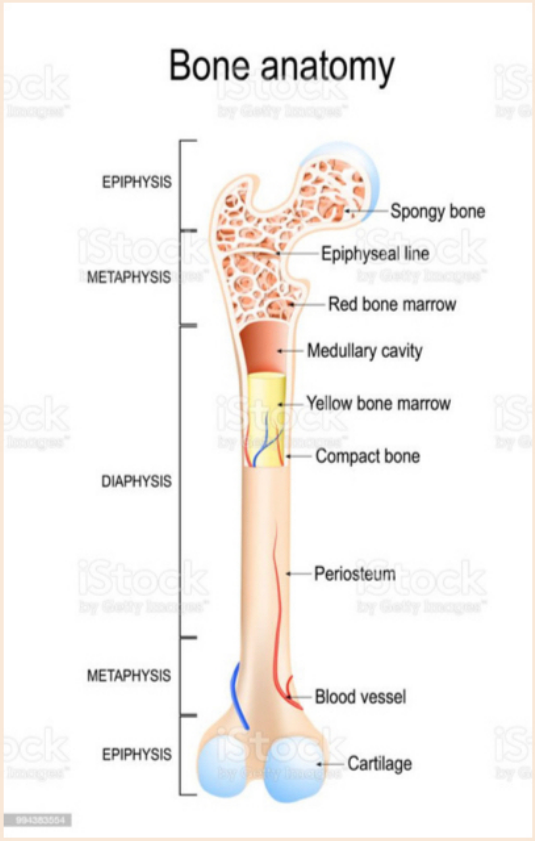
1)which consists mainly of hematopoietic tissue, Red blood cells, platelets, and most white blood cells arise in red marrow

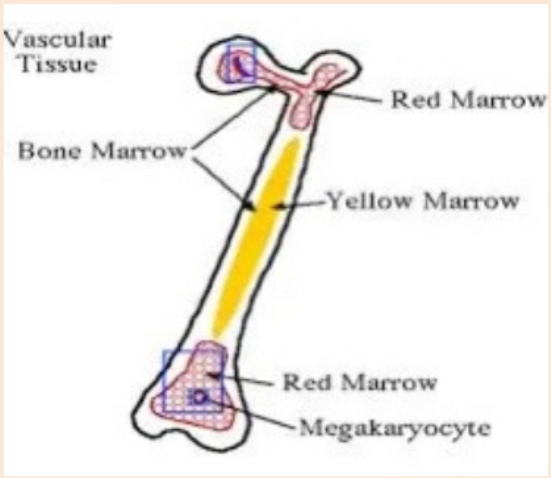
2)Red marrow is found mainly in the flat bones, such as the pelvis, sternum, cranium, ribs, vertebrae and scapulae, and at the epiphyseal ends of long bones such as the femur and humerus

- Stroma; any tissue not associated to blood production as fatty marrow, fibroblast, osteoclast and osteoblast.

Tala Iyad

Adaptive immune system:

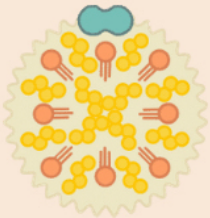




- Yellow marrow:

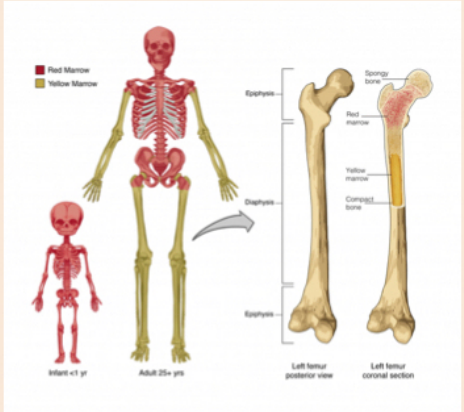
1) which is mainly made up of fat cells

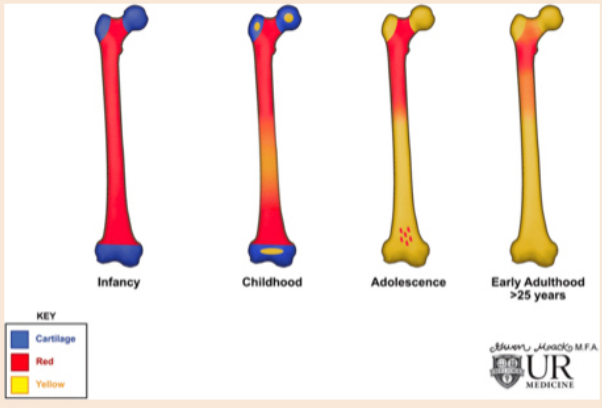
2) Yellow marrow is found in the hollow interior of the middle portion of long bones.



Red marrow vs yellow marrow

- At birth, all bone marrow is red. With age, more and more of it is converted to the yellow type; only around half of adult bone marrow is red.
- In cases of severe blood loss, the body can convert yellow marrow back to red marrow to increase blood cell production





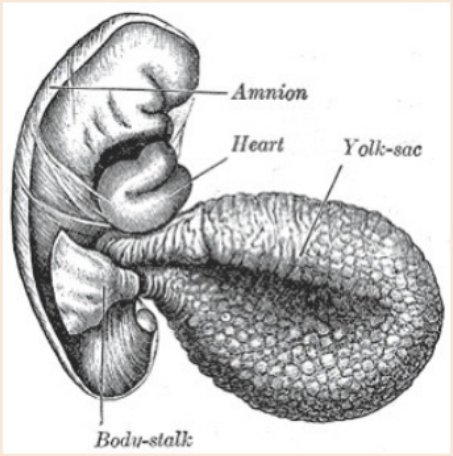
Tala Iyad

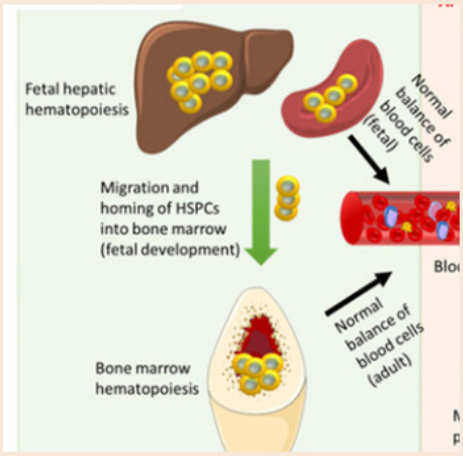
Adaptive immune system:

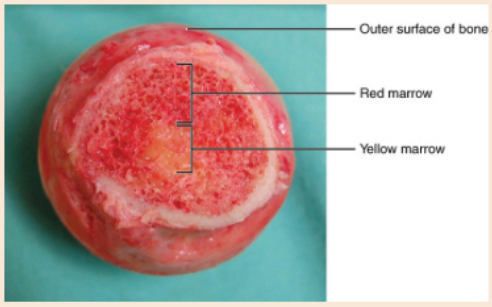
Hematopoiesis :

- the formation of blood cellular components .

- hematopoiesis start in childhood (YOLK SAC AND mesenchyme(orBgin of C.T), then liver and spleen and finally the bone marrow in puberty) and get maximum in adult age







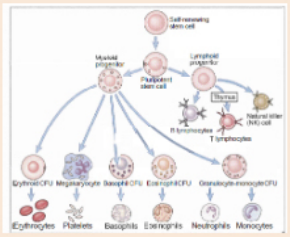
- In cases of excess demand liver and spleen help the BM (the extramedullaryhematopoiesis).

- Hematopoietic stem cells (HSCs) give rise to two kinds of multipotent progenitor cells, one that generates lymphoid and another that produces myeloid cells,
- •The common lymphoid progenitor gives rise to committed precursors of T cell, B cell
- •The common myeloid-megakaryocyte- erythroid progenitors give rise to committed precursors of the erythroid, megakaryocytic, granulocytic, and monocytic lineages,

Tala Iyad

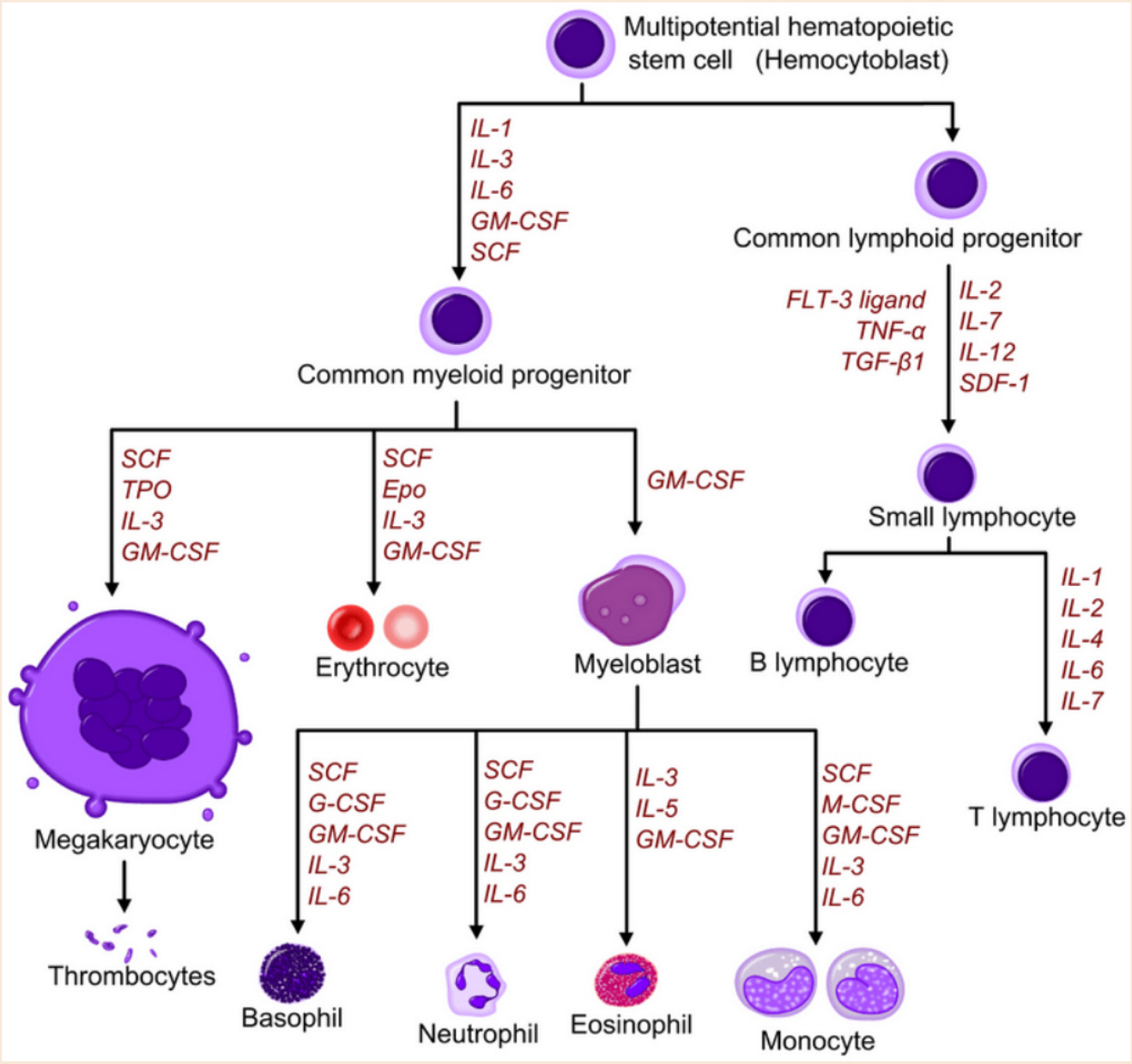
Adaptive immune system:

Hematopoiesis :



- Stem cells express 2 main proteins, CD34 and stem cell antigen-1 .

- Hematopoietic cytokines called Colony stimulating factors are the influencing factors for stem cell differentiation and maturation e.g; G-CSF, M-CSF and GM-CSF
-



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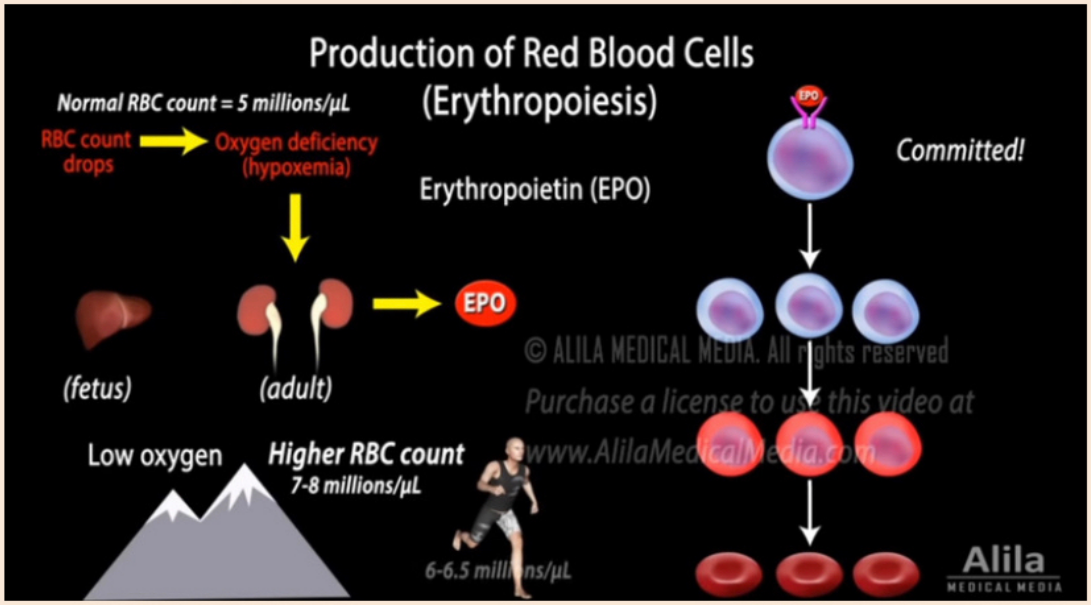
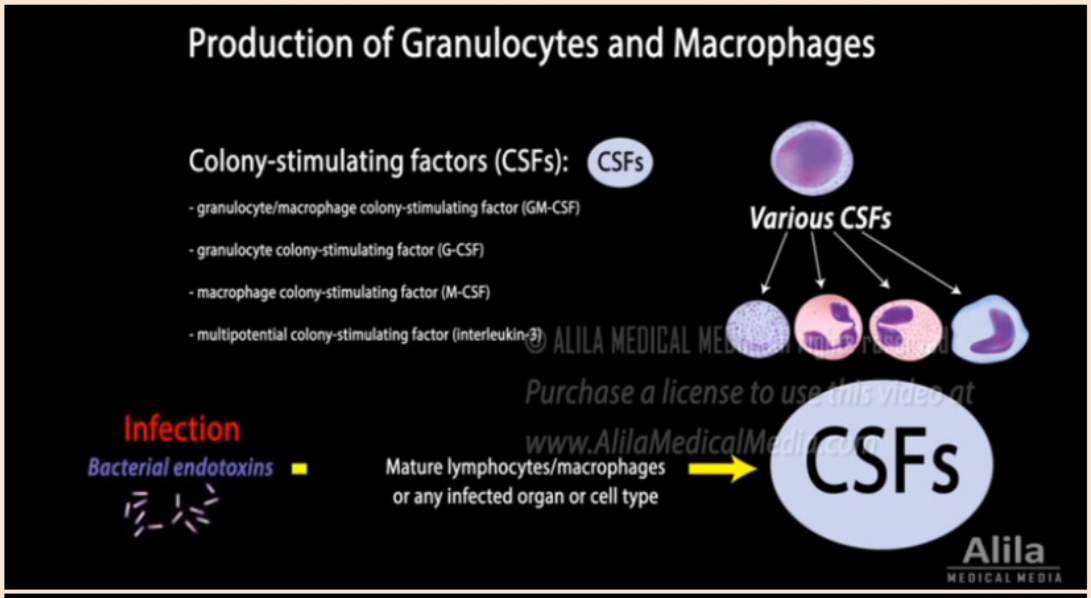
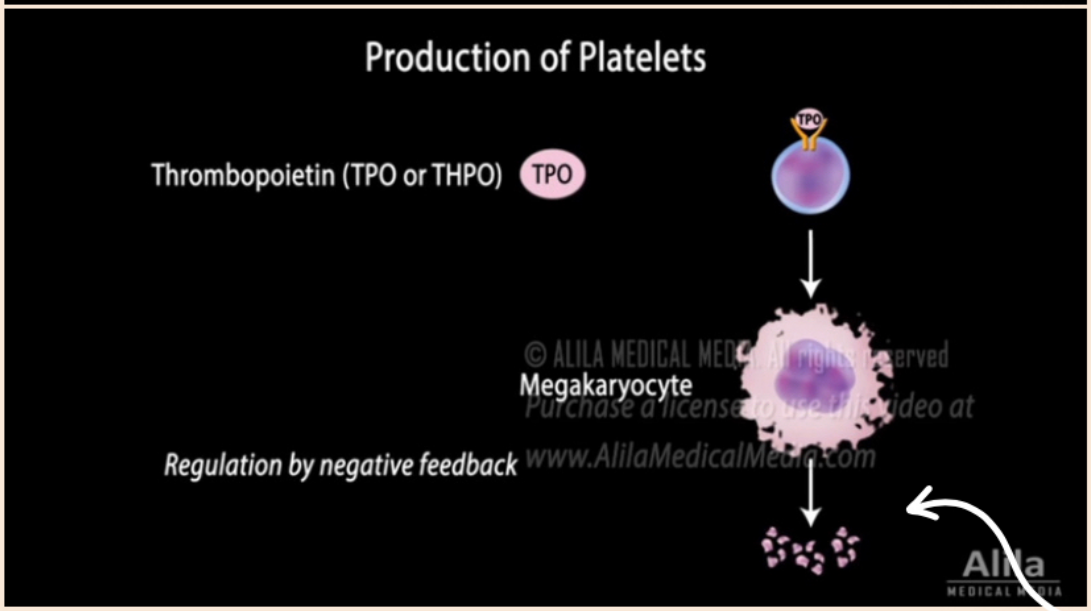
Adaptive immune system:

Hematopoiesis : maintain normal blood cells count







Cells bind to specific stimulus that produced in response to condition in the body and stimulate its differentiation into specific type as required

Platelets are anucleate cytoplasmic discs derived from megakaryocytes that circulate in the blood

Tala Iyad

Adaptive immune system:

Organs of immune response :

primary organs :

1) Bone marrow

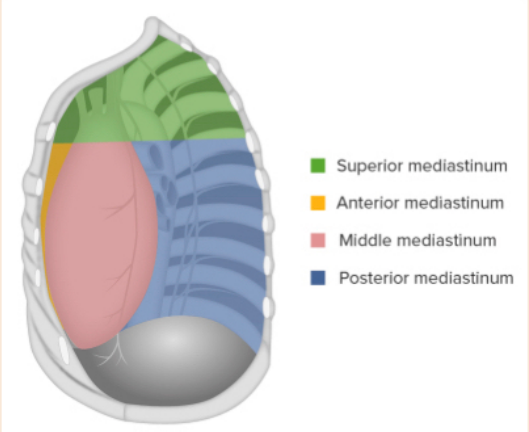
2) thymus

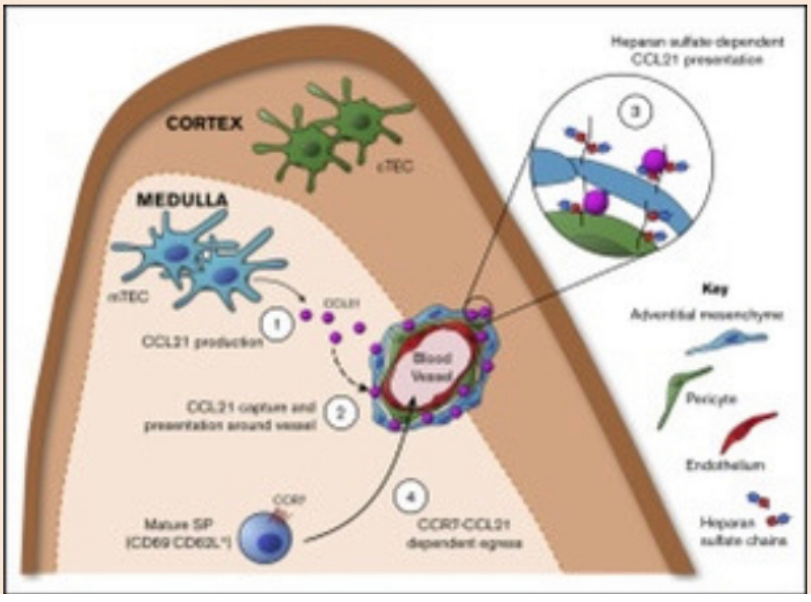
2) thymus :

functions :

- Where T cell defferetionation to mature
- T cellmaturation and formation of T cell antigen receptors

- The thymus gland is found in the thorax in the anterior mediastinum. It gradually enlarges during childhood but after puberty it undergoes a process of involution resulting in a reduction in the functioning mass of the gland. It continues to function throughout life, however.

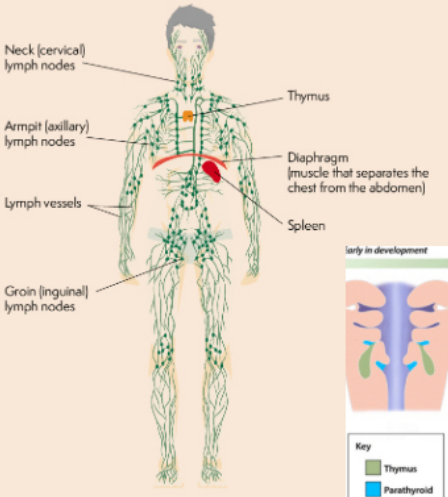


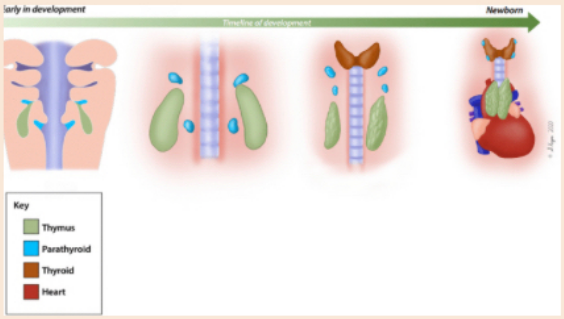


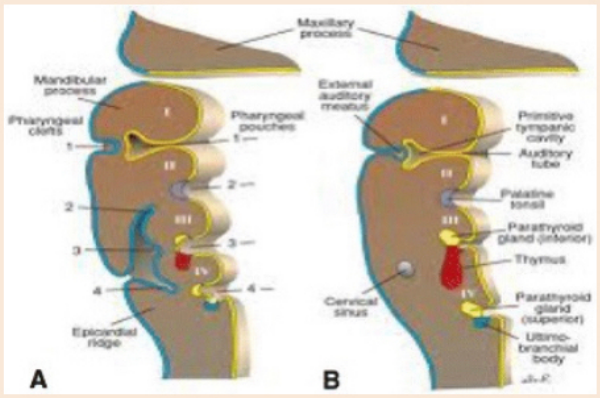
Tala Iyad

Adaptive immune system:

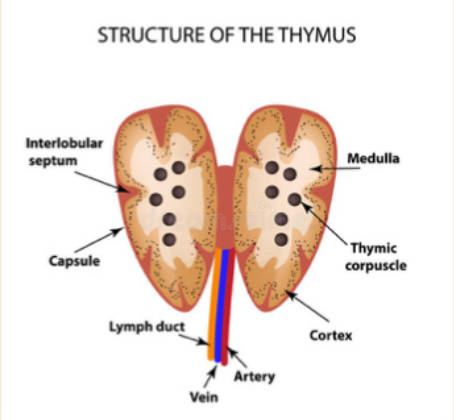
- The thymus has a rich vascular supply and efferent lymphatic but no afferent vessels .. that drain into mediastinal lymph nodes. The thymus is derived from invaginations of the ectoderm in the developing neck and chest of the embryo, forming structures called branchial clefts.

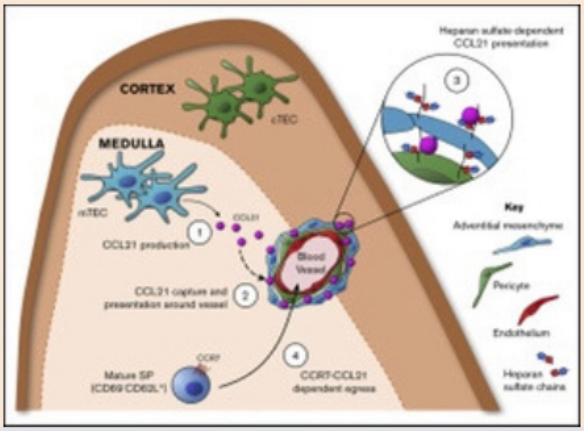






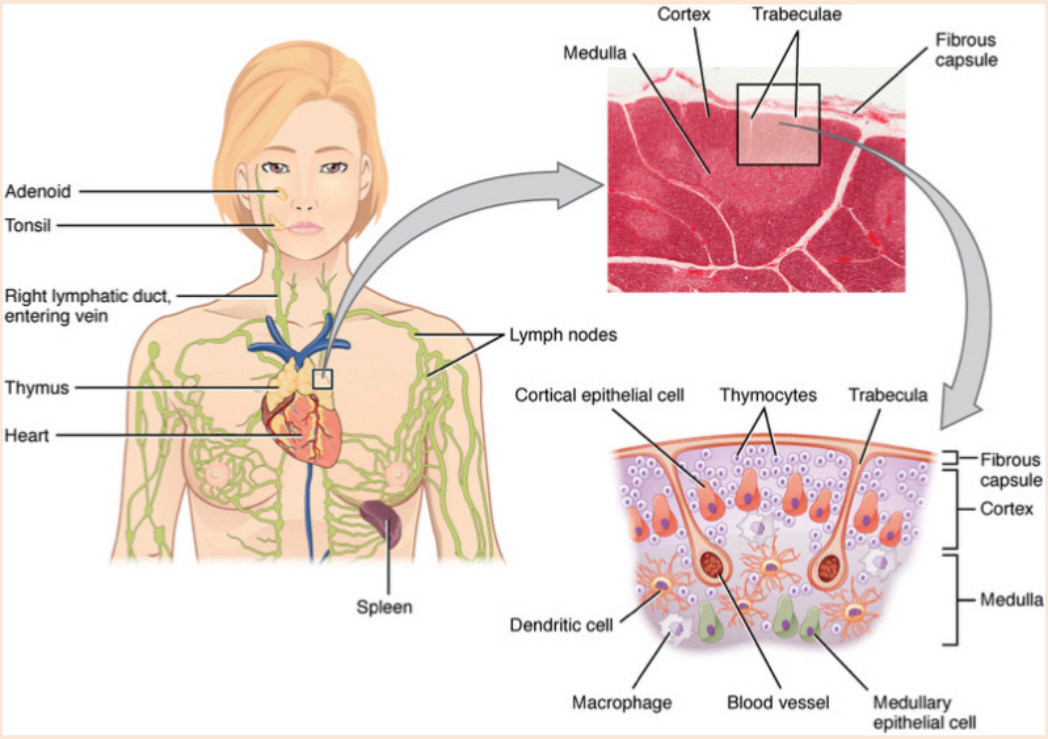
- Histology: The thymus gland is surrounded by a fibrous capsule, and arranged into an outer, more cellular, cortex and an inner, less cellular, medulla. Cells involved
- •The most immature T cells in the cortex. As thymocytes or T cells mature, they migrate toward the medulla, then to circulation
- •Epithelial cells
- •Macrophages and lymphoid dentritic cells



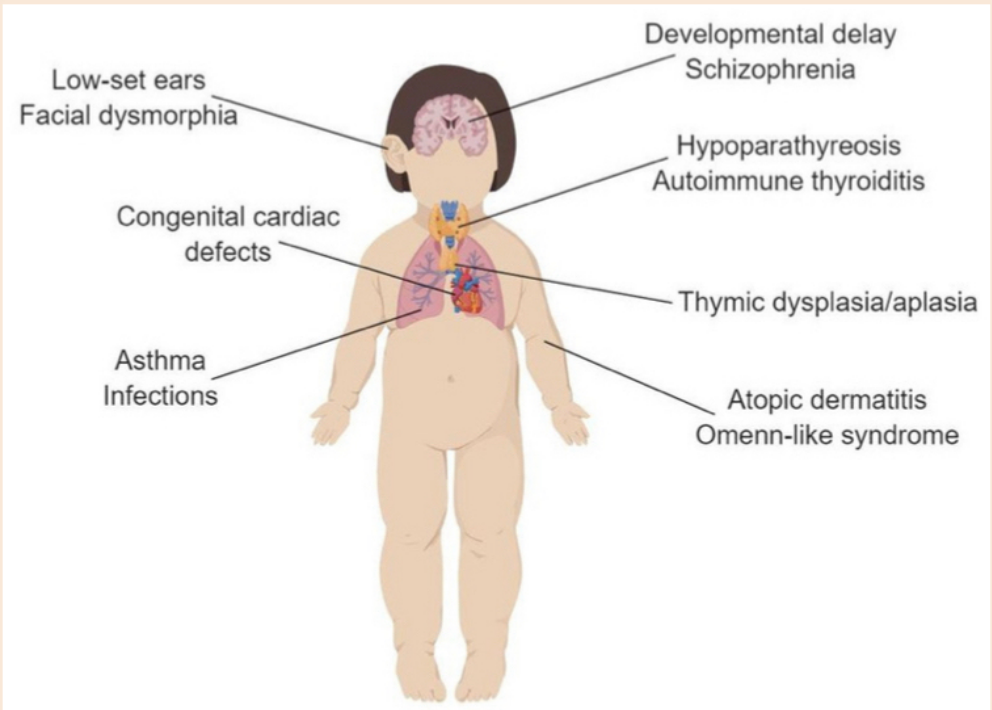


Tala Iyad

Adaptive immune system:



- Digeorge syndrome (genetic defect in development of 3rd pharyngeal pouch in embryo); T cell deficient as a result of impaired thymus development, plus parathyroid gland defect



Tala Iyad

Adaptive immune system:

SECONDARY LYMPHOID ORGANS :

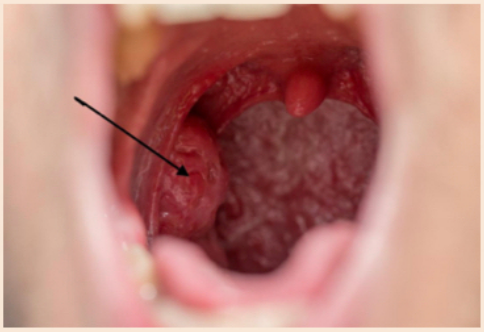
- spleen
- lymph node
- MALT

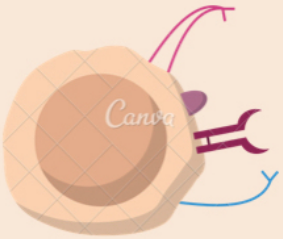
functions :

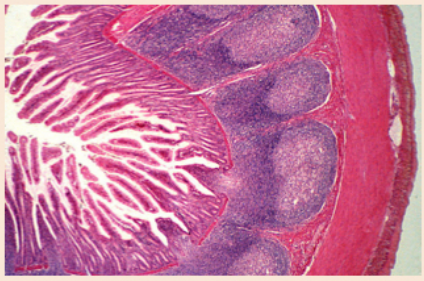
- maintain mature naive lymphocytes and initiate an adaptive immune response.
- the sites of lymphocyte activation by antigen.
- It is exemplified by the lymph nodes, and the lymphoid follicles in tonsils, Peyer's patches, spleen, adenoids, skin, etc. that are associated with the mucosa-associated lymphoid tissue (MALT)

Note :

naive lymphocytes:
Lymphocytes that have not encountered antigen are known as naïve lymphocytes. They circulate continuously through the blood and lymphatic vessels and into the peripheral tissues.







Tala Iyad

Adaptive immune system:

Lymph nodes and lymphatic system (peripheral or 2nd lymphatic sys.):

- function to concentrate antigens that are introduced through the common portals of entry (skin and gastrointestinal and respiratory tracts).
- •They Are places where the innate cells carry the antigen and present it to the adaptive immune system
- •Site of lymphocyte activation by antigen

Structure of lymph nodes:

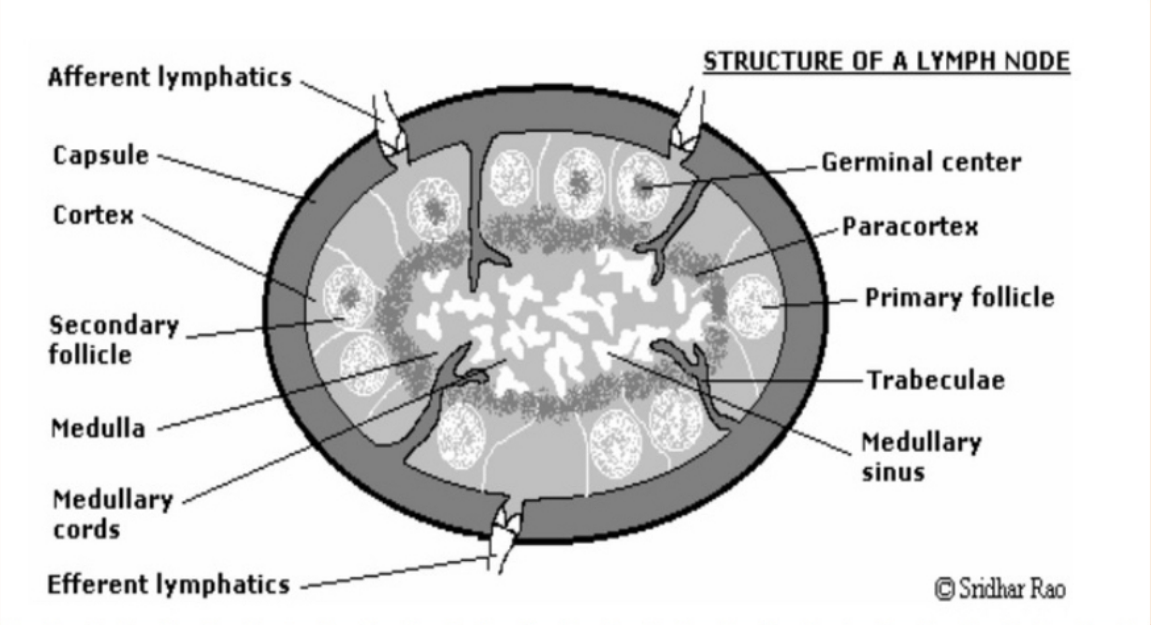
- lymph nodes, which are clustered at sites such as the groin, armpits and neck and along the small intestine, and collect antigen from the tissues;

- The node is made up of three components:
- •lymphatic sinuses the Lymph flows from afferent vessels cortical sinuses, into the medullary sinuses and into efferent lymphatic vessels
- • , blood vessels
- • parenchyma (cortex, paracortex, medulla)

Tala Iyad

Adaptive immune system:

Lymph nodes and lymphatic system (peripheral or 2nd lymphatic sys.):

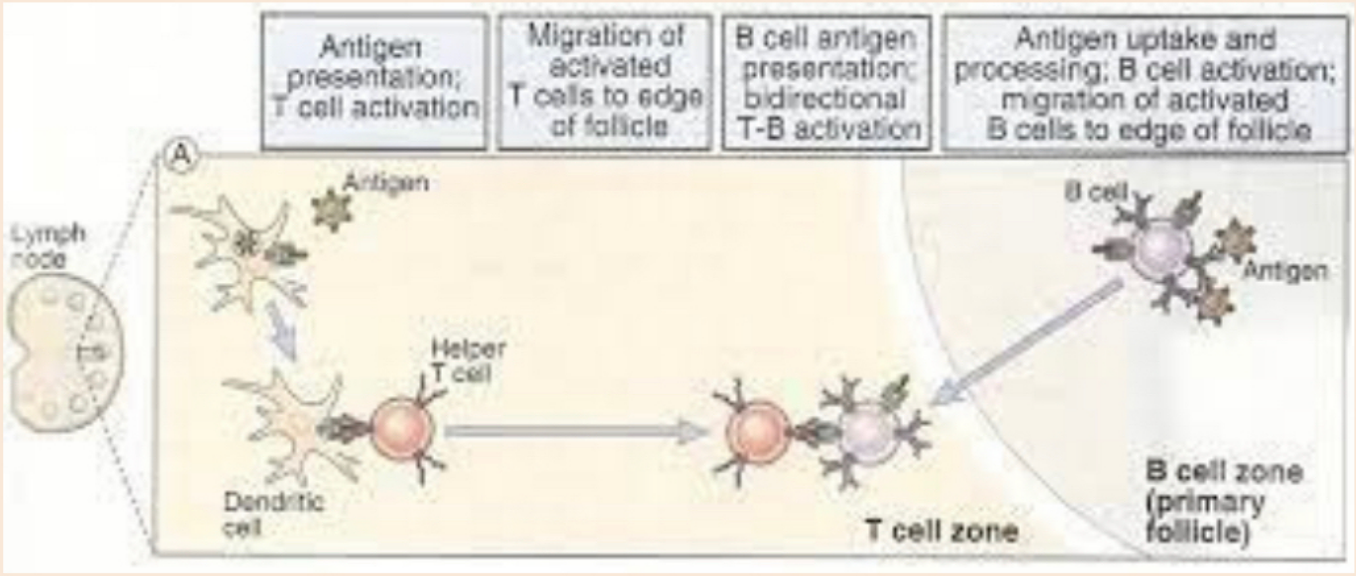


- Structure of the lymph node
- Cortex
- •Cortex consists of primary follicles and secondary follicles (with germinal center).
- •Germinal center formed from stimulated B cells and follicular dendritic cells. Whereas primary follicles have only mature but not activated B cells
- •Stimulated mature B cells change into plasma cells or memory B cells which reside in medulla and antibody that move to the circulation.

Tala Iyad

Adaptive immune system:

Lymph nodes and lymphatic system (peripheral or 2nd lymphatic sys.):



- Paracortex
- •The paracortex contains T lymphocytes and macrophages
- •T cells: The various types of T cell enter the node from the blood via the HEVs. When activated they form lymphoblasts which divide to produce a clone of T cells responding to a specific antigen. Activated T cells then pass into the circulation to reach peripheral sites.
- • Medulla
- •The medulla comprises:
- •large blood vessels
- •medullary cords and sinuses
- •plasma cells

- A lymphocyte that has gotten larger after being stimulated by an antigen. Lymphoblast also refers to an immature cell that can develop into a mature lymphocyte

Tala Iyad

Adaptive immune system:

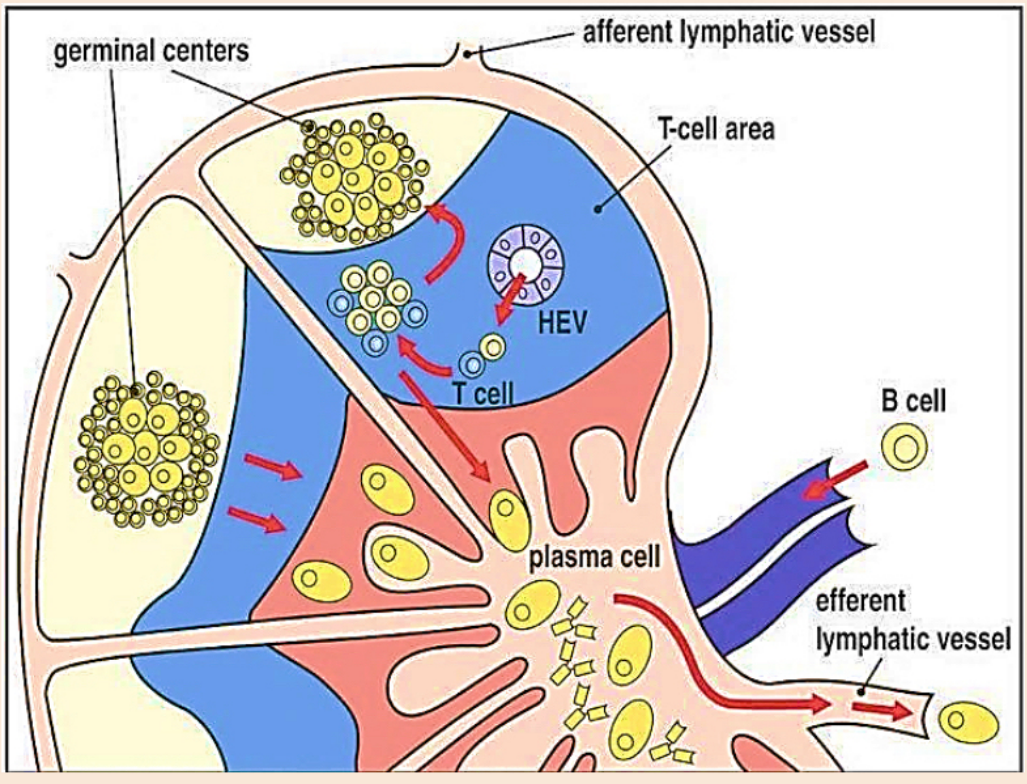
Lymph nodes and lymphatic system (peripheral or 2nd lymphatic sys.):

- Paracortex:
- • between the cortex and medulla
- •Is called the Thymus dependent zone of
- the lymph node, contains T cells that have migrated from the thymus [T lymphocytes

High endothelial venules (HEV): is a post- capillary venule

.

is the point of entry of T cells from bloc
• its endothelial lining is unusual
• is cuboidal to facilitate movement
ofT cells into LN



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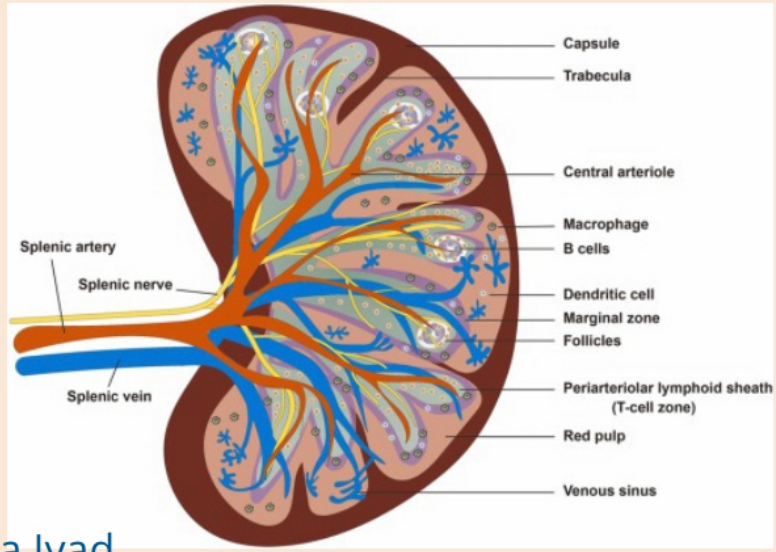
Adaptive immune system:

spleen :

- the spleen, which collects antigen from the bloodstream;
- spleen
- •Weigh 150g, in left upper quadrant
- •Immune response against blood borne antigens
- •Consist of white pulp(inner)
- • peri-arteriolar lymphoid sheath;PALS (T cell Zone)
- •follicles (B cells Zone).
- • Marginal Zone in between red and white pulp, have both B and T cells and macrophages.
- •Red pulp; outer, splenic artery, vascular sinusoid, splenic vein. consist of old erythrocytes and macrophages, It is the place where aged RBC is destroyed by macrophages
- •The splenic artery enters the red pulp through a web of small blood vessels, and blood-borne microorganisms are trapped in this loose collection of cells until they are gradually washed out through the splenic vein
- •No afferent lymphatic vessel in spleen.



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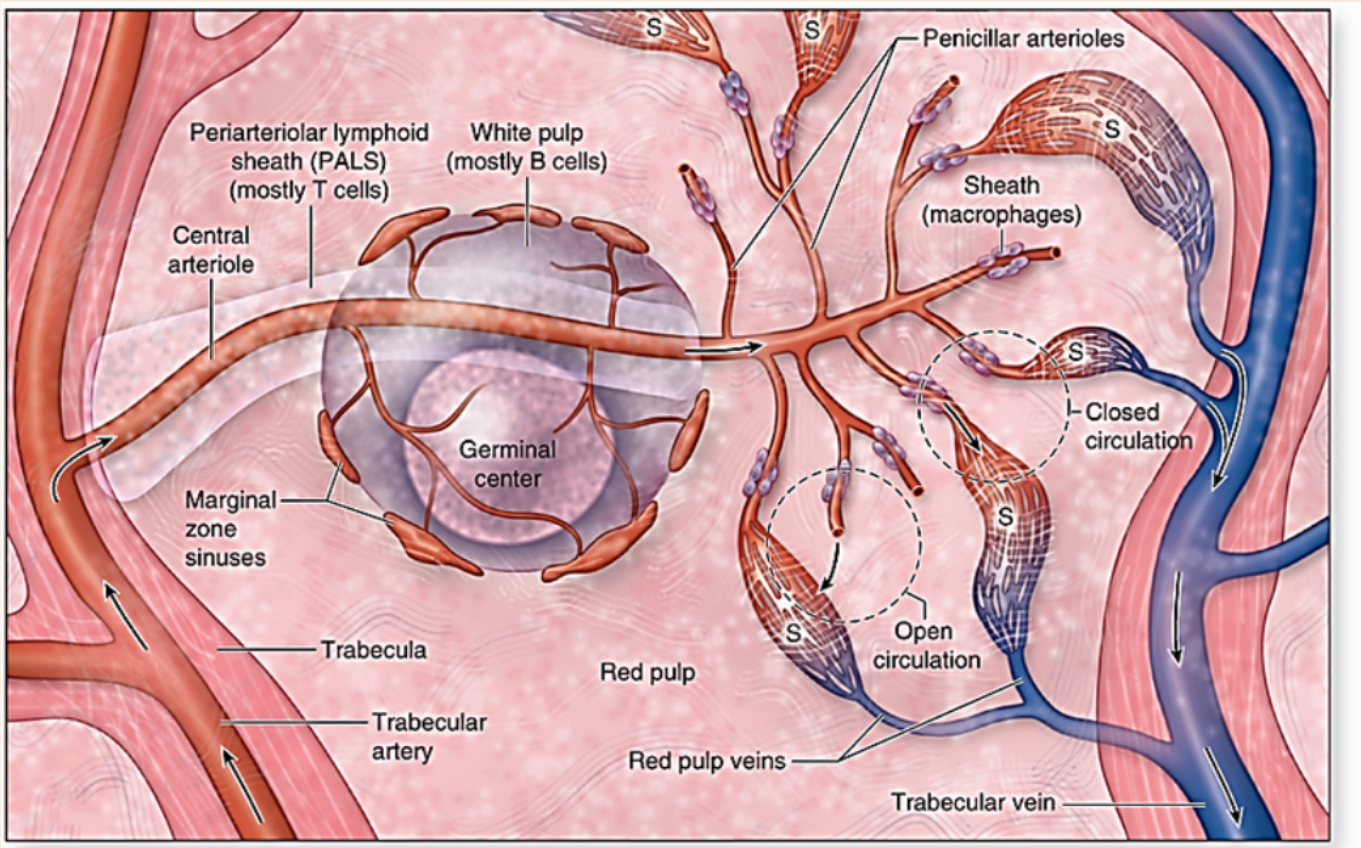
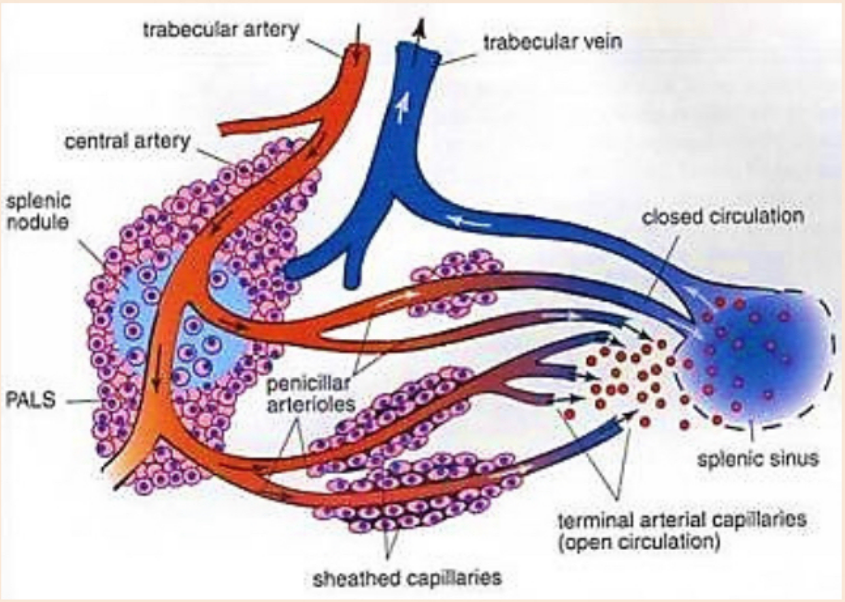
Adaptive immune system:

spleen :





- Splenic artery → trabecular arteries → central arterioles → penicillinar arterioles enter the red pulp and they terminate as:
- ➢Closed circulation when terminate directly into splenic sinusoids
- ➢Open circulation when terminate in splenic cords

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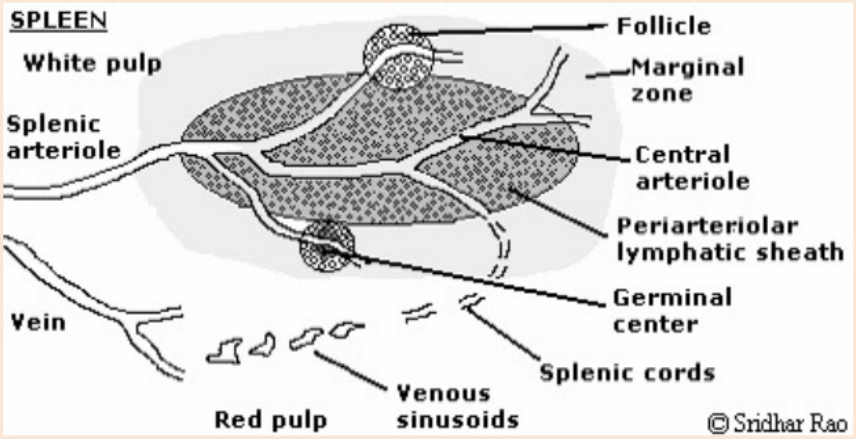
Adaptive immune system:

spleen :

spleen functions :

- It is the major site for killing antibody coated microbesand destroying the damaged RBC
- •Storage of RBCs and lymphocytes
- •Individuals lacking a spleen are extremely susceptible to infections with encapsulated bacteria such as pneumococci and meningococci because such organisms are normally cleared by opsonization and phagocytosis, and this function is defective in the absence of the spleen



triple vaccine:

- Pneumococcal, meningococcal, and Haemophilus influenzae (Hib) vaccinations are indicated for patients after splenectomy.

and the mucosa-associated lymphoid tissues (MALT), which collect antigen from the respiratory, gastrointestinal and urogenital tracts and are particularly well organized in the small intestine, in structures known as Peyer's patches

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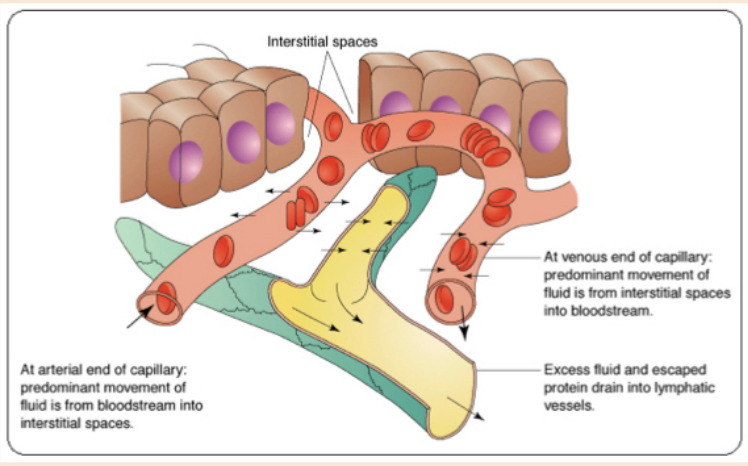
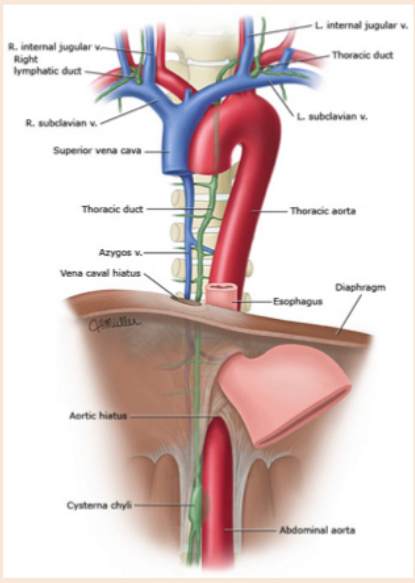
Adaptive immune system:

Innate and T cells migration

- Lymph (macrophage and DC) from tissues (mainly innate cells carrying antigens) passes into the nearby node through the afferent lymphatic vessel
- In the node they activate T and B cells
- B and T cells are produced migrate to secondary lymphoid tissues through High endothelial venules ;HEVs,
- Then the innate cells go into the cortical sinuses then marginal sinus to reach the medullary sinuses before leaving via the efferent lymphatic.
- If the T cells recognize antigen, they are activated, and they return to the circulation through the efferent lymphatics, to the thoracic or right lymphatic ducts, and finally into the superior vena cava or right subclavian vein.





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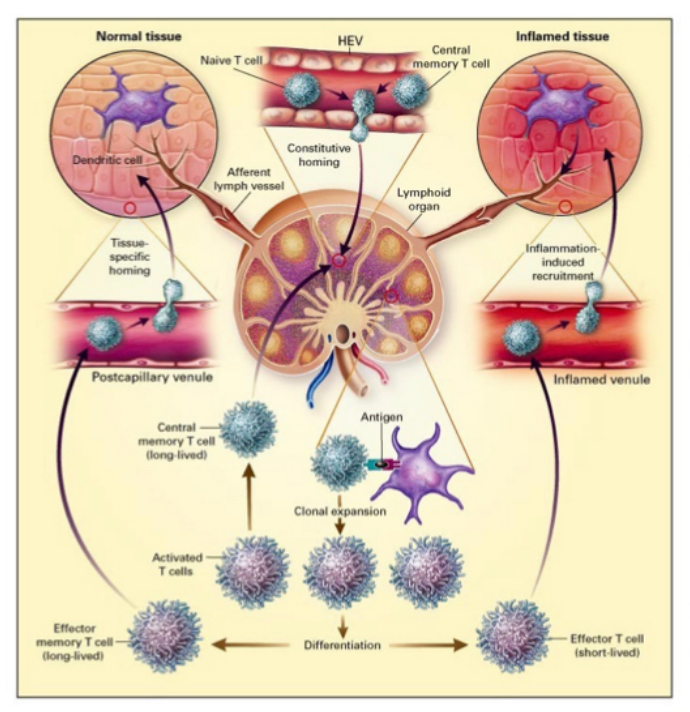
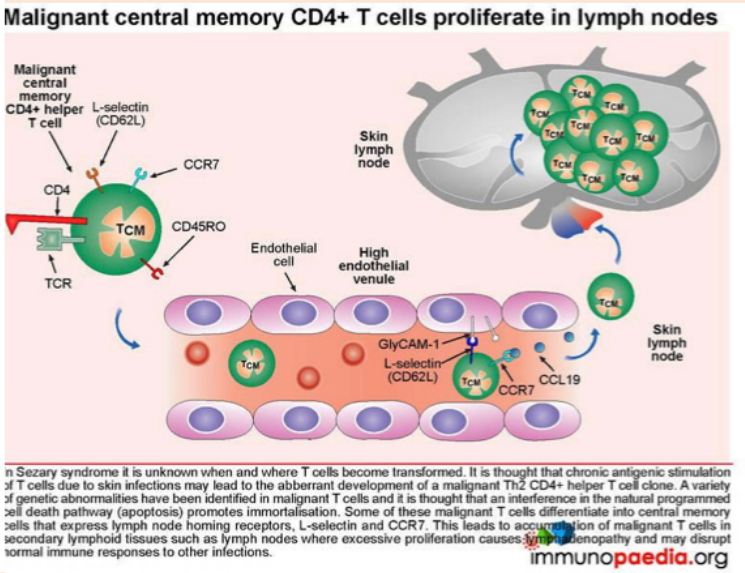
Adaptive immune system:

Effector (Effector T cells include CD8+ cytotoxic T cells and CD4+ helper T cells ;TH1, TH2, and TH17 subsets) and memory T cells preferentially leave the blood and enter peripheral tissues through venules at sites of inflammation.

•Whereas naïve T cells recirculate and reenter the LN agai

•the two molecules needed for selective entry of T cells into secondary lymphoid organs through HEV (CCR7 and L-selectin) are reduced on effector T cells, and high in naïve cells therefore these cells do not readily reenter lymphoid tissues.





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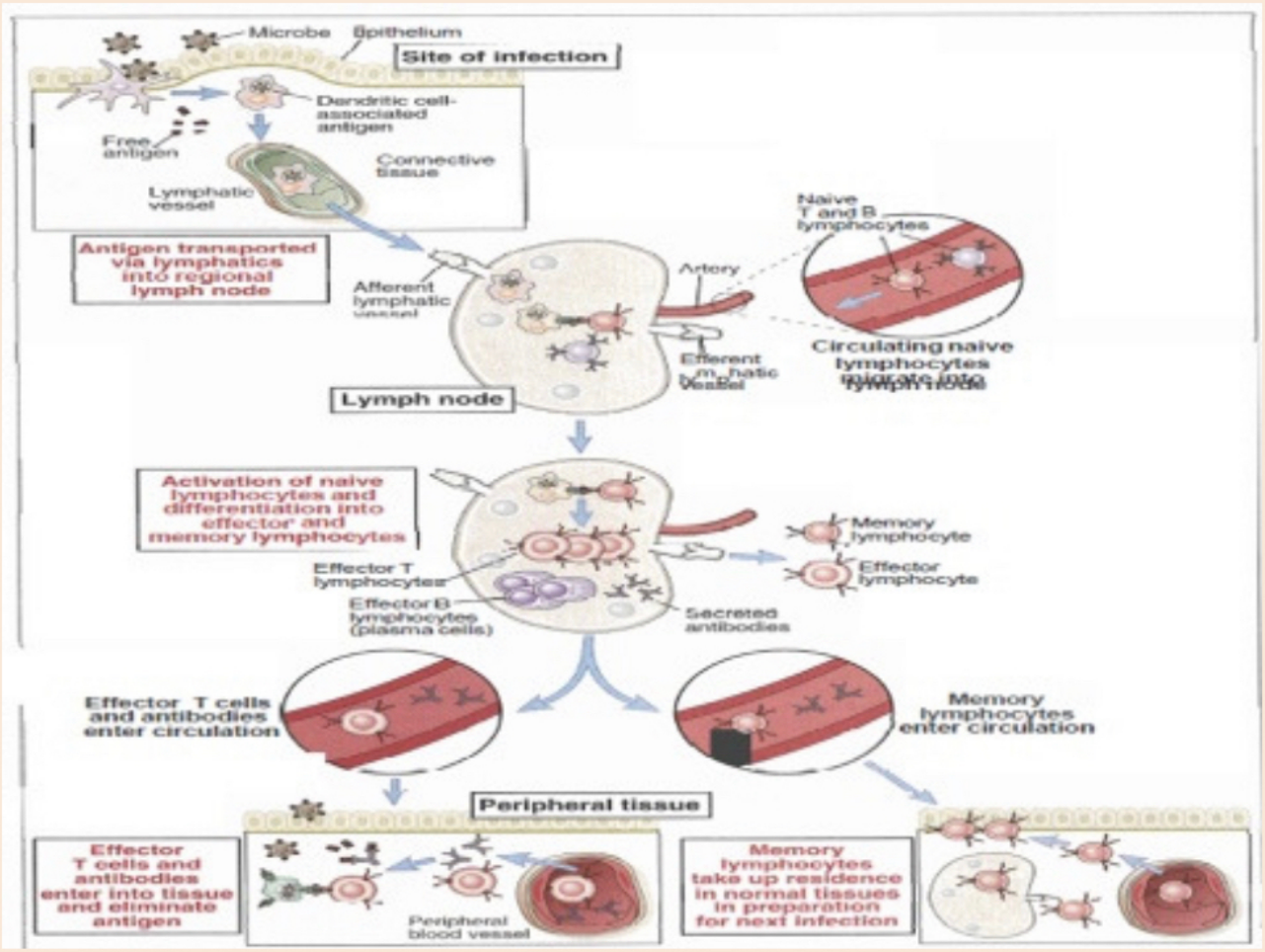
Adaptive immune system:

B cells migration

- B cells migrate into follicles, the site where they may encounter antigen and become activated.
- After B cell activated they reside in germinal center where they secret antibodies and Many antibody-producing plasma cells and memory cells reside in medulla or migrate to the bone marrow through efferent L. V. to circulation where they secrete antibodies for long periods.



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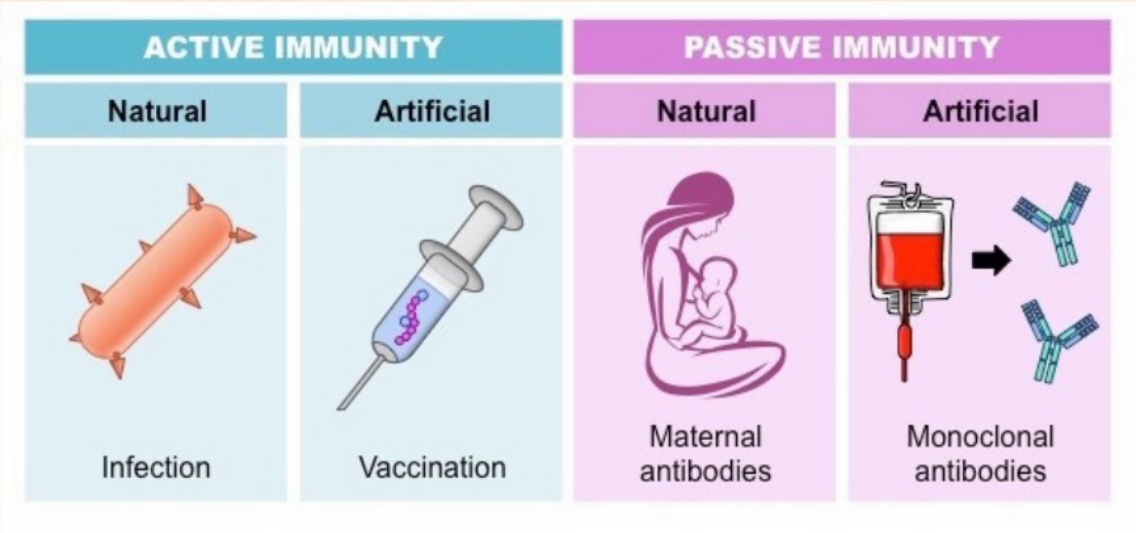
Immunity against certain microbe

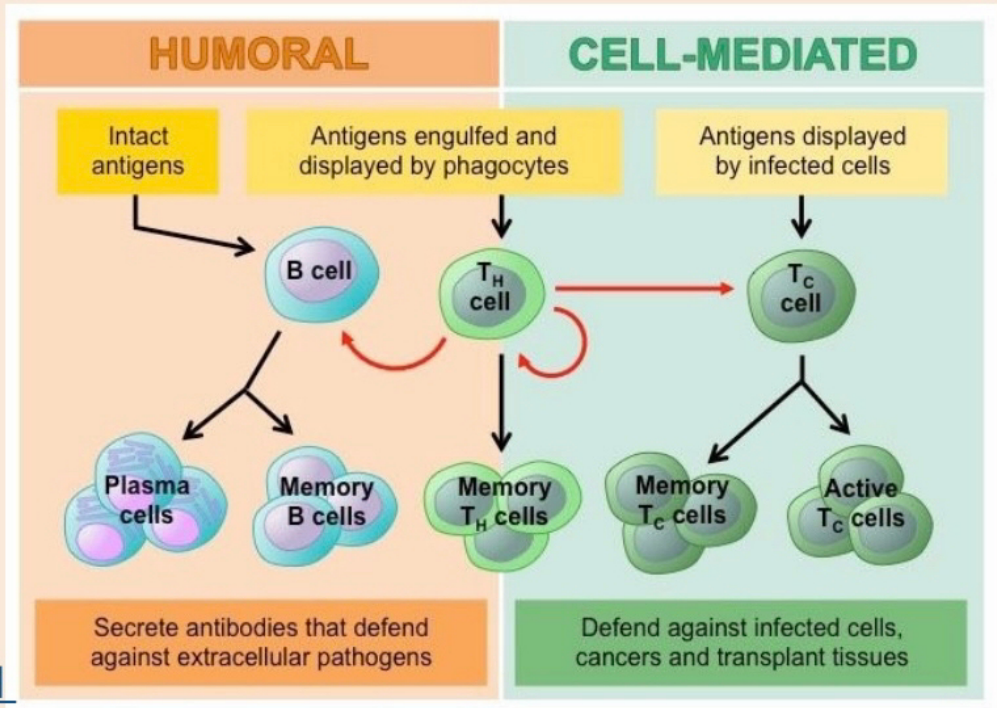
Immunity can be active or passive

- Active; induced by previous exposure to an antigen and host immune cells respond and form antibodies and memory cells (AB produced inside the body)
- Passive, transfer serum or lymphocytes from specifically immunized individual to not-exposed person (naïve).

Maternal Ab to fetus (Abs isn't produced in the body)



Humeral immunity vs cell mediated immunity:



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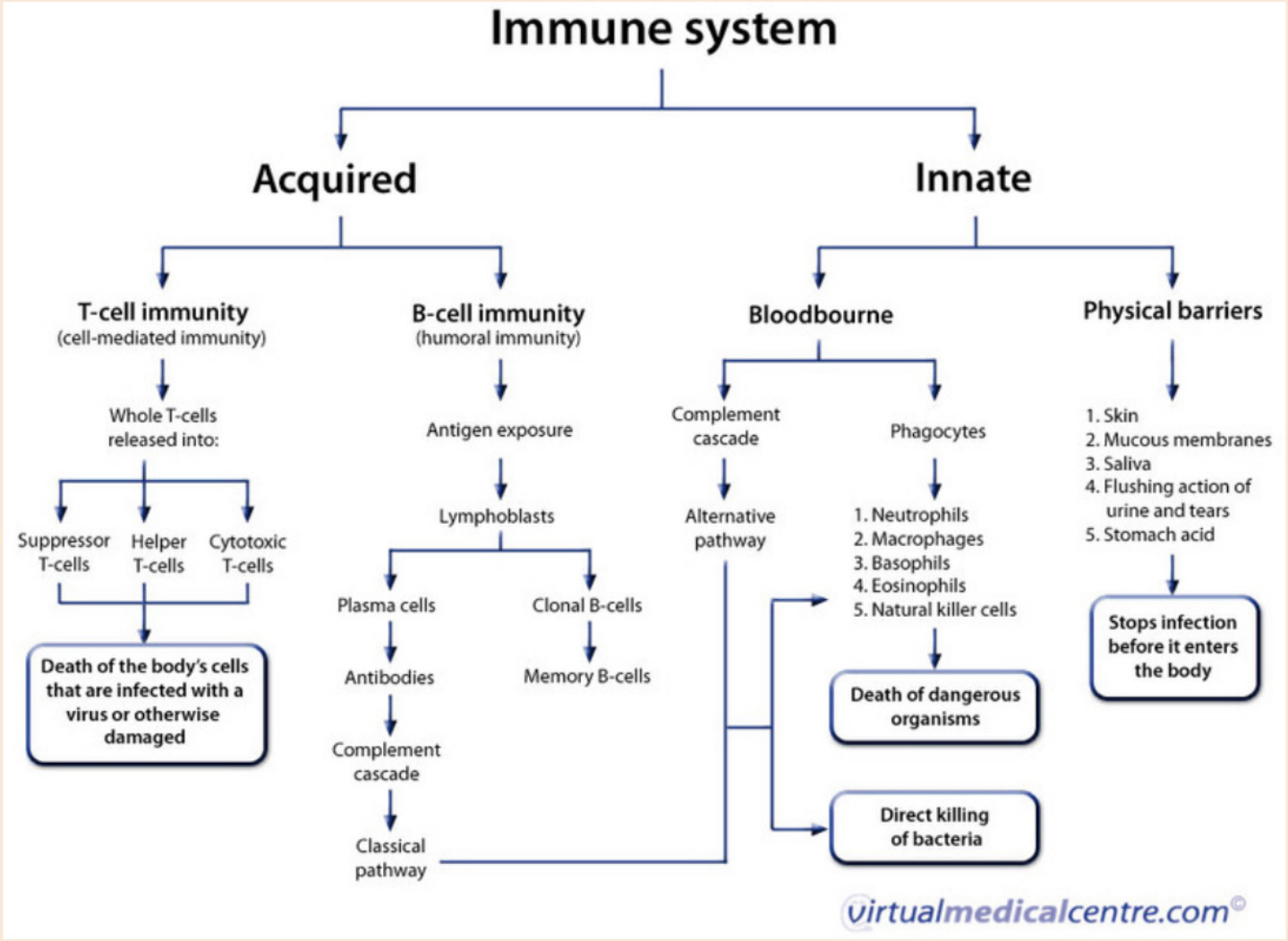
Innate immunity vs adaptive immunity

Immunity in practice

—The innate immune system (the first to act;),
•consists of physical, chemical and cellular defenses against pathogens(complements and cells)
•present and act the same in all people against general antigens.
•it is monotonic; the same magnitude and speed of response each time,
•not specific, act against common microbial antigens..
—The second is adaptive immune system (T and B cells),
•it is specific act against certain antigen,
•increasing in magnitude and speed of response in re-exposure to the same antigen (memory)



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Innate immunity vs adaptive immunity

Innate and Adaptive

•Innate immune response is better than adaptive in recognizing self from non-self.
Because non specific for all microbes and quick .

•Innate immune responses to a foreign microbe are immediate and do not require prior exposure to the microbe

•effective adaptive immune responses to a newly introduced microbe develop over several days as T and B lymphocytes are activated by some activated innate cells and they undergo expansion and differentiate into functional effector Th and Tc cells and antibody producing B cells.

•The targets of the innate immune response is essential for the survival of the microbes

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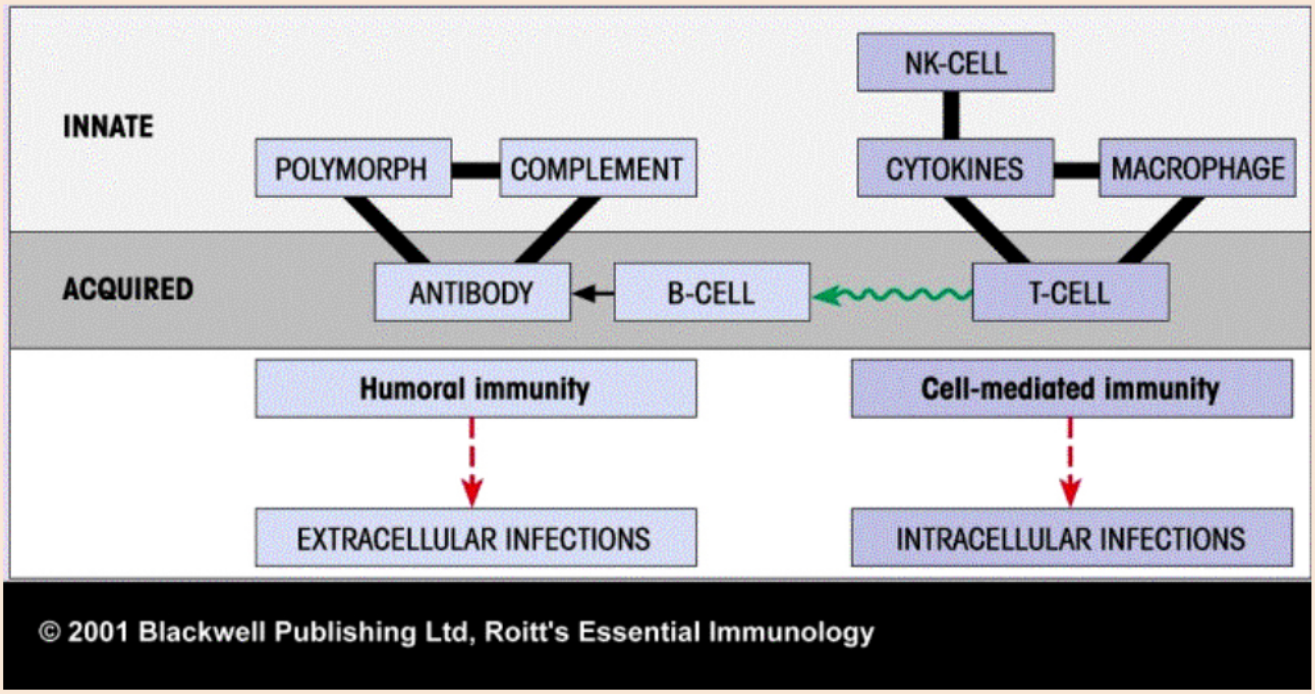
Innate immunityThe link between innate and adaptive immunity

1.The innate stimulate the adaptive (macrophage secret IL-12 and/ or IL-4 that activate T cells. C3d complement activate B cell. Antigen presentation to T cell by macrophages.

2.The adaptive immune response use some innate cells to eliminate the antigen (T cells secret IFN gamma that activate macrophages)

vs adaptive immunity



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Innate immunity vs adaptive immunity

TABLE 1-3 Comparison of adaptive and innate immunity

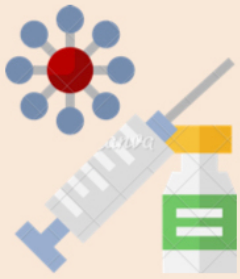
	Innate	Adaptive
Response time	Hours	Days
Specificity	Limited and fixed	Highly diverse, improves during the course of immune response
Response to repeat infection	Identical to primary response	Much more rapid than primary response

history :

Immunity: protection from infectious microbes or foreign macromolecules; proteins and polysaccharides

•Immune system constitutes of cells, tissues and small molecules

•The first application in immunology is done by edward jenner's vaccination against smallpox when he injected parts of cowpox microbe into small boy who is later became resistant to smallpox disease in 1798 (vaccine)



•This was crowned in 1980 when the WHO announce the smallpox have been eradicated worldwide.

important definition :

The immune system Cells in our bone marrow, thymus, and the lymphatic system of ducts and nodes, spleen, and blood that function to protect us.

Antigen Anything causing an immune response, usually foreign material but may be our own tissues.

Pathogen Any disease causing micro-organism.

Tolerance Non-reactivity of the immune system, usually refers to "self" but may include foreign tissue in organ transplants.

Autoimmunity A failure of tolerance, the immune system reacts to self.

Chemokines Molecules released by pathogens and infected tissues to attract cells of the immune system.

Cytokines Signaling molecules released by one cell to cause a response in another. Signaling is extremely important in our immune response.

Innate immunity Protection that is always present. Includes phagocytic (cells that eat other cells) macrophages and dendritic cells.

Adaptive immunity Protection that arises by an immune response, including humoral immunity producing antibodies and cellular immunity.

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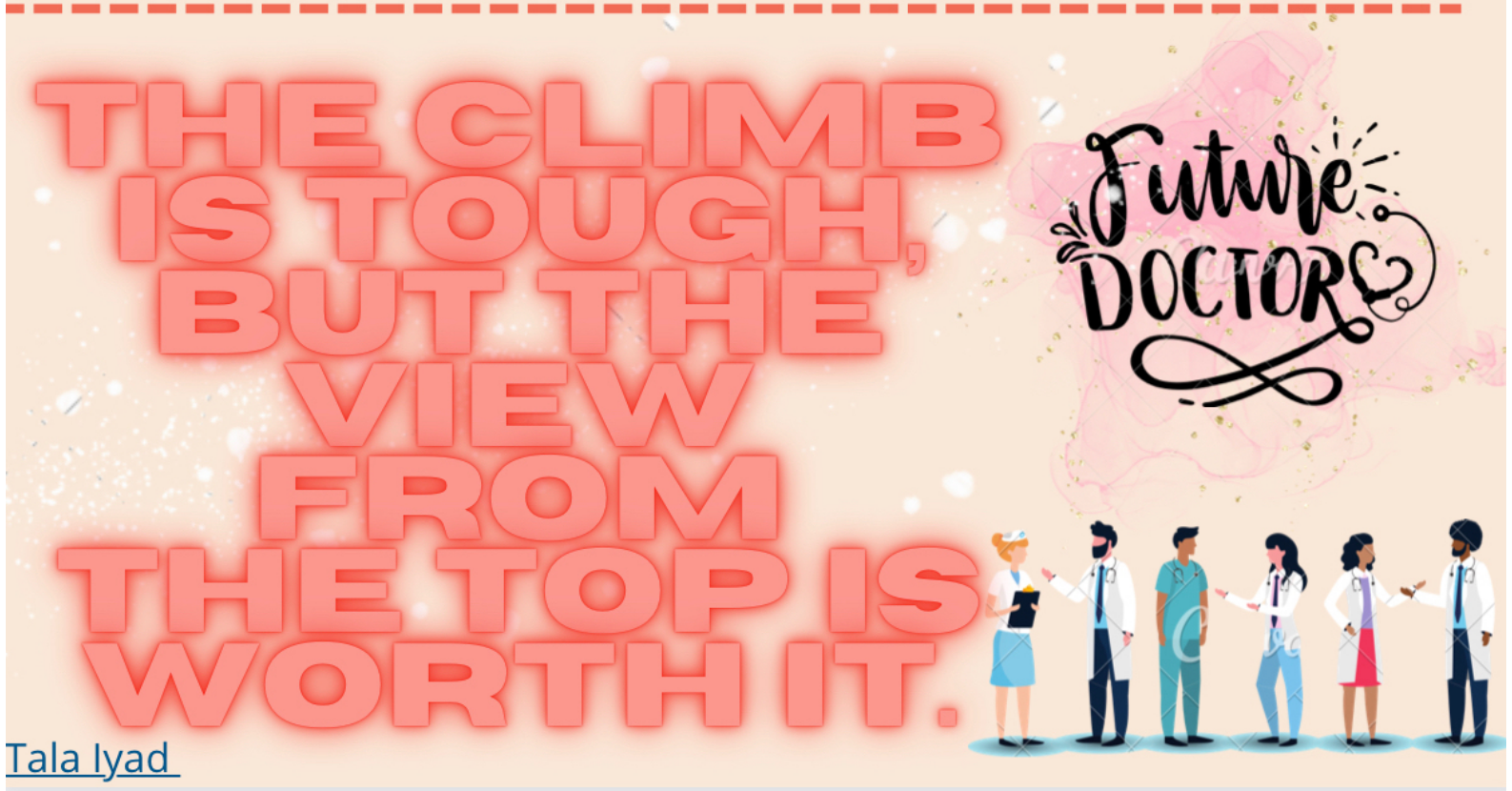
Innate immunity vs adaptive immunity

TABLE 1-1 Nobel Prizes for immunologic research

Year	Recipient	Country	Research
1901	Emil von Behring	Germany	Serum antitoxins
1905	Robert Koch	Germany	Cellular immunity to tuberculosis
1908	Elie Metchnikoff Paul Ehrlich	Russia Germany	Role of phagocytosis (Metchnikoff) and antitoxins (Ehrlich) in immunity
1913	Charles Richet	France	Anaphylaxis
1919	Jules Border	Belgium	Complement-mediated bacteriolysis
1930	Karl Landsteiner	United States	Discovery of human blood groups
1951	Max Theiler	South Africa	Development of yellow fever vaccine
1957	Daniel Bovet	Switzerland	Antihistamines
1960	F. Macfarlane Burnet Peter Medawar	Australia Great Britain	Discovery of acquired immunological tolerance
1972	Rodney R. Porter Gerald M. Edelman	Great Britain United States	Chemical structure of antibodies
1977	Rosalyn R. Yalow	United States	Development of radioimmunoassay
1980	George Snell Jean Daussct Baruj Benacerraf	United States France United States	Major histocompatibility complex
1984	Cesar Milstein Georges E. Köhler	Great Britain Germany	Monoclonal antibody
	Niels K. Jerne	Denmark	Immune regulatory theories
1987	Susumu Tonegawa	Japan	Gene rearrangement in antibody production
1991	E. Donnall Thomas Joseph Murray	United States United States	Transplantation immunology
1996	Peter C. Doherty Rolf M. Zinkernagel	Australia Switzerland	Role of major histocompatibility complex in antigen recognition by by T cells



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