innate immunity and immune organs

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NK cells

- 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.
- 10 % of mononuclear cells in blood and spleen and rare in lymphoid organs
- 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

NK receptors

1. Killer activation receptors (KAR) of NK cells detect alteration in host cells as cancers. recognize stress related molecules as MICA, MICB
2. Killer inhibition receptors (KIR) of NK cells, used to detect the presence of MHC 1 protein on host cells any binding means inhibition

killing is the net result from the activating receptors (KAR) and inhibitory receptors (KIR)

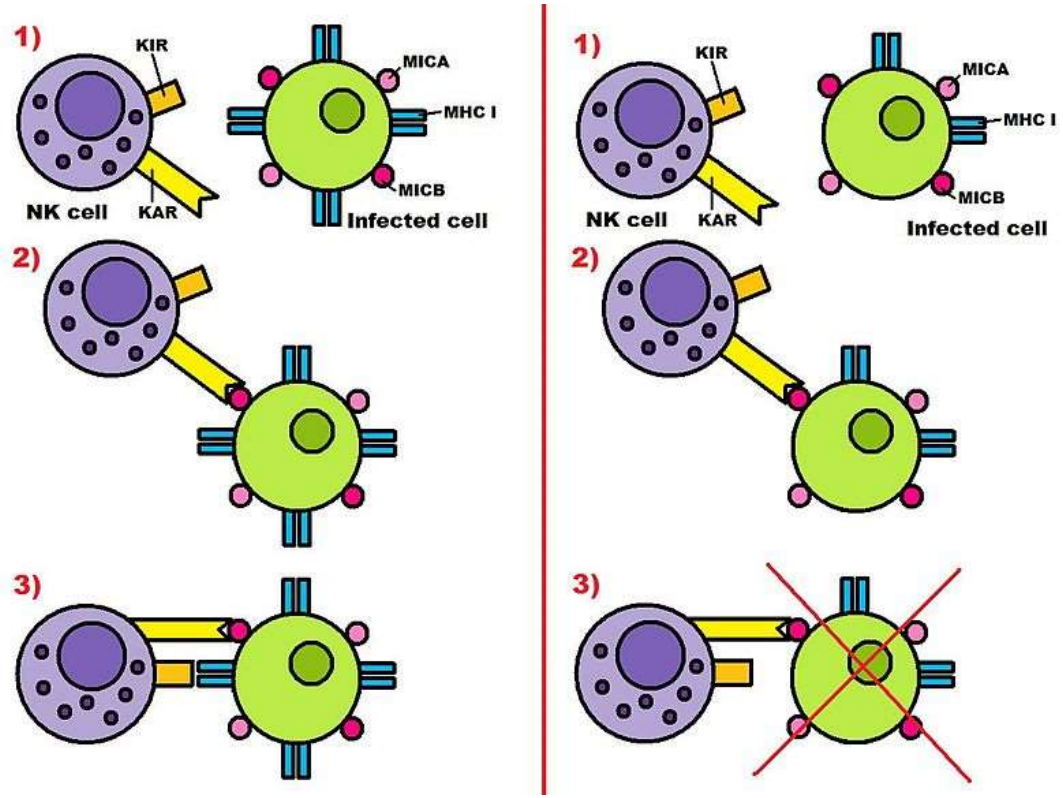
The action depend on the 2nd receptor

3. ,Opsonin receptors for antibodies; and kill these opsonin- coated cells, this is called antibody dependent cell mediated cyto-toxicity (ADCC)

4. 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)

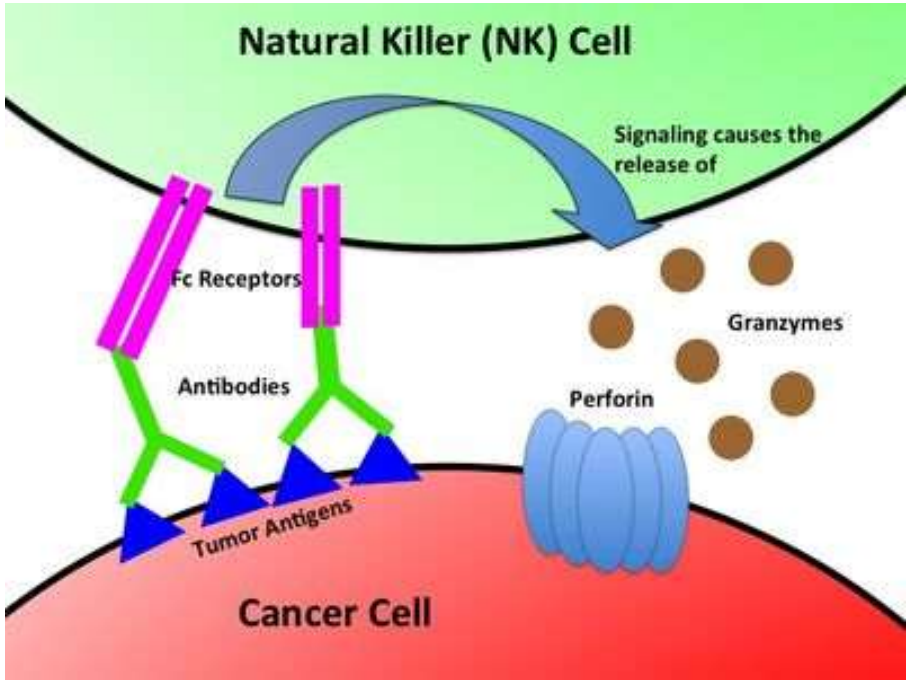
NK cells

- Effecter functions of NK cells
  - Direct extracellular killing by secretion
    - Perforins; making pores then osmotic lysis
    - Granzymes, enzymes enter through perforin pores and activate caspases leading to cell death
  - Indirect killing . increase macrophage phagocytosis and killing of microbe by secreting IFN gamma

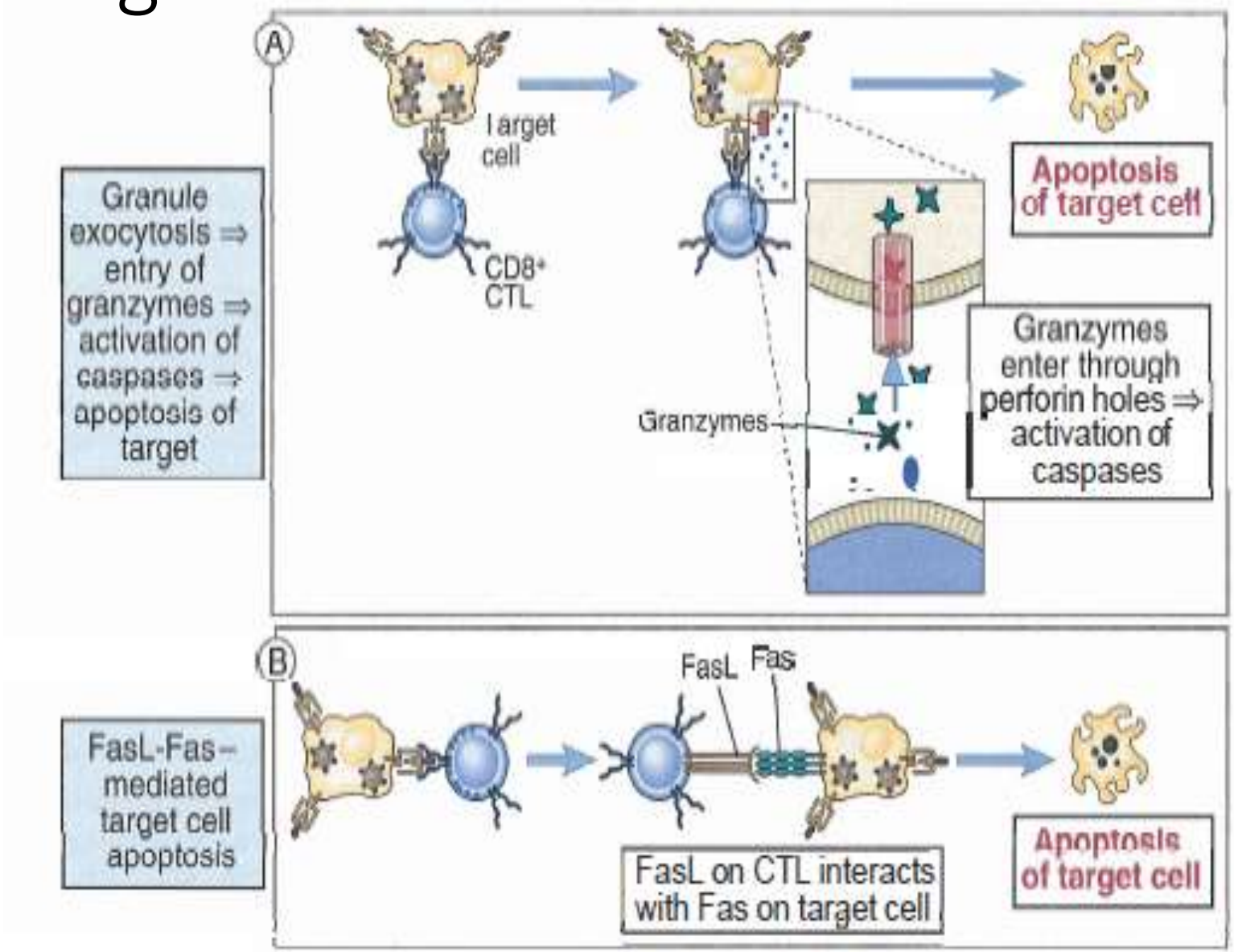


When a KAR binds to MICA and MICB molecules on the surface of an infected cell (or a tumor cell), a KIR examines the levels of MHC class I of this target cell. If the MHC class I levels are enough, killing of the cell doesn't proceed (left), but if they aren't, the killing signal proceeds and the cell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

Direct killing by NK cells

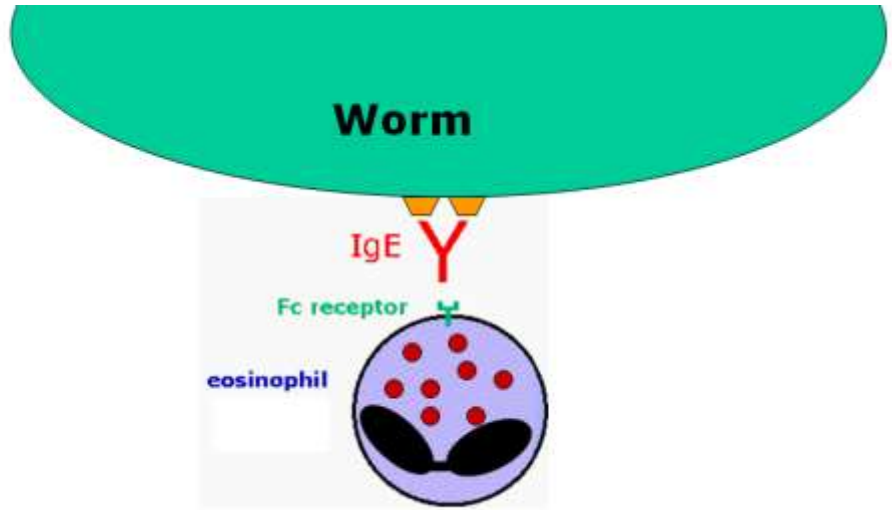


NK killing


A
Target cell
CD8+ CTL
Granule exocytosis ⇒ entry of granzymes ⇒ activation of caspases → apoptosis of target
Apoptosis of target cell
Granzymes
Granzymes enter through perforin holes ⇒ activation of caspases
B
FasL
Fas
FasL-Fas–mediated target cell apoptosis
FasL on CTL interacts with Fas on target cell
Apoptosis of target cell

EOSINOPHILS

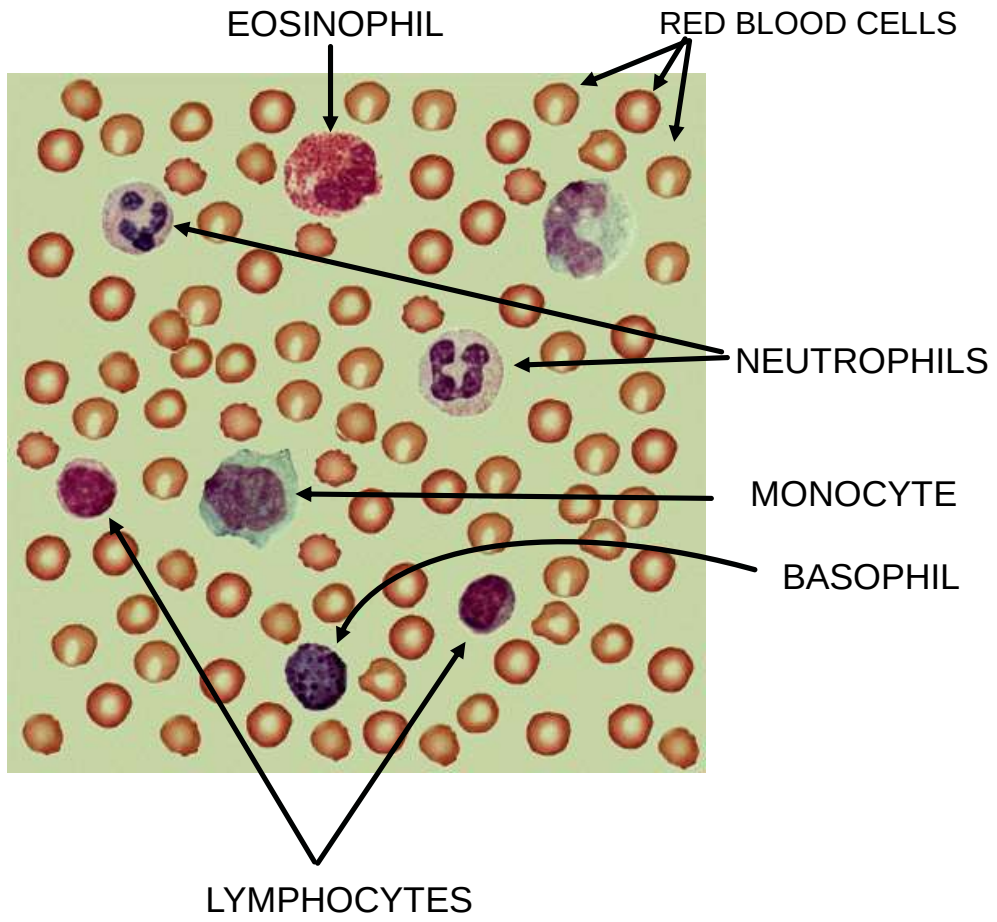
- These cells are eosinophilic or "acid-loving" as shown by their affinity to coal tar dyes: Normally transparent, it is this affinity that causes them to appear brick-red after staining with eosin, a red dye,
- Eosinophils kill extracellularly
- 2 functions
  - When eosinophils bind to IgE on the surface of a worm, the cell is triggered to degranulate. The contents of the granules cause damage to the worm.
  - Other function is in allergy.
- 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).


Worm
IgE
Fc receptor
eosinophil

Basophils and mast cells

- Granulocytes, have acidic proteoglycan, Lobed nucleus--more variable, large coarse granules stain blue with basic dye methylene blue.
- Mast cells is the cessile form whereas basophils is the circulating form
- 2 types of mast cells
  - Connective tissue
  - Mucosal mast cells, act in allergy and is T cell dependent to degranulat and produce histamine.
- 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;

Cells of the blood



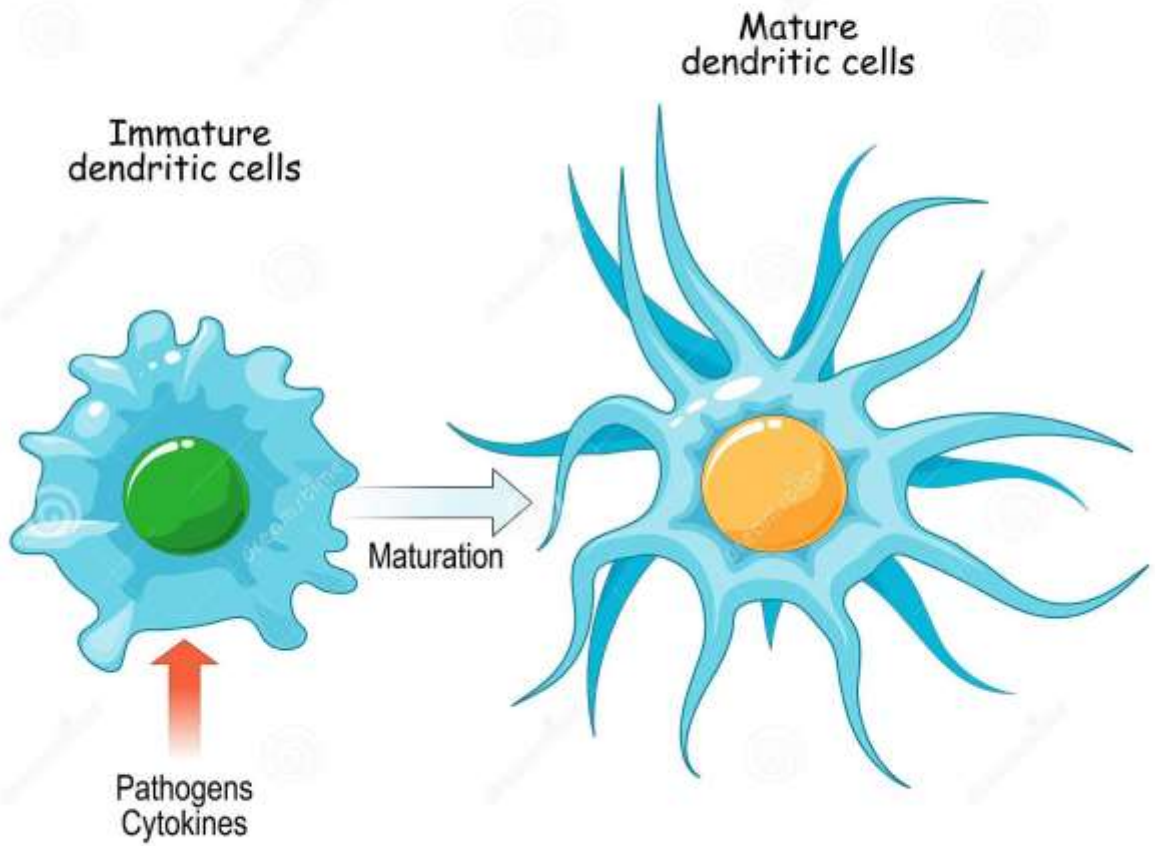
Dendritic cells (DCs)

- 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,

DC or dentritic cells

- 4 types
  - 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 dendritic cells, are early cellular responders to viral infection. They have potent antiviral activities.

Dendritic cells



Cellular Components of all immune system in percents

1. Lymphocytes(30%); T cells (60%), B cells (30%) (high N:C ratio) and large granular lymphocytes called natural killer cells(10%) low N:C ratio and granular)
2. Mononuclear phagocytes; macrophages (5.3%)
3. Granulocytes; neutrophils (62%), eosinophils(2.3%) and basophils (0.4%)

receptors of acquired immune- cells

- 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 10^{10} 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.

- The 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)

Organs of the immune response

- Primary lymphoid organs
  A. Bone marrow; where the immune cells originate
  B. Thymus; where T cells differentiation to mature
- Secondary lymphoid organs
  - 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).

Primary immune organs; Bone marrow and thymus

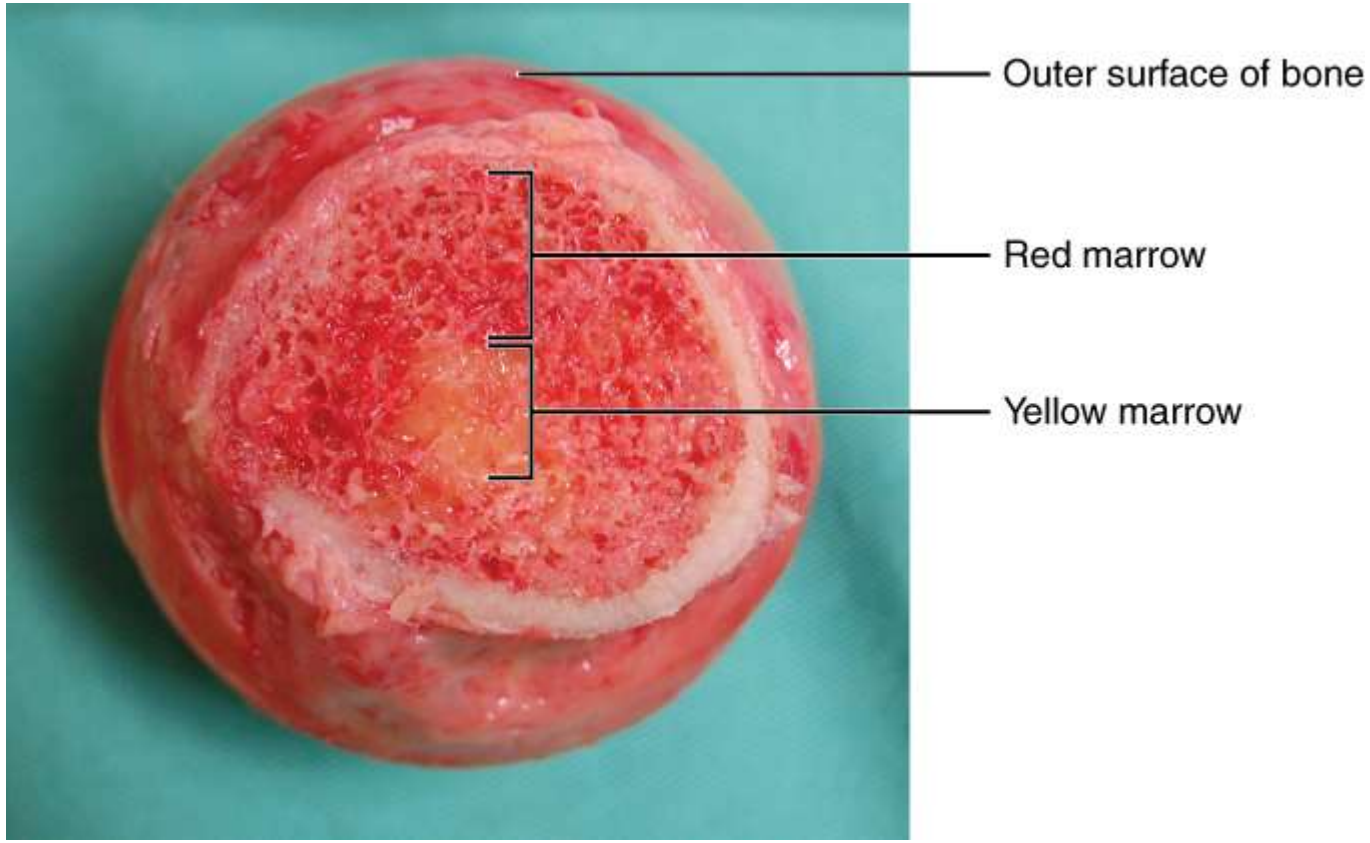
- Bone marrow functions
  - Leukocytes production, B cells maturation. hematopoiesis start in childhood (YOLK SAC AND mesenchyme, then liver and spleen and finally the bone marrow in puberty) and get maximum in adult age, most common site of BM is sternum, vertebrae, iliac bones and ribs.
  - In cases of excess demand liver and spleen help the BM (the extramedullary hematopoiesis).
- Thymus
  - T cell maturation and formation of T cell antigen receptors

Bone marrow components

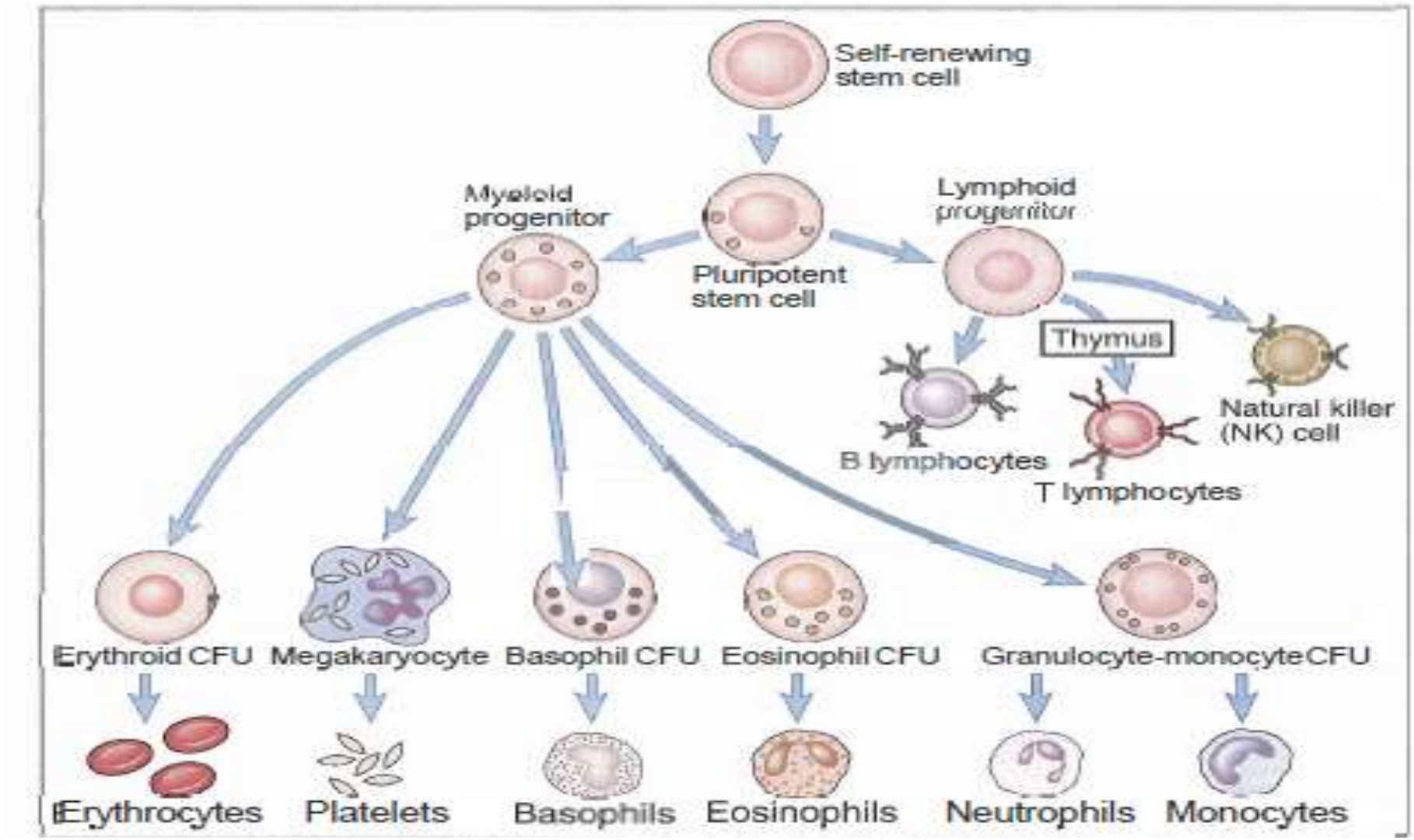
- The two components of bone marrow are
  - "**red marrow**" which consists mainly of hematopoietic tissue, Red blood cells, platelets, and most white blood cells arise in red marrow Red marrow is found mainly in the flat bones, such as the pelvis, sternum, cranium, ribs, vertebrae and scapulae, and at the epiphyseal ends of long bones such as the femur and humerus
  - and "**yellow marrow**", which is mainly made up of fat cells. 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.. Yellow marrow is found in the hollow interior of the middle portion of long bones. In cases of severe blood loss, the body can convert yellow marrow back to red marrow to increase blood cell production
  - Stroma; any tissue not associated to blood production as fatty marrow, fibroblast, osteoclast and osteoblast.

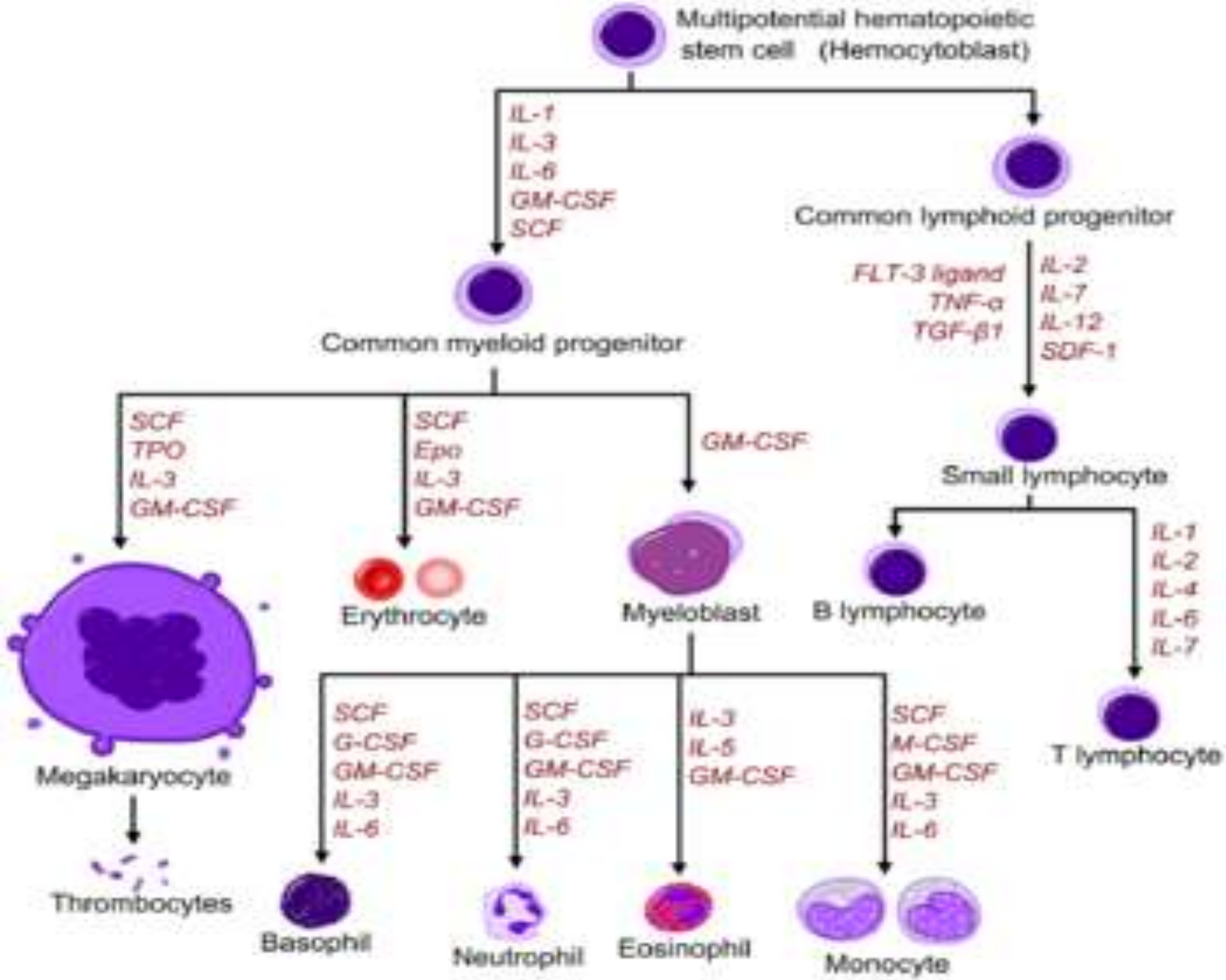
- Hematopoietic stem cells (HSCs) give rise to two kinds of multipotent progenitor cells, one that generates lymphoid and another that produces myeloid cells,
- The common lymphoid progenitor gives rise to committed precursors of T cell, B cell
- The common myeloid-megakaryocyte- erythroid progenitors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

BM



Blood cells precursors




Multipotential hematopoietic stem cell (Hemocytoblast)
IL-1
IL-3
IL-6
GM-CSF
SCF
Common lymphoid progenitor
FLT-3 ligand
TNF-α
TGF-β1
IL-2
IL-7
IL-12
SDF-1
Common myeloid progenitor
Small lymphocyte
SCF
TPO
IL-3
GM-CSF
SCF
Epo
IL-3
GM-CSF
GM-CSF
IL-1
IL-2
IL-4
IL-6
IL-7
Erythrocyte
Myeloblast
B lymphocyte
T lymphocyte
Megakaryocyte
SCF
G-CSF
GM-CSF
IL-3
IL-6
SCF
G-CSF
GM-CSF
IL-3
IL-6
IL-3
IL-5
GM-CSF
SCF
M-CSF
GM-CSF
IL-3
IL-6
Thrombocytes
Basophil
Neutrophil
Eosinophil
Monocyte

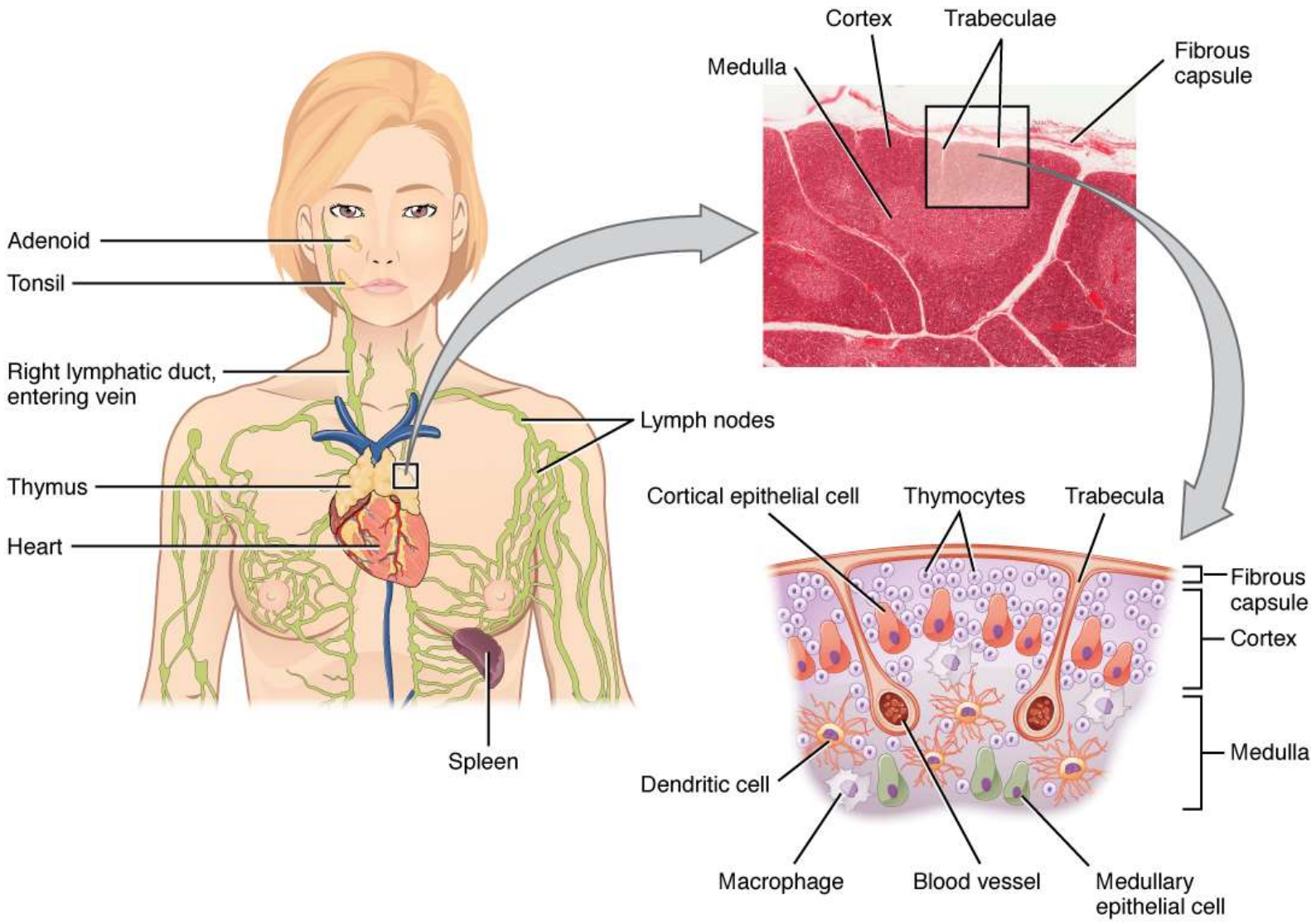
Thymus

- 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.
- The thymus has a rich vascular supply and efferent lymphatic 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.

Thymus

- **A. Anatomy;** The thymus is composed of two identical lobes and is located anatomically in the anterior superior mediastinum, in front of the heart and behind the sternum
- **B. 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
- 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

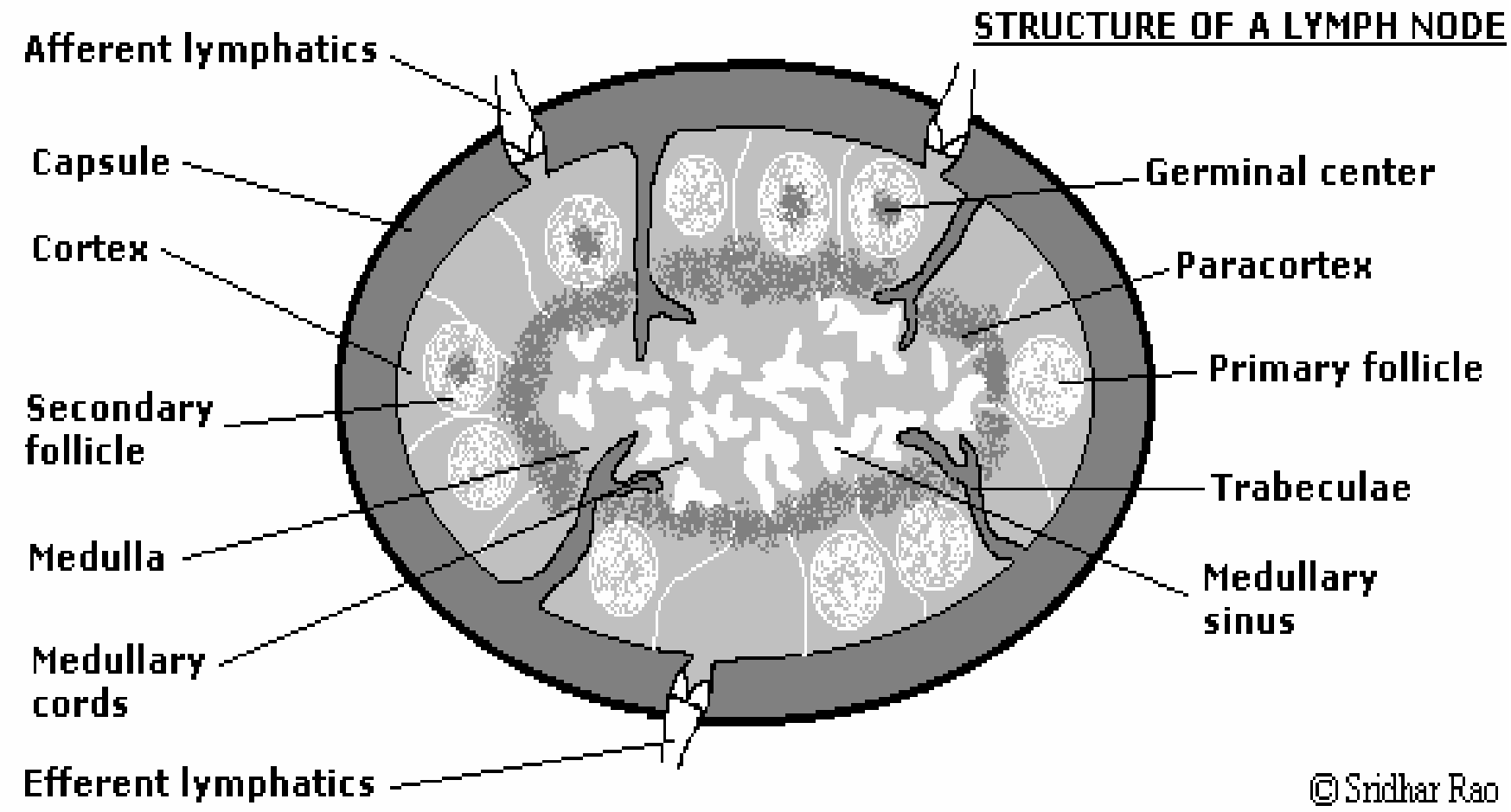
Thymus


Adenoid
Tonsil
Right lymphatic duct, entering vein
Thymus
Heart
Spleen
Lymph nodes
Cortex
Trabeculae
Medulla
Fibrous capsule
Cortical epithelial cell
Thymocytes
Trabecula
Fibrous capsule
Cortex
Medulla
Dendritic cell
Macrophage
Blood vessel
Medullary epithelial cell

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

- Secondary lymphoid tissues consist of the
  - **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 **spleen**, which collects antigen from the bloodstream;
  - 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**
- 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)


STRUCTURE OF A LYMPH NODE
Afferent lymphatics
Capsule
Cortex
Secondary follicle
Medulla
Medullary cords
Efferent lymphatics
Germinal center
Paracortex
Primary follicle
Trabeculae
Medullary sinus
© Sridhar Rao

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.

- **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.

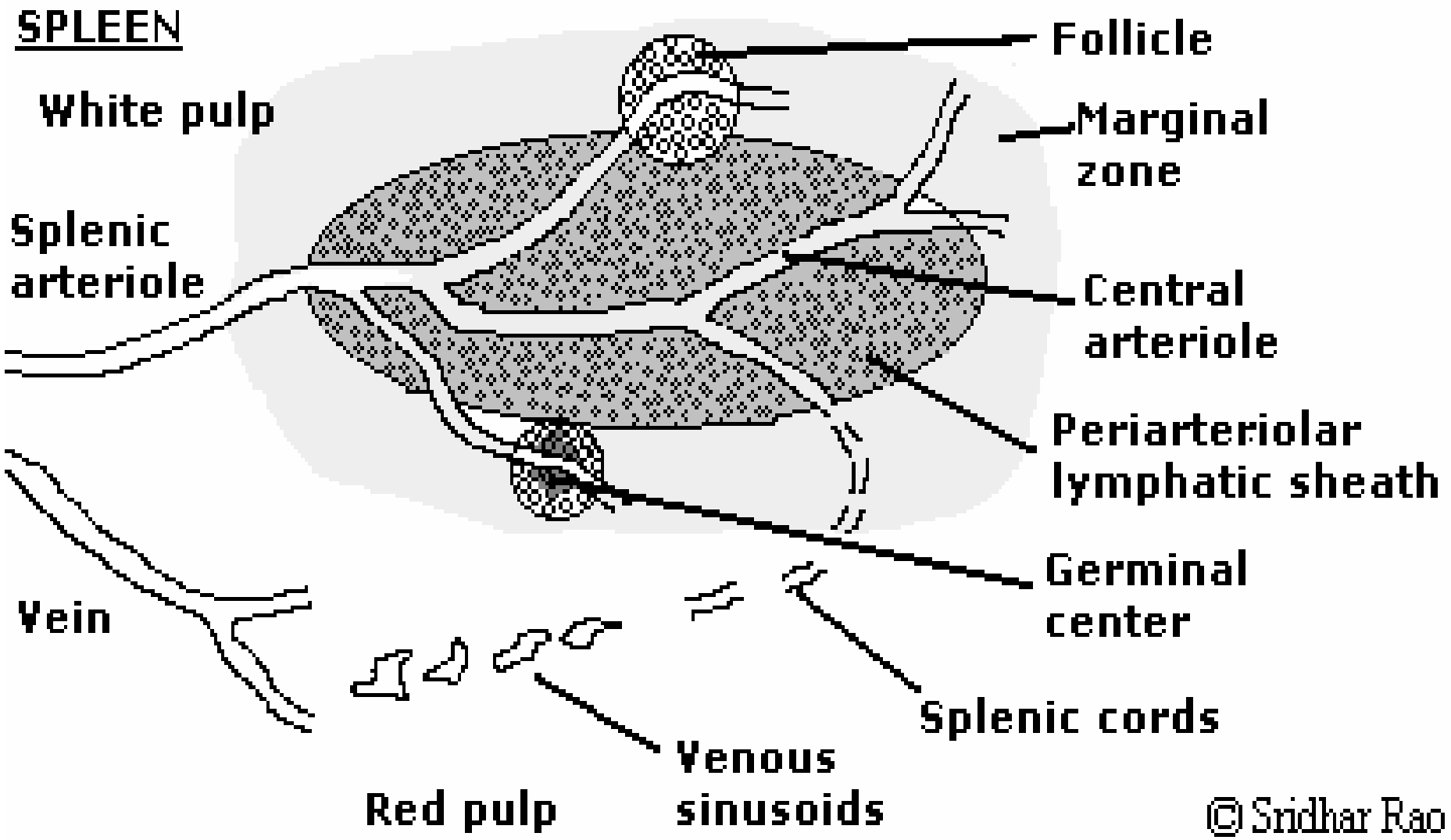
- **Medulla**
- The medulla comprises:
  - large blood vessels
  - medullary cords and sinuses
  - plasma cells

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.

Spleen functions

- 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


SPLEEN
White pulp
Follicle
Marginal zone
Splenic arteriole
Central arteriole
Periarteriolar lymphatic sheath
Germinal center
Vein
Splenic cords
Venous sinusoids
Red pulp
© Sridhar Rao

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.

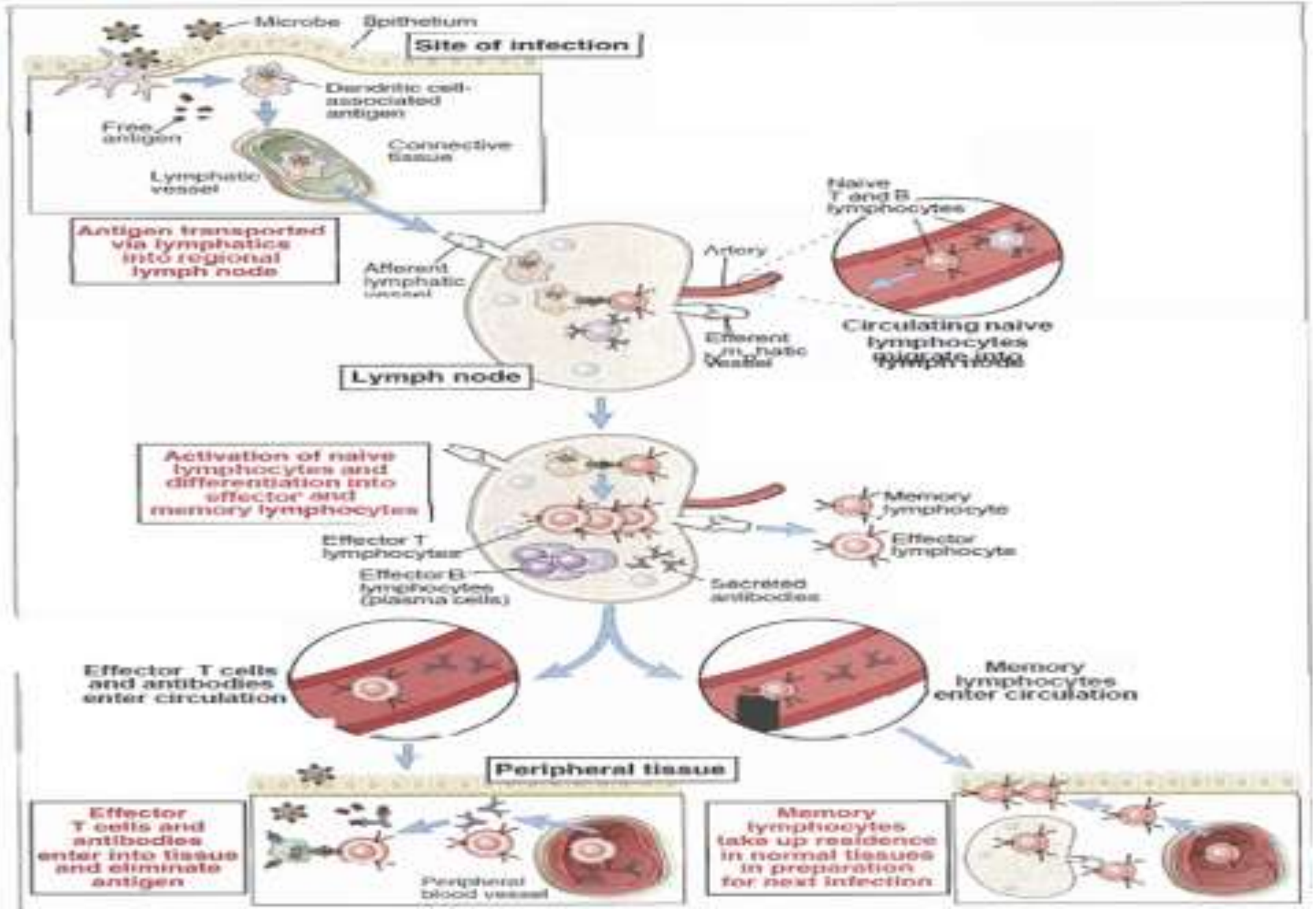
- Effector (Effector T cells include CD8+ cytotoxic T cells and CD4+ helper T cells ;TH1, TH2, and TH17 subsets) and memory T cells preferentially leave the blood and enter peripheral tissues through venules at sites of inflammation.
- Whereas naïve T cells recirculate and reenter the LN agai
- the two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

Memory T cells

- Central memory T cells were defined as human T cells that express high levels of CCR7 and L-selectin;
- effector memory T cells were defined as T cells that express low levels of CCR7 and L-selectin
- So Central cells recirculate back to peripheral node and reside there
- And the effector cell reside in tissues

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.


Microbe
Epithelium
Site of infection
Dendritic cell-associated antigen
Free antigen
Connective tissue
Lymphatic vessel
Antigen transported via lymphatics into regional lymph node
Afferent lymphatic vessel
Artery
Efferent lymphatic vessel
Lymph node
Naive T and B lymphocytes
Circulating naive lymphocytes
Activation of naive lymphocytes and differentiation into effector and memory lymphocytes
Effector T lymphocytes
Effector B lymphocytes (plasma cells)
Secreted antibodies
Memory lymphocyte
Effector lymphocyte
Effector T cells and antibodies enter circulation
Memory lymphocytes enter circulation
Peripheral tissue
Effector T cells and antibodies enter into tissue and eliminate antigen
Peripheral blood vessel
Memory lymphocytes take up residence in normal tissues in preparation for next infection

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
  - Passive, transfer serum or lymphocytes from specifically immunized individual to not-exposed person (naïve). Maternal Ab to fetus

Important definitions

- **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.

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 Dausset 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