(Lecture 1)

→ 1: Common terms (Just understand):

Immunity: resistance to disease / Immune system: The collection of biological structures in an organism that resists infections/ immune response: coordinated reaction of the biological structures to infectious microbes/ Immunology: the study of the immune system in any organism

→ 2: Roles of the immune system:

a) the main function is to target foreign antigens This is done through three steps:
1. Recognize self from nonself, 2. Restore 3. Remember
Fighting infections can be boosted by vaccination and can be weakened by immunodeficiencies (AIDS)
b) Fighting tumors: An important application is immunotherapy (treating cancer by boosting the immune system)
c) Injure cells and induce pathological inflammation (bad effect): Best examples are allergies & autoimmune diseases
d) Fight new implanted tissues and organs: a big challenge for gene therapy and transplantation
e) Keeping homeostasis (Important)

→ 3: Components of the immune system: (there is some communication between them) (Extremely important)

	Innate immunity	Adaptive Immunity
Components	 1. Physical and chemical barriers 2. Phagocytic leukocytes 3. Dendritic cells 4. Natural Killer cells 5. Plasma proteins (complement)	 1. Humoral immunity (B cells, which mature into antibody secreting plasma cells) 2. Cell-mediated immunity (T cells, which mature into effector helper and cytotoxic T cells)
Activity	Always present	Normally silent
Response and potency	Immediate response, but has a limited and lower potency	Slower response (over 1-2 weeks, but is much more potent
Specificity	General: can recognize general classes of pathogens (i.e. bacteria, viruses, fungi, parasites) but cannot make fine distinctions	Recognizes highly specific antigens
Course	Attempts to immediately destroy the pathogen, and if it can't, it contains the infection until the more powerful adaptive immune system acts.	Slower to respond; effector cells are generally produced in 1 week and the entire response occurs over 1-2 weeks. However, this course can vary somewhat during different responses in an individual.

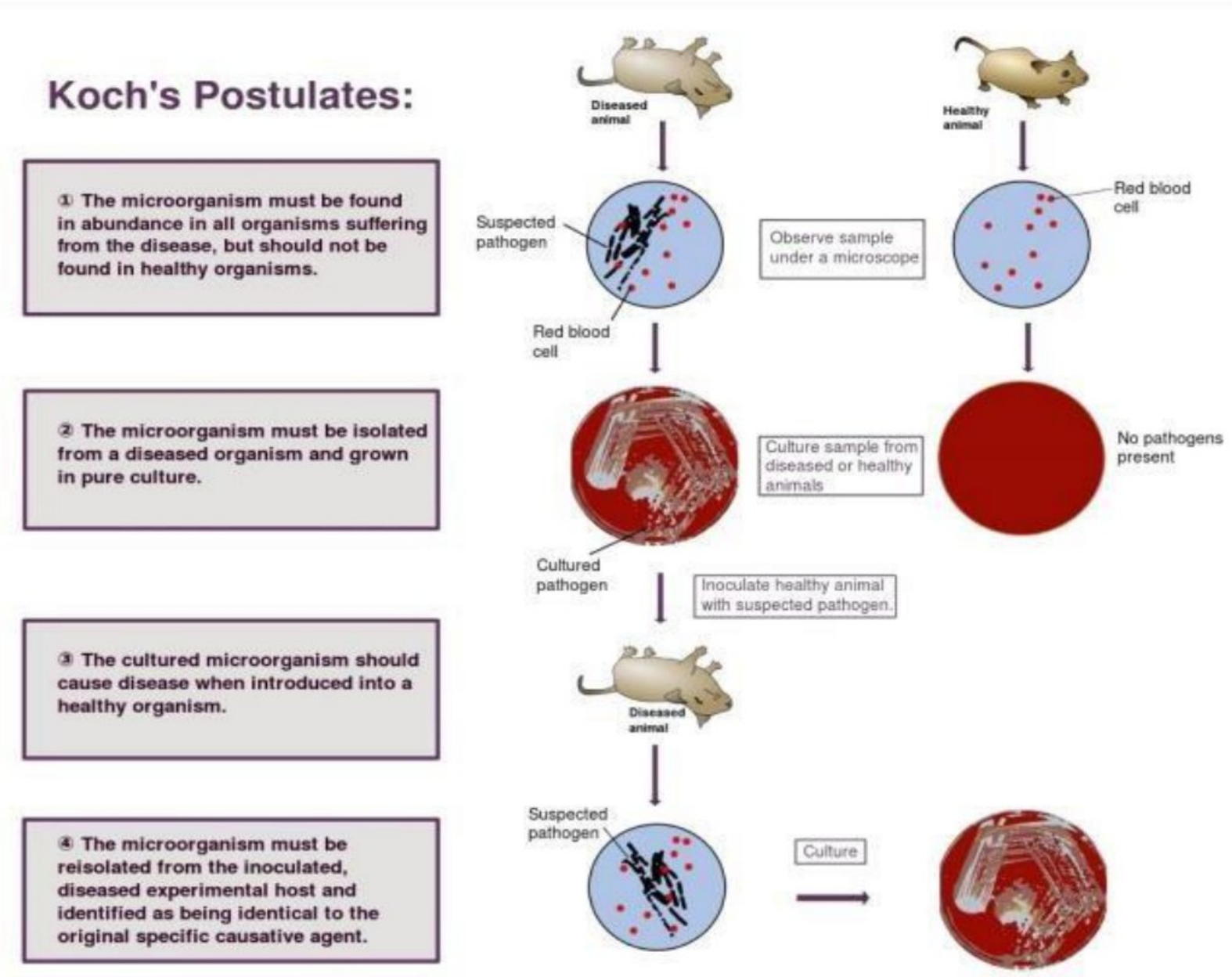
→ 4: Origin of the immune system: The cells of the immune system originate from the bone marrow from cells called "hematopoietic stem cells", in the bone marrow there are stem cells that can differentiate into lymphoid stem cells and myeloid stem cells
- Innate immunity is almost found in all living organisms, but adaptive immunity is not
- with time, the immune system becomes more complex because of the huge number of bacteria, and as a result, both the bacteria and the immune system are always becoming more complex

→ 5: Location of the immune system:
- The duty of the immune system is to survey the whole body so it should be present everywhere.
- There are sites where immune cells collect to fulfill their function. For example, in the small intestine, there is lymphatic tissue that surveys intestinal pathogens called Peyer's patches.
- The bone marrow is an important place for the generation of immune and non-immune blood cells.

→ 6: Antigens & Antibodies: (Somehow important)
◦ Antigens are any substance that may stimulate the immune system to produce antibodies, there are two types of antigens: self and non-self
◦ Normally, the immune system is stimulated vs. non-self antigens, but in some diseases, it may be stimulated vs. self-antigens
◦ Epitope also known as antigenic determinant, is the part of an antigen that is recognized by the immune system.
◦ Antibodies, also called immunoglobulins: the Y-shaped molecules are proteins that are manufactured by the body that help fight against antigens.

→ 7: History of immunology (Not important)
◦ In 1798, **Edward Jenner**, noticed that milkmaids were protected from smallpox if they had been first infected with cowpox microbe.
◦ **Pasteur** is renowned for his discoveries of the principles of vaccination, microbial fermentation, and pasteurization, he was responsible for disproving the doctrine of spontaneous generation.

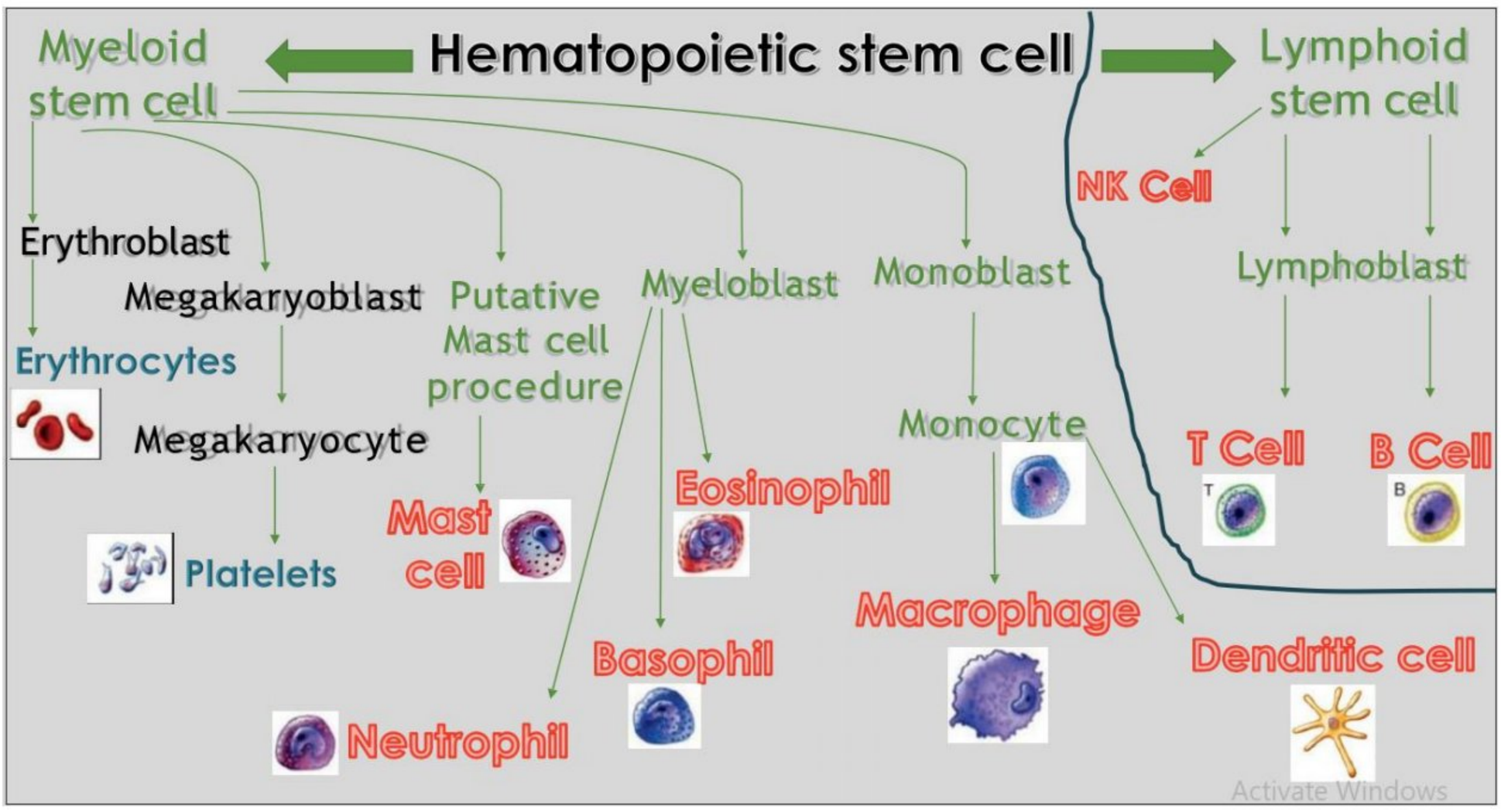
◦ Robert Koch was one of the main founders of modern bacteriology. He identified the specific causative agents of tuberculosis, cholera, and anthrax and gave experimental support for the concept of infectious disease (germ theory), which included experiments on humans and other animals.



◦ **Paul Ehrlich** and others, recognized that a specific antigen elicited the production of a specific antibody. Ehrlich hypothesized that these antibodies were specialized molecular structures with specific receptor sites that fit each pathogen like a lock and key. Thus, the first realization that the body had a specific defense system was introduced.
◦ The idea that specific cells could be directly involved with defending the body was first suggested in 1884 by **Élie Metchnikoff**. he conducted experiments on animals where he would inflict some injuries, and he would later notice while examining under the microscope that there are some cells trying to treat the injury.
◦ However, it was not until the 1940s that his theories were accepted and the cell-mediated, as opposed to the humoral, immune response was recognized.

(Lecture 2)

→ 1: Origin of immune cells:



→ 2: Some terms:
◦ Granulocytes: Neutrophils, Basophils, and Eosinophils. (mast cells can be considered as a granulocyte)
◦ Lymphocytes: NK cells, T and B cells
◦ Leukocytes: Granulocytes, Lymphocytes, monocytes, and NK cell
◦ Phagocytes: Macrophages and neutrophils
◦ Antigen-presenting cells: Macrophages and dendritic cells

(We will study four categories in this and the next lecture: a) Phagocytes/ b) Mast Cells, Basophils& Eosinophils/ c) Antigen-Presenting Cells/ d) Lymphocytes)

→ 3: a)Phagocytes:

a1- Neutrophils (3 main sub-topics: Main properties/types of granules/ mechanism of fighting)

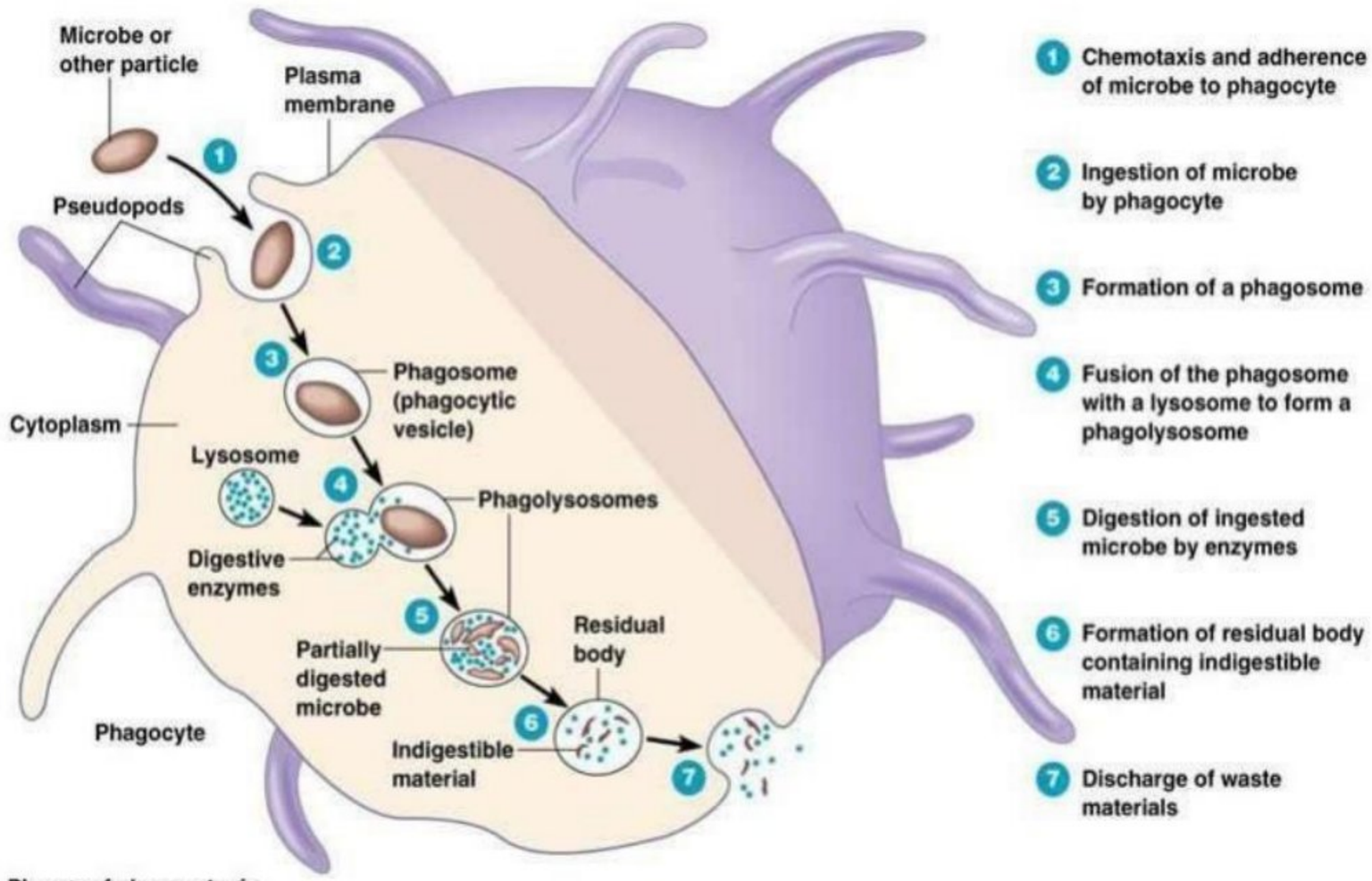
- Main properties: 1- its granules don't stain (neutral) / 2- most abundant WBC (70%)/ 3- most early response / 4- short lifespan (6 hours) then cleared by macrophages/ 5- 100 billion neutrophils per day produced/ 6- Production is stimulated by granulocyte colony-stimulating factor(G-CSF)/ 7- polymorphonuclear leukocyte (the nucleus is segmented into 3-5 lobes)

- Contain two types of granules:

1) Specific granules (major): filled with many enzymes such as:
a- lysozyme: Breaks glycosidic bonds between NAM and NAG in bacterial cell wall
b- Collagenase: breaks the peptide bond in the collagen
c- Elastase: Breaks elastic fibers
2) azurophilic granules: lysosomes containing enzymes and other microbicidal substances

- Mechanism of fighting

1) It keeps circulating until it reaches an infection side, then it migrates into the infected tissue by using collagenase and elastase to break the ECM and move easily.
2) Have three mechanisms to fight the pathogen:
a- Phagocytosis (Chemotaxis: process in which the phagocyte will follow a certain gradient from a molecule in the bacteria.)



Phases of phagocytosis

Neutropenia is an abnormally low concentration of neutrophils in the blood. Neutropenia has many causes and can be congenital and acquired (e.g. cancer treatment, autoimmune diseases)

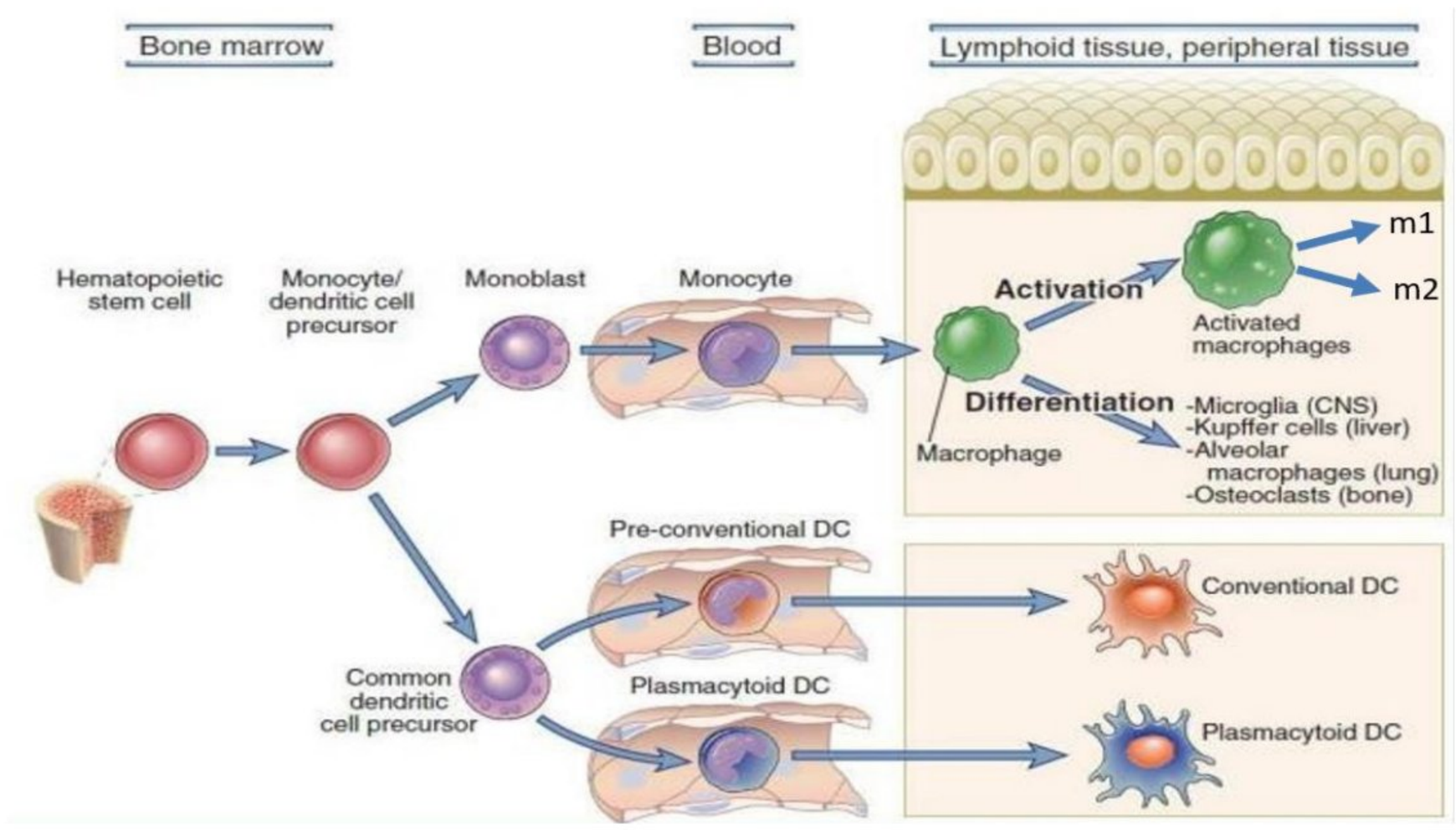
b- Releasing enzymes from granules to ECM which can harm bacterial cells
c- Neutrophil extracellular traps (NETs): some neutrophils may get their DNA out of the cell and cover a large area harming microbes by some DNA components such as s histones, ROS, and Myeloperoxidase (MPO)

a2- Macrophages (Contain 3 topics: function / Formation/types)

- Function of macrophages:

1) Phagocyte pathogens & present some of their particles on their surface
2) Phagocyte dead host cells
3) Secrete cytokines (Signaling proteins for stimulating the immune system)
4) promote repair (angiogenesis & fibrosis)

- Formation of macrophages:

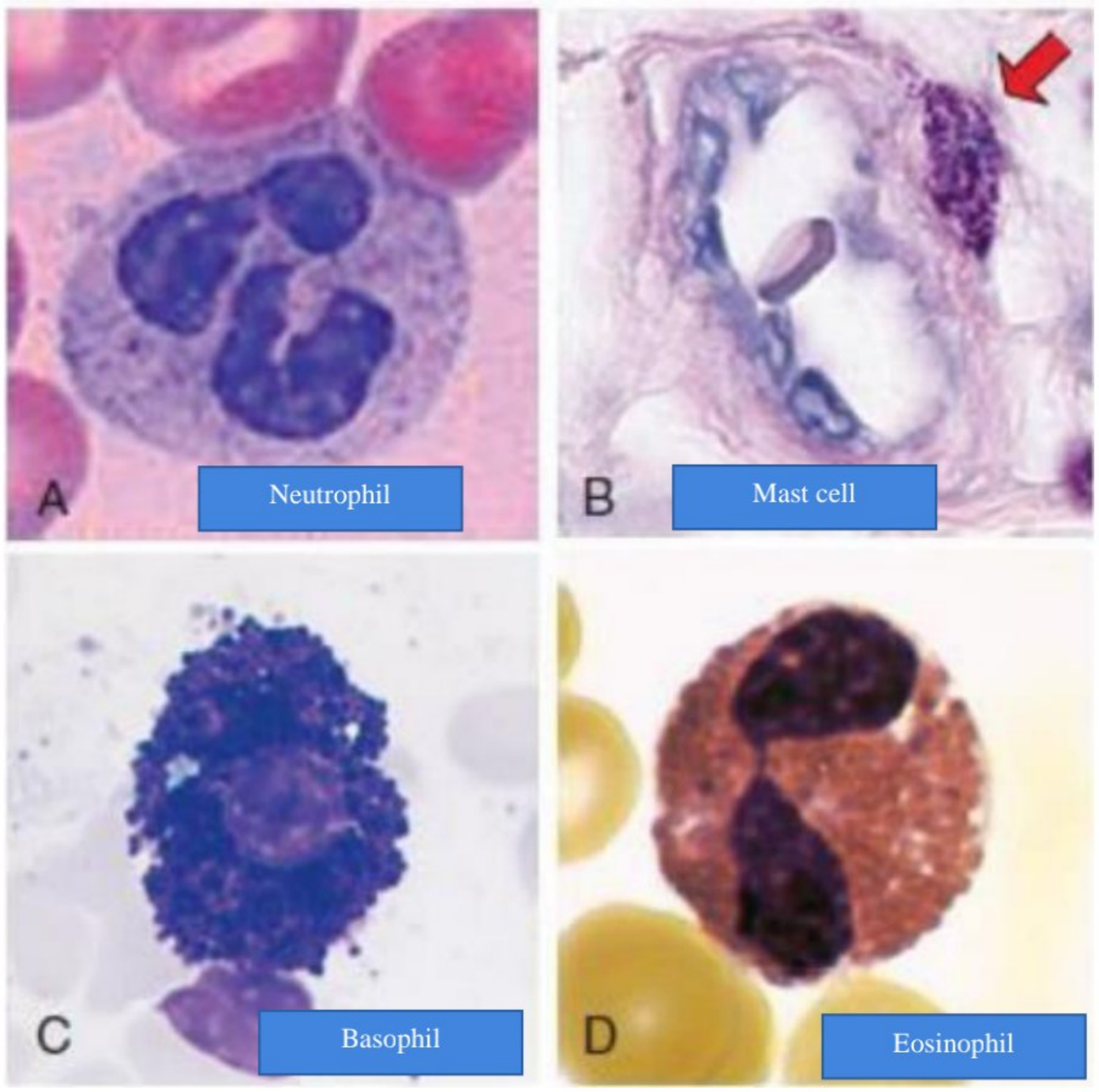


- Types of activated macrophages:

◦ If it finds microbes or interferon-gamma (IFNγ) or LPS, it will differentiate into **M1** which has a microbicidal activity and secrete inflammatory cytokines to stimulate the immune response, and this is called **classical activation** of the macrophage **Immunostimulation**.

◦ If the inflammation already took place, it will differentiate to **M2** by IL-10 & glucocorticoid hormones, and produce proteins that are responsible for **immunoregulation**, this is called **alternative activation**

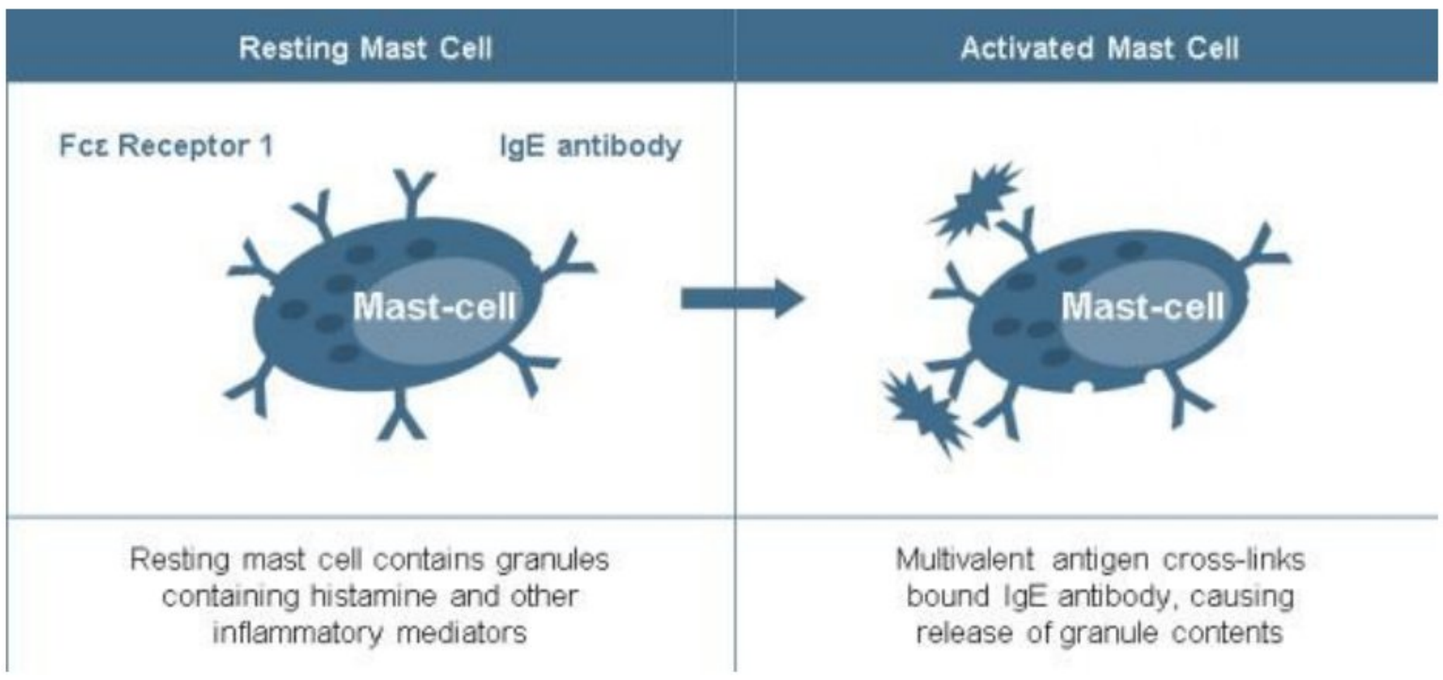
→ 4: b) Mast Cells, Basophils & Eosinophils:



B1- Mast cells: (Most abundant) present in healthy skin and mucosal epithelium adjacent to blood vessels and nerves

◦ Structure: contain granules filled with cytokines such as histamine mainly and have some antibodies on its surface like IgG and IgE that are bound on certain receptors

◦ Cause allergic diseases (HOW?) the antigen (allergen) binds to the antibodies in themast cell surface activating it, then the mast cell releases the contents of the granules like histamine, producing allergy



B2- Basophils are blood granulocytes with many structural and functional similarities to mast cells.

◦ Like mast cells, basophils express IgG and IgE receptors, bind IgE, and can be triggered by antigen binding to the IgE

◦ Basophils constitute less than 1% of blood leukocytes, normally not present in tissues and their importance is uncertain.

B3- Eosinophils are blood granulocytes that express cytoplasmic granules containing enzymes that are harmful to the cell walls of parasites but can also damage host tissues.

◦ Several lines of evidence suggest that deficiency of eosinophils is not associated with any characteristic abnormality.

(Lecture 3)

→ 1: c) Antigen-Presenting Cells: cells that capture foreign antigens and display them to lymphocytes to activate them (Link between innate and adaptive immunity) (5 TYPES: a) dendritic cell, b) Macrophages, c) B cells, d) some endothelial cells, & e) thymus epithelial cells)
(Sub-topics covered: Dendritic cells/ macrophages/ B cells/ MHC)

- Dendritic cells: (types: a1) classical (conventional) dendritic cells -most important-, a2) Follicular dendritic cells, and a3) plasmacytoid dendritic cells)
◦ classical (conventional) dendritic cells:
-) features: Have membranous projections and phagocytic capabilities
-) Location: lymphoid tissues, mucosal epithelium, skin, and organ parenchyma.
-) Function: In response to activation by microbes, conventional dendritic cells in the skin, mucosa, and organ parenchyma become mobile, migrate to lymph nodes, and display microbial antigens to T lymphocytes. activating naive T cells by presenting antigens to them on MHC II molecule
◦Follicular dendritic cells: are also dendritic cells that present antigens, BUT they differ from conventional dendritic cells in many things such as a) Origin: they originate from mesenchymal cells rather than monocytes b) Motility: they are nonmigratory c) Location: they're found in germinal centers in lymph nodes d) Function: they play an important role in B lymphocytes maturation
◦ plasmacytoid dendritic cells: expert in type I interferon synthesis upon viral stimulation

- Macrophages: present antigen to already activated helper T lymphocytes for more activation, so T cells secrete cytokines that help the macrophage to digest bacteria that are resisting killing.

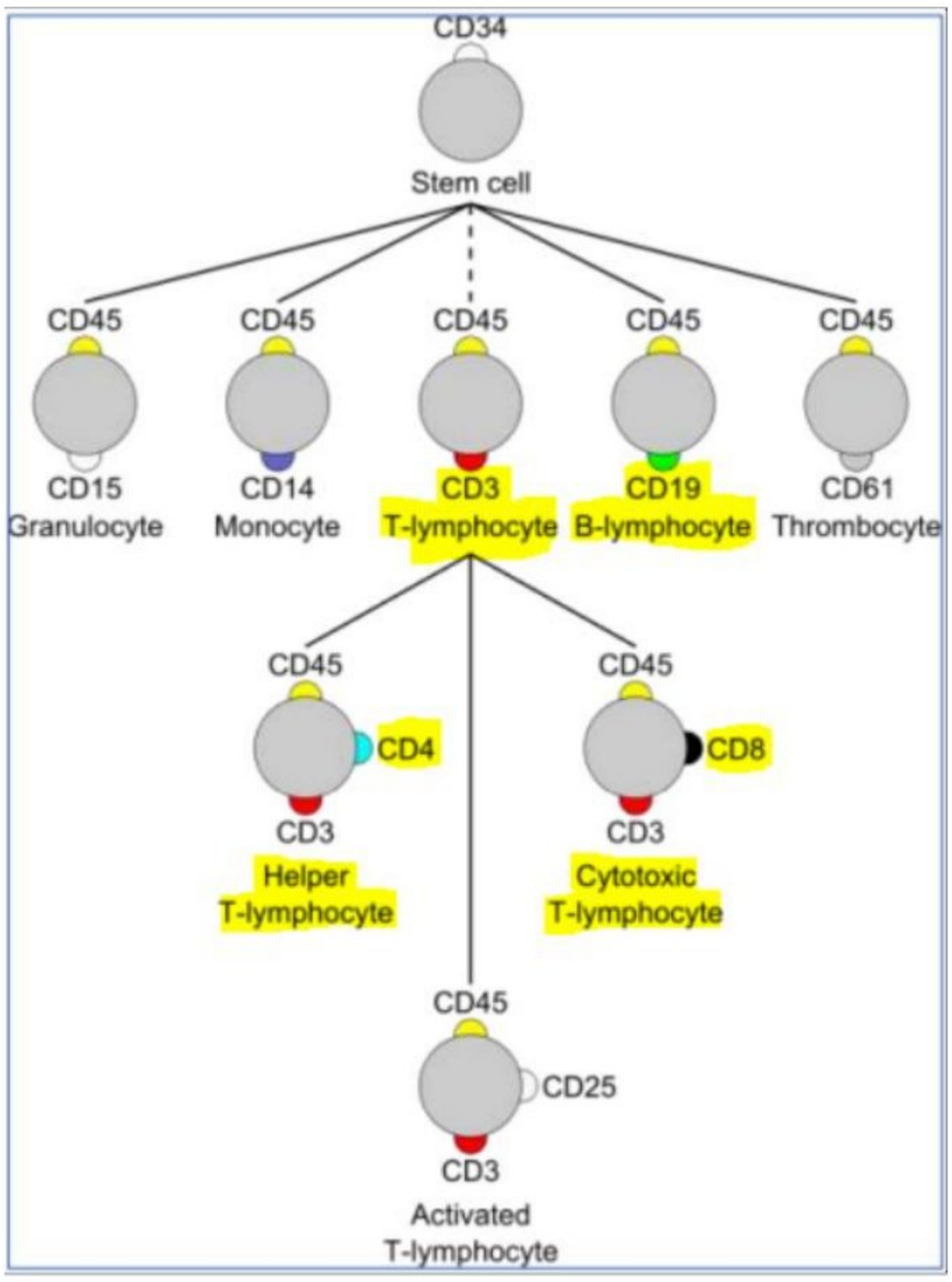
- B cells present antigens to helper T cells which helps in humoral immunity

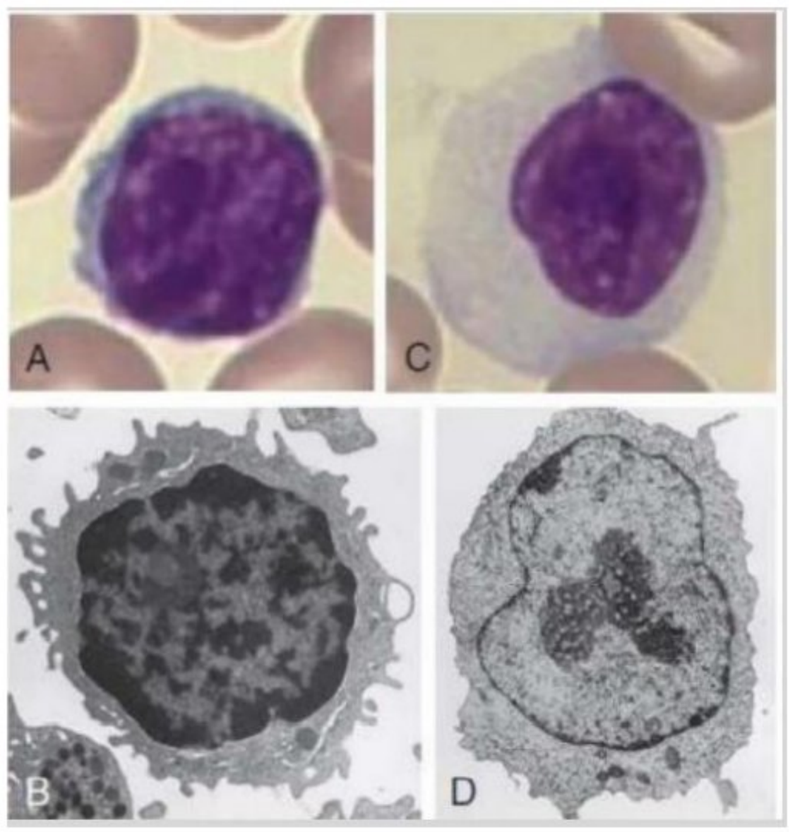
- MHC (major histocompatibility complex)

	MHC I	MHC II
Location	found on almost all cells	found on professional antigen-presenting cells such as **classical** dendritic cells, Macrophages, B cells, and some endothelial cells.
Antigen presented	Intracellular proteins	extracellular proteins
Function	activating cytotoxic T cells (CD8+) if there is an infection	activate helper T cells (CD4+)
How do they accomplish their function?	1) Normally cytoplasmic proteins are degraded by proteasomes enzymes continuously. 2) Degraded proteins are translocated from the cytoplasm to the ER and attached to the MHC I molecule. 3) MHC I is released on the surface of the cell and detected by CD8+ T cells, if the protein is abnormal (Infected cell or cancer cell) then the CD8+ will start attacking this cell.	The microbe is destroyed by phagocytosis, then some of its proteins are released on the surface of the cell attached to the MHC II molecule which will be detected by CD4+ T cells.

→ 2: d) Lymphocytes (NK, T & B cells)
- Natural killer (NK) cells are lymphocytes distinct from T and B cells that play important roles in innate immune responses mainly against intracellular viruses and bacteria/ No need for clonal expansion and differentiation/ Inhibited by MHC 1 so it kills cells that downregulate them such as some virally infected cells

- T & B cells: (Topics we will cover: general information/ morphology/ origin/ location/ function/ replication)
a) General info: B cells are responsible for humoral immunity by secreting antibodies. / T cells are responsible for cell-mediated immunity./ Most important two types of T cells are: Cytotoxic T cells and Helper T cells, the less common types are: regulatory T cells./ They are activated once they are exposed to a specific antigen.
b) Morphology: B& T cells are morphologically similar, so we use "cluster of differentiation or CD" to distinguish between them/ CD molecules may be receptors or ligands and sometimes adhesion molecules.





c) Origin:

T cell:

Formation in the bone marrow → Mature in the Thymus but remain naive → Go to a lymph node, spleen, mucosal and skin lymphoid tissues until they find their antigen and become activated

B cell:

Formation in the bone marrow → Early maturation in the Bone marrow → Fully maturated in the lymph nodes and convert into plasma cells

d) Location: most lymphocytes are found in the lymphoid organs (mainly the lymph nodes and spleen) /2% are in the blood

e) Function:

- Function of B cells: produce antibodies in blood & mucosa, important in the neutralization of microbes, phagocytosis, complement activation
- Function of cytotoxic t cells: Killing of infected cells: 1) Produce perforin that will pierce the cell membrane of the cell 2) Produce granzymes that will penetrate through holes produced by perforin 3) granzymes cleave caspase cascade which leads to apoptosis
- Function of helper t cells: produce cytokines that help in 1) Activating macrophages: to kill bacteria that are resisting killing 2) inducing inflammation & 3) activating the differentiation and proliferation of B & T cells

f) Replication: there are 2 important features regarding those types of cells: clonal expansion & gene rearrangement

(Lecture 4)

Lymphoid organs and tissues are divided into primary & secondary

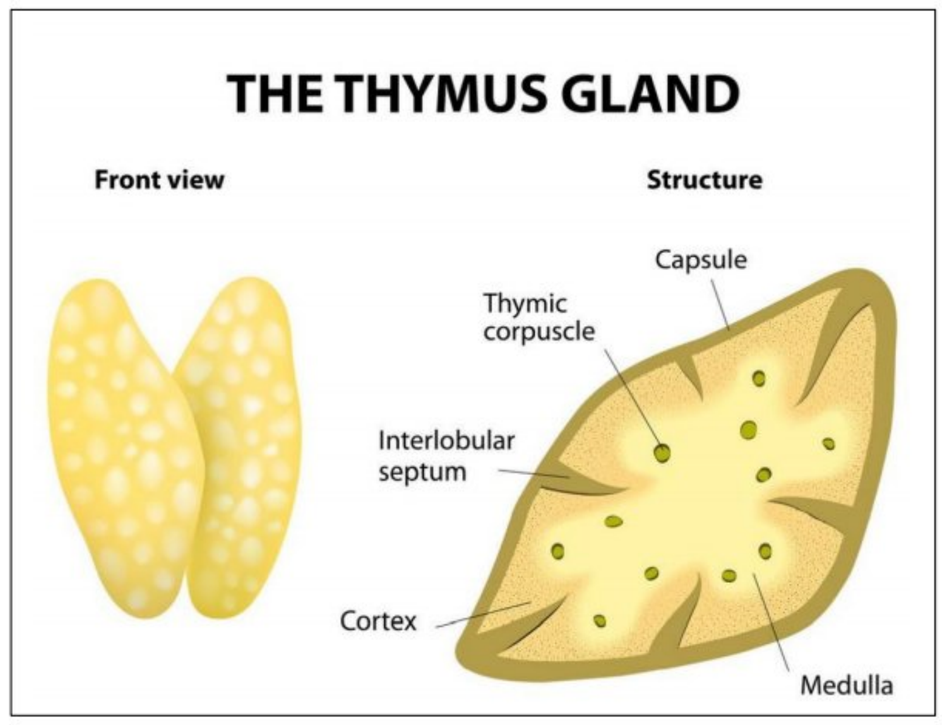
→ 1: Primary lymphoid organs

- Functions: 1- Formation of immune cells 2- Maturation of immune cells
- There are two types: a) Bone marrow and b) Thymus

a) Bone marrow:
- Site of developing most blood and immune cells (Hematopoiesis)+site of early events in B cell maturation
- Site of Hematopoiesis during life: Yolk sac and para-aortic mesenchyme → Liver → Bone marrow → Bone marrow of flat bones

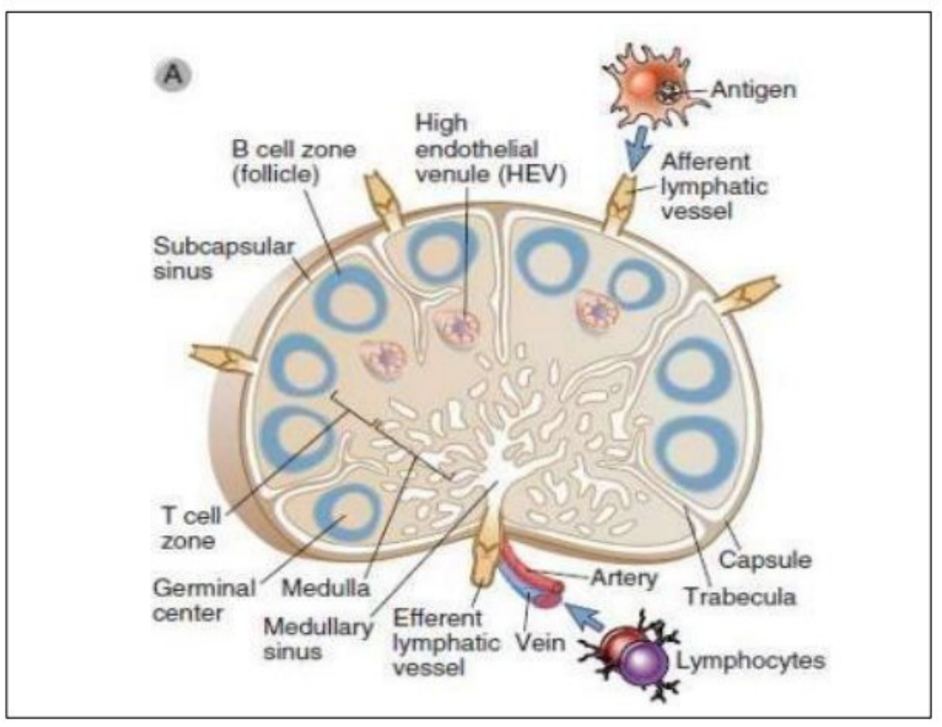
b) Thymus: Site of T cell maturation

Location: anterior mediastinum/ Shape: bilobed organ, Each lobe is divided into multiple lobules by fibrous septa, and each lobule consists of a cortex and a medulla. The medulla contains TME cells that present self-antigens to T cells, if any T cell activates, then TME cells eliminate this T cell

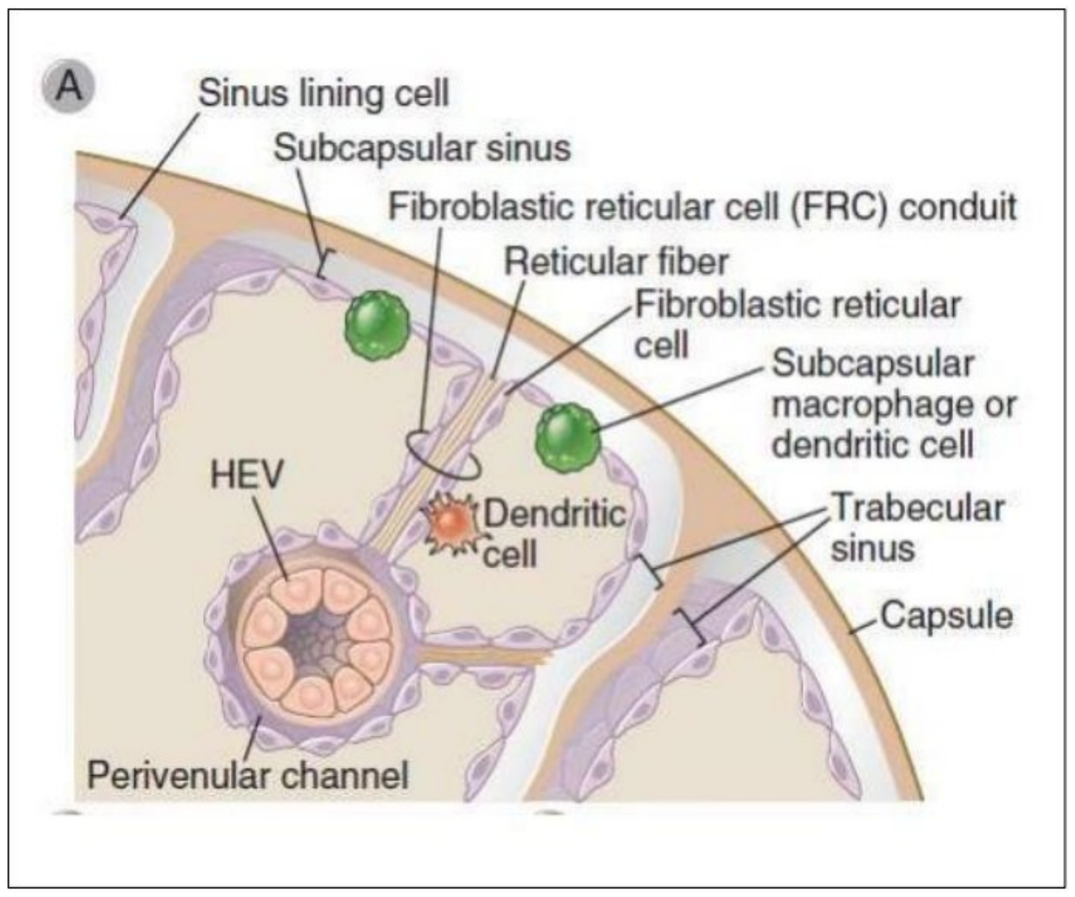


→ 2: Secondary lymphoid tissues and organs
function in activating lymphocytes
- They form 3 structures: a) Lymph nodes, b) Lymphatic tissues and c) spleen

A) Lymph nodes: encapsulated, vascularized secondary lymphoid organs
◦ Cells in the lymph nodes: B cells, T cells, special macrophages, and dendritic cells
◦ Parts of the lymph node: Medulla and the cortex, the cortex is divided into follicular and parafollicular zones.
◦ How do T and B cells reach lymph nodes? After they're released into the circulation from the bone marrow and the thymus, they enter the lymph nodes from the high endothelial venule and follow certain chemokines (type of cytokines) to sit in their proper place waiting for their antigens.
◦ How do T and B cells reach lymph nodes? After they're released into the circulation from the bone marrow and the thymus, they enter the lymph nodes from the high endothelial venule and follow certain chemokines (type of cytokines) to sit in their proper place waiting for their antigens
◦ Now antigens will reach lymph nodes either free antigens or presented on the surface by dendritic cells and macrophages
◦ There are some macrophages and dendritic cells that are resident in the lymph nodes, they'll catch some of the free antigens and present them to the lymphocytes



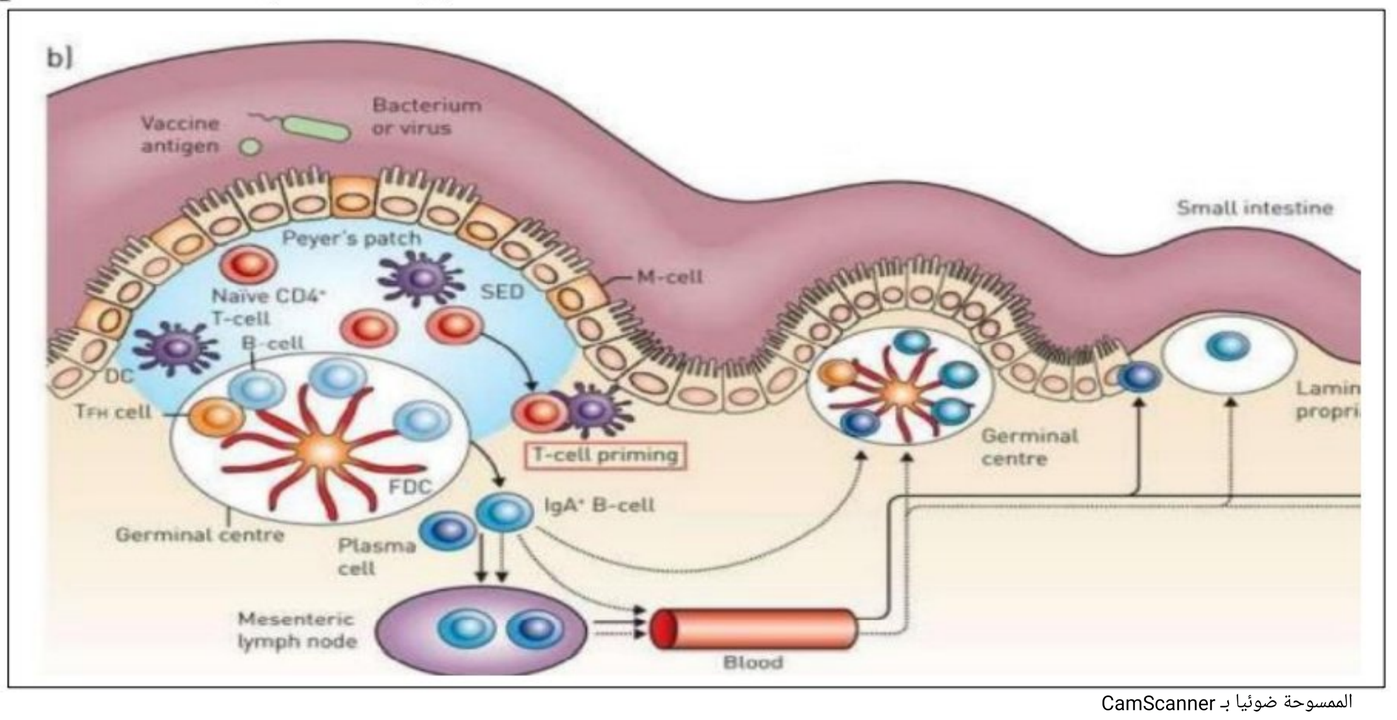
◦ So, antigens presented to lymphocytes are either: 1. Free antigens (Only to B cells)/ 2. Antigens presented on Dendritic cells and macrophages that came from the skin and mucosal tissues (Only to T cells)/ 3. Antigens presented on Dendritic cells and macrophages that are resident in the lymph nodes
◦ How antigens are presented to B lymphocytes? Viruses and other high molecular weight antigens are taken up by sinus (subcapsular) macrophages and dendritic cells and presented to cortical B lymphocytes. Small molecular-weight antigens are detected as free antigens by B cells
◦ How antigens are presented to T lymphocytes? Low-molecular-weight soluble antigens are transported to resident dendritic cells that extend processes and capture and pinocytose soluble antigens. The contribution of this pathway of antigen delivery may be important for initial T cell immune responses to some microbial antigens, but larger and sustained responses require delivery of antigens to the node by tissue dendritic cells



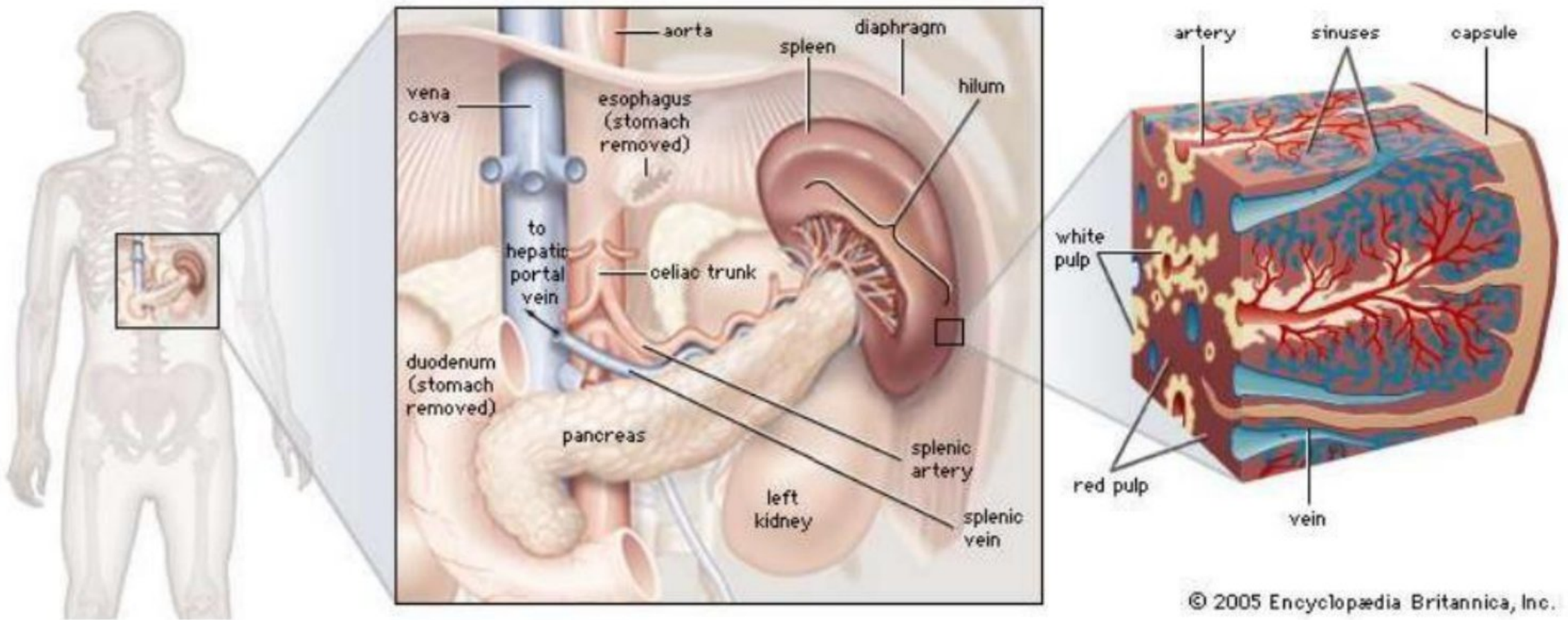
b) Regional lymphatic tissues: special non-encapsulated lymphoid structures found on the major epithelial barriers of the body (e.g. Mucosa-associated lymphoid tissue (MALT))

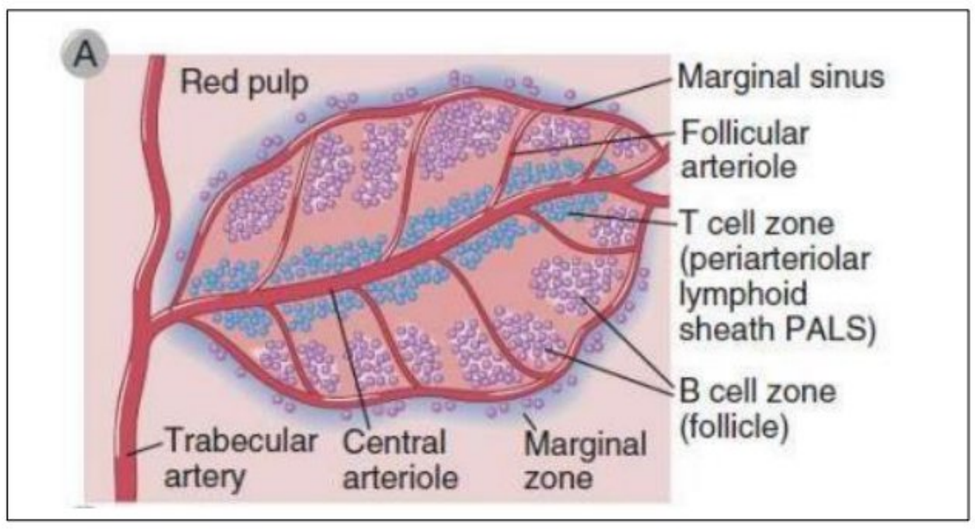
Normal small intestine histology with Peyer's patches. b) Initiation of the immune response in the gut: antigens are taken up by microfold (M)-cells and process to the resident dendritic cells (DCs) in Peyer's patches.

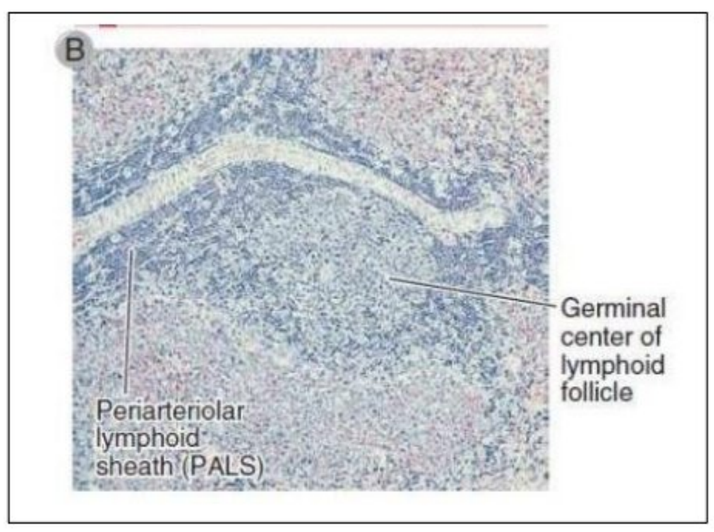
T-follicular helper (TFH) cells interact with B-cells and follicular dendritic cell (FDC) thus forming a germinal center. Antigen specific plasma cells and memory B-cells are generated and migrate through the blood and mesenteric lymph nodes



c) Spleen:







→ a highly vascularized organ whose function is an immune response, it weighs about 150 g in adults and is located in the left upper quadrant of the abdomen, it receives blood from the splenic artery that pierces the capsule at the hilum and divides into progressively smaller branches that remain surrounded by protective and supporting fibrous trabeculae

→Spleen consists of two parts: 1- red pulp and 2- white pulp. 2) Secondary lymphoid tissues

◦ 1- Red pulp: contains macrophages that serve as an important filter for the blood, it removes: Aging RBCs, Damaged cells, and microbes (specially opsonized)

→ Individuals lacking a spleen are highly susceptible to infections with encapsulated bacteria

◦ 2- White pulp: Rich-Lymphocyte pulp that functions in promoting adaptive immune responses to blood-borne antigens.

→ The white pulp is organized around central arteries, derived from the splenic artery, several smaller branches of each central artery pass through the lymphocyte-rich area and drain into a marginal sinus.

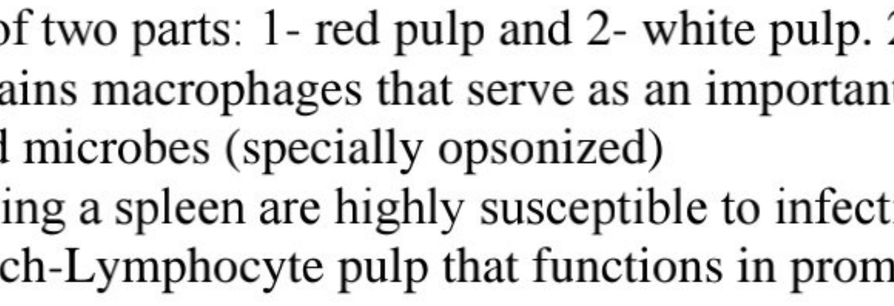
→ marginal zone: specialized cells form a boundary between the red and white pulp

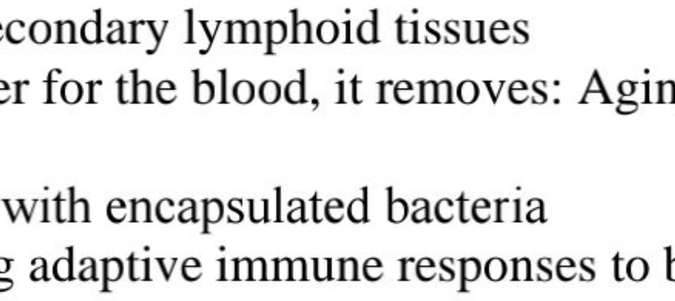
(Lecture 5)

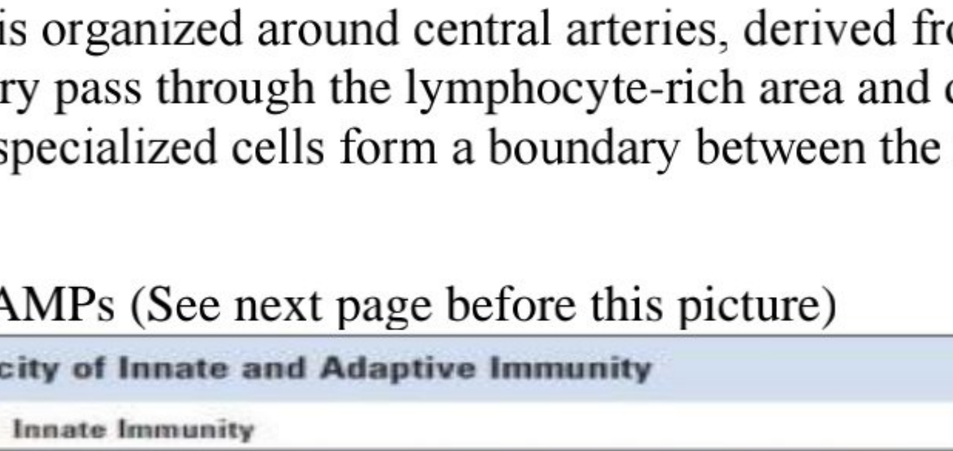
→ 1: PAMPs & DAMPs (See next page before this picture)

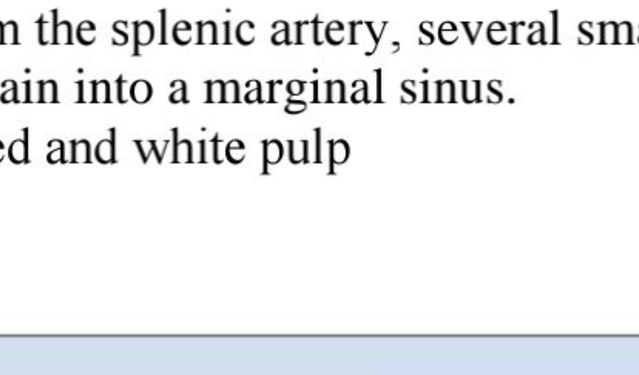
TABLE 4–1 Specificity of Innate and Adaptive Immunity

	Innate Immunity	Adaptive Immunity
Specificity	For structures shared by classes of microbes (pathogen-associated molecular patterns)	For structural detail of microbial molecules (antigens); may recognize nonmicrobial antigens
Receptors	Encoded in germline; limited diversity (pattern recognition receptors)	Encoded by genes produced by somatic recombination of gene segments; greater diversity
Distribution of receptors	Nonclonal: identical receptors on all cells of the same lineage	Clonal: clones of lymphocytes with distinct specificities express different receptors
Discrimination of self and non-self	Yes; healthy host cells are not recognized or they may express molecules that prevent innate immune reactions	Yes; based on elimination or inactivation of self-reactive lymphocytes; may be imperfect (giving rise to autoimmunity)





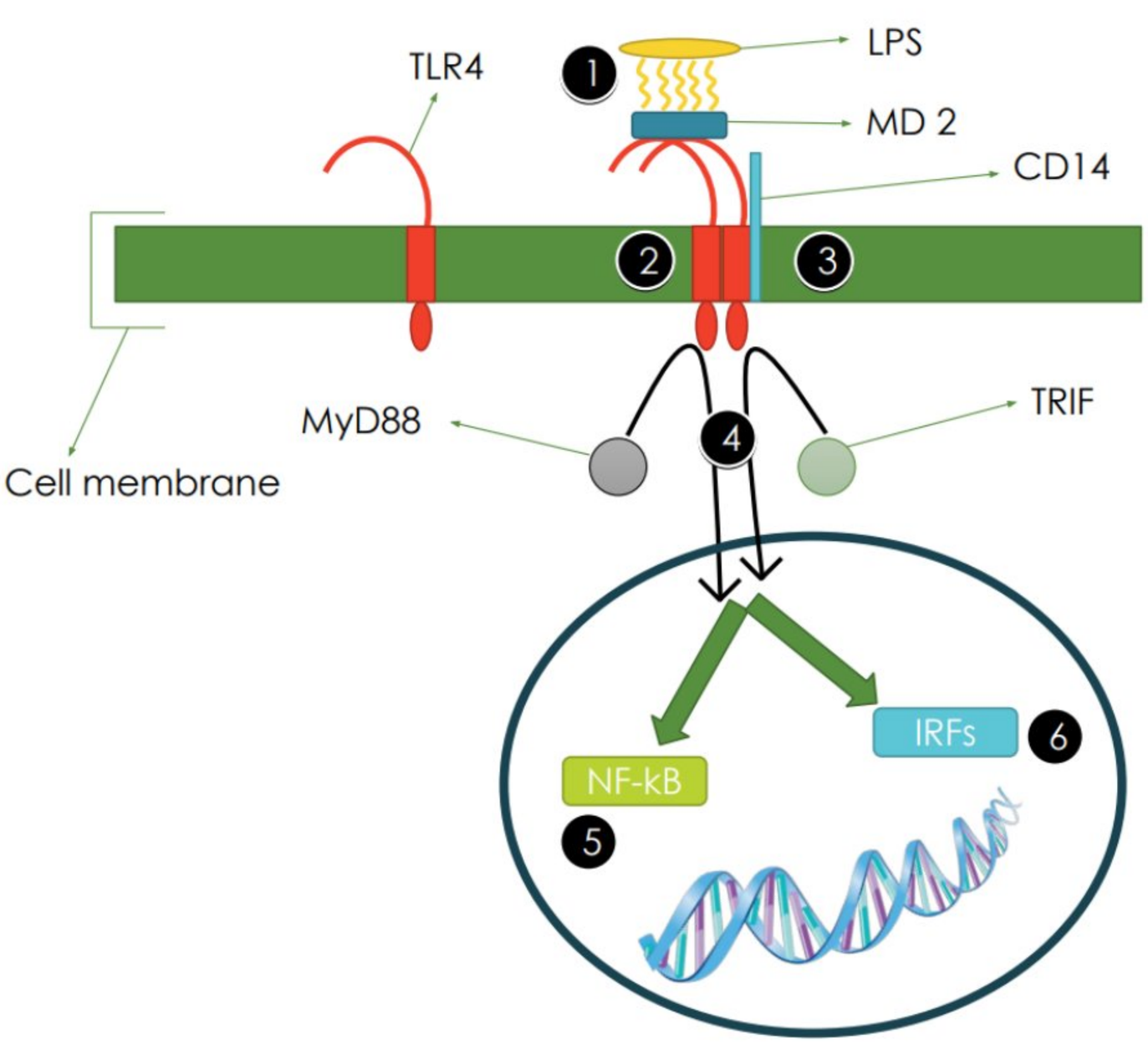




- a) PAMPs: Pathogen-associated molecular pattern/ often essential for pathogen life & not found in mammalian cells
- Type of PAMPs:
1- Nucleic acids that are unique to microbes, such as double-stranded RNA found in replicating viruses and unmethylated CpG DNA sequences found in bacteria
2- Proteins that are found in microbes, such as initiation by N-formyl methionine, which is typical of bacterial proteins.
3- Complex lipids and carbohydrates that are synthesized by microbes but not by mammalian cells, such as lipopolysaccharide (LPS) in gram-negative bacteria, lipoteichoic acid or peptidoglycan (PGN) in Gram-positive bacteria, and mannose-rich oligosaccharides.
- b) DAMPs: Damage-associated molecular pattern - not released by apoptosis - e.g. HMGB1(transcription factor)

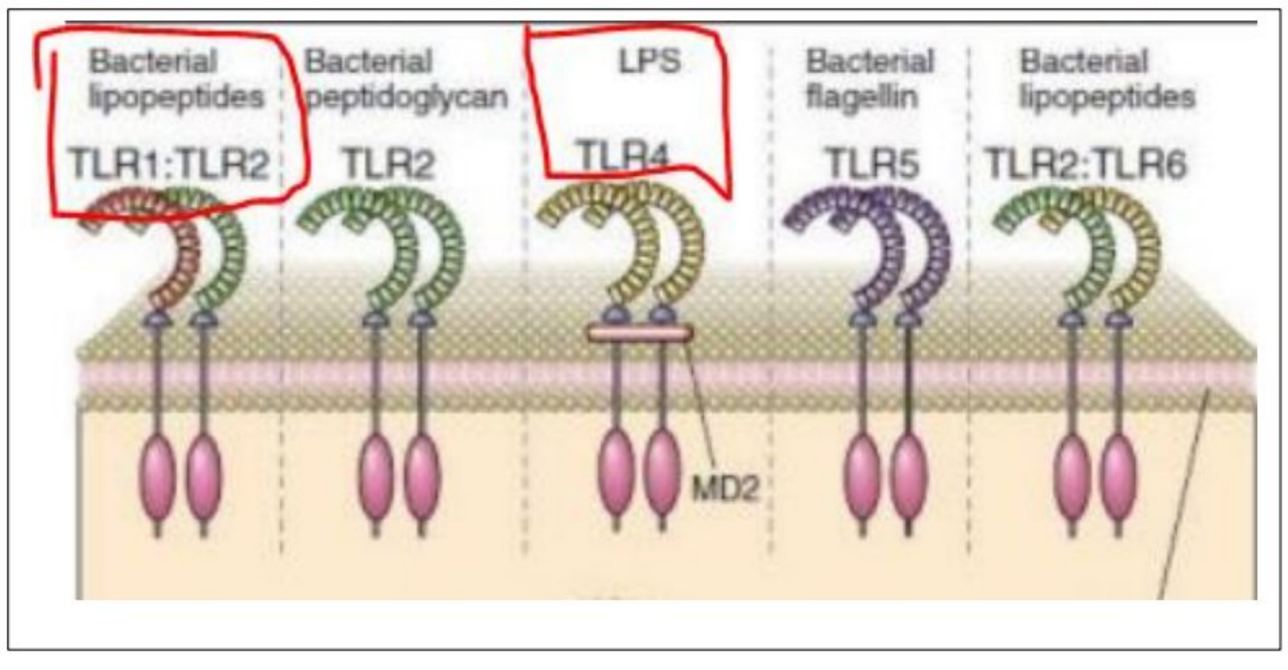
→ 2: Pattern recognition receptors
◦They are proteins expressed, mainly, by cells of the innate immune system, such as dendritic cells, macrophages, monocytes, neutrophils, and in many times epithelial cells, endothelial cells, and fibroblasts.
◦ two main mechanisms to work: promoting inflammation and achieving an anti-viral state. / detect PAMPs & DAMPs
◦ Types of PRRs:
1) cell bound: May be found on:
a- Cellular membranes (mainly on the plasma membrane, but can be found in the phagosome and the endosome)
b- in the cytosol
2) Soluble in the extracellular matrix
◦ We will start speaking in this lecture about cell-bound PPRs that are found on cellular membranes, they are 4 types:
a1- Toll-like receptors, a2- Receptors for Carbohydrates, a3- Scavenger receptors, and a4- N-Formyl met-leu-phe receptors

a1- Toll-like receptors: activating antimicrobial defense mechanisms in the cells in which they are expressed./ like a protein called "toll" found in some fruit flies/ found on the plasma membrane and in the endosomes/ Consists of 1) Leucine-rich domain, 2) intramembranous domain, and 3) cytoplasmic domain/ There are 9 types of TLRs from (1-9), e.g. TLR1, TLR2 …etc, and each one binds to certain PAMPs, the most important one is TLR4 that binds to Lipopolysaccharide.



□ How does TLR4 works?
1) Lipopolysaccharide binds to TLR4 by an adaptor protein (MD2)
2) TLR4 forms a homodimer with another TLR4 and transmit signal to inside the cell.
3) CD14 is a co-receptor that also send a signal inside the cell, so the whole signal will be stronger
4) The signal is transmitted through the cytoplasm to the nucleus by adaptor proteins (MyD88 –mainly- and TRIF), the signal will reach some transcription factors such as NF-kB and IRFs and activate them by facilitate the recruitment and activation of various protein kinases.
5) NF-kB will stimulate transcription of inflammatory genes that will induce inflammation by various effects (e.g. producing chemokines and cytokines such as IL-1, IL-6 and TNF)
6) IRFs will transcribe interferon genes producing interferons that will induce an anti-viral state in the neighboring cells (Less important than NF-kB)

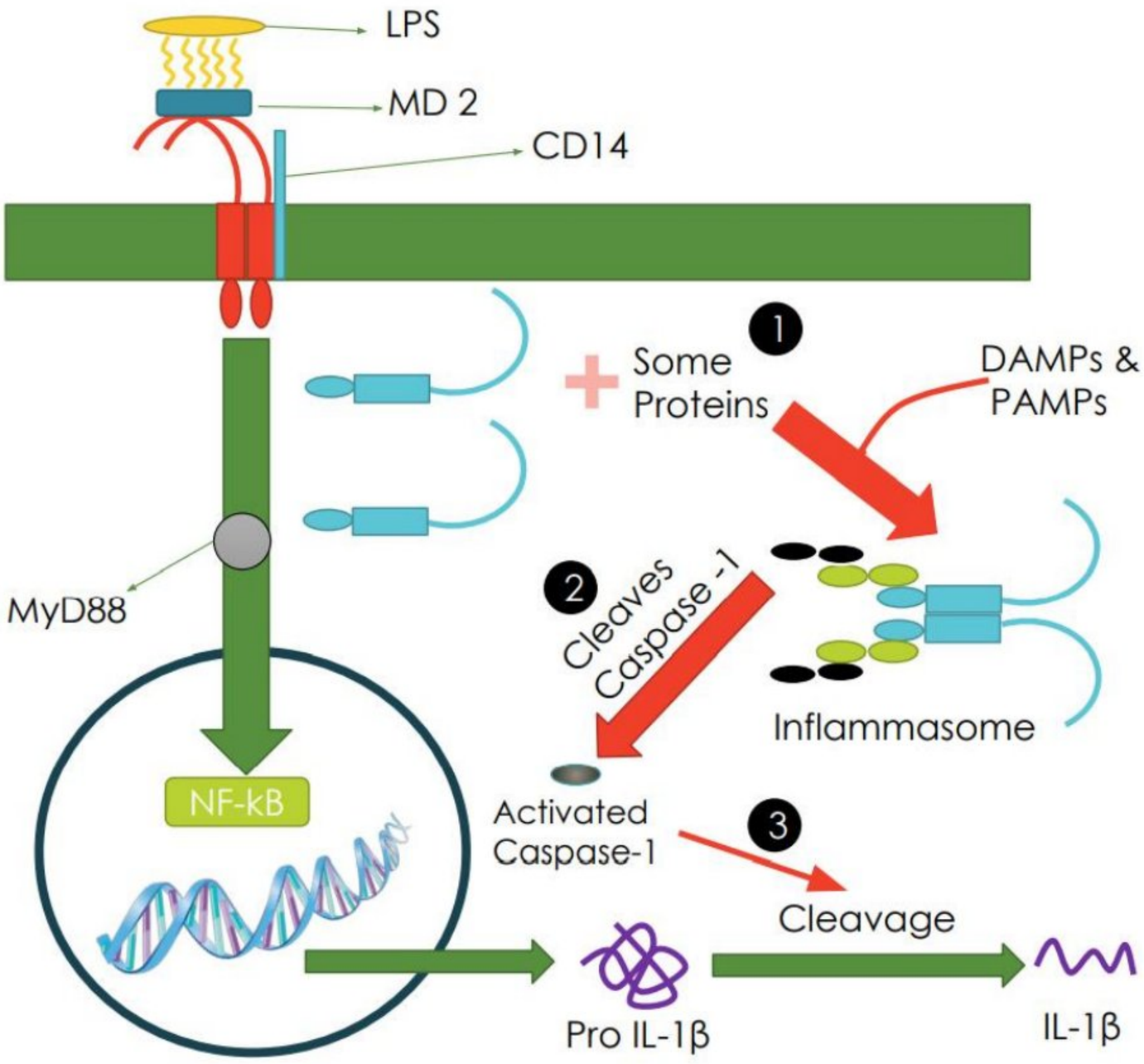
◦ TLRs in endosomes detect mainly the nucleic acid of the pathogens
◦ MD2 is an abbreviation for myeloid differentiation protein 2
◦ All TLRs except TLR3 signal through MyD88 and are therefore capable of activating NF-κB and inducing an inflammatory response. TLR3 signals through TRIF and therefore activates IRF3 and



induces expression of type I interferons

◦ a2- Receptors for Carbohydrates recognize carbohydrates on the surface of microbes, they facilitate the phagocytosis of the microbes and stimulate subsequent adaptive immune responses. These receptors belong to the C-type lectin family, so-called because they bind carbohydrates (hence, lectins) in a Ca++-dependent manner (hence, C-type). Some of these are soluble proteins found in the blood and extracellular fluids; others are integral membrane proteins found on the surfaces of macrophages, dendritic cells, and some tissue cells. (examples, mannose and lectin receptors).
◦ a3- Scavenger receptors comprise a structurally and functionally diverse collection of cell surface proteins found mainly on macrophages, they detect microbial diglycerides.
◦ a4- N-Formyl met-leu-phe receptors, expressed by neutrophils and macrophages, recognize bacterial peptides containing N-formyl methionyl residues and stimulate the directed movement of the cells. (i.e those residues are chemoattractants that help phagocytic cells trace the bacteria producing it)

b- in the cytosol (contains two major classes of receptors: b1- NOD-like receptors and b2- RIG-like receptors)
Function: obligate intracellular pathogens (viruses & some bacteria)/ bacteria that escape phagosomes/ stress in a cell releasing DAMPs
b1- NOD-like receptors (NLRs): recruit other proteins to form signaling complexes that promote inflammation.
◦ Examples of NLRs:
1) NOD1 and NOD2, are expressed in the cytoplasm of several cell types including mucosal epithelial cells and phagocytes, and they respond to bacterial cell wall peptidoglycans.
2) The NLRP subfamily of NLRs (mainly NLRP3) respond to cytoplasmic PAMPs and DAMPs by forming signaling complexes called inflammasomes, which generate active forms of the inflammatory cytokine IL-1.
- The inflammasome is a multiprotein intracellular complex that detects pathogenic microorganisms and sterile stressors and activates the highly pro-inflammatory cytokines interleukin1b (IL-1b) and IL-18. Dysregulation of inflammasomes is associated with a number of autoimmune diseases. (There is some evidence to create NLRP3 inhibitors to treat some auto-immune diseases)



2- Pattern recognition receptors

How does NLRP3 work?
1) They sense some DAMPs and PAMPs (e.g. some viruses, bacteria, raised ion concentration … etc) and join with another NLRP3 and some proteins forming the inflammasome
2) The inflammasome will cleave caspase-1 activating it
3) Caspase-1 will cleave pro IL-1β cytokine producing IL-1β that will induce inflammation

◦ b2- RIG-like receptors (retinoic acid-inducible gene)
◦ RLRs are cytosolic sensors of viral RNA that respond to viral nucleic acids by inducing the production of the antiviral type I interferons.
◦ RLRs can recognize double-stranded and single-stranded RNA, which includes the genomes of RNA viruses and RNA transcripts of RNA and DNA viruses
◦ RLRs also can discriminate viral single-stranded RNA from normal cellular single-stranded RNA transcripts.
◦ Location: RLRs are expressed in a wide variety of cell types, including bone marrow-derived leukocytes and various tissue cells.

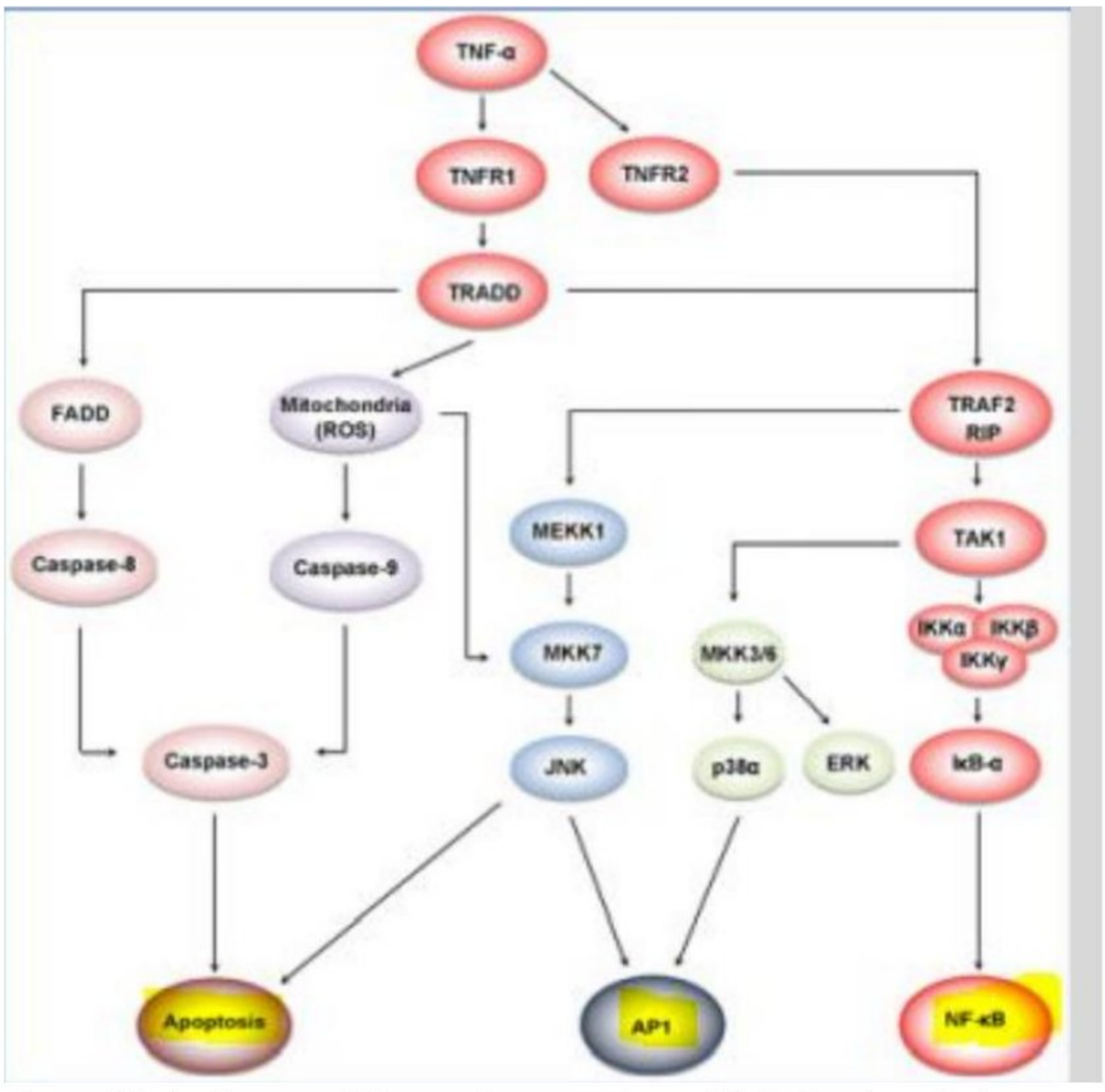
→ 3: Cytokines: the language of immune communication between cells/ produced by many immune and non-immune cells/ include chemokines, interferons, interleukins, lymphokines, and tumor necrosis factors

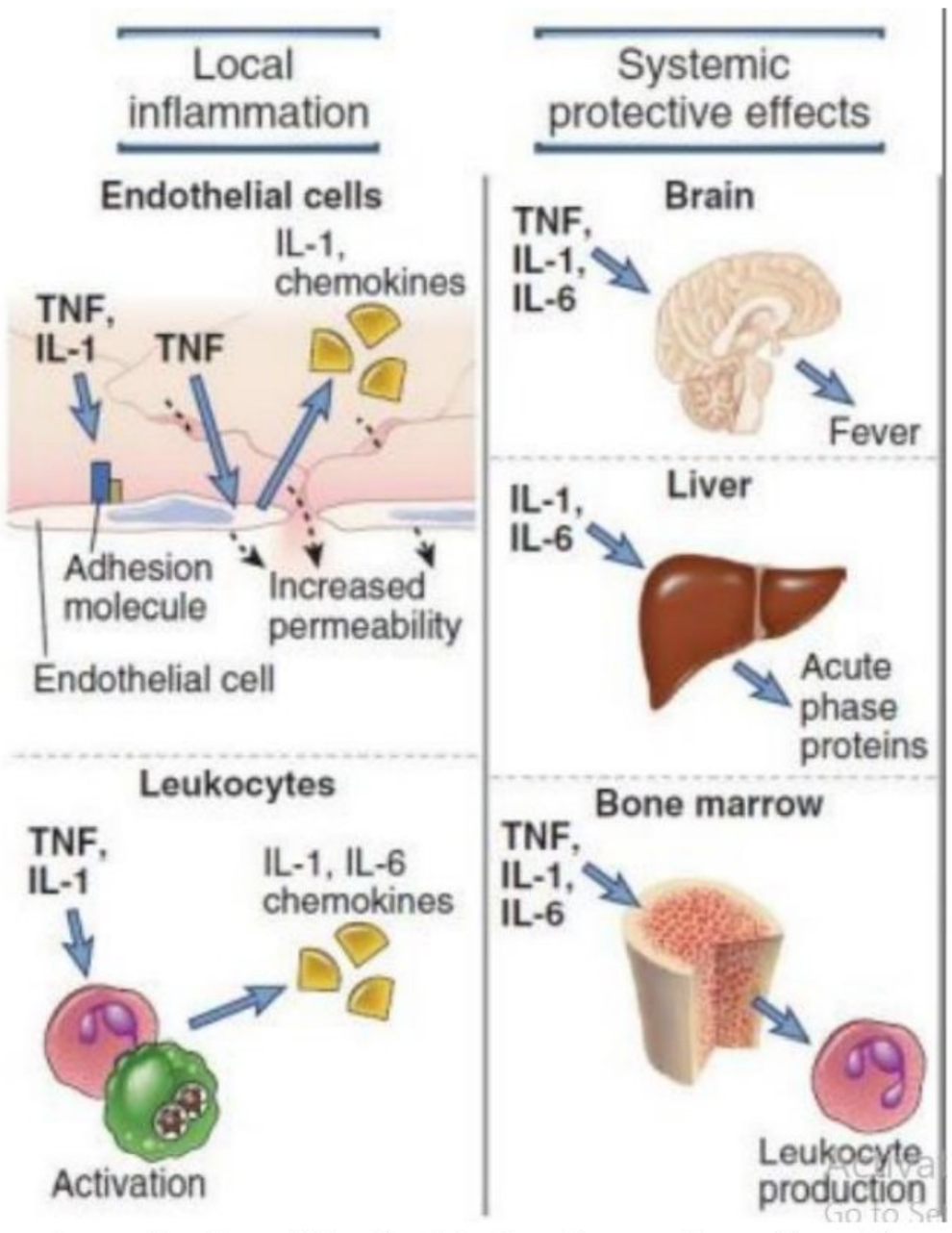
◦We will talk in this lecture about the following cytokines: 1) Tumor necrosis factor 2) Interleukins: mainly IL-1 & IL-6 (Produced mainly by macrophages and mast cells, sometimes by endothelial and epithelial cells)

TABLE 2–2 Some Cytokines Acting in Infection

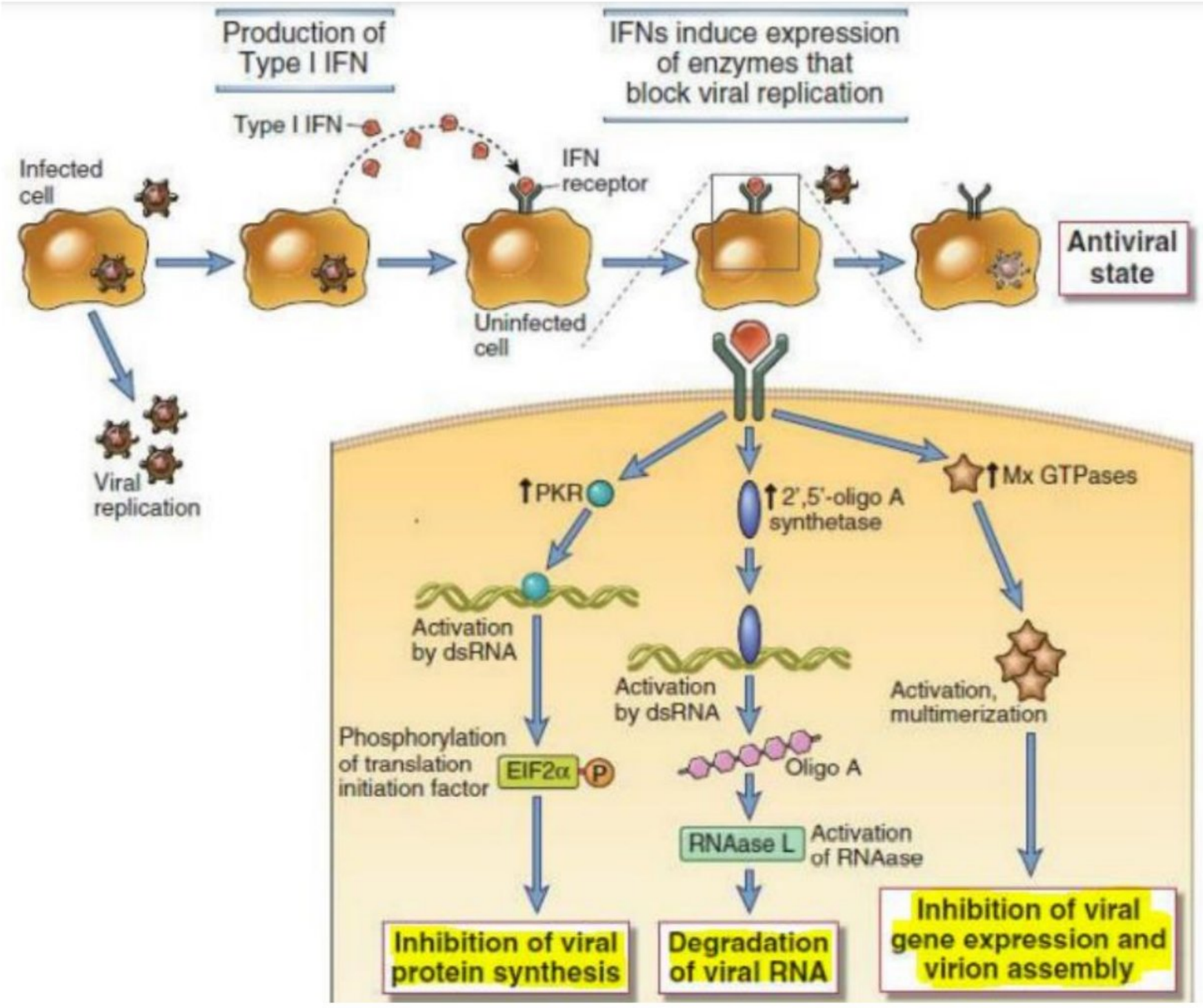
	CELL SOURCE	FUNCTIONS
Interleukins (IL)		
IL-1	Macrophages, endothelium, fibroblasts, epithelial	Differentiation and function of immune effectors, PMN response (T_H17)
Interferons (IFN)		
IFN-α/β	T cells, B cells, macrophages, fibroblasts	Antiviral activity, stimulates macrophages, MHC class I expression
Tumor Necrosis Factor (TNF)		
TNF-α	T cells, macrophages, NK cells	Expression of multiple cytokines, (growth and transcription factors), stimulates inflammatory response, cytotoxic for tumor cells

◦ Tumor necrosis factor is a mediator of the acute inflammatory response to bacteria and other infectious microbes.
◦ Produced: mainly by macrophages.
◦ Stimulated: by PAMPs and DAMPs. TLRs, NLRs, and RLRs
◦ Functions: 1) Inducing apoptosis in cancer cells causing their death 2) Produce AP1 that will help in the proliferation of many immune cells. 3) Activating FN-kB that will enhance producing interleukins and more of TNF 4) Producing adhesion molecules on endothelial cells of the blood vessels in the side of the infection 5) Production and activation of leukocytes 6) Stimulation of the hypothalamus resulting in fever
◦Interleukin-1 (IL-1) is also a mediator of the acute inflammatory response and has many similar actions as TNF.
◦ Produced: by many cell types other than macrophages, such as neutrophils, epithelial cells (e.g., keratinocytes), and endothelial cells.
◦ There are two forms of IL-1, called IL-1α and IL-1β, The main biologically active secreted form is IL-1β.
◦IL-1 mediates its biological effects through a membrane receptor called the type I IL-1 receptor
◦ Functions: 1) IL-1β gene transcription is induced by TLR and NOD signaling pathways that activate NF-κB, whereas pro–IL-1β cleavage is mediated by the NLRP3 inflammasome.
◦ Functions of IL-1: 1) IL-1β gene transcription is induced by TLR and NOD signaling pathways that activate NF-κB, whereas pro–IL- 1β cleavage is mediated by the NLRP3 inflammasome. 2) Producing adhesion molecules on endothelial cells of the blood vessels in the side of the infection 3) Production and activation of leukocytes 4) Stimulation of the hypothalamus resulting in fever 5) Inducing liver to produce acute phase proteins
◦IL-6 is another important cytokine in acute inflammatory responses that has both local and systemic effects 1) including the induction of liver synthesis of a variety of other inflammatory mediators 2) the stimulation of neutrophil production in the bone marrow 3) and the differentiation of IL-17–producing helper T cells 4) Stimulation of the hypothalamus resulting in fever





◦type I interferons: The major way by which the innate immune system deals with viral infections, they function in 1) Achieve antiviral state: Type I interferons, signaling through the type I interferon receptor, activate transcription of several genes that confer on the resistance of the cell to viral infection, called an antiviral state. 2) cause sequestration of lymphocytes in lymph nodes, thus maximizing the opportunity for an encounter with microbial antigens. 3) increase the cytotoxicity of NK cells and CD8+ CTLs 4) Upregulate expression of class I MHC molecules and thereby increase the probability that virally infected cells will be recognized and killed by CD8+ CTLs



(Lecture 6)

→ 1: Soluble pattern recognition receptors

 General functions: 1)Opsonization 2) bring more phagocytes to sites of infections 3) directly kill microbes and infected cells

Types:

A) Natural antibodies: part of innate immunity, opsonizers that are secreted by B1 Features: 1- secreted without overt exposure to foreign antigens 2- recognize common and limited molecular patterns 3- Most of them are IgM antibodies

B) Acute-phase proteins (APPs): are a class of proteins whose plasma concentrations increase in response to inflammation. This response is called the acute-phase reaction.

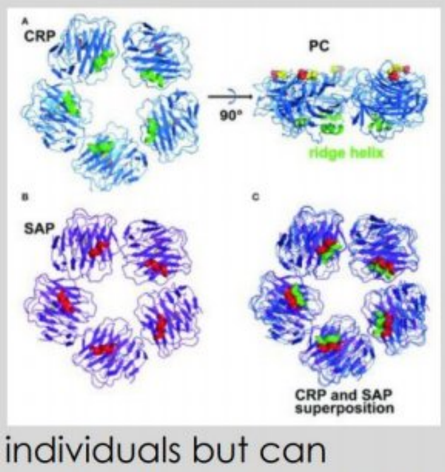
◦How are they produced? In response to injury or infection, local inflammatory cells (neutrophil granulocytes and macrophages) secrete a number of cytokines into the bloodstream, most notable of which are the interleukins IL1, IL6, and TNFα. The liver responds by producing a large number of acute-phase reactants.

◦ The pentraxin family: is a pentameric proteins that forms important part of the Acute Phase Proteins.

◦ Prominent members of this family:
1) C-reactive protein (CRP)
2) serum amyloid P (SAP)
3) the long pentraxin PTX3.

◦ Both CRP and SAP bind to a few PAMPs and DAMPs

◦ Function: activate the complement system by binding to C1q and initiate the classical pathway. .



◦ Plasma concentrations of CRP are very low in healthy individuals but can increase up to 1000-fold during infections and in response to other inflammatory stimuli.

C) Collectins and Ficolins: they're soluble PRRs that bind carbohydrate PAMPs

 An important example of collectins is mannose-binding lectins, they bind with terminal mannose (sometime fucose) and activate the lectin pathway of complement activation.

d) complement system (See next picture)

Notes on the picture:

◦How do C3a & C5a induce inflammation? 1- Bind to mast cells and degranulate them 2- Bind to mast cells enhancing their phagocytosis action 3- affect endothelial cells increasing their permeability and helping them produce adhesion molecules 4- Bind sometimes to B cells

◦ The MAC can bind to host cells without killing them, they function in signaling

◦ Clinical notes about the complement system: 1) People with a deficient complement system will have immunodeficiency 2) People with low rates of C1q will have an auto-immune disease that is called "systemic lupus erythematosus", it's caused because C1q won't remove died cells, so they will accumulate stimulating the immune cell to fight our own cells. 3) Helps in forming connections between neurons

◦ To know the amount of activation of the complement system, we measure the rate of C3 & C5 in the blood, they are low if there is a disease because they're cleaved

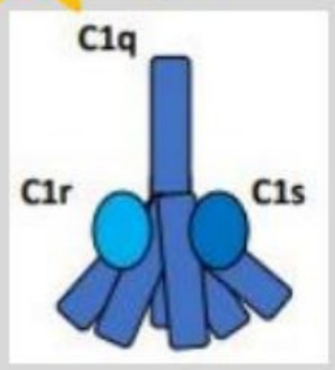
1

CRP & SAP

PAMPs & DAMPs

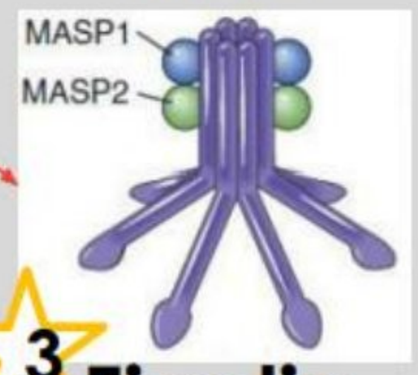
Immune complex

2 C1

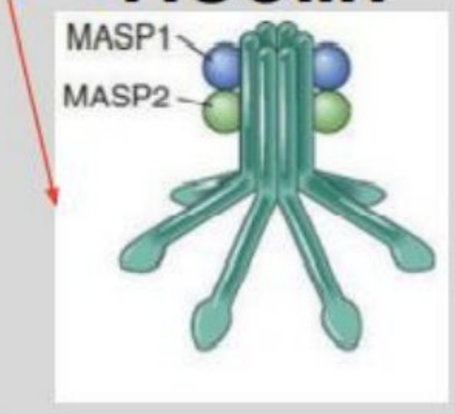


Classical pathway

MBL



3 Ficolin



Lectin pathway

Factor H

15

C3b Or iC3b

+ Factor b

+ Factor d

Alternative pathway

13

Join together forming:

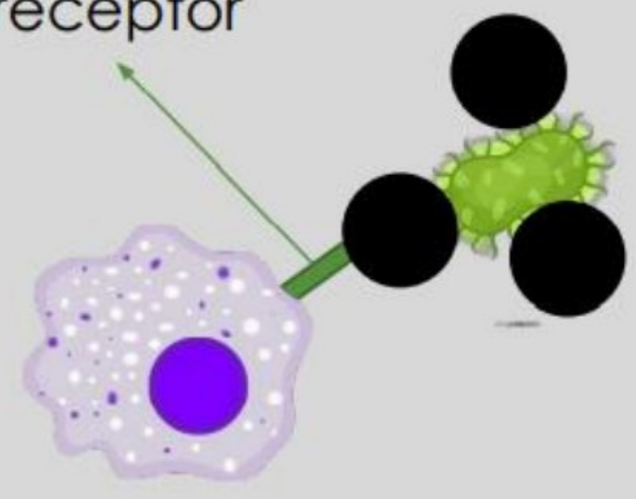
C3 convertase

Will act as the upper convertase

4

Cleaves C4 & C2

CR1 receptor



CD46

CD55

14

C4b & C2b forms:

5

C3 convertase

Cleaves C3 forming: C3a & C3b

6

C3b

Opsonize

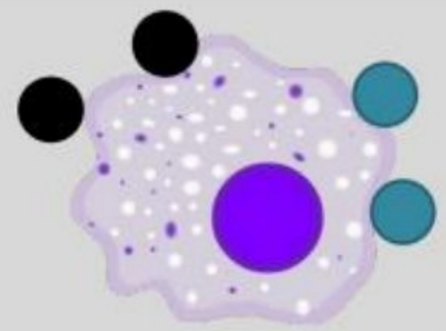
8

Inflammation

7 C3a

C3 convertase join with properdin

9



C5 convertase

Cleaves C5 forming: C5a & C5b

10

Terminal pathway

Inflammation

C5a

11

C5b

12

Forms MAC with (C 6-9)

16

CD59

Can inhibit the formation of MAC