Cihan University/ Sulaymaniyah

College of Health Science

Medical Laboratory Analysis

4th Stage- 1st Semester

Clinical Immunology

Lecture- 2: An Overview of the Immune System (Part-1)

Internal Defense Line

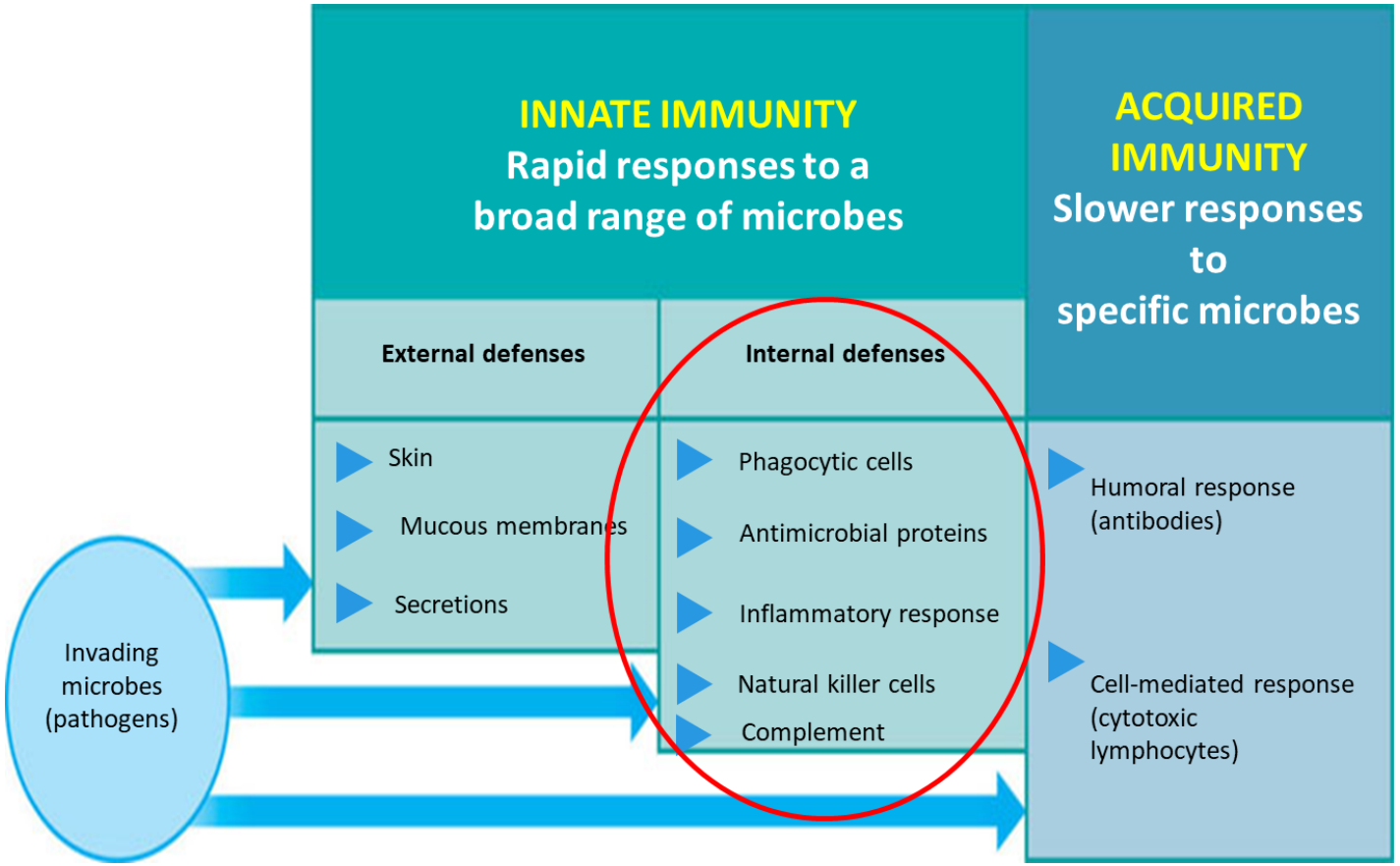
2023- 2024

Lecturer: Mohammed T. Salih

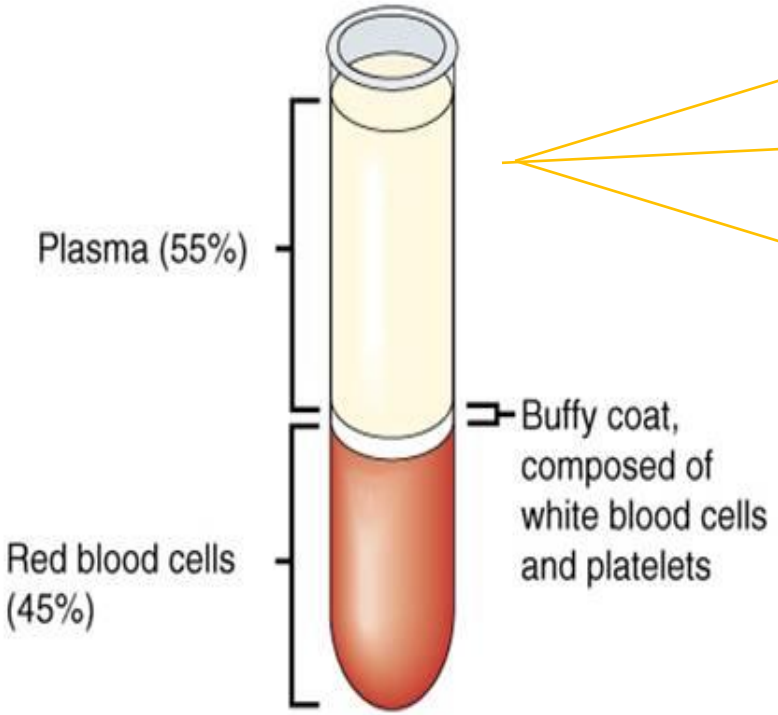
Second Line of Defense:

Internal Defense Line

Inflammation, Phagocytosis, Complement System and Natural Killer cells.



Innate Immune System: Components of Blood



Complement proteins

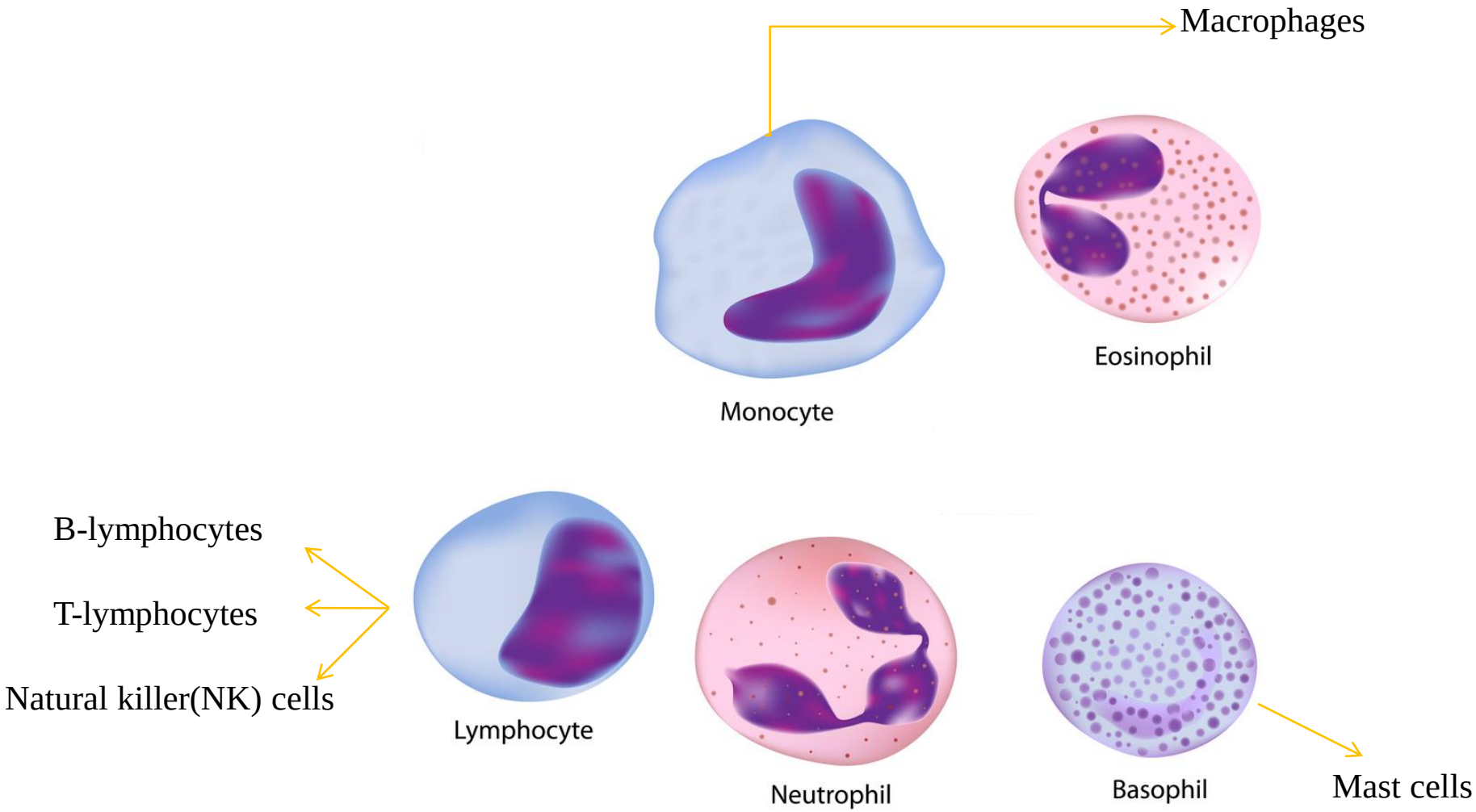
Coagulation proteins

Cytokines

Extracellular

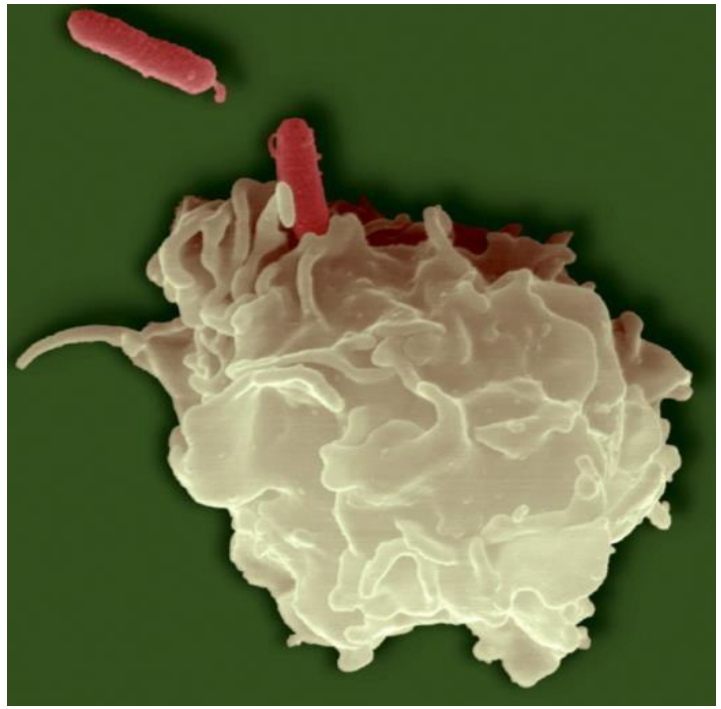
WBCs

White blood cells (WBCs)



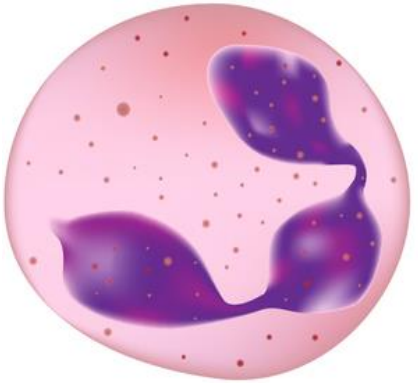
Phagocytes: Neutrophils and Monocytes/ Macrophages

- Immune cells that perform phagocytosis.
- There are two types of circulating phagocytes, neutrophils and monocytes
- These are blood cells that are recruited to sites of infection, where they recognize and ingest microbes for intracellular killing.
- Phagocytes catch the invaders using its cytoplasmic extensions.

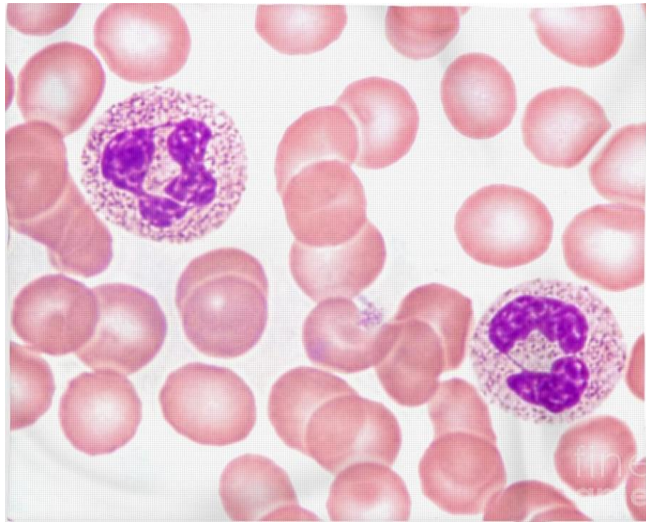


Neutrophils

- Neutrophils, also called polymorphonuclear leukocytes (PMNs),
- The most abundant leukocytes in the blood, numbering 4,000 to 10,000 per μL.
- Large numbers released during infection, particularly bacterial and fungal infections,
- Attracted to chemicals released by bacteria also necrotic (dying) tissue during infection and are the first to arrive during an inflammatory response.
- The production of neutrophils is stimulated by cytokines, known as colony-stimulating factors (CSFs),

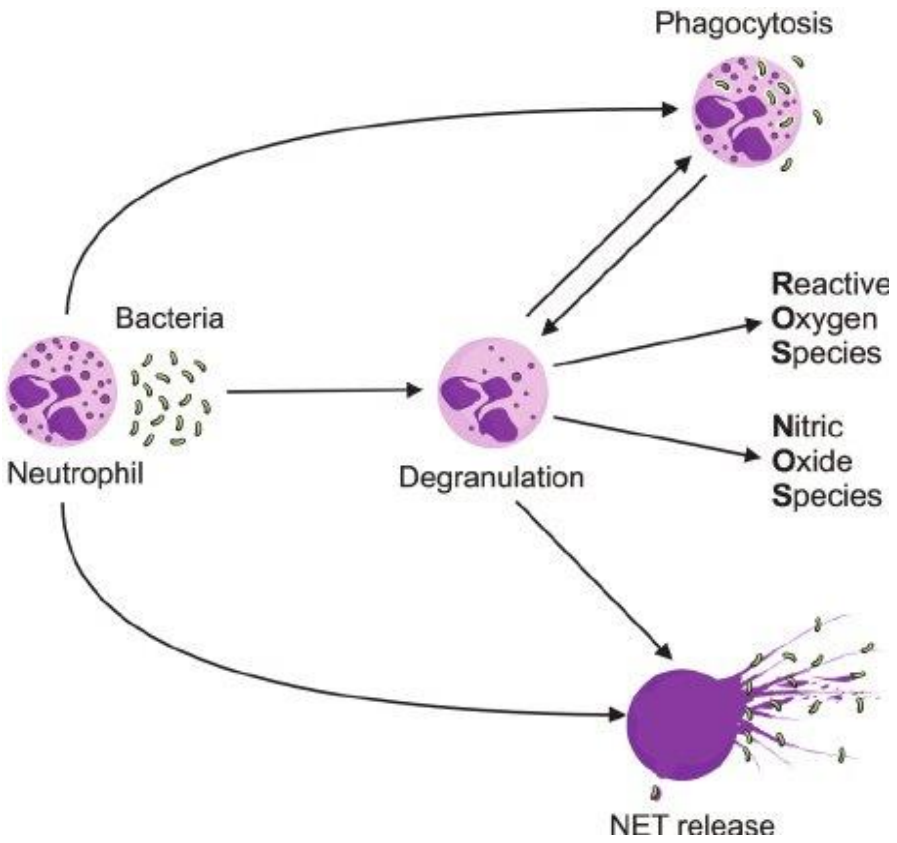


Neutrophil



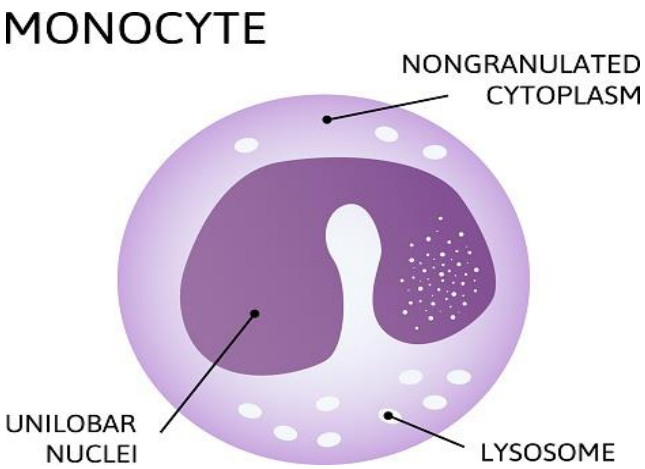
Neutrophils

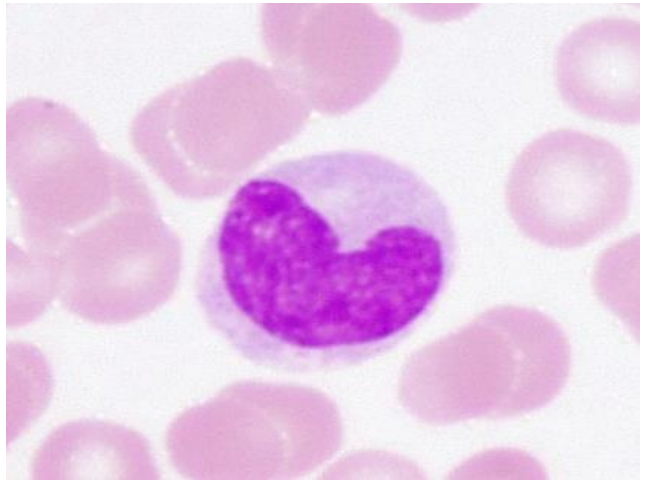
- Unfortunately, this results in the death of the neutrophil as well. as they die after digesting bacteria. Because of this, neutrophils have a lifespan that ranges from a few hours to a few days.
- Dead neutrophils make up a large proportion of pus.
- Also secrete pro-inflammatory cytokines when exposed to inflammatory mediators.
- Every day, 10 billion neutrophils are produced in the bone marrow making them the most abundant white blood cells.

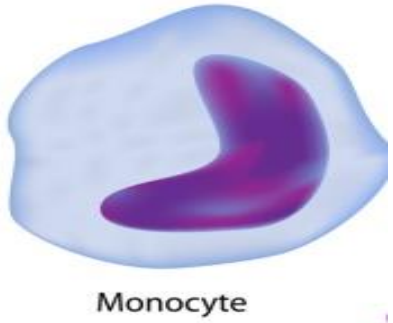


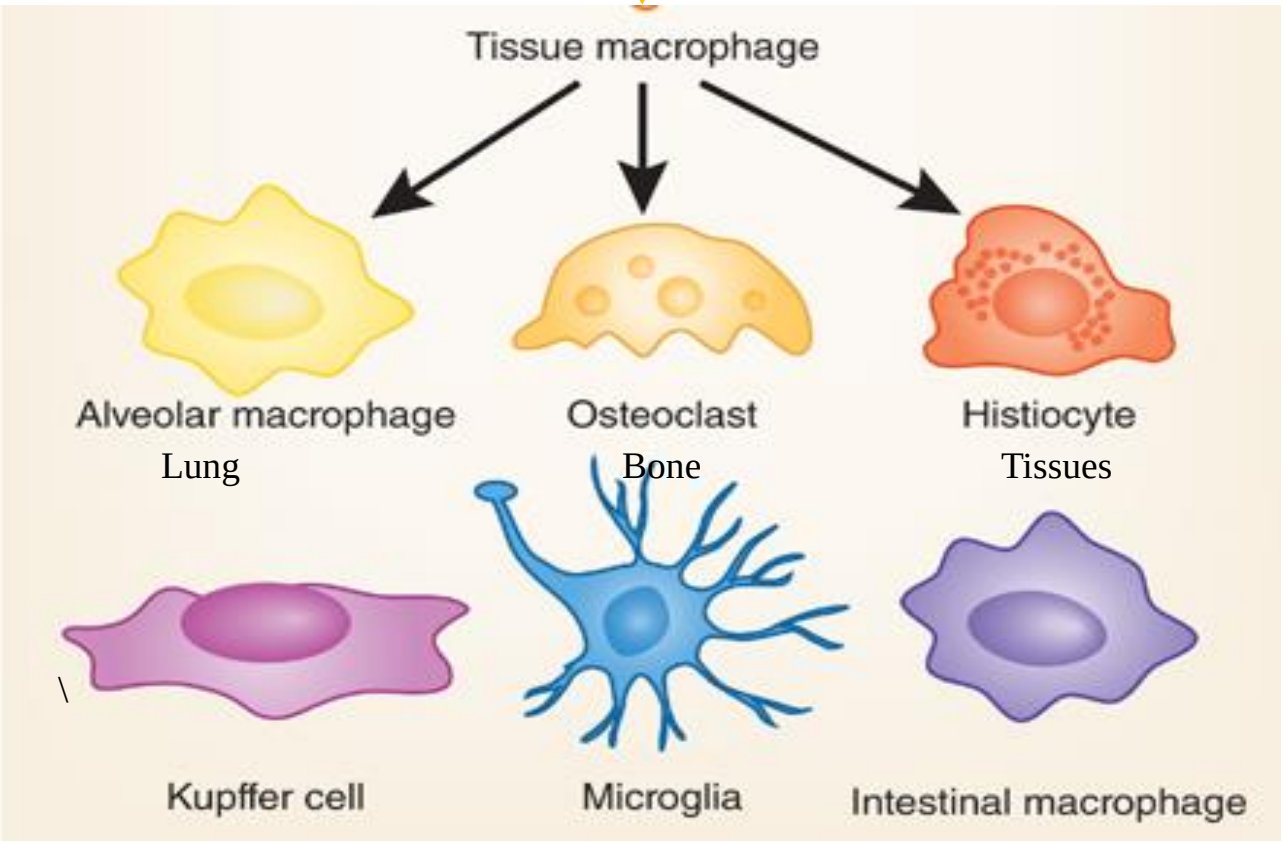
Monocytes

- Less abundant in the blood than neutrophils, numbering 500 to 1000 per μL.
- They also ingest microbes in the blood and in tissues.
- During inflammatory reactions, monocytes enter extravascular tissues and differentiate into cells called macrophages (fixed types),
- Some resident macrophages such as in the brain, liver, and lungs, are derived from progenitors in the yolk sac or fetal liver early during the development of the organism.






Monocyte


Tissue macrophage
Alveolar macrophage
Lung
Osteoclast
Bone
Histiocyte
Tissues
Kupffer cell
Liver
Microglia
Brain
Intestinal macrophage
intestine

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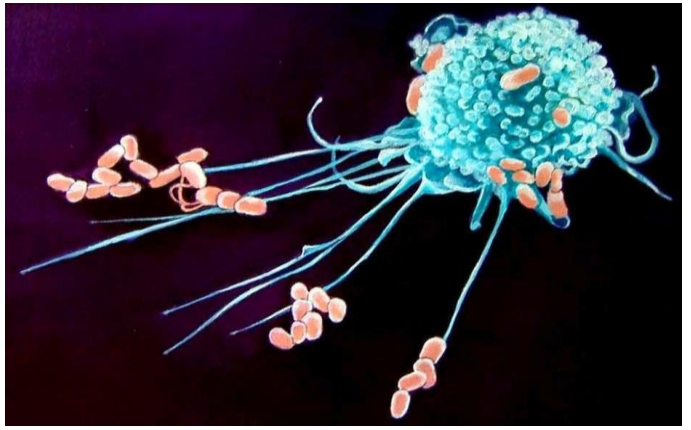
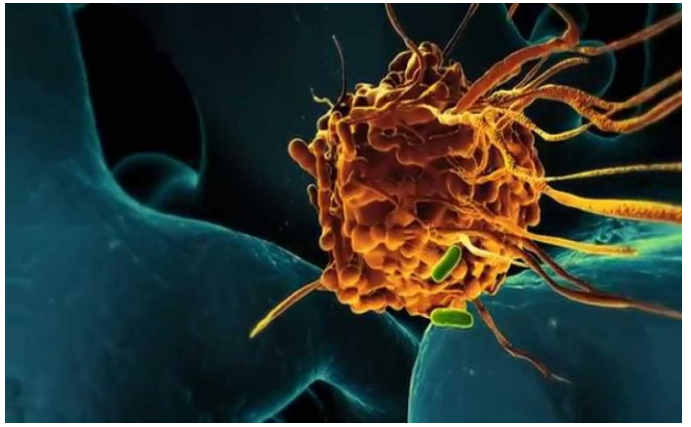
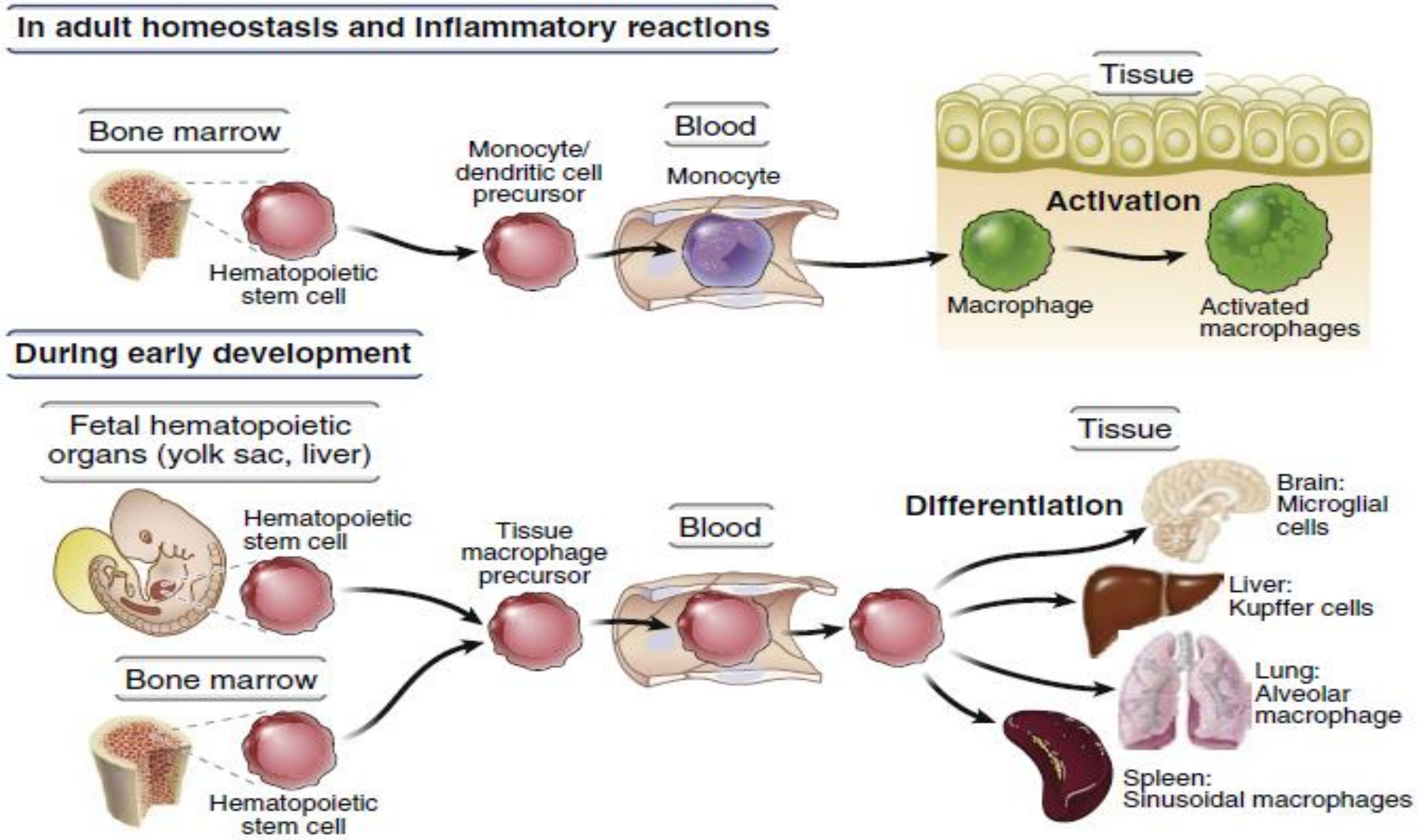
Macrophages

- From the Greek word meaning ‘big eaters’.
- Macrophages digest the microbes much slower than neutrophils and do not self- destruct during the digestion process.
- Also secrete pro-inflammatory cytokines when exposed to inflammatory mediators.
- Macrophages are more durable and long-lived than neutrophils.
- Life span: months to years
- Most tissues in the body contain resident populations of macrophages that protect the tissue from infection.
- Initiate adaptive immune responses as they display antigens from the pathogens to the lymphocytes (as APC).



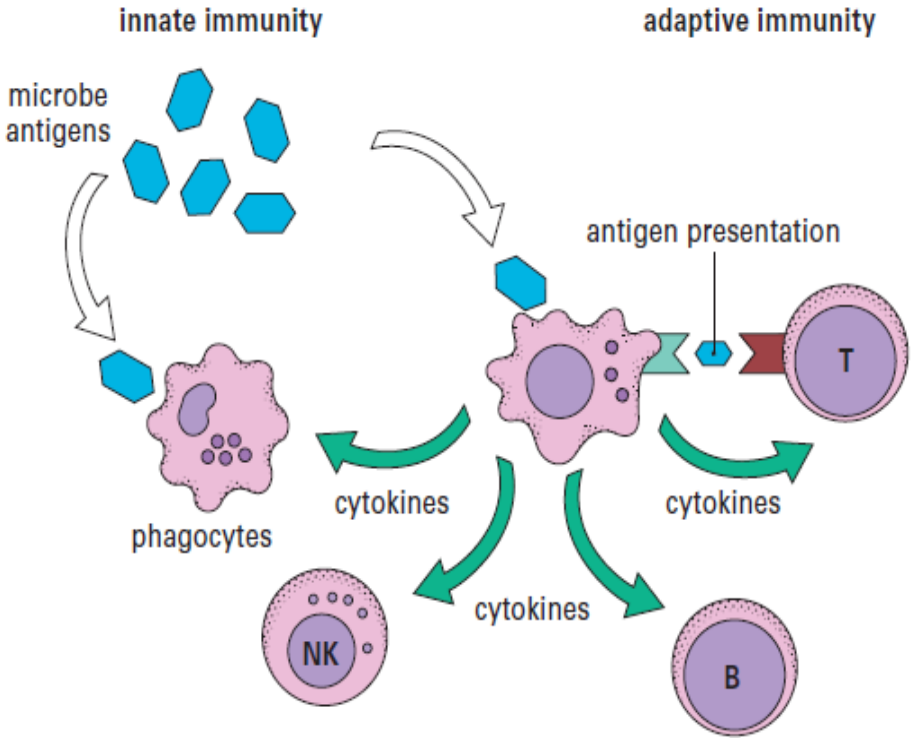


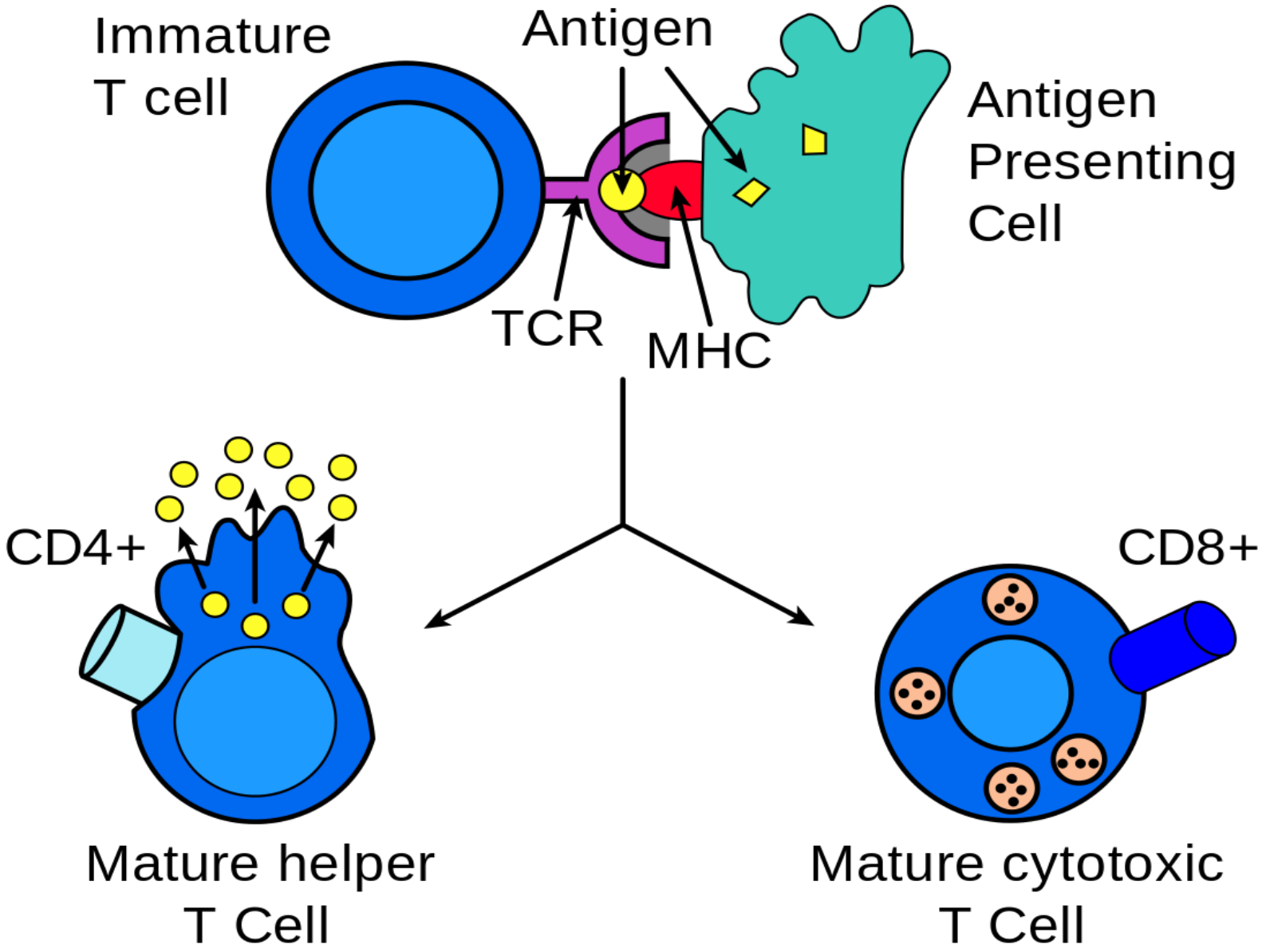
SEM of a macrophage white blood cell engulfing bacteria.


In adult homeostasis and inflammatory reactions
Bone marrow
Hematopoietic stem cell
Monocyte/ dendritic cell precursor
Blood
Monocyte
Tissue
Activation
Macrophage
Activated macrophages
During early development
Fetal hematopoietic organs (yolk sac, liver)
Hematopoietic stem cell
Bone marrow
Hematopoietic stem cell
Tissue macrophage precursor
Blood
Tissue
Differentiation
Brain: Microglial cells
Liver: Kupffer cells
Lung: Alveolar macrophage
Spleen: Sinusoidal macrophages

Antigen-presenting cells (APC)

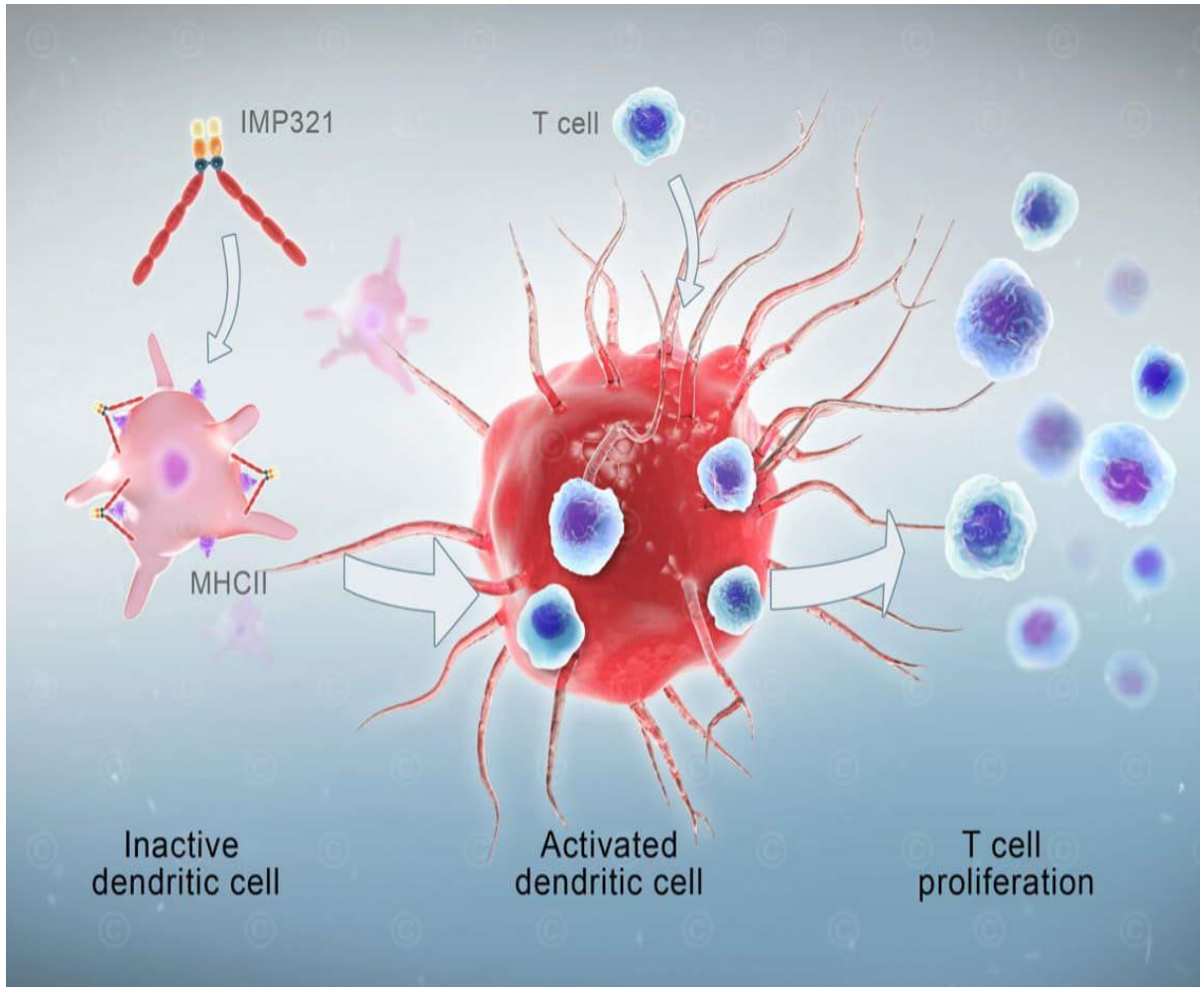
- Antigen-presenting cells (APCs) are a heterogeneous group of immune cells that mediate the cellular immune response by processing and presenting antigens for recognition by T cells.
- Classical APCs include **dendritic cells**, **macrophages**, and **B cells**.
- An antigen-presenting cell (APC) displays foreign antigen complex (parts of the digested invaders) with MHC (Major histocompatibility complex) II on its surface.
- T-cells recognize this complex using their T-cell receptor (TCR).




Immature
T cell
Antigen
Antigen
Presenting
Cell
TCR
MHC
CD4+
CD8+
Mature helper
T Cell
Mature cytotoxic
T Cell

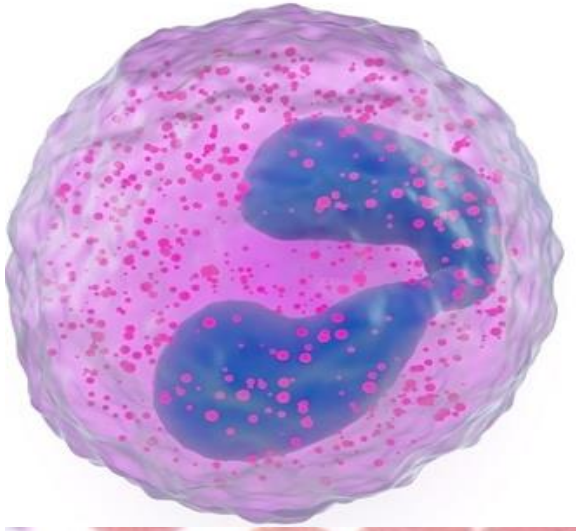
Dendritic cells

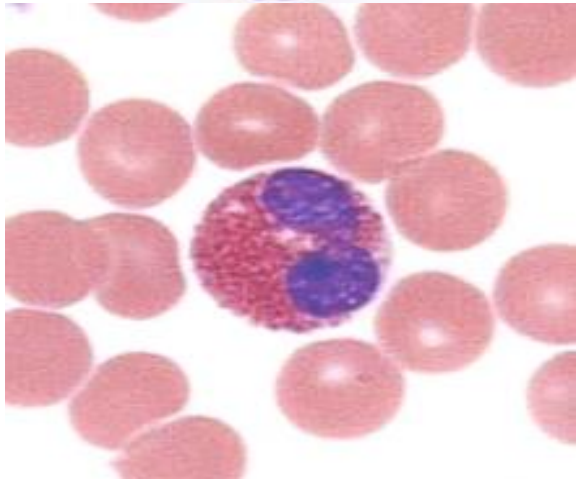
- More efficient APCs than macrophages.
- These cells reside in the structural compartment of the lymphoid organs such as the thymus, lymph nodes and spleen.
- It can also be found in the bloodstream and other tissues of the body.
- It captures antigen then bring it to the lymphoid organs to start-up the adaptive immune response.



Eosinophils

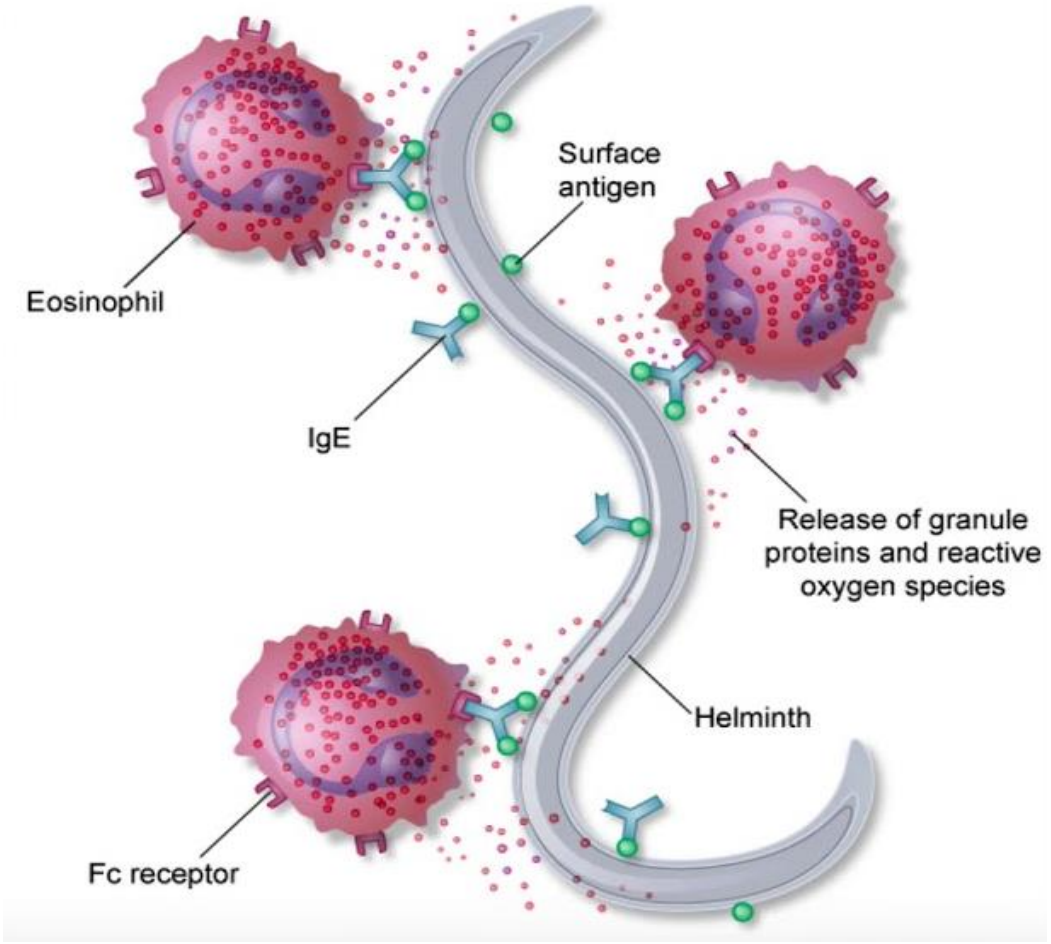
- These cells have the purpose of fighting parasites such as helminths and in allergic reactions.
- Primary location: intravascular circulation
- Life span: days
- Release pro-inflammatory mediators and toxic-substances against non-phagocytosable surfaces (too large for phagocytes).
- May balance immediate hypersensitivity reactions by degrading or inactivating mediators released by mast cells.





Eosinophils (Cont.)

- The eosinophils release various substances from their eosinophilic granules.
- The granule contents are capable of damaging the parasite membrane.
- It contains many granules rich in:
    1. Major basic protein (MBP)
    2. Cationic proteins
    3. Peroxidase
    4. Arylsulphatase B, phospholipase D
    5. Histaminase
    6. Cytokines



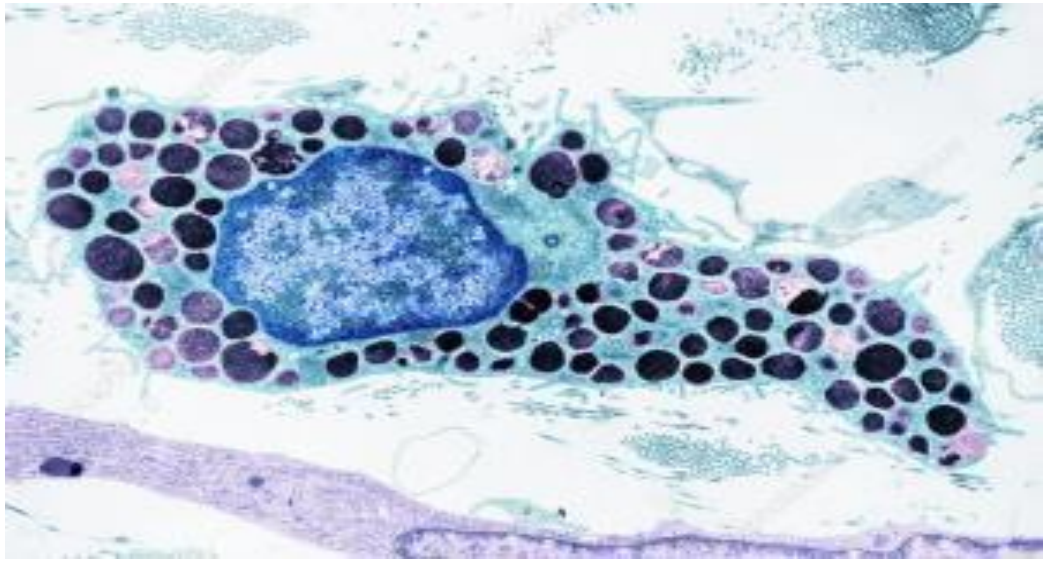
Basophils

- Play a role in host defense, particularly against parasites, and allergic responses.
- Release inflammatory mediators.
- Primary location: intravascular circulation.
- Life span: days
- Contains many granules rich in:

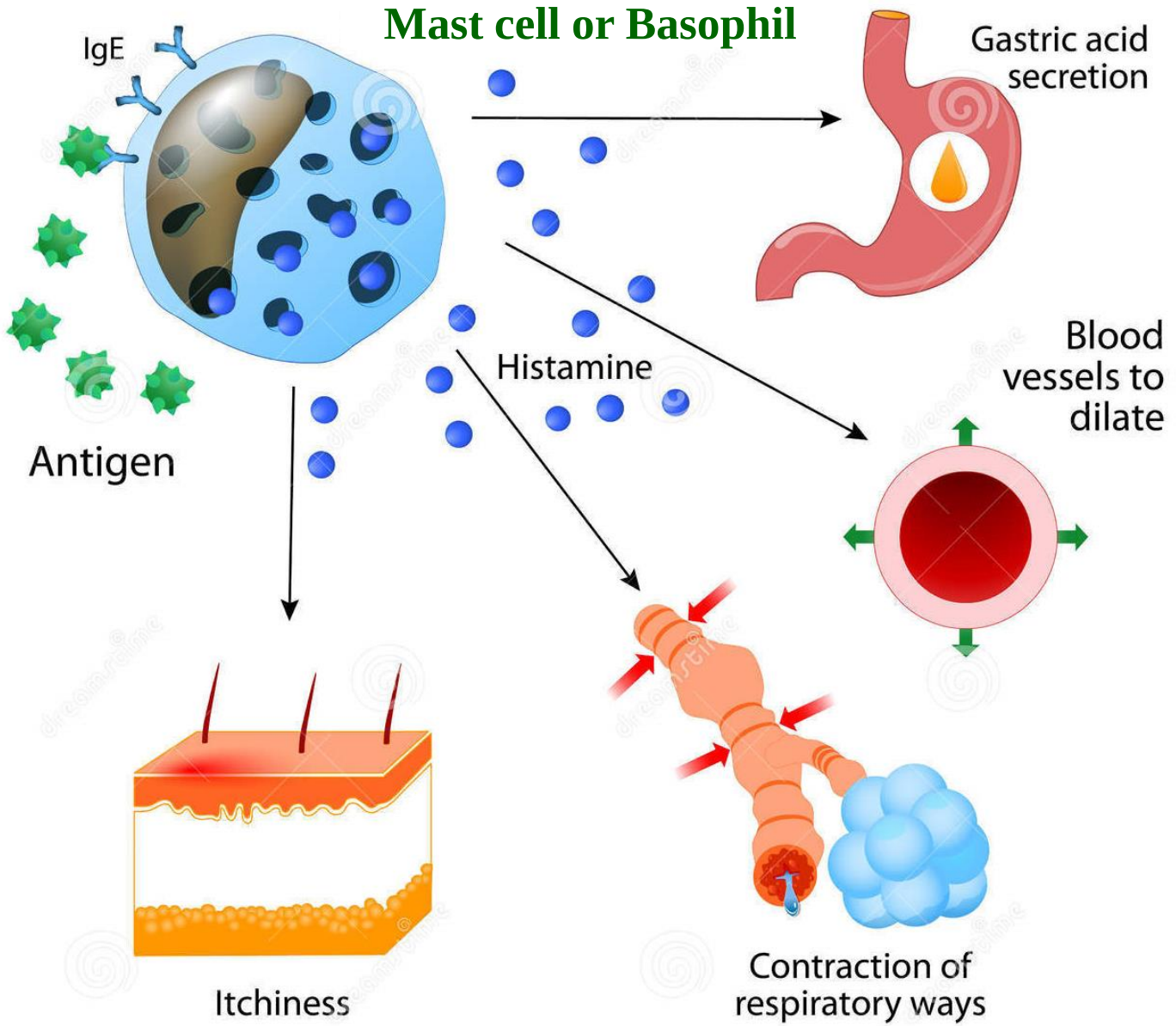
    1. Heparin
    1. Histamine
    2. Serotonin
    3. Interleukins

Mast cells

- Play a key role in the inflammatory process and wound healing.
- Its play an important role in immediate hypersensitivity - allergy and anaphylaxis.
- Young basophils settle into tissues and become mast cells.
- Primary location: tissues
- Life span: months
- Contains many granules rich in:
    1. Heparin
    1. Histamine
    2. Serotonin
    3. Serine proteases
    4. Prostaglandin D2



TEM of a section through a mast cell, with vacuoles (dark) containing histamine or heparin

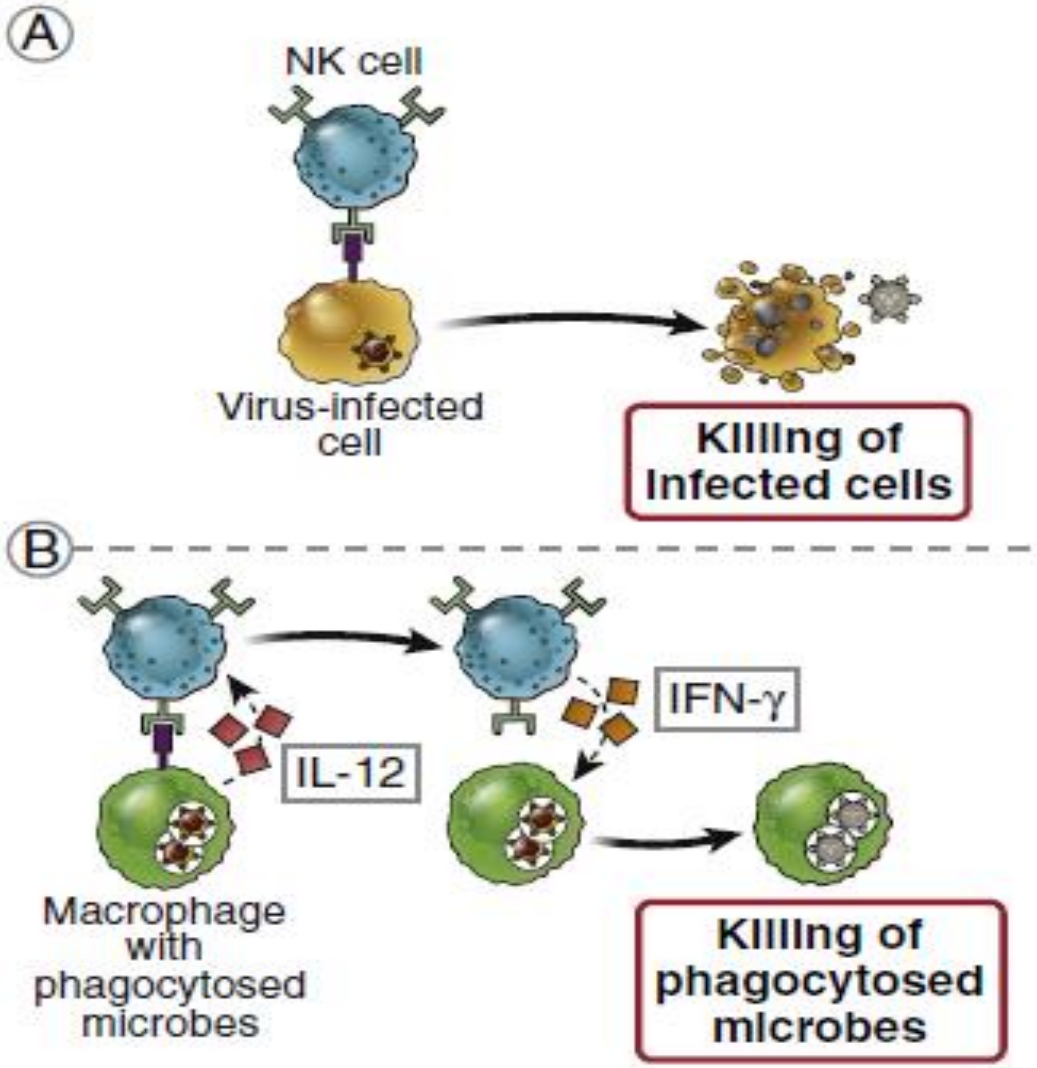

Mast cell or Basophil
IgE
Antigen
Histamine
Gastric acid secretion
Blood vessels to dilate
Itchiness
Contraction of respiratory ways

Natural Killer Cells (NK cells)

- Guard the body against own body cells that are viruses infected or have become cancerous.
- Roaming all over the body looking for abnormal cells to kill.
- NK cells know if our cells became abnormal by scanning their MHC I, abnormal cells that have a different MHC I, or not expressing MHC I, will be killed.
- Life span: weeks
- NK cells will poke and made many holes on the abnormal cells until it died from apoptosis.
- Use cytolytic proteins such as perforin.
- Called natural killer cells because even though they are a type of T cells, they exhibit spontaneous killing of abnormal cells without the need for specific antigen activation as required by T-cells in the adaptive immune response.
- NK cells are important in defense against viral infections and malignancies.

Natural Killer Cells (NK cells)- Cont.

- NK cells recognize **infected** and **stressed cells** and respond by killing these cells by secreting the **macrophage-activating cytokine IFN-γ**.
- Activated NK cells empty the contents of their cytoplasmic granules into the extracellular space at the point of contact with the infected cell.
- The granule proteins then enter infected cells and activate enzymes that induce **apoptosis**.



Second Line of Defense: Internal Defense Line

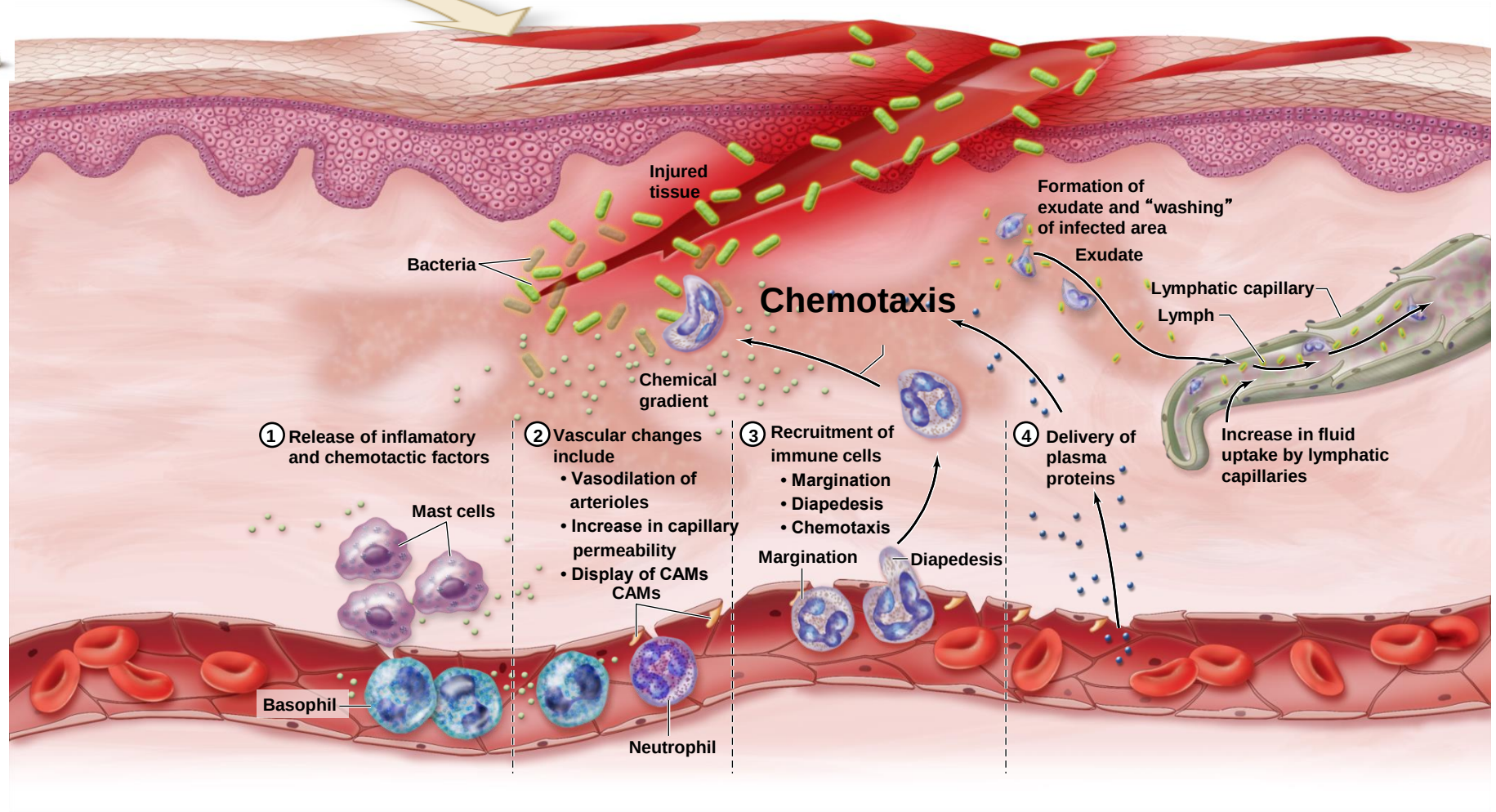
Inflammatory Response, Complement System

Inflammatory response

- Activate the body ‘alarm’ using chemicals.
- Biological response of the immune system that can be triggered by a variety of factors:

  1. Pathogens,
  2. Damaged cells,
  3. Toxic compounds,

Inflammation



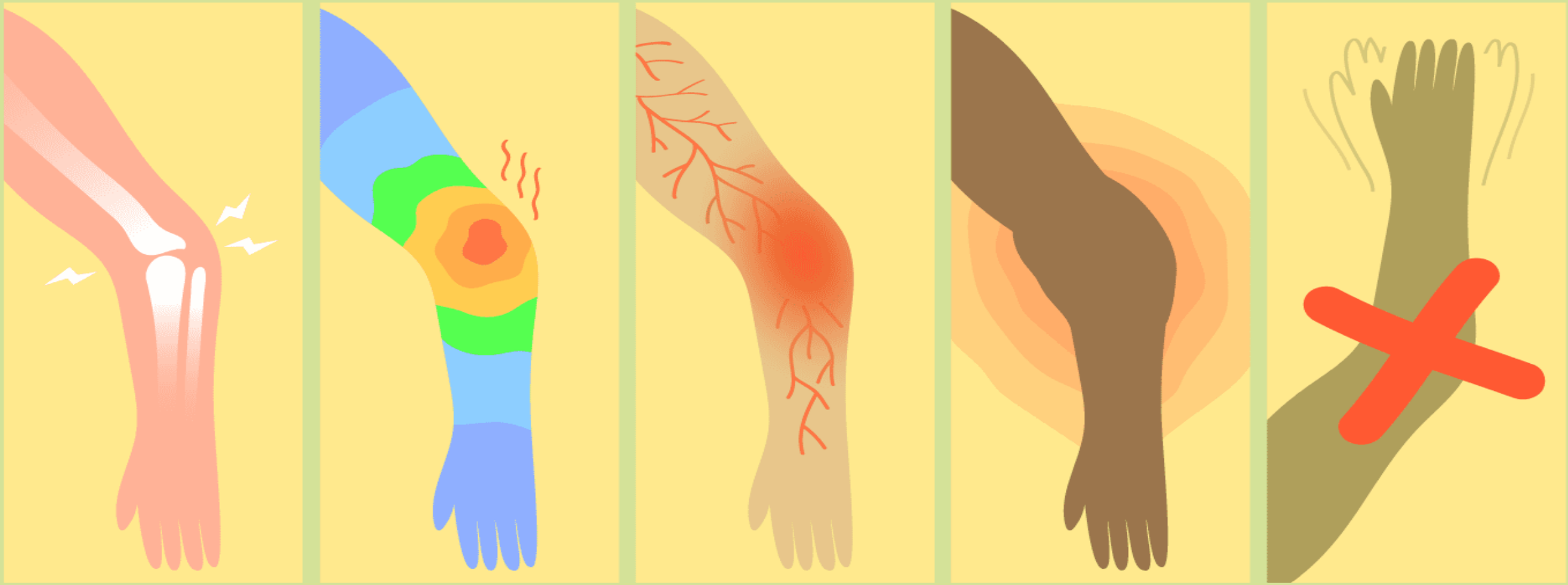
Inflammation has two main components

1. The cellular component involves the movement of white blood cells from blood vessels into the inflamed tissue. extravasate (filter out) phagocytes, picking up bacteria and cellular debris.
2. The exudative component involves the movement of fluid, usually containing many important proteins such as fibrin and immunoglobulins (antibodies).

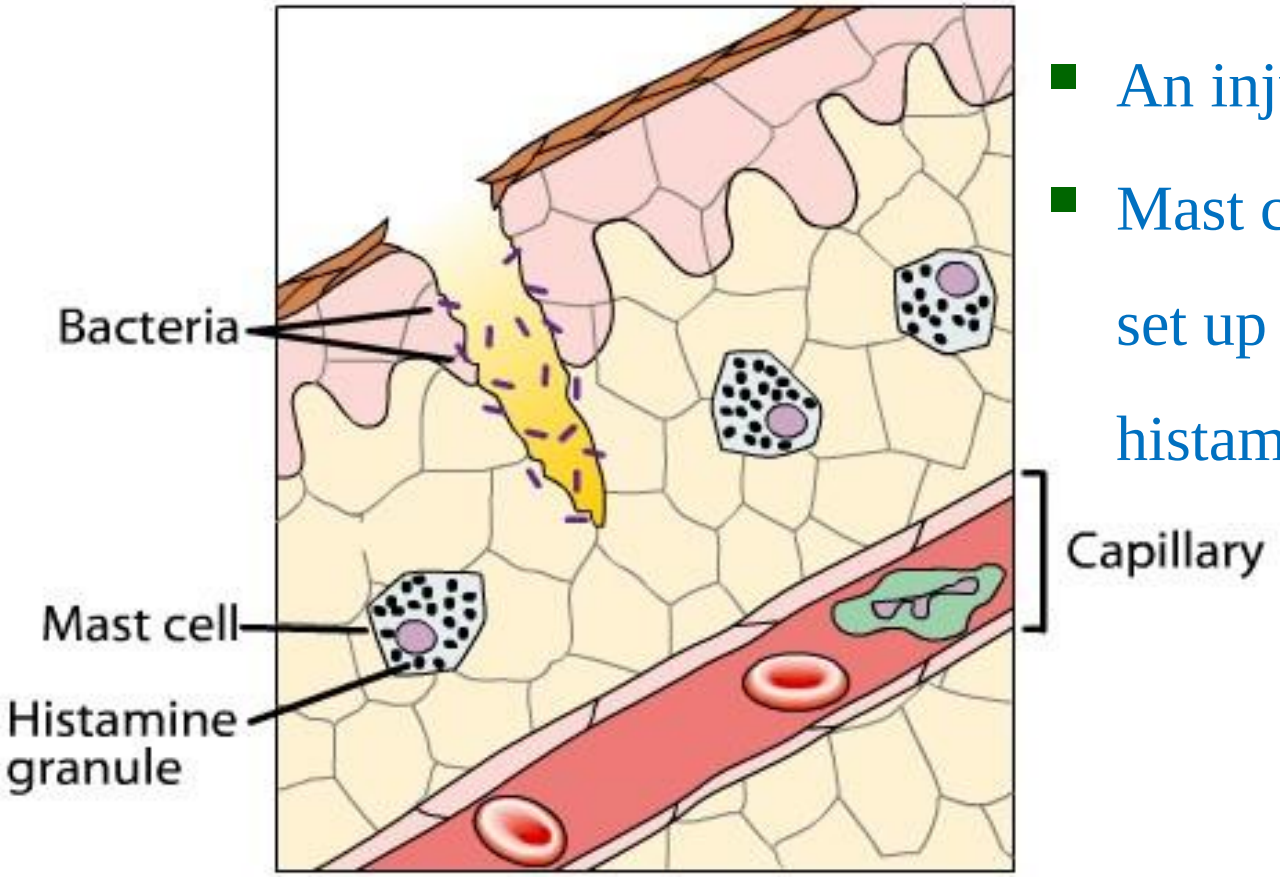
The Signs and Symptoms Include:

- Redness (Rubor)- raised blood flow.
- Swelling (Tumor)– leakage of fluids to the tissue.
- Heat (Calor) – raised blood flow, leakage of fluids to the tissue, release of inflammatory mediators.
- Pain (Dolor)– stimulation of pain receptors by inflammatory mediators, injury of nerve fibres, and irritation by toxic chemicals released by microbes.
- To some extent, loss of tissue function (Functio laesa)– pain, disruption of tissue structure, fibroplasia, metaplasia.

5 Cardinal Signs of Inflammation



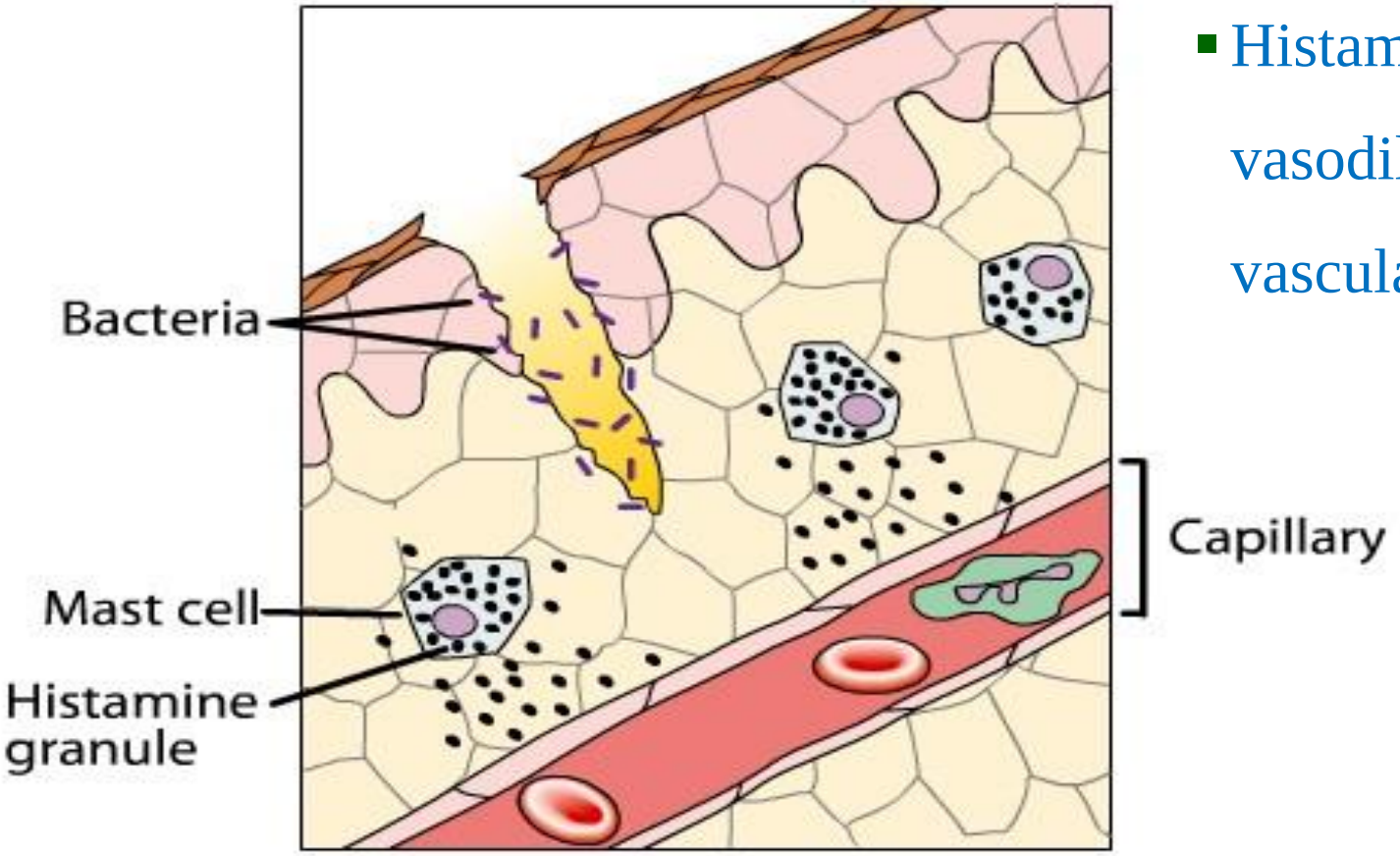
1- Release of soluble mediators



The tissue damage triggers mast cells to release histamine from their histamine granules into the surrounding tissue.

- An injury site exposed to invaders.
- Mast cells and the injured vascular epithelium will set up the inflammatory response by releasing histamine and other vasoactive substances.

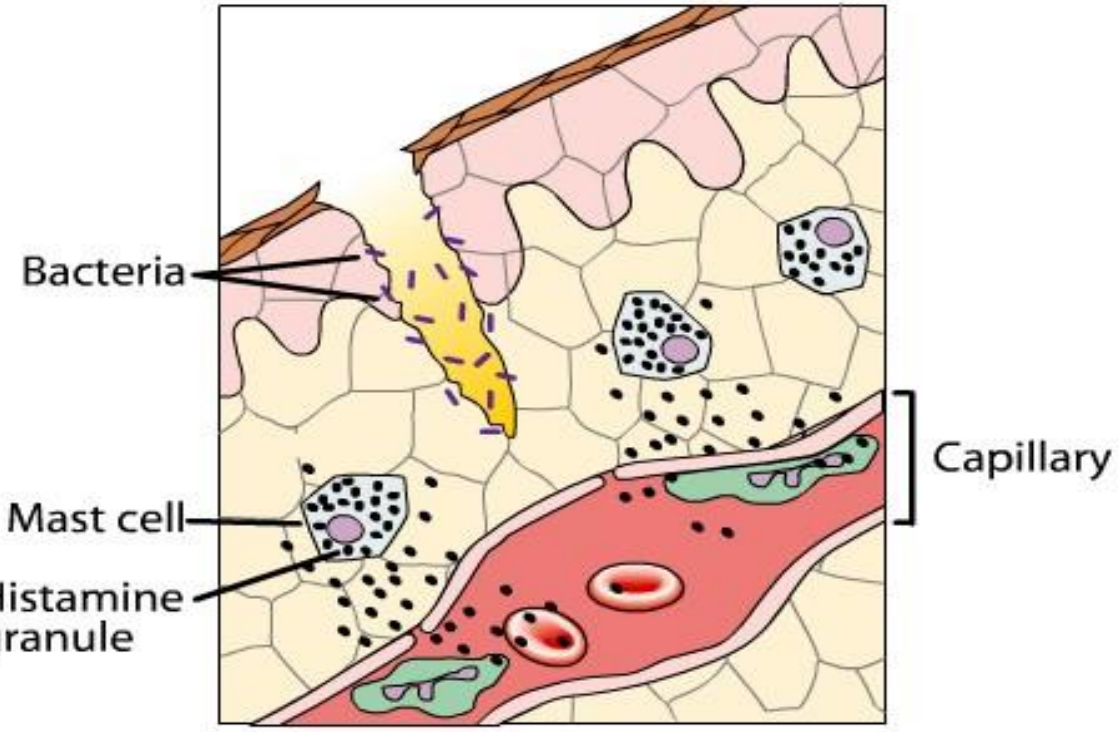
2- Vasodilation



Histamine diffuses into capillaries, causing them to dilate and become leaky. As capillaries dilate, the area appears red. As plasma leaks into the tissue, the area swells.

- Histamine main effect is to activate vasodilation, which leads to the leakage of vascular fluid to the site of injury.

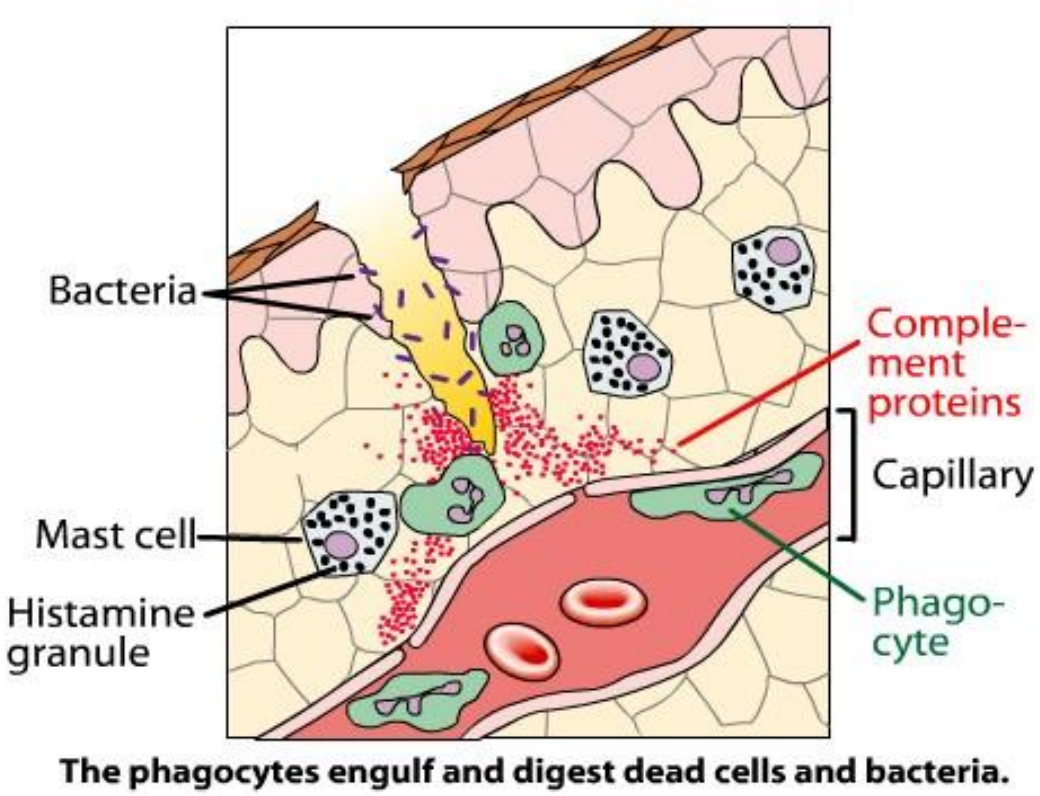
3- Increased blood flow and Extravasation



In damaged or infected tissue, activated proteins called complement proteins and other chemicals attract phagocytes to the area.

1. The reason is to floods the area with serum proteins that contain:
2. Inflammatory mediators (prostaglandins, kininogen, complement, cytokines etc.)
3. Antimicrobial proteins (defensins, hepcidins, cathelicidin etc.)
4. Chemoattractant (C3a, C5a, leukotriene etc.)

4- Migration of Phagocytes (Chemotaxis)



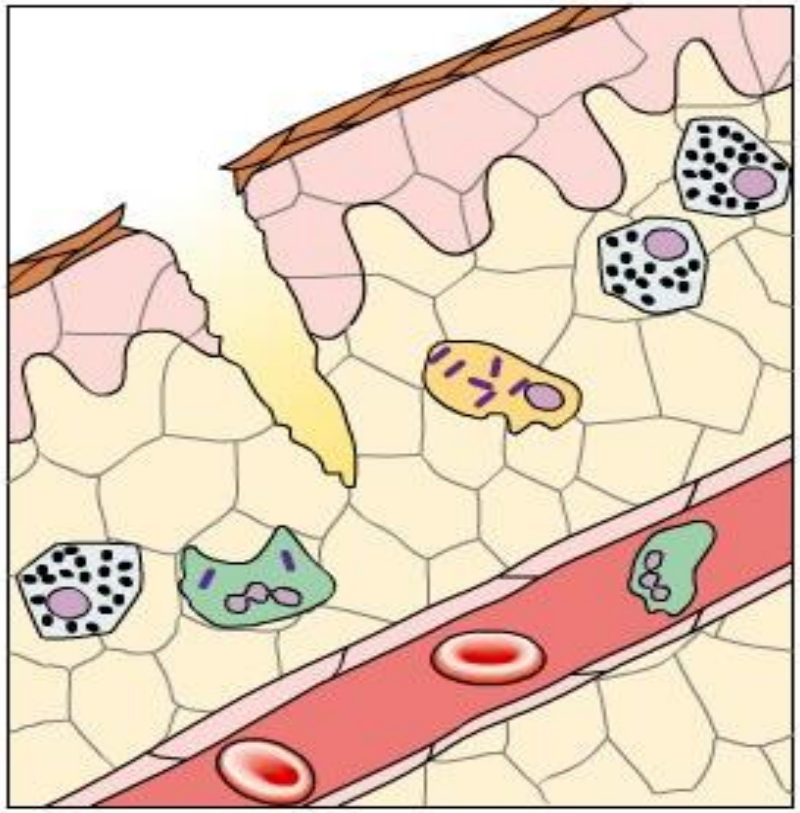
The phagocytes engulf and digest dead cells and bacteria.

Monocytes, neutrophils and other effector cells from the blood attracted to the sites of infection or tissue damage by chemo-attractants.

Helps by the:

- Increased margination (the gap between the cells)
- Leakage of serum fluids to the infected area.

5- Tissue Repair



Histamine and complement signaling cease, and phagocytes are no longer attracted to the area. The tissue returns to normal.

Inflammatory response continues until the foreign material is eliminated and the injury is repaired.

Benefits of the inflammatory response

- Protective Role:

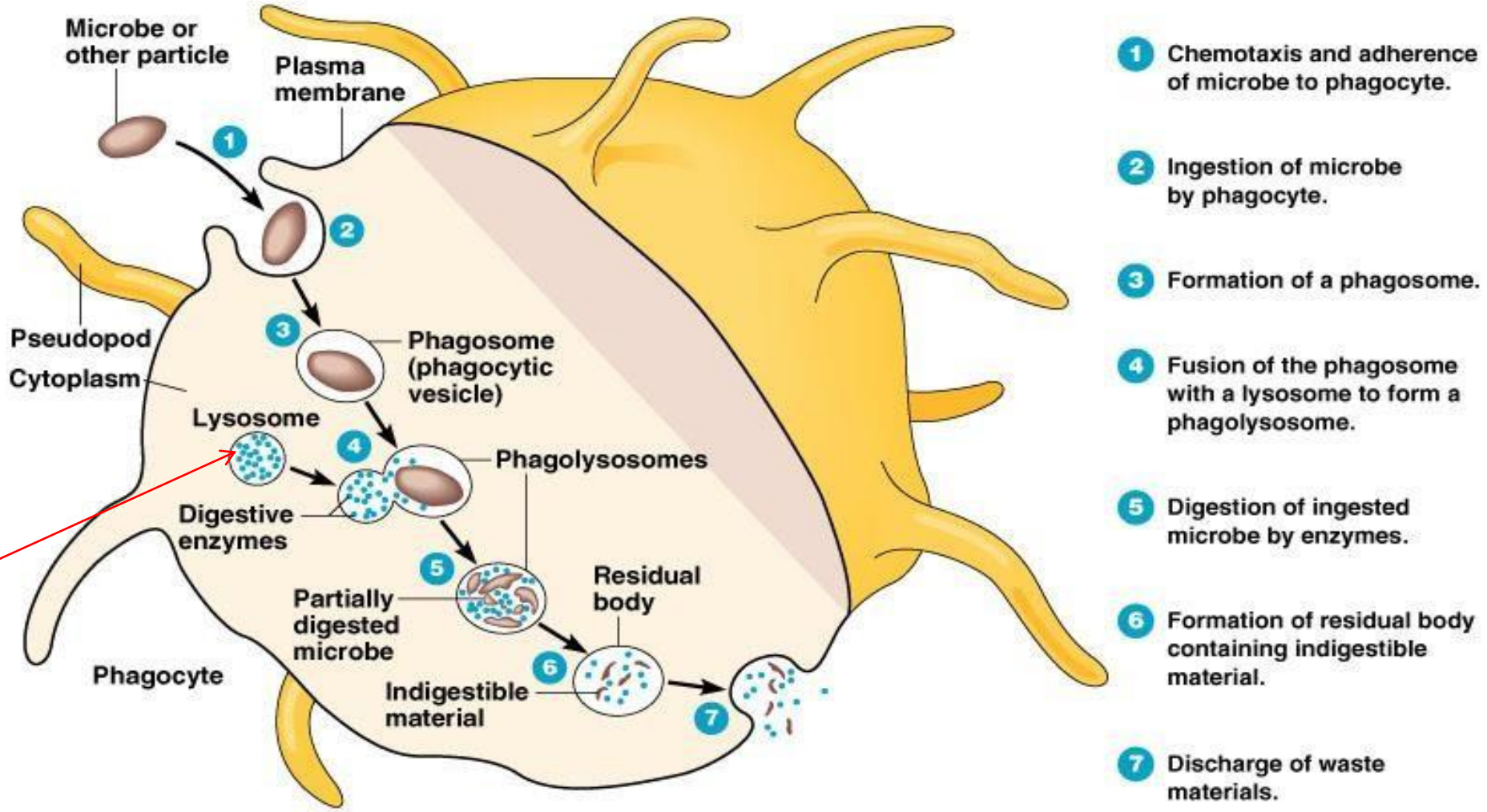
  1. Prevents the spread of damaging agents to nearby tissues,
  2. Clearance of foreign or damaged material,
  3. Encourages repair,

- The downside of the inflammatory reaction is that it is nonspecific and the inflammatory compounds released are also harmful to the host.
- Because of this, inflammation is under tight regulatory control in the body.

Phagocytosis

- Phago = to eat
- Cyte = cell
- WBCs (eg. Neutrophils) – find, eat and digest microbes!
- The process by which phagocytes ingest or engulf other cells or particles.
- Resting phagocytes become activated by inflammatory mediators.
- This activated full of energy phagocytes moves towards the chemical attractant (chemoattractant).
- Majority of the eaten microbes will be digested into debris, while small parts of it will be processed then presented into adaptive immune cells.

Phases of Phagocytosis



Granules

What's in the granules ? **Lysozyme – digests bacterial cell wall; other antimicrobial proteins.**

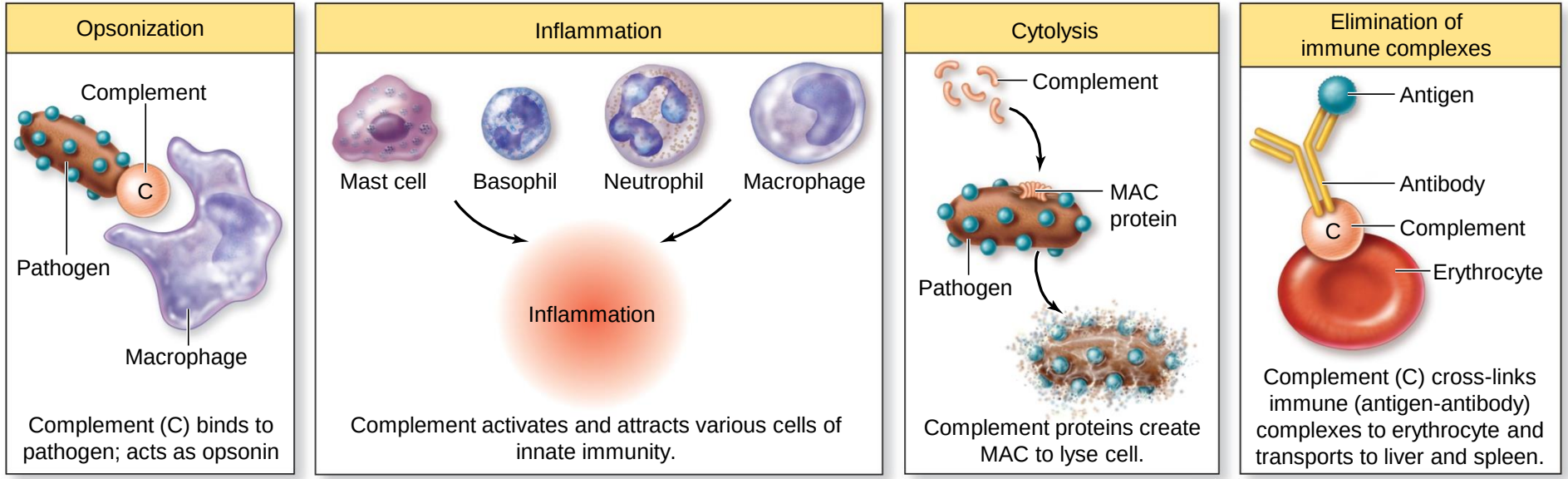
Serum proteins: Complement (C`)

- They are a large number of distinct plasma proteins produced by the liver that react with one another (C1 thro' C9)
- Circulated in blood plasma and tissues
- System of plasma proteins that can be activated:
  - ✓ Directly by pathogens
  - ✓ Indirectly by pathogen-bound antibody
- Activation leading to a cascade of reactions that occurs on the surface of pathogens and generates active components with various effector functions
- Complement can bind to microbes and coat the microbes,
- Essential part of innate immune response,
- Enhances adaptive immune response.

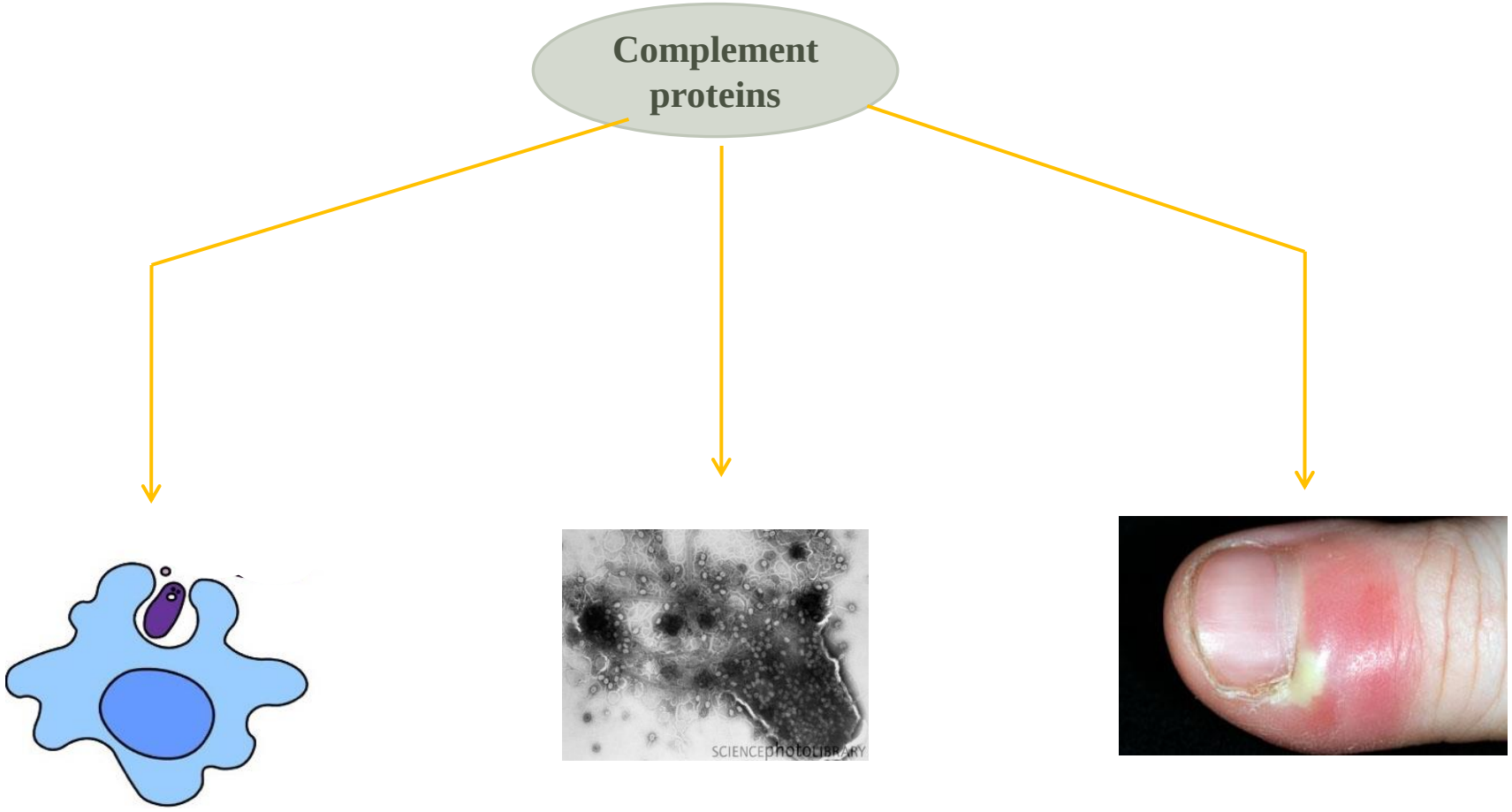
The Functions of Complement

1. Lysis of cells, bacteria, and viruses,
2. Opsonization, which promotes phagocytosis of particulate antigens,
3. Binding to specific complement receptors on cells of the immune system, triggering specific cell functions, inflammation, and secretion of immunoregulatory molecules,
4. Immune clearance, which removes immune complexes from the circulation and deposits them in the spleen and liver.

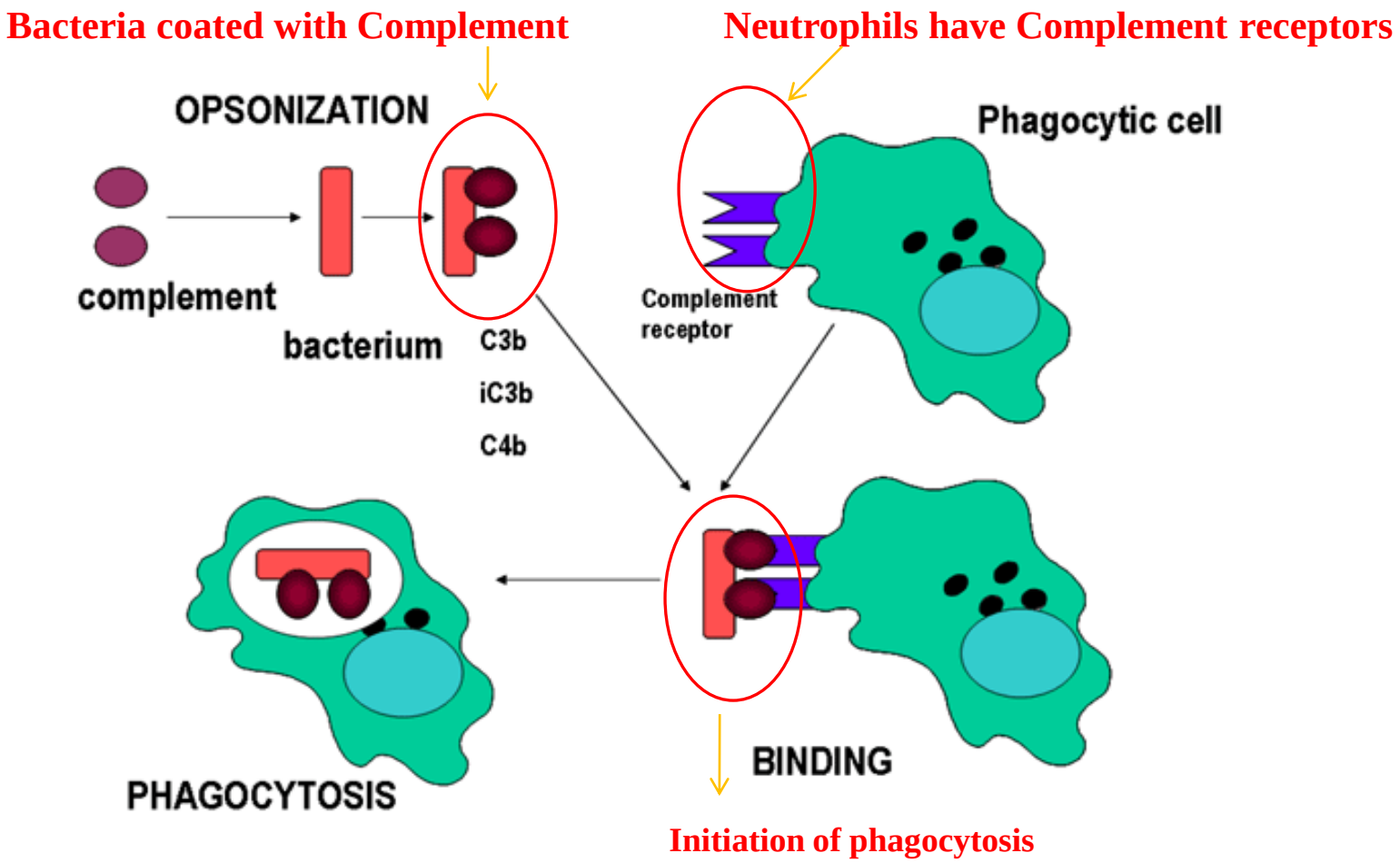
Complement Proteins



Complement proteins: Role in innate immune system

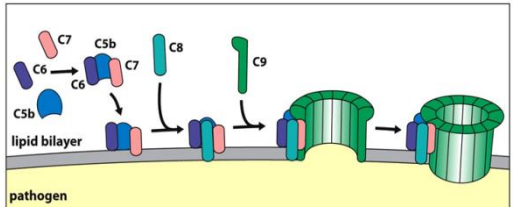


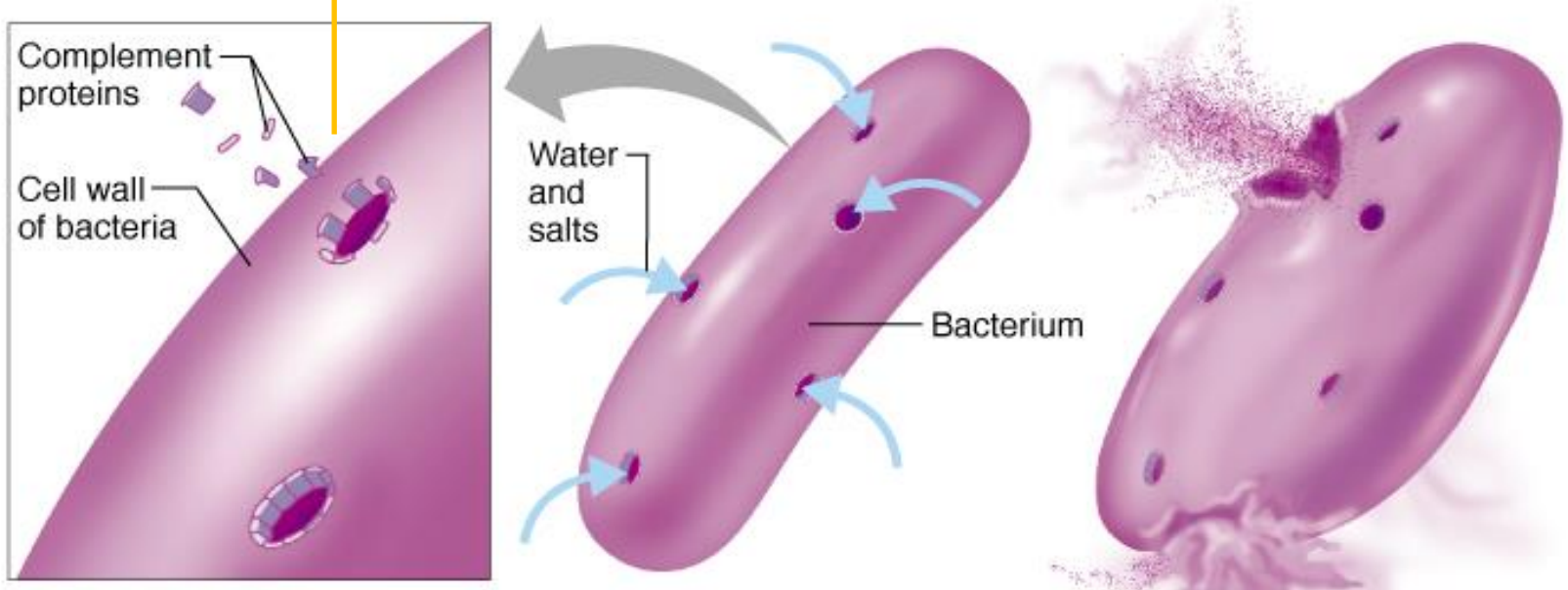
How do Complement Proteins Facilitate Phagocytosis ?



How do Complement Proteins Lyse Pathogens?

Membrane attack complex formed by c` proteins





① Activated complement proteins form complexes of proteins that create holes in the bacterial cell wall.

② Water and salts diffuse into the bacterium through the holes.

③ The bacterium swells and eventually bursts.

References

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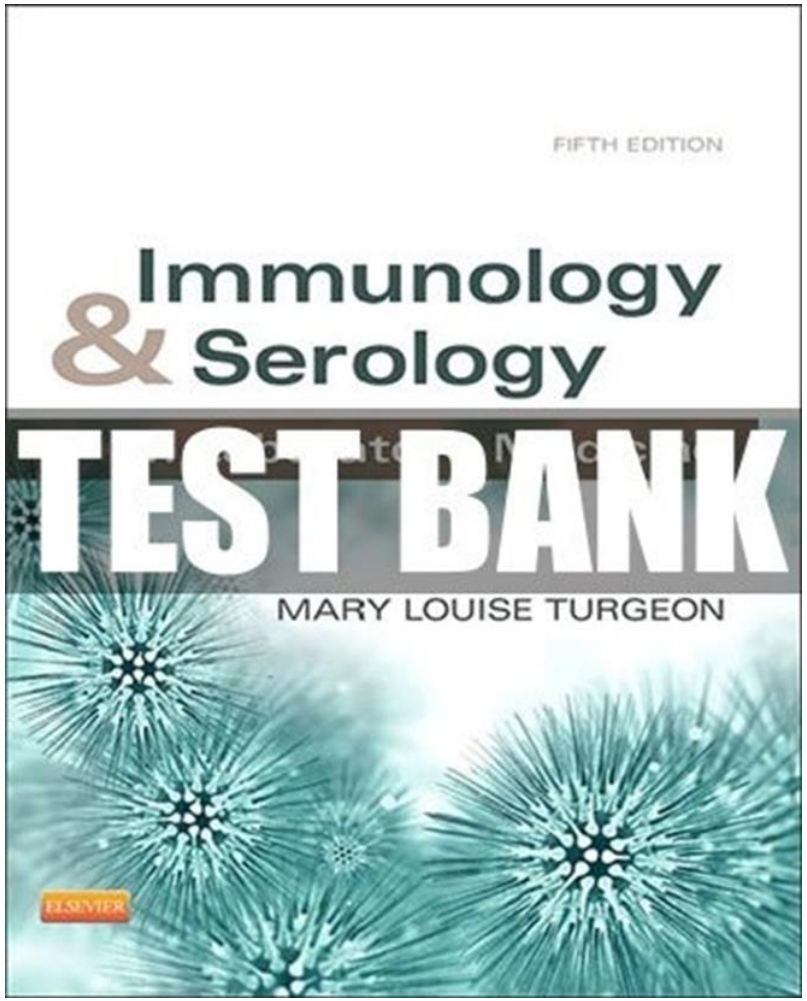

Here is the required reading for this lecture