Cihan University/ Sulaymaniyah

College of Health Science

Medical Laboratory Analysis

4th Stage- 1st Semester

Clinical Immunology

Lecture- 2: Innate Immunity

Internal Defense Line (2nd line of defense)

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The Internal Defense System

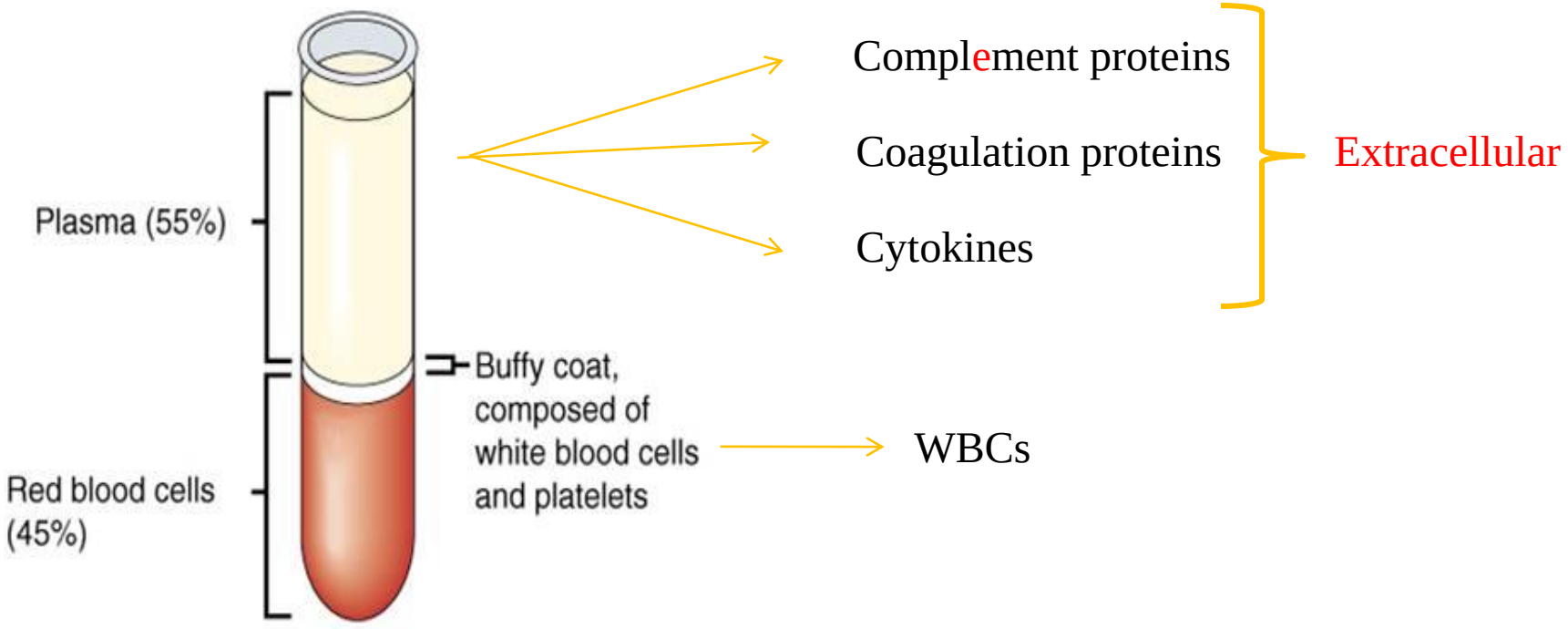
- It is composed of both **cells** and **soluble factors** that have specific and essential functions.

A- Cells; that are capable of phagocytosis play a major role in the internal defenses.

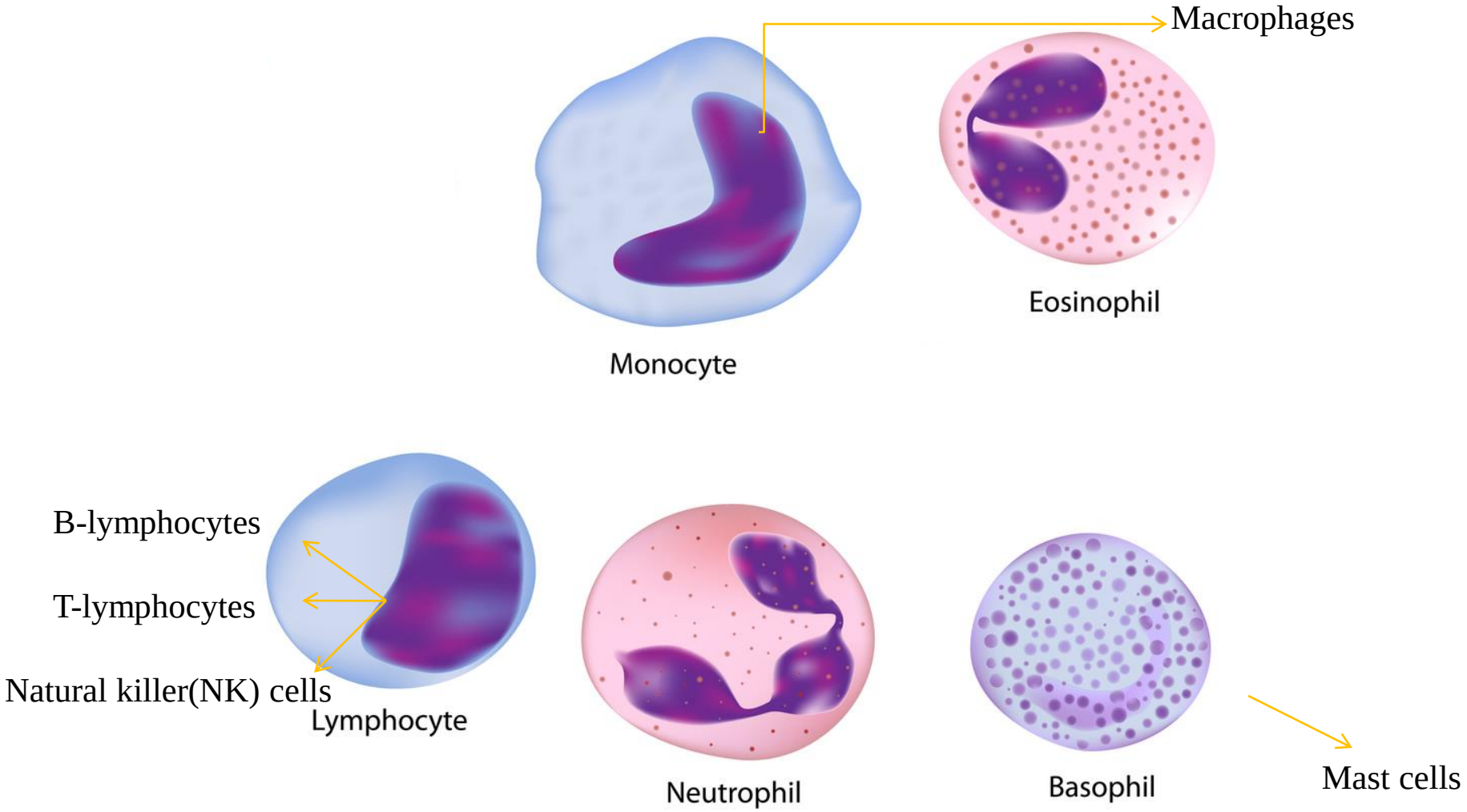
- ✓ Phagocytic cells engulf and destroy most of the foreign cells or particles that enter the body; this is the most important function of the internal defense system.
- ✓ Phagocytosis **is enhanced** by **specific receptors on cells** that capture invaders through **identification of unique microbial substances**.

B- Soluble factors; called **acute-phase reactants** act by several different mechanisms to **facilitate contact between microbes and phagocytic cells** and to bind to and recycle important proteins after the process of phagocytosis has taken place.

Innate Immune System: Components of Blood



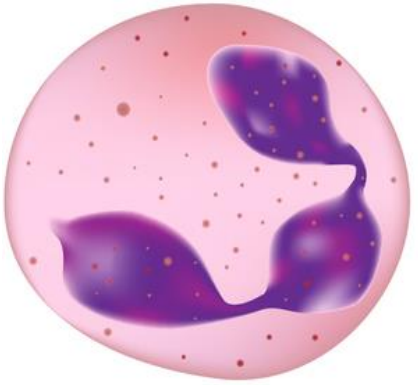
White blood cells (WBCs)



A- Cells of the Innate Immune System

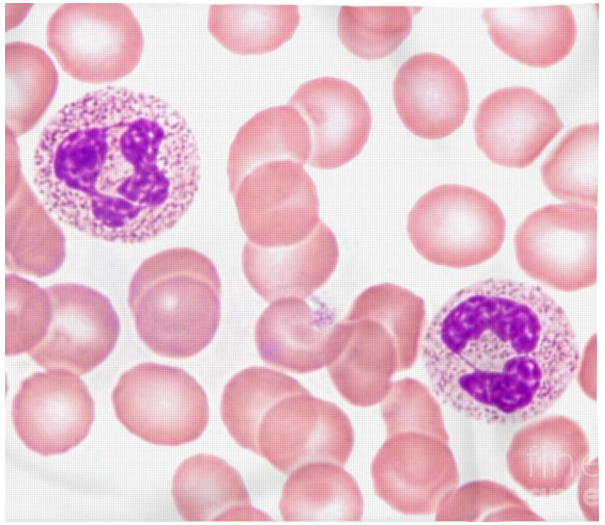
1- Circulating Blood Cells

a. Neutrophils



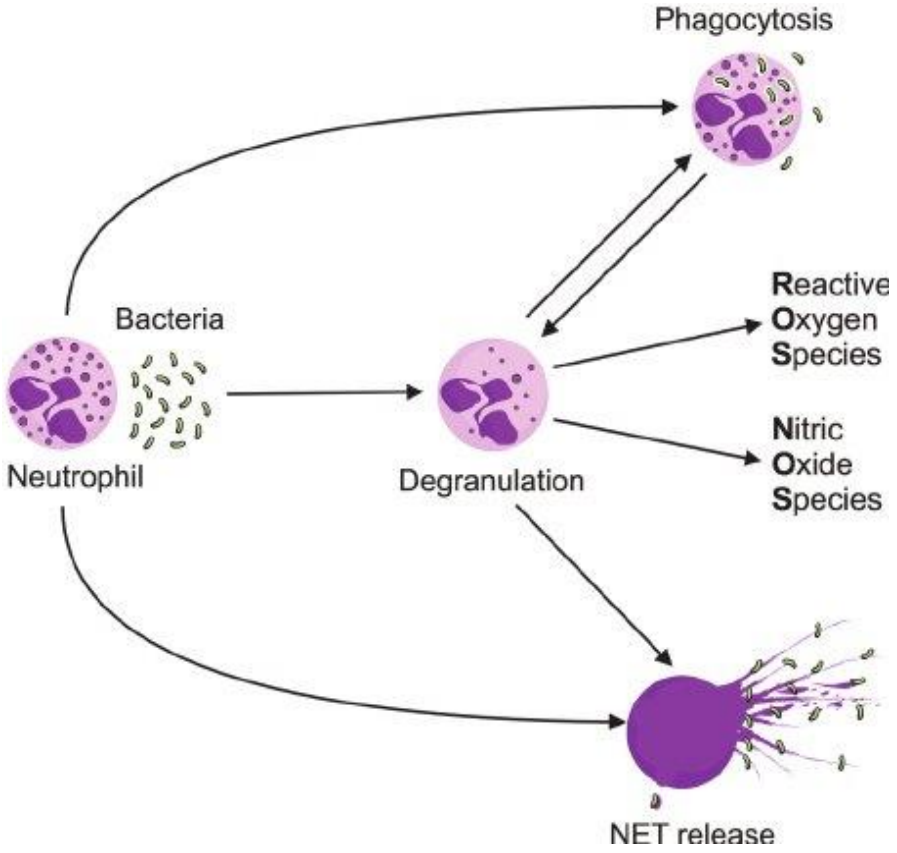
Neutrophil

- 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.
- The main function of neutrophils is phagocytosis, resulting in the destruction of foreign particles.
- Normally, half of the total neutrophil population in peripheral blood is found in a marginating pool adhering to blood vessel walls, whereas the rest of the neutrophils circulate freely for approximately 6 to 8 hours.
- Margination occurs to allow neutrophils to move from the circulating blood to the tissues through a process known as **diapedesis**, or movement through blood vessel walls.
- They are attracted to a specific area by chemotactic factors.



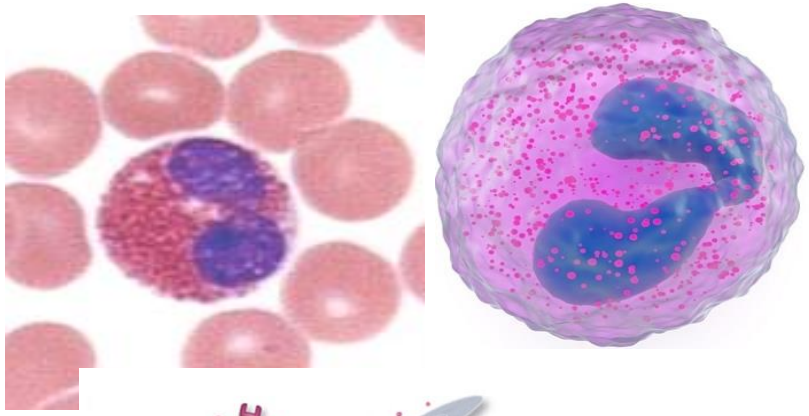
a. Neutrophils- cont.

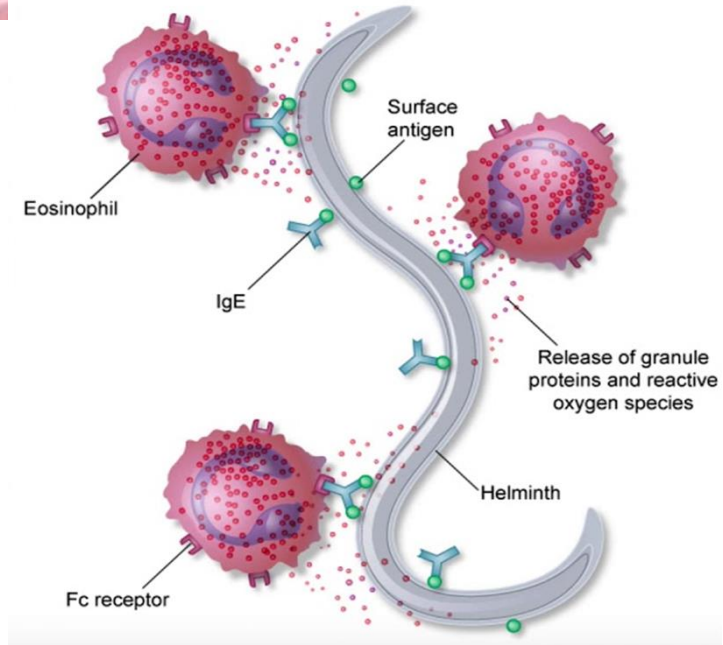
- Neutrophil die after digesting bacteria. Because of this, neutrophils have a lifespan that ranges from a few hours to a few days.
- Dead neutrophils make up a large proportion of pus.
- Also secrete pro-inflammatory cytokines when exposed to inflammatory mediators.
- Every day, 10 billion neutrophils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



b. 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.





c. Basophils

- Basophils are the least numerous of the WBCs found in peripheral blood, representing less than 1% of all circulating WBCs.
- 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

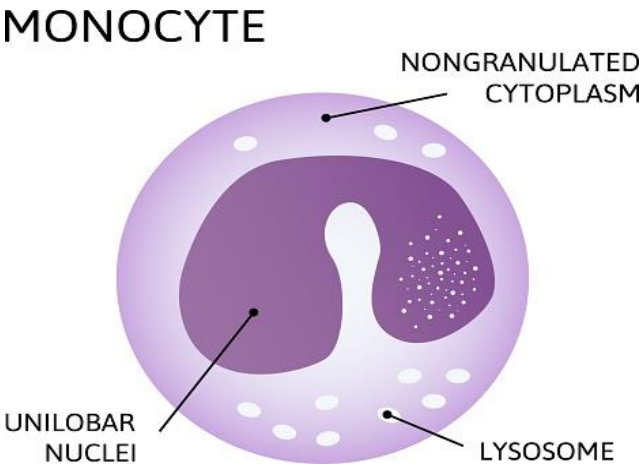
  1. Histamine

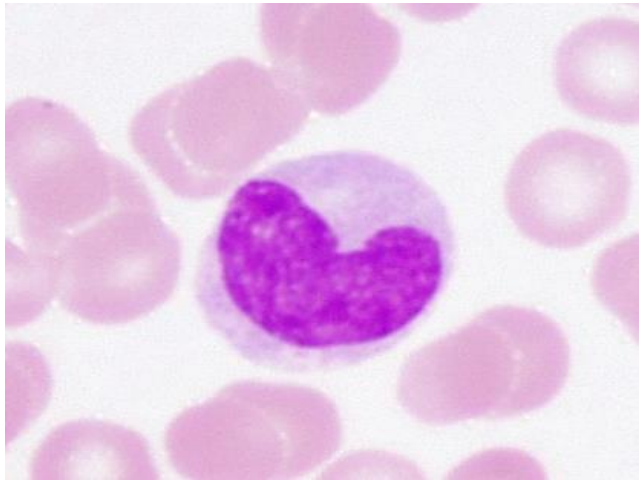
  2. Serotonin

  3. Interleukins

d. 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.



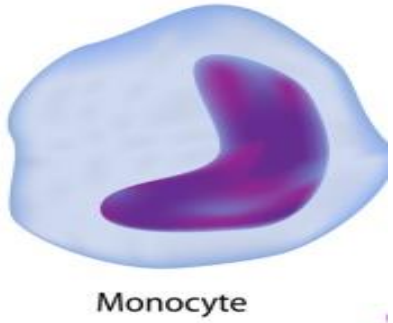


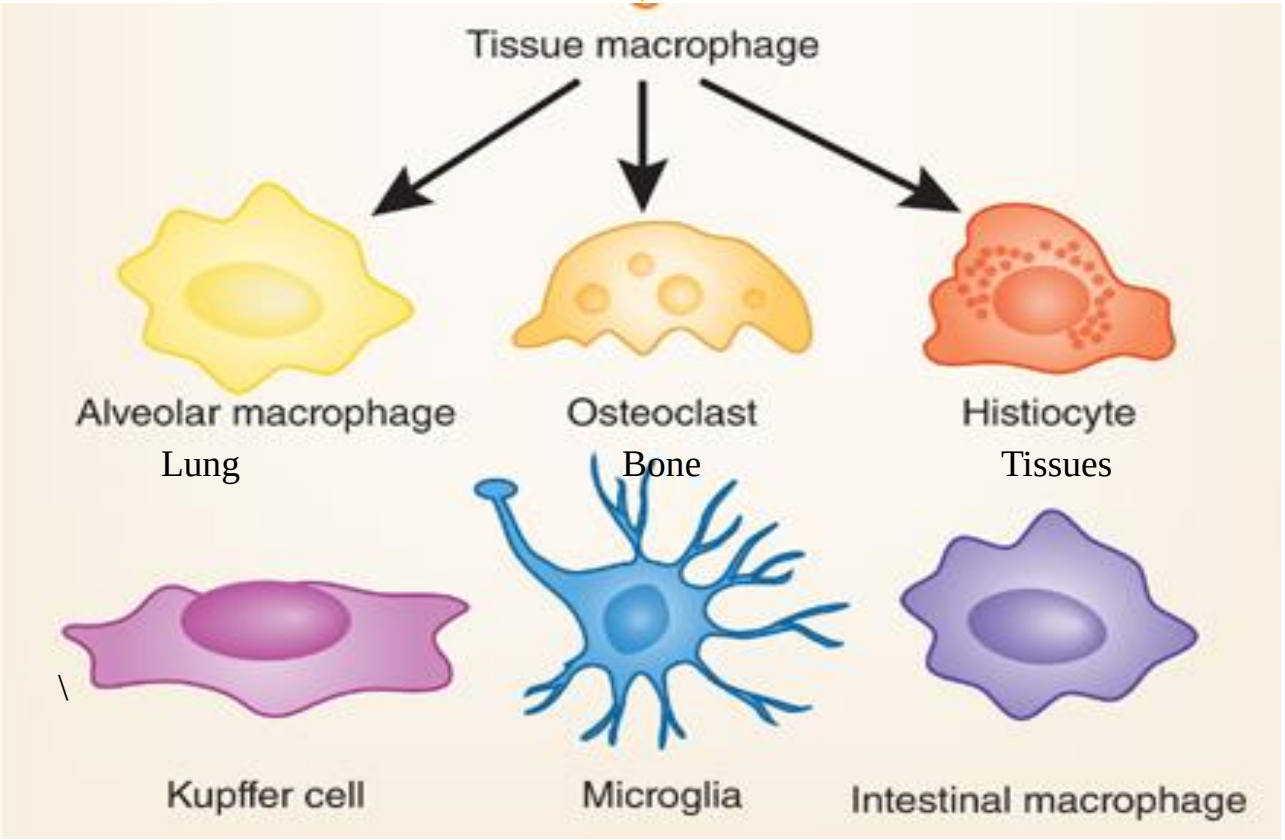
A. Cells of the Innate Immune System

2. Tissue Cells

a- Macrophages

- All macrophages arise from monocytes, which can be thought of as macrophage precursors, because additional differentiation and cell division take place in the tissues.
- Macrophages may not be as efficient as neutrophils in phagocytosis because their motility is slow compared with that of the neutrophils.
- Their innate immune functions include **phagocytosis**, **microbial killing**, **anti-tumor activity**, **intracellular parasite eradication**, and **secretion of cell mediators**.
- Macrophages play a major role in the adaptive immune response by presenting phagocytosed antigens to T lymphocytes.


Monocyte


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

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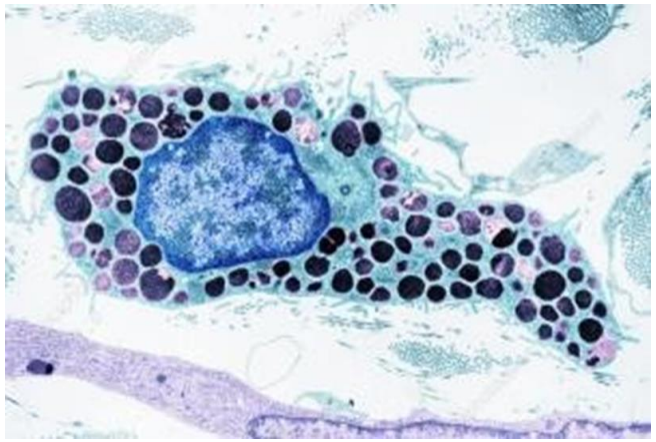
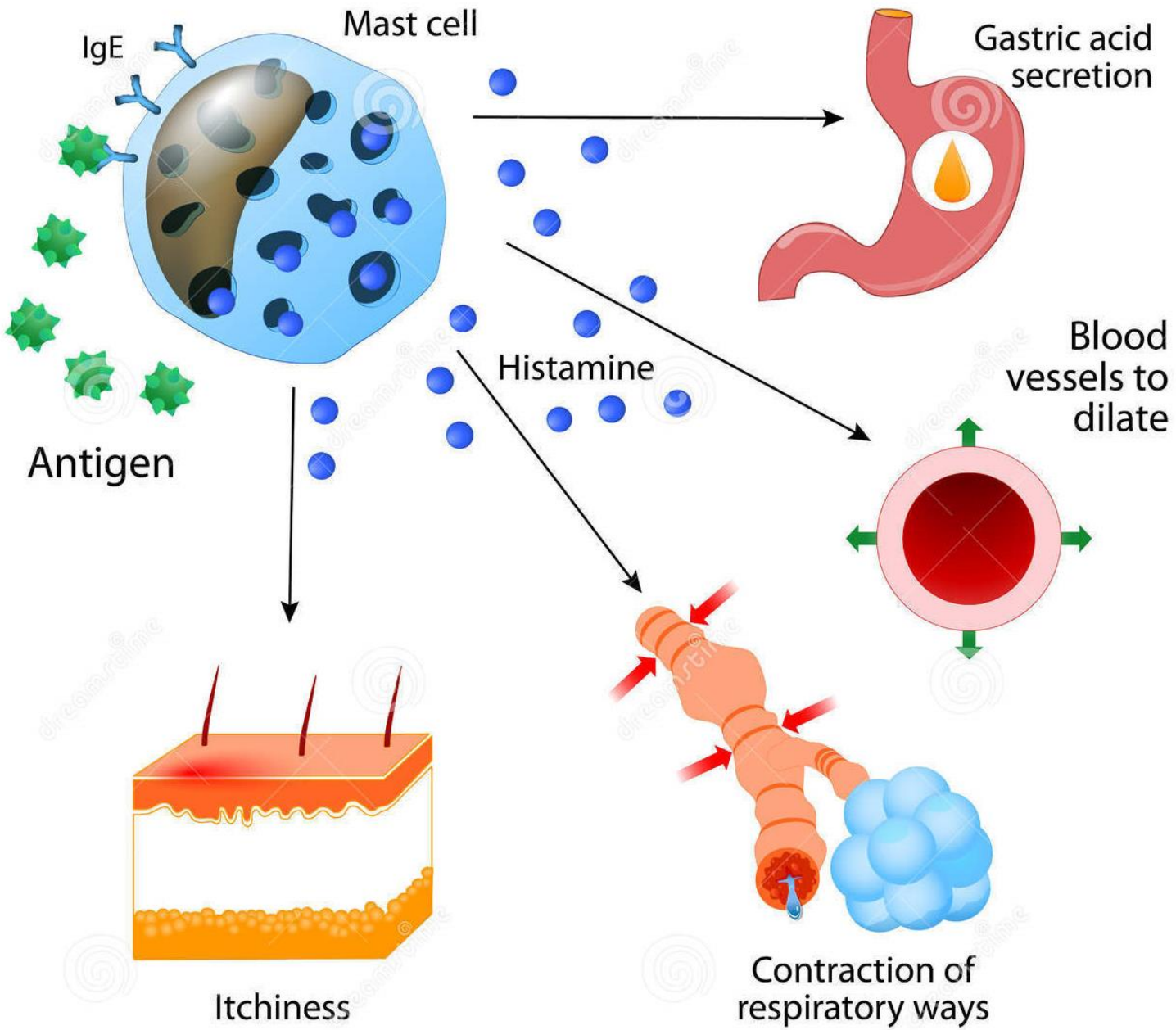
b. Mast Cells

- Tissue mast cells resemble basophils, but they come from a different lineage.
- Mast cells are distributed throughout the body in a wide variety of tissues, such as skin, connective tissue, and the mucosal epithelial tissue of the respiratory, genitourinary, and digestive tracts.

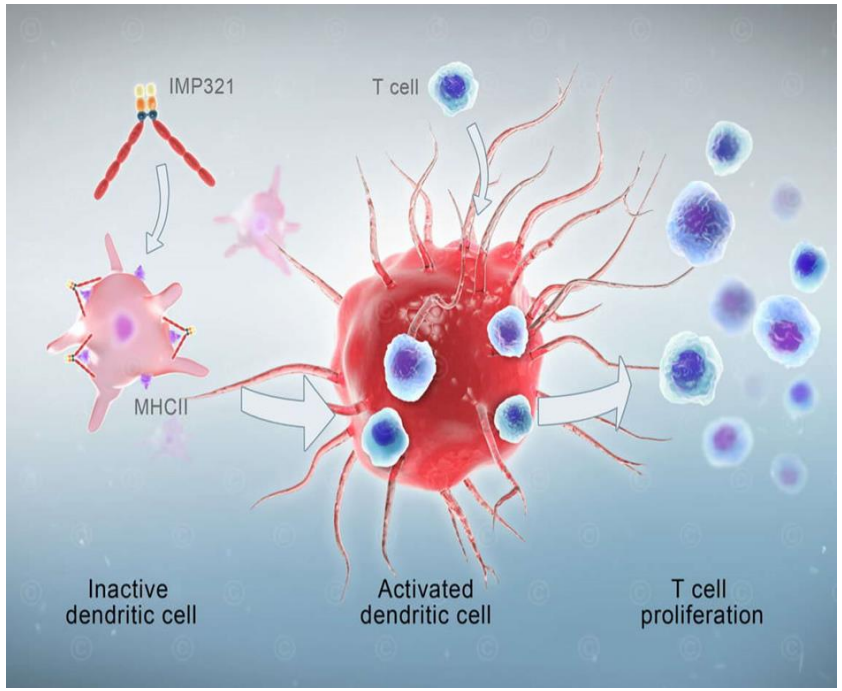


- They have a long life span of between 9 and 18 months.
- The enzyme content of the granules in mast cells helps to distinguish them from basophils because they contain serine proteases, heparin, and neutrophil chemotactic factor, as well as histamine.
- Act to increase vascular permeability and increase blood flow to the affected area.
- Play a key role in allergic reactions, as well as functioning as antigen-presenting cells (APCs).
- Their function as a major conduit between the innate and adaptive immune systems.


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

c. Dendritic Cells

- Dendritic cells are so named because they are covered with long, membranous extensions that resemble nerve cell dendrites.
- After capturing an antigen in the tissue by phagocytosis or endocytosis, dendritic cells travel to the nearest lymph node and present the antigen to T lymphocytes to initiate the adaptive immune response in a similar way as macrophages.
- Dendritic cells, are considered the most effective APC in the body, as well as the most potent phagocytic cell.



d. Innate Lymphoid Cells and Natural Killer Cells

- The innate lymphoid cells are a family of related cells that have important roles in innate immunity and tissue remodeling.
- These cells share three main properties:

  1. They have a lymphoid morphology,
  2. They do not possess antigen-specific receptors, and
  3. They do not have myeloid and dendritic cell markers.

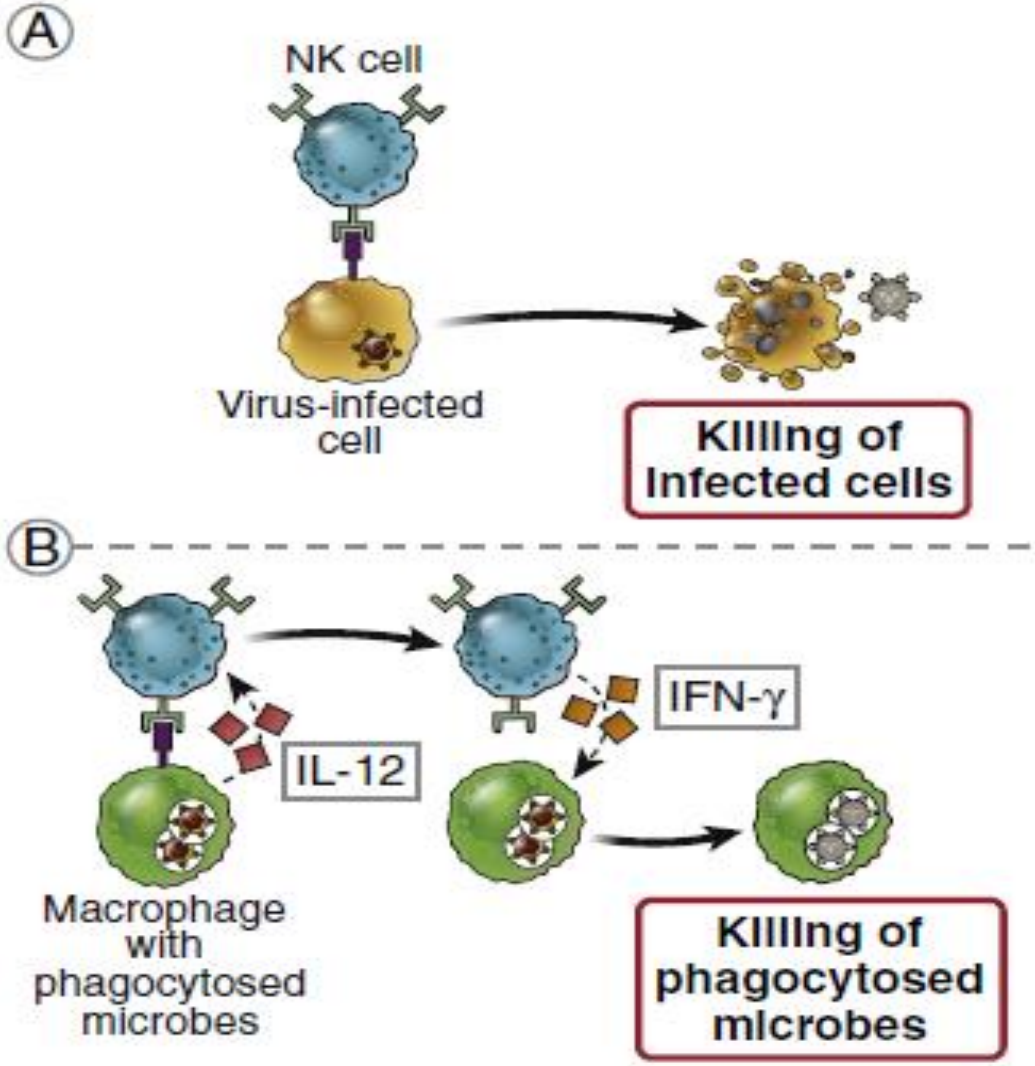
- A principal type of innate lymphoid cell is the natural killer (NK) cell.

Natural Killer Cells (NK cells)

- NK cells are so named because they have the ability to kill target cells without prior exposure to them.
- Do not require the thymus for development but appear to mature in the bone marrow itself.
- Human natural killer (NK) cells can be subdivided into different populations based on the relative expression of the surface markers CD16 and CD56.
- By the presence of CD16, NK cells are able to make contact with and then lyse any cell coated with antibodies.
- They are continuously scan for protein irregularities on host cells, and they represent the first line of defense against **virally infected cells** and **tumor cells**.
- NK cells are also capable of recognizing **foreign cells** and destroying them.
- They are thought to play an important role as a transitional cell that bridges the innate and the adaptive immune responses against pathogens.

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**.



B. Soluble Factors (Acute-phase Reactants)

- In addition to the **cells and receptors** that enhance the destruction of pathogens, the internal defense system also consists of **soluble factors** called **acute-phase reactants** that contribute to the innate immune response.
- **Acute-phase reactants** are normal serum constituents that rapidly increase or decrease in concentration because of infection, injury, or trauma to the tissues.
- Those that **increase** are termed **positive acute-phase reactants**, whereas those that **decrease**, such as **albumin** and **transferrin**, are known as **negative acute-phase reactants.**
- Many of these proteins act by binding to microorganisms and promoting adherence, the first step in phagocytosis.

B. Soluble Factors (Acute-phase Reactants)- cont.

- Some of the most important positive acute-phase reactants are:
  1. C-reactive protein (CRP),
  2. Serum amyloid A (SAA),
  3. Complement components,
  4. Alpha1- antitrypsin (AAT),
  5. Haptoglobin,
  6. Fibrinogen,
  7. Ceruloplasmin.

- They are **produced primarily by hepatocytes (liver parenchymal cells) within 12 to 24 hours** in response to an increase in cytokines.

- The major cytokines involved in inflammation are **interleukin-1 (IL-1), interleukin-6 (IL-6),** and **tumor necrosis factor-α (TNF-α),** all of which are **produced by monocytes** and **macrophages**.

C-Reactive Protein

- C-reactive protein (CRP) is a **trace constituent of serum.**
- **CRP promotes phagocytosis by binding to specific receptors** found on monocytes, macrophages, and neutrophils.
- Elevated levels are found in conditions such as **bacterial infections, rheumatic fever, viral infections, malignant diseases, tuberculosis, and after a heart attack.**
- Because the **levels rise and then decline so rapidly**, CRP is the most widely **used indicator of acute inflammation**.

Serum Amyloid A

- Serum amyloid A (SAA) is another major protein whose concentration can increase almost a thousand-fold in response to infection or injury. It is an apolipoprotein that is synthesized in the liver.
- It has a **high affinity for high density lipoprotein (HDL)** cholesterol and is **transported by HDL to the site of infection**.
- **Act as a chemical messenger**, similar to a cytokine, and it **activates monocytes** and **macrophages** to **produce products that increase inflammation**.
- It has been found to increase significantly more in bacterial infections than in viral infections.
- SAA can also be **increased because of chronic inflammation**, **atherosclerosis**, and **cancer**.
- Elevated levels may predict a worse outcome for the patient.

Complement System

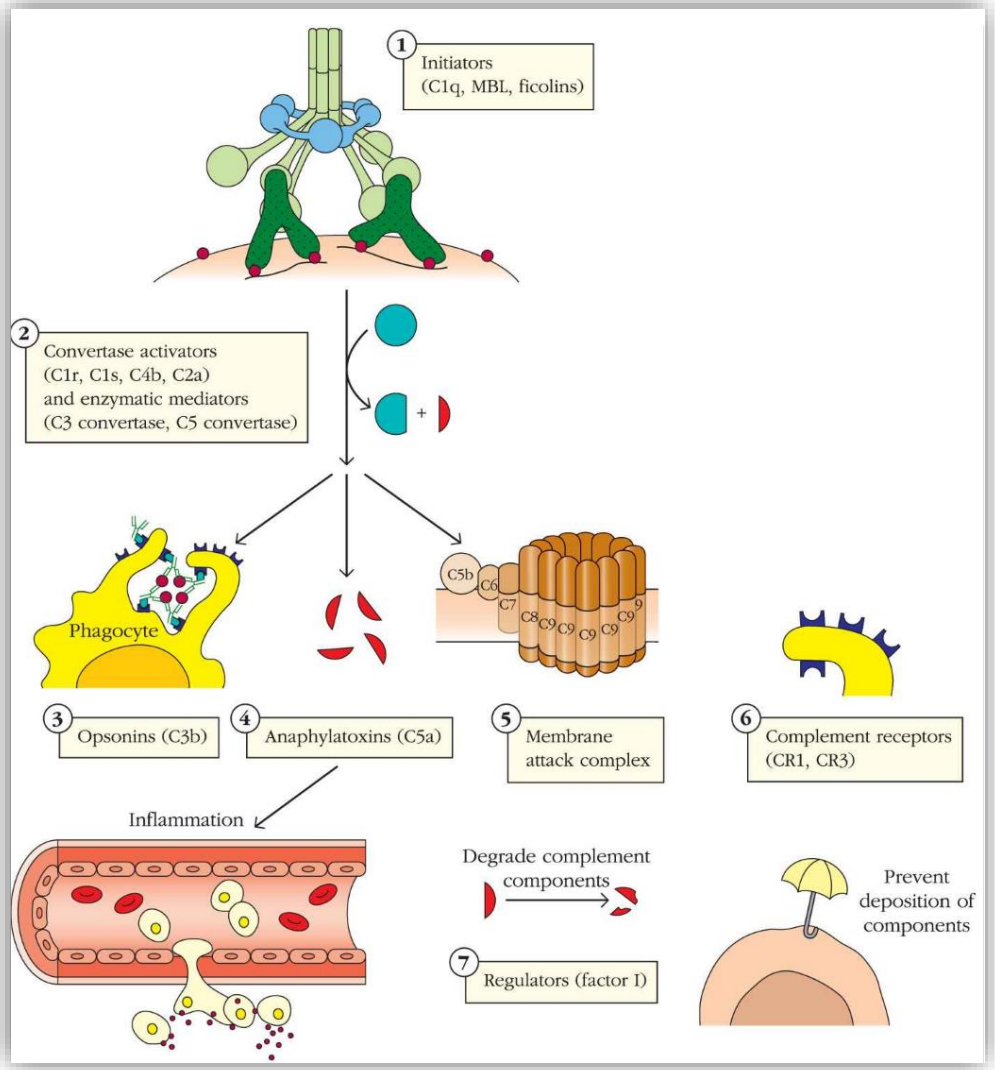
The major functions of complement are:

❖ Host benefit:

1. Opsonization to enhance phagocytosis
2. Phagocyte attraction and activation
3. Lysis of bacteria and infected cells
4. Regulation of antibody responses
5. Clearance of immune complexes
6. Clearance of apoptotic cells

❖ Host detriment:

1. Inflammation,
2. Anaphylaxis



Alpha1-Antitrypsin

- Alpha1-antitrypsin (AAT) is a protein that is **primarily synthesized in the liver**.

  a. **It is a general plasma inhibitor of proteases released from leukocytes. For example Elastase**, one such protease, is an **enzyme secreted by neutrophils during inflammation** that can **degrade elastin and collagen**.

  b. **It also regulates the expression of proinflammatory cytokines such as TNF-α, interleukin-1β**, and **interleukin-6**. Therefore, activation of monocytes and neutrophils is inhibited, limiting the harmful side effects of inflammation.

- AAT deficiency can result in **premature emphysema**, especially in individuals who smoke or who have frequent exposure to **noxious chemicals**.

- In such a deficiency, **uninhibited proteases remain in the lower respiratory tract**, leading to destruction of parenchymal cells in the lungs and to the development of emphysema or idiopathic pulmonary fibrosis.

Haptoglobin

- Haptoglobin is an **alpha2-globulin** with a molecular weight of 100,000 daltons. It **binds irreversibly to free hemoglobin** released by **intravascular hemolysis**.
- It **acts as an antioxidant to provide protection against oxidative damage** mediated by free hemoglobin. Once bound, the complex is cleared rapidly by macrophages in the liver.
- A two- to tenfold **increase in haptoglobin** can be seen following **inflammation, stress, or tissue necrosis**.
- Early in the **inflammatory response**, however, **haptoglobin levels may drop because of intravascular hemolysis**, consequently masking the protein's behavior as an acute-phase reactant.

Fibrinogen

- Fibrinogen is an **acute-phase protein** involved in the **coagulation pathway**. A **small portion is cleaved by thrombin** to **form fibrils** that make up a **fibrin clot**.
- The clot increases the strength of a wound and stimulates endothelial cell adhesion and proliferation, which are critical to the healing process.
- Formation of a **clot creates a barrier that helps prevent the spread of microorganisms** further into the body. Fibrinogen makes blood more viscous and serves to promote aggregation of red blood cells (RBCs) and platelets.
- Increased levels may contribute to an increased risk for developing coronary artery disease.

Ceruloplasmin

- Ceruloplasmin consists of a **single polypeptide chain**.
  1. It is the **principal copper-transporting protein** in human plasma, binding more than 70% of the copper found in plasma by attaching Six Cupric Ions per molecule.
  2. It **acts as an enzyme, converting the toxic ferrous ion (Fe2+) to the nontoxic ferric form (Fe3+).**
- Normally, **circulating copper is absorbed out of the circulation by the liver** and either **combined with ceruloplasmin** and returned to the plasma or **excreted into the bile duct**.

References

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