

Courses of signalisation molecular and cellular (Pr S.ZERIZER)

Part one

I OVERVIEW OF THE IMMUNE SYSTEM

We are constantly being exposed to infectious agents and yet, in most cases, we are able to resist these infections.

It is our immune system that enables us to resist infections.

The immune system is composed of two major subdivisions:

1-the innate or non-specific immune system

2-the adaptive or specific immune system

The innate immune system is our first line of defense against invading organisms while the adaptive immune system acts as a second line of defense and also affords protection against re-exposure to the same pathogen (table 01).

Table 01: The difference between the innate immune system and the adaptive immune system is

1-the innate or non-specific immune system	2-the adaptive or specific immune system
1-The innate immune system is our first line of defense against invading organisms	The adaptive immune system is the second line of defense .
2-the innate immune system does not demonstrate immunological memory	-immunological memory . It “remembers” that it has encountered an invading organism and reacts more rapidly on subsequent exposure to the same organism.

3-Each of the major subdivisions of the immune system has both cellular and humoral components by which they carry out their protective function.

In addition, the innate immune system also has anatomical features that function as barriers to infection.

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4-Responds within minutes to infection).

requires some time to react to an invading organism, (Response develops over days).

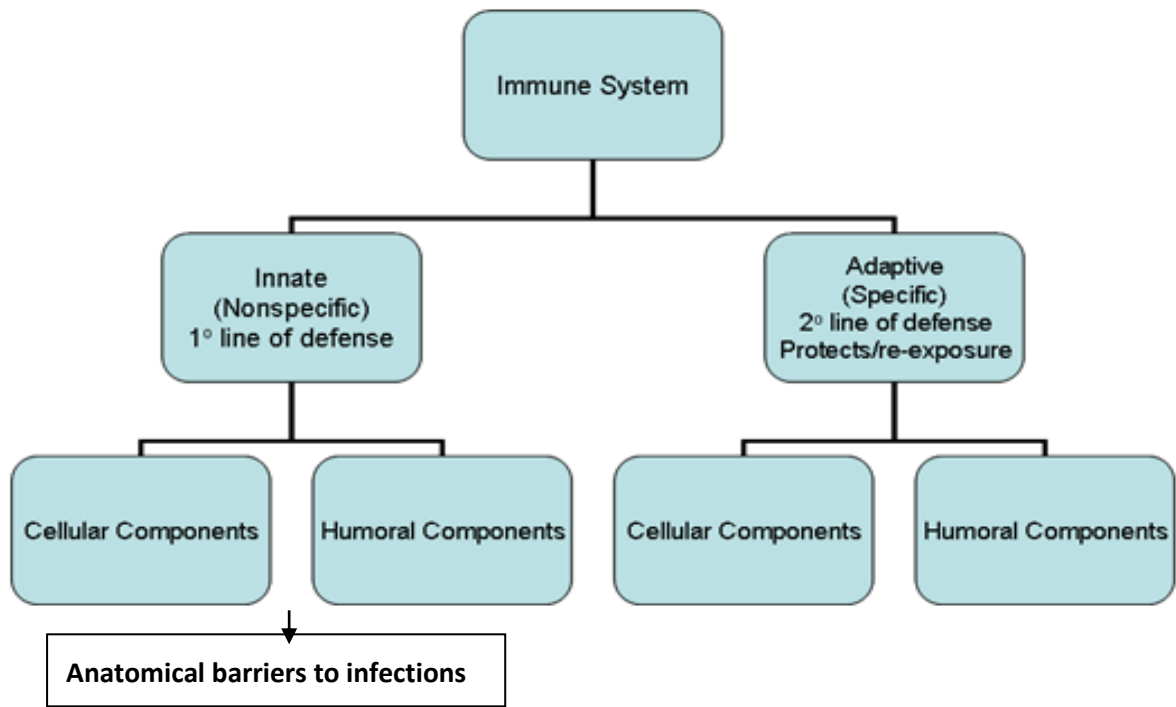


Figure 1 : Overview of the immune system

Cells of the immune system

All cells of the immune system have their origin in the bone marrow and they include myeloid (neutrophils, basophils, eosinophils, macrophages and dendritic cells) and lymphoid (B lymphocyte, T lymphocyte and Natural Killer) cells (Figure 2), which differentiate along distinct pathways (Figure 3). The myeloid progenitor (stem) cell in the bone marrow gives rise to erythrocytes, platelets, neutrophils, monocytes/macrophages and dendritic cells whereas the lymphoid progenitor (stem) cell gives rise to the NK, T cells and B cells. For T cell development the precursor T cells must migrate to the thymus where they undergo differentiation into two distinct types of T cells, the CD4+ T helper cell and the CD8+ pre-cytotoxic T cell. Two types of T helper cells are produced in the thymus the TH1 cells, which help the CD8+ pre-cytotoxic cells to differentiate into cytotoxic T cells, and TH2 cells, which help B cells, differentiate into plasma cells, which secrete antibodies.

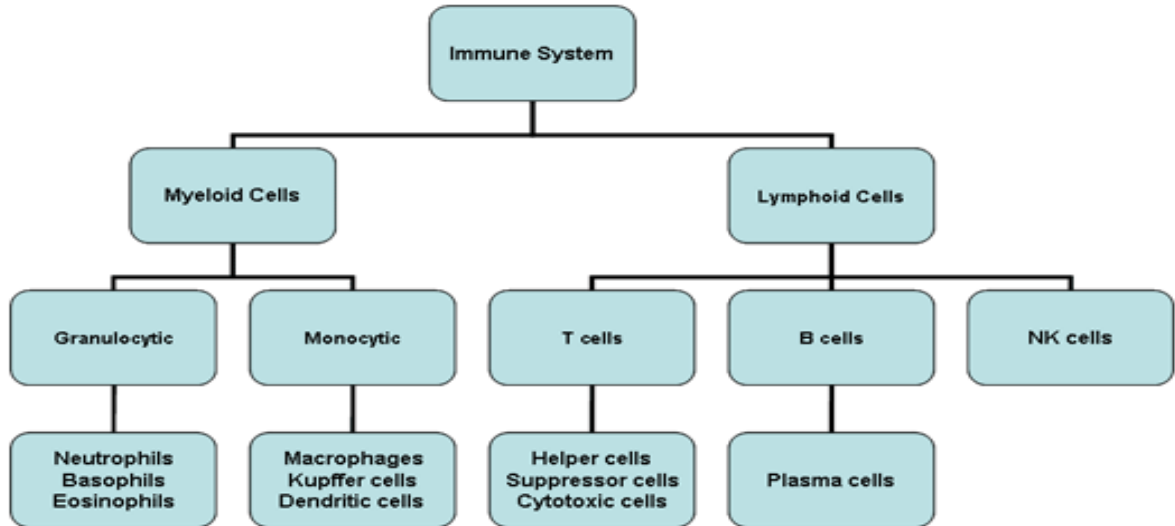


Figure 2: Cells of the immune system

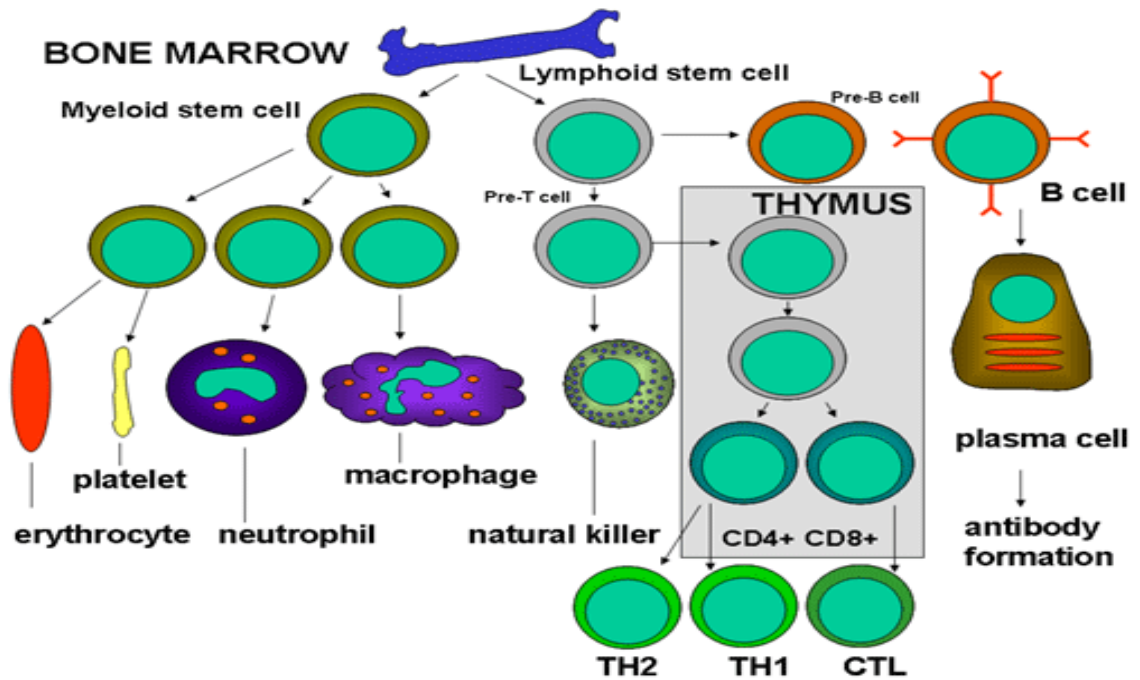


Figure 3: Development of the cells of the immune system

II-INNATE (NON-SPECIFIC) IMMUNITY

The elements of the innate (non-specific) immune system (Table 2) include anatomical barriers, secretory molecules and cellular components. Among the mechanical anatomical barriers are the skin and internal epithelial layers, the movement of the intestines and the oscillation of broncho-pulmonary cilia. Associated with these protective surfaces are chemical and biological agents.

A. Anatomical barriers to infections

1. Mechanical factors

The epithelial surfaces form a physical barrier that is very impermeable to most infectious agents. Thus, the skin acts as our first line of defense against invading organisms. The desquamation of skin epithelium also helps remove bacteria and other infectious agents that have adhered to the epithelial surfaces. Movement due to cilia or peristalsis helps to keep air passages and the gastrointestinal tract free from microorganisms. The flushing action of tears and saliva helps prevent infection of the eyes and mouth. The trapping effect of mucus that lines the respiratory and gastrointestinal tract helps protect the lungs and digestive systems from infection.

2. Chemical factors

Fatty acids in sweat inhibit the growth of bacteria. lysozyme and phospholipase found in tears, saliva and nasal secretions can breakdown the cell wall of bacteria and destabilize bacterial membranes. The low pH of sweat and gastric secretions prevents growth of bacteria. Defensins (low molecular weight proteins) found in the lung and gastrointestinal tract have antimicrobial activity. Surfactants in the lung act as opsonins (substances that promote phagocytosis of particles by phagocytic cells).

3. Biological factors

The normal flora of the skin and in the gastrointestinal tract can prevent the colonization of pathogenic bacteria by secreting toxic substances or by competing with pathogenic bacteria for nutrients or attachment to cell surfaces.

B. Humoral barriers to infection

- The anatomical barriers are very effective in preventing colonization of tissues by microorganisms. However, when there is damage to tissues the anatomical barriers are breached and infection may occur.
- Once infectious agents have penetrated tissues, another innate defense mechanism comes into play, namely acute inflammation. Humoral factors play an important role in inflammation, which is characterized by edema and the recruitment of phagocytic cells. These humoral factors are found in serum or they are formed at the site of infection.
- 1. Complement system – The complement system is the major humoral non-specific defense mechanism. Once activated complement can lead to increased vascular permeability, recruitment of phagocytic cells, lysis and opsonization of bacteria.
- 2. Coagulation system – Depending on the severity of the tissue injury, the coagulation system may or may not be activated.
- Some products of the coagulation system can contribute to the non-specific defenses because of their ability to increase vascular permeability and act as chemotactic agents for phagocytic cells.
- In addition, some of the products of the coagulation system are directly antimicrobial. For example, beta-lysin, a protein produced by platelets during coagulation can lyse many Gram positive bacteria by acting as a cationic detergent.
- 3. Lactoferrin and transferrin – By binding iron, an essential nutrient for bacteria, these proteins limit bacterial growth.
- 4. Interferons – Interferons are proteins that can limit virus replication in cells.
- 5. Lysozyme – Lysozyme breaks down the cell wall of bacteria.

6. Interleukin-1 – Il-1 induces fever and the production of acute phase proteins, some of which are antimicrobial because they can opsonize bacteria.

C. Cellular barriers to infection

- Part of the inflammatory response is the recruitment of polymorphonuclear Neutrophils and macrophages to sites of infection.
- These cells are the main line of defense in the non-specific immune system.

III PHAGOCYTOSIS AND INTRACELLULAR KILLING

A. Phagocytic cells

1. Neutrophils/Polymorphonuclear cells

Neutrophils/Polymorphonuclear are motile phagocytic cells have lobed nuclei they can be identified by their characteristic nucleus or by an antigen present on the cell surface called CD66.

They contain two kinds of granules , the primary granules, which are abundant in young newly formed PMNs, contain defensins that can kill bacteria, proteolytic enzymes like elastase, and cathepsin G to breakdown proteins, lysozyme to break down bacterial cell walls, and myeloperoxidase, which is involved in the generation of bacteriocidal compounds.

The second type of granule found in more mature PMNs is the secondary or specific granule. These contain lysozyme, NADPH oxidase components, which are involved in the generation of toxic oxygen products, and characteristically lactoferrin, an iron chelating protein and B12-binding protein.

- **2. Monocytes/Macrophages**

Macrophages are phagocytic cells that have a characteristic kidney-shaped nucleus. They can be identified morphologically or by the presence of the CD14 cell surface marker. Unlike Neutrophils they do not contain granules but they have numerous lysosomes which have contents similar to the PMN granules.

- **B. Response of phagocytes to infection**

- **1-Circulating PMNs and monocytes**

- Respond to danger (SOS) signals generated at the site of an infection,
- SOS signals include N- formyl –methionine containing peptides released by bacteria, clotting system peptides, complement products and cytokines released from tissue macrophages that have encountered bacteria in tissue.
- Some of the SOS signals stimulate endothelial cells near the site of the infection to express cell adhesion molecules such as ICAM-1 and selectins which bind to components on the surface of phagocytic cells and cause the phagocytes to adhere to the endothelium.
- Vasodilators produced at the site of infection cause the junctions between endothelial cells to loosen and the phagocytes then cross the endothelial barrier by “squeezing” between the endothelial cells in a process called diapedesis (Figure 04).
- Once in the tissue spaces some of the SOS signals attract phagocytes to the infection site by chemotaxis (movement toward an increasing chemical gradient). The SOS signals also activate the phagocytes, which results in increased phagocytosis and intracellular killing of the invading organisms.

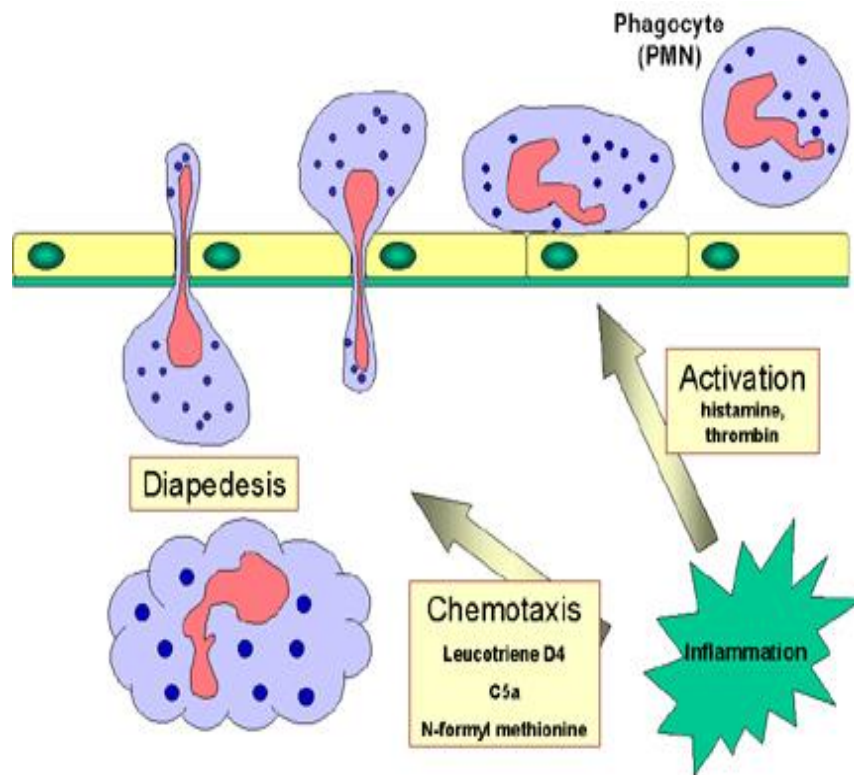


Figure 04 : Chemotactic response to inflammatory stimulus

B. Initiation of Phagocytosis

Phagocytic cells have a variety of receptors on their cell membranes through which infectious agents bind to the cells. These include:

1. Fc receptors – Bacteria with IgG antibody on their surface have the Fc region exposed and this part of the Ig molecule can bind to the receptor on phagocytes.

Binding to the Fc receptor requires prior interaction of the antibody with an antigen. Binding of IgG-coated bacteria to Fc receptors results in enhanced phagocytosis and activation of the metabolic activity of phagocytes (respiratory burst).

- 2. Complement receptors – Phagocytic cells have a receptor for the 3rd component of complement, C3b.

Binding of C3b-coated bacteria to this receptor also results in enhanced phagocytosis and stimulation of the respiratory burst.

3. Scavenger receptors – Scavenger receptors bind a wide variety of polyanions on bacterial surfaces resulting in phagocytosis of bacteria.

- 4. Toll-like receptors – Phagocytes have a variety of Toll-like receptors (Pattern Recognition Receptors or PRRs) which recognize broad molecular patterns called PAMPs (Pathogen Associated Molecular Patterns) on infectious agents.

Binding of infectious agents via Toll-like receptors results in phagocytosis and the release of inflammatory cytokines (IL-1, TNF-alpha and IL-6) by the phagocytes (figure 05).

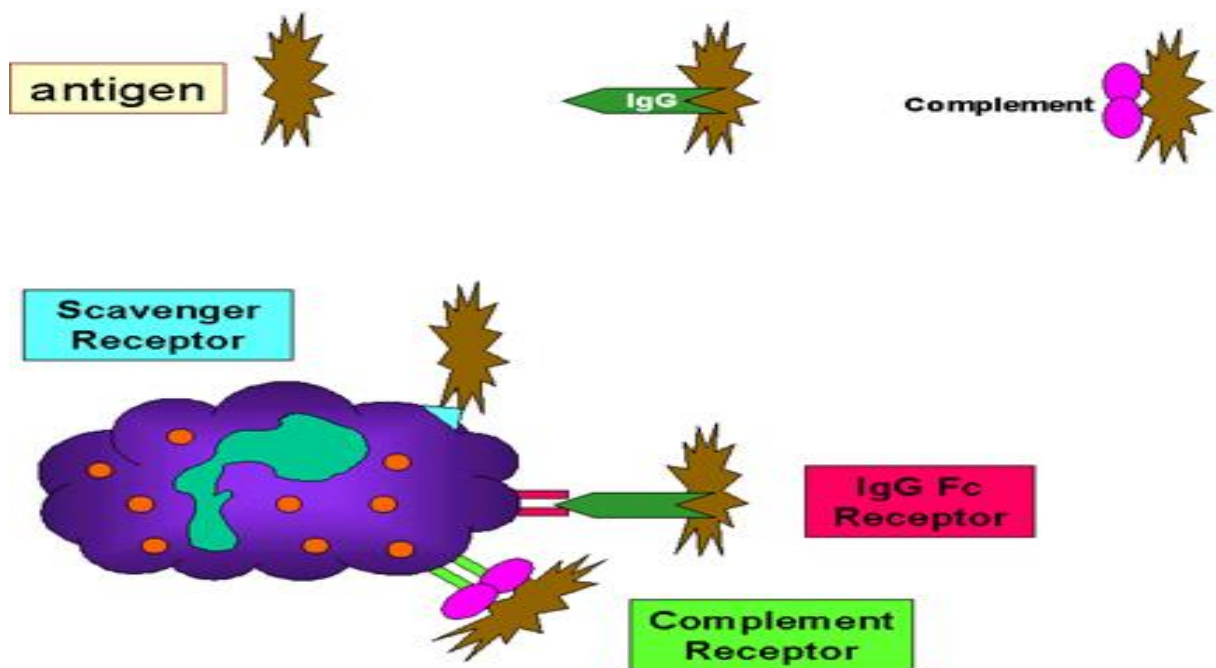


Figure 05: Adherence of bacteria via receptors

D. Phagocytosis

After attachment of a bacterium, the phagocyte begins to extend pseudopods around the bacterium. The pseudopods eventually surround the bacterium and engulf it, and the bacterium is enclosed in a phagosome. During phagocytosis the granules or lysosomes of the phagocyte fuse with the phagosome and empty their contents. The result is a bacterium engulfed in a phagolysosome which contains the contents of the granules or lysosomes.

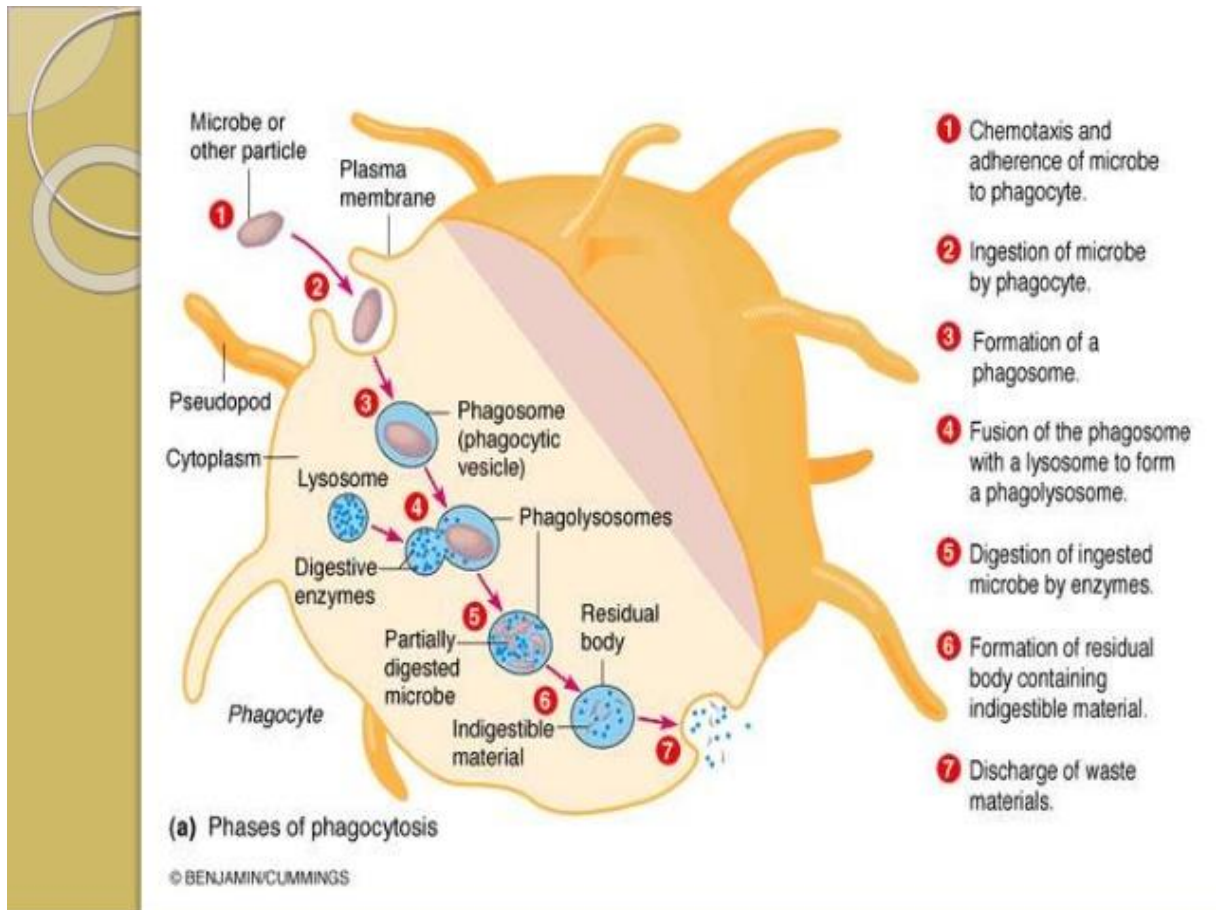


Figure 06 : Process of phagocytosis