Chapter IV. The non-specific immune response

The innate immune system includes cells and mechanisms that provide immediate defense against infectious agents. Unlike the adaptive immune system, which exists only in vertebrates, the innate immune system is present in all organisms in both the plant and animal kingdoms.

The main functions of the innate immune system in vertebrates are:

1. Establishing a physical and chemical barrier against infectious agents.
2. Detecting infectious agents and recruiting immune cells to the site of infection.
3. Eliminating dead cells or immune complexes.
4. Identifying and removing foreign bodies present in the organism, tissues, blood, and lymph through white blood cells.
5. Activating adaptive immunity through antigen presentation.

The innate immune system includes:

1. Natural barriers

A. Physical barriers

- Skin
- Mucous membranes

B. Chemical barriers

- Biological secretions (saliva, sweat, sebum, tears, mucus, etc.)

C. Microbiological barriers

- Intestinal flora and skin flora.

2. Innate immune cells

The cells involved in innate immunity are:

A. Tissue-resident cells: Macrophages, mast cells, dendritic cells.

B. Circulating cells in the blood: Monocytes, granulocytes (polymorphonuclear cells), Natural Killer (NK) cells.

Chapter IV. The non-specific immune response

Table 1: The main roles of innate immune cells

Les Cellules	Principaux rôles
Cellule dendritique	-phagocytose -cellule présentatrice d'antigéne CPA -sécrétion des médiateurs chimiques de l'inflammation
Granulocyte	-phagocytose -sécrétion de médiateurs chimiques de l'inflammation
Monocyte	-CPA -peuvent traverser la paroi des vaisseaux et se transformer en macrophage
Macrophage	-provenant des monocytes sanguins - CPA -phagocytose -sécrétion des médiateurs chimiques de l'inflammation
Mastocyte	-sécrétion d'histamine, héparine et de prostaglandine -provoque la vasodilatation et la diapédèse -rôle caractéristique dans le allergies
Cellule NK	- tue les cellules infectée qui ont perdu leur CMH-1

IV.1. Molecules of innate immunity

IV.1.1. The complement system

IV.1.1.1. Definition

The complement system, designated by the symbol "C," is a complex system of plasma proteins that plays a fundamental role in pathogen opsonisation and the activation of the inflammatory response. As a component of natural immunity, the complement system exists in an inactive form, with most of its factors synthesized by macrophages and hepatocytes.

IV.1.1.2. Complement activation pathways

There are three distinct pathways through which the complement system can be activated: the classical pathway, the alternative pathway, and the lectin pathway. These pathways are activated by different cascades that ultimately converge on the same set of effector molecules.

A. Classical pathway

- ***A.1. Activators of the classical pathway:*** This pathway is activated by antigen-antibody (Ag-Ab) complexes in which the antibody is of the IgM or IgG type.
- ***A.2. Components of the classical pathway:***
    - **C1:** A macromolecular complex composed of three proteins: C1q, C1r, and C1s.

- **C1q:** The heaviest part of the complement (410 kDa), consisting of a complex of six polypeptide subunits, each with a tulip-like structure ending in a globular part that binds to the Fc regions of antibodies.
- **C1r and C1s:** Pro-enzymes capable of activation, forming a tetramer in the presence of Ca^{2+}: $(C1r)_2$-Ca^{2+}-$(C1s)_2$.
- **C4 and C2:** Two proteins specific to the classical pathway (a decrease in their serum levels indicates pathological activation of this pathway).

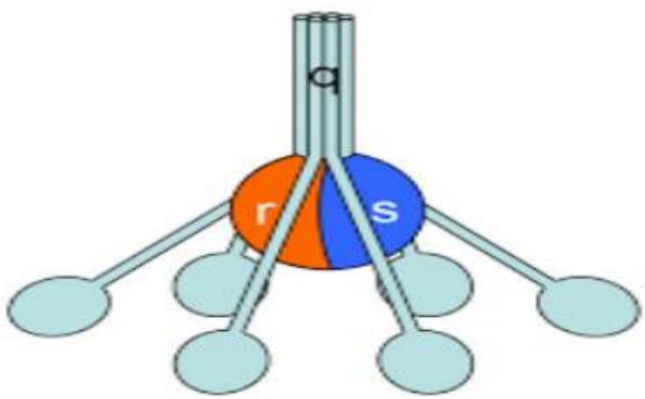

Fig 15. C1 complex structure.

A.3. Classical pathway cascade

C1q binds to the Fc fragment of IgM and IgG, leading to the activation of C1r, which transitions from a pro-enzyme state to an enzymatic state. C1r then cleaves C1s into two polypeptides: C1sa (34 kDa) and C1sb (76 kDa). The smaller subunit is a serine esterase. C1s acts as an enzyme capable of cleaving the two molecules C4 and C2 into C4a, C4b, and C2a, C2b.

The two fragments, C4b and C2a, together form **the classical C3 convertase (C4b2a)**. This reaction occurs in the presence of Mg^{2+} ions. The C3 convertase cleaves C3 into two parts: C3a and C3b. The C3b fragment binds to the surface of the target cell at the Ag-Ab-C4b2a complex. The complex **C4b2a3b** represents **the C5 convertase**, which has

opsonization and adhesion properties. The fragments C4a, C3a, and C5a have **anaphylatoxic** and **chemotactic** properties.

Activation of the lytic complex: When C5 binds to C3b, it becomes a substrate for both the classical and alternative C5 convertases, which cleave it into two fragments: C5a and C5b. The C5b fragment (171 kDa) binds to the membrane of the target cell. Around it, other complement molecules (C6 to C9) attach. This process consists of non-enzymatic reactions since these components circulate in the plasma in an active form.

The C5, C6, and C7 complex attaches firmly to the membrane, then recruits C8, which inserts itself into the membrane. Several C9 molecules (poly-C9 or (C9)n) fuse with the C5, C6, C7, and C8 complex, forming a pore in the target membrane. This entire complex—C5, C6, C7, C8, and (C9)n—is called the **Membrane Attack Complex (MAC).**

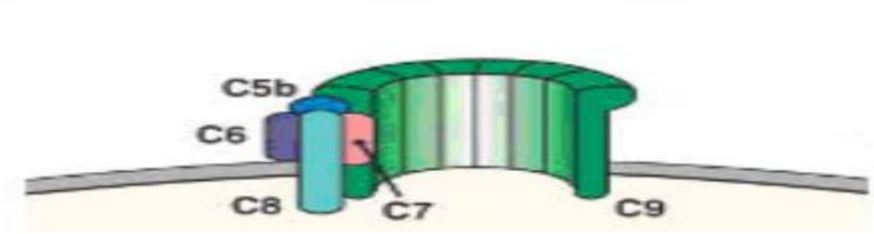

Fig 16. Membrane Attack Complex (MAC) Structure.

B. Alternative pathway

- ***B.1. Activators of the alternative pathway:***

1. Virus-infected cells.
2. Bacterial endotoxins.
3. Yeasts, parasites, and cobra venom.
4. Aggregates of IgA and IgE (which do not bind C1).

- ***B.2. Components of the alternative pathway:***

The main proteins involved in the alternative pathway are:

1. **Factor B:** A 95 kDa protein (with a serum concentration of 250 µg/L).
2. **Factor D:** A 25 kDa globulin.
3. **Properdin (Factor P):** A protein composed of four identical subunits, which stabilizes the alternative C3 convertase.
4. **The C3b component of the complement system.**

B.3. Alternative pathway cascade:

1. Factor B is cleaved by Factor D into two fragments: **Ba** and **Bb**. The binding of C3b and Bb in the presence of Mg^{2+} ions forms the **alternative C3 convertase**.
2. The **C3b-Bb** complex is stabilized by properdin.
3. C3 is then cleaved into C3a and C3b by the C3 convertase.
4. The **C3bBbC3b** complex has the proteolytic function of **C5 convertase**, which hydrolyzes C5 into C5a and C5b.
5. After the formation of C5b, the components C6, C7, C8, and C9 attach in the same manner as in the classical pathway.

C. The lectin pathway

The lectin pathway is activated by the carbohydrate structures of microorganisms. It is similar to the classical pathway. The recognition protein in this case is **MBL (Mannan-Binding Lectin),** which is associated with serine esterases called **MASP-1, MASP-2, and MASP-3 (Mannan-Associated Serine Protease).** These enzymes share a strong homology with C1s and C1r.

Once activated, MASPs gain the ability to cleave C4 and C2 proteins, contributing to the formation of **C3 convertase (C4b2a),** identical to that formed through activation of the classical pathway.

IV.1.1.3. Biological consequences of complement activation

1. **Lysis of certain bacteria** by the **Membrane Attack Complex (MAC),** formed through the activation of terminal components C5 to C9.
2. **Opsonisation** through the deposition of **C3b,** which facilitates phagocytosis.
3. **Pro-inflammatory activity** mainly linked to the anaphylatoxins **C3a and C5a.**

IV.1.2. Cytokines

Cytokines are soluble or membrane-bound mediators that facilitate communication between cells. During the innate immune response, all immune cells, as well as epithelial and endothelial cells, can produce cytokines. They are mainly classified into:

1. **Pro-inflammatory cytokines**, such as **TNF, IL-1, IL-6, IL-12, IFN-α, IFN-β, IFN-γ, IL-15, and IL-17.**
2. **Chemoattractant cytokines (chemokines)**, such as **CXCL8 (IL-8).**

3. **Regulatory cytokines** involved in inflammation control, such as **IL-10 and TGF-β.**

The targets of these innate immunity cytokines include:

- **Innate immune cells themselves**, for self-maintenance and inflammation regulation.
- **Organs**, such as:
  - **The liver**, which synthesizes acute-phase proteins like **CRP (C-reactive protein).**
  - **The hypothalamus**, which induces **fever.**
  - **Endothelial cells**, which activate **coagulation.**

IV.1.2.1. Cytokines modes of action

A. Pleiotropy: A single cytokine can exert different biological effects on different types of cells.

Fig 17. Pleiotropy.

B. Redundancy: A specific biological activity can be induced by different cytokines.

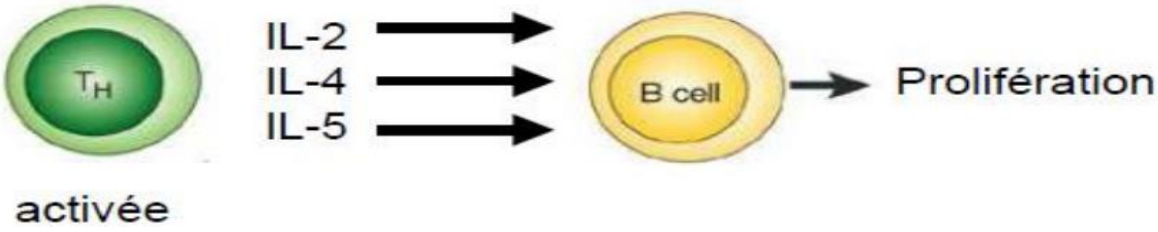

Fig 18. Redundancy.

C. Synergy: A combination of cytokines produces a greater effect than the sum of their individual effects.

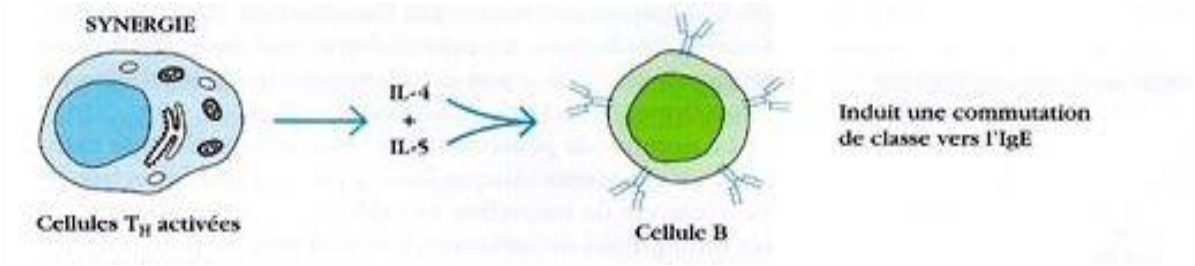

Fig 19. Synergy.

D. Antagonism: When one cytokine inhibits the effect of another cytokine.

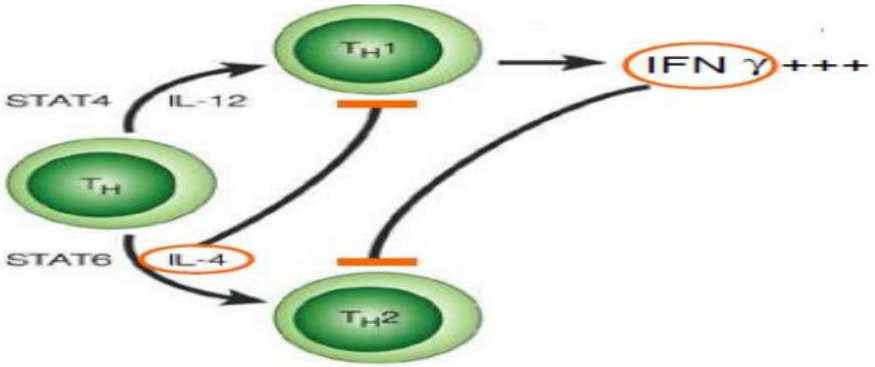

Fig 20. Antagonism.

E. Cascade Action: Cytokines often influence the synthesis of other cytokines.

F. A single cytokine can have an activating effect on one receptor and an inhibitory effect on another receptor.

G. Some receptors are specific to a single cytokine, while others can respond to multiple cytokines.

H. The same receptor can be present on different types of cells.

IV.1.2.2. Secretion modes

A. Double Ubiquity: The same cytokine can be produced by different cell types, and a given cell can produce multiple different cytokines.

B. Autocrine: The cytokine acts on the cell that secreted it.

C. Paracrine: The cytokine acts on nearby cells surrounding the secreting cell.

D. Endocrine: The cytokine enters the bloodstream to act on cells located far from its production site.

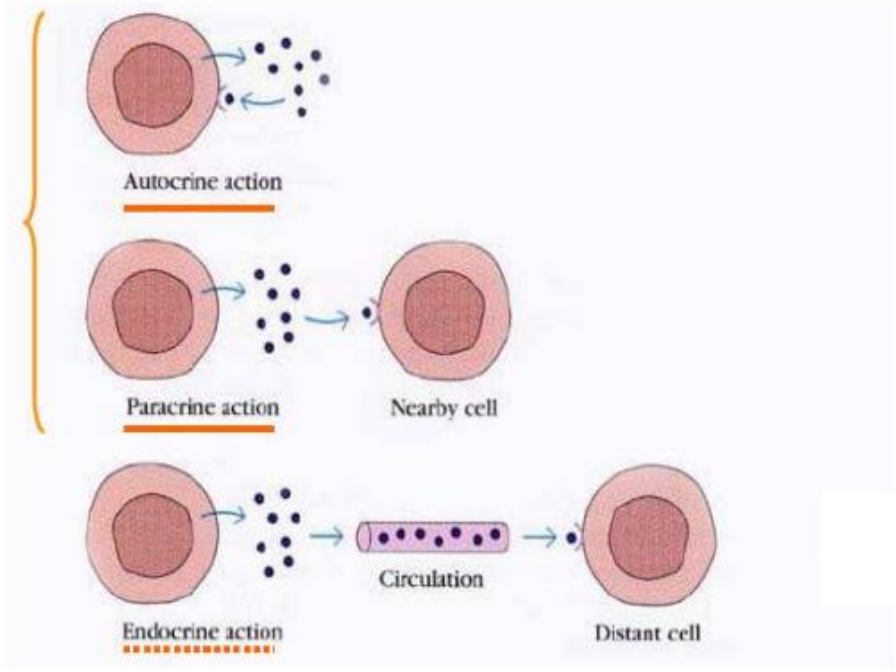

Fig 21. Cytokines secretion modes

IV.2. The inflammatory response (Inflammation)

Inflammation is the set of defensive reaction mechanisms through which the body recognizes, destroys, and eliminates all foreign substances. The causes of inflammation are numerous and varied, including infectious agents, inert foreign substances, physical agents, and post-traumatic cellular or tissue injury.

IV.2.1. Inflammation clinical effects

A. Redness and Heat: Caused by the dilation of blood vessels and increased blood flow.

B. Pain: Results from a combination of:

- Pressure on nerve endings.
- The direct effect of chemical mediators released during the inflammatory response.

C. Swelling (Edema): Caused by the accumulation of exudates, mainly the fluid component.

IV.2.2. Stages of inflammation

- ***Step 1:*** Skin injury allows pathogens to bypass the natural barrier. Bacteria cross the epidermis and reach the dermis.

- ***Step 2:*** Contamination leads to the penetration of microorganisms, which begin to multiply. This marks the start of the infection.
- ***Step 3:*** Specific recognition of the pathogen by immune (sentinel) cells, triggering the production of chemical mediators.
- ***Step 4:*** Local dilation of blood capillaries due to histamine and prostaglandin secretion by mast cells. This causes swelling and redness of the wound (**erythema and edema**) and induces **diapedesis**. Nerve endings are stimulated, sending a pain signal to the brain.
- ***Step 5: Diapedesis*** – Granulocytes and monocytes circulating in the blood vessels cross the vessel walls and move toward microorganisms through **chemotaxis**, following the release of chemical mediators (cytokines).
- ***Step 6: Phagocytosis*** – Macrophages are activated, bind to microorganisms via receptors on their surface, internalize them, and then digest them.

IV.3. Phagocytosis

Phagocytosis is the cellular process by which phagocytes can ingest solid foreign particles on a micrometric scale.

IV.3.1. Stages of phagocytosis

1. ***Adhesion:*** Recognition of the pathogen by a phagocyte.
2. ***Ingestion:*** Internalization of the pathogen into a **phagosome** through endocytosis.
3. ***Digestion:*** Destruction of the pathogen by fusion of the **phagosome** with lysosomes (**phagolysosome**).
4. ***Exocytosis:*** Expulsion of waste materials.

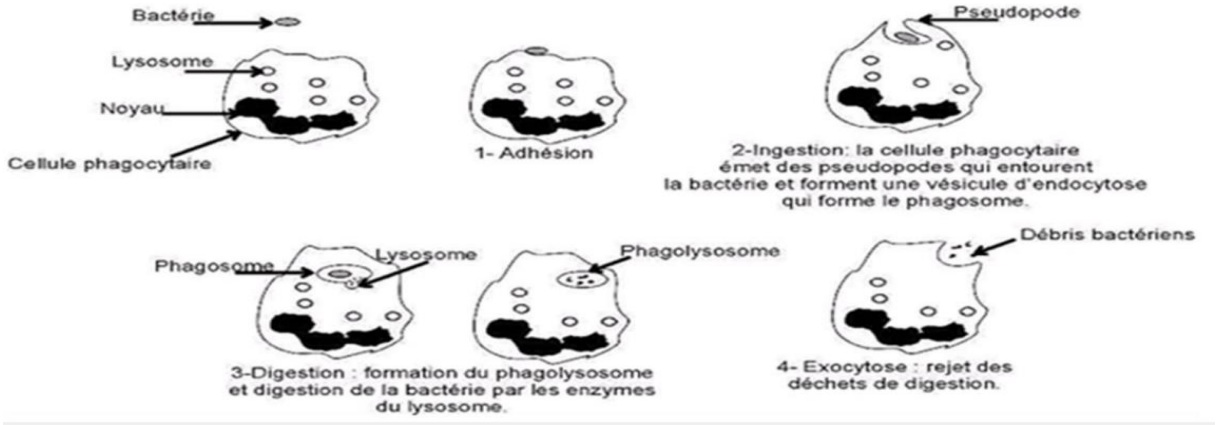

Fig 22. Phagocytosis.