Chapter V: The Specific Immune Response

Innate immunity does not always allow the elimination of foreign elements that can then infect the body. Diseases appear that will usually be fought within a week. The body sets up an adaptive Immunity targeted to a specific antigen. Adaptive immunity is a set of specialized cells, the purpose of which is to recognize and memorize the non-self in order to provide a specific response to each case Adaptive immunity is not immediate: the effector molecules that contribute to the elimination of the foreign element do not exist before the infection and do not appear until a few days after it. Adaptive immunity includes:

A. Cellular immunity.

- ❖ The effector cells are the LT
- ❖ The major defense mechanism is Cell Toxicity.

B. Humoral immunity:

- ❖ The effector cells are the LT
- ❖ The antibodies

V.1. Cellular immunity.

Cellular immunity, or cell-mediated immunity, is the adaptive immunity in which T cells play a central role.

V.1.1. T-cells

- ➢ Plays a role in cellular immunity especially against intracellular non-self.
- ➢ Represent 70-80% of lymphocytes.
- ➢ Some so-called "memory" cells with a long lifespan.
- ➢ Plays an important role in cytokine production.

There are 2 types of T cells:

A. T4 lymphocytes (LT4, LTCD4, LTh)

- ➢ Has a CD4 surface marker.
- ➢ Respond to Ag in combination with MHC II.
- ➢ Recognize the Ags presented by the CPAs

B. T8 lymphocytes (LT8, LTCD8, LTcytox)

- ➢ Has a CD8 surface marker.
- ➢ Respond to Ag in combination with MHC II.
- ➢ Recognizes tumor cells, virus-infected cells and destroys them.

V.2. Humoral immunity

Humoral (humors = liquids) such as: blood (serum, plasma), CSF, tears, secretions (mucous membranes, milk) all extracellular liquids.

Serum limited in principle to serum but much wider in scope, due to its easy exploration and connection (balance) with all extra-cellular compartments of the body.

V.2.1. B lymphocytes

B lymphocytes support the humoral adaptive immunity which is immunity transferable by serum and presented by the release of Antibodies (Ab) capable of binding specifically to antigens (Ag). Ab is secreted by **activated LB** or **Plasmocytes**.

- LBs play a role in Toxin Neutralization.
- BL represents 12% of lymphocytes
- BLs can respond to peptide, carbohydrate or glycolipid antigens.

V. 2. 2. Antibodies

- These are soluble glycoproteins produced in response to an antigen that specifically combines with the antigen (which induced its formation).
- These are immunoglobulins that are produced by plasma cells in response to an immunogen. - Present in serum and tissue fluids or on cell membranes.
- On B cells immunoglobulins serve as BCR antigen receptors and play the key role in B cell differentiation.
- Contributes to the elimination of their specific antigen or the lysis of microorganisms carrying these antigens by activating the effector mechanisms.

A. The structure of the Abs

The three-dimensional structure of the Abs, itself determined by the AA sequence of the 4 chains that make them up:

- **2 L-light chains** have 2 domains:
  - The amino acid sequences of the first domain are highly variable: they define **the variable domain of the L chains (VL).**
  - The domain whose amino acid sequence is conserved is called the domain **constant** of the L chains **(CL).**

❖ There are 2 types of light chains designated by the letters **κ (Kappa)** and λ**(Lambda)**

➢ **2 heavy chains H** have 4 or 5 domains:

- The amino acid sequences of the first domain are highly variable: they define **the variable domain of the H chains (VH).**
- **The constant domains of the H chains** are: **CH1, CH2, CH3** (and CH4 for IgM and IgE).

❖ There are five types of heavy chains, designated by the Greek letters **γ (gamma), α (alpha), μ (mu), δ (delta), ε (epsilon).**

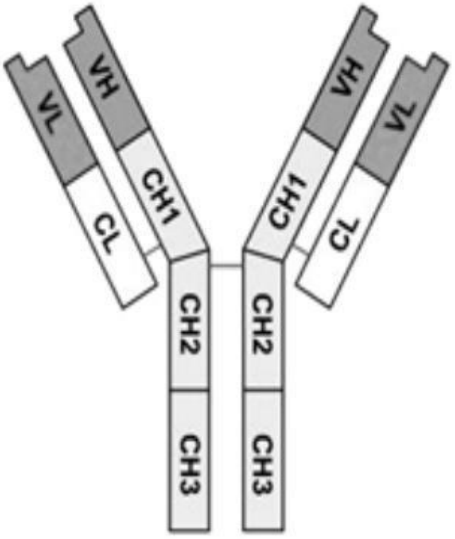

Figure 23: The structure of antibodies.

B. Immunoglobulin classes

Immunoglobulins can be divided into five different classes according to the constant regions of the heavy chains.

1. **IgG** : heavy chain "Gamma" **γ**
2. **IgM** : heavy chain "Mu" μ
3. **IgA**: heavy chain "Alpha" **α**
4. **IgD** : heavy chain "Delta" **δ**
5. **IgE**: heavy chain "Epsilon" **ε**

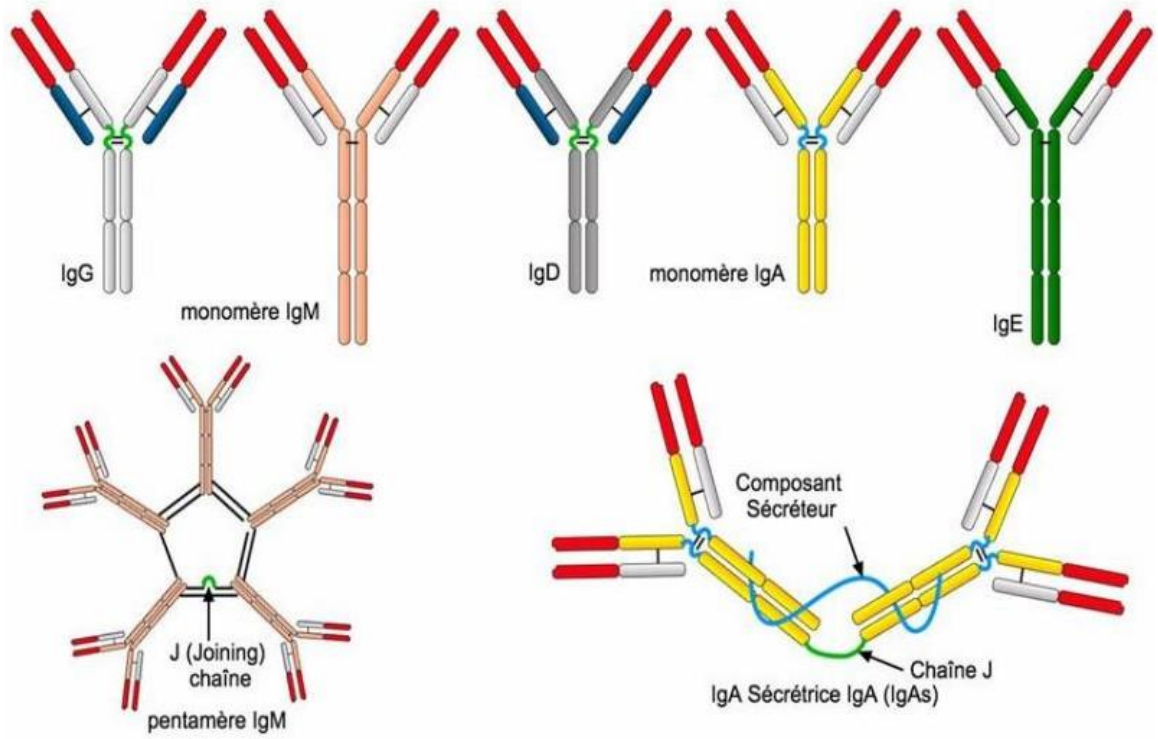

Figure 24: Immunoglobulin classes

C. The effector functions of antibodies

1- The immune complex (AC-Ag) activates the classical complement pathway that induces the elimination of bacteria and viruses.

2- The opsonisation of pathogens i.e., by binding to their surface, antibodies (only IgG) promote the phagocytosis of pathogens.

3- Antibodies bound to virus-infected cells can promote their recognition and lysis by NK cells.

4- Neutralization of toxins by preventing them from entering the cell and exercising their toxic power.

V.3 Cellular and humoral cooperation

The different objectives of cell cooperation are:

- Allow the development of an adaptive immune response.
- Make the immune response effective.
- Ensure the control of the immune response.

This is possible thanks to:

- **Co membrane signals**: Co stimulation molecules
- **Soluble co signals**: cytokines, chemokines (cell migration)

V.3.1 Activation, Lymphocyte

After being subjected to positive and then negative selection in the thymus, the T cells entering the circulation are called naive, because they have not yet encountered the antigen recognized by their Antigen Receptor (TCR).

In order to be activated and increase their number, they must meet professional Antigen Presenting Cells (APCs), the dendritic cells that present the specific antigen on its Major Histocompatibility Complex (MHC) molecules. The interaction of T cells with dendritic cells is enhanced by a large number of accessory and adhesion molecules .

A. The first activation signal

Naïve T cells sweep the surface of the dendritic cells present. They can establish low affinity bonds with the dendritic cell.

- If no high-affinity binding is established between the TCR and any of the peptide-MHC complexes present, the naive T lymphocyte leaves the lymph node through the efferent lymphatic vessel. This process takes 12-18 hours.

- Conversely, if the TCR specifically recognizes one of the peptide-CMH complexes, with sufficient affinity, the T lymphocyte can activate This interaction between the TCR and the peptide-CMH complex of the Self or **first signal** of T lymphocyte activation ensures its **specificity**.

The affinity between the paratope of the TCR and the epitope present in the groove of the MHC molecule plays a major role in the stability of this binding, reinforced by the binding **of the CD4 and CD8 co-receptors** to the MHC molecules of class II or class I respectively. Other molecules such as CD2 and LFA-1 adhesion molecules will also promote the CPA/naive T lymphocyte interaction and prolong the duration of the first signal.

Un 1er Signal **d'activation**: liaison entre
CMH II + Ag (cellules dendritique) ⟶ (LT4) TCR + CD4

B. The second Co-stimulation signal

A **second signal** is required to continue this specific antigen activation. This Co-stimulation **signal** is essential to protect T cells from **anergy** or early apoptosis that occurs in its absence. Dendritic cells in the lymph node weakly express **CD80** and **CD86** molecules on their surface. These molecules bind to the **CD28** molecule, expressed on the surface of T lymphocytes. Intracellular signaling from the binding of CD28 amplifies/completes the signals from the TCR allowing optimal production of IL-2 necessary for T lymphocyte proliferation. In the absence of Co-stimulation by CD28, the T lymphocyte becomes **functionally "paralyzed"** and resistant to subsequent activation (**state of anergy**). Signaling involving TCR and CD28 also induces expression of **CD40-Ligand** (CD154) on the surface of the T cell. Binding to CD40 expressed on dendritic cells induces an increase in CD80/CD86 expression, which in turn enhances the signal induced by CD28.

Un 2eme signal **de Co stimulation** : liaison entre
B7 (CD80/CD86) (cellules dendritique) ⟶ (LT4) CD28
CD40 (cellules dendritique) ⟶ (LT4) CD40L

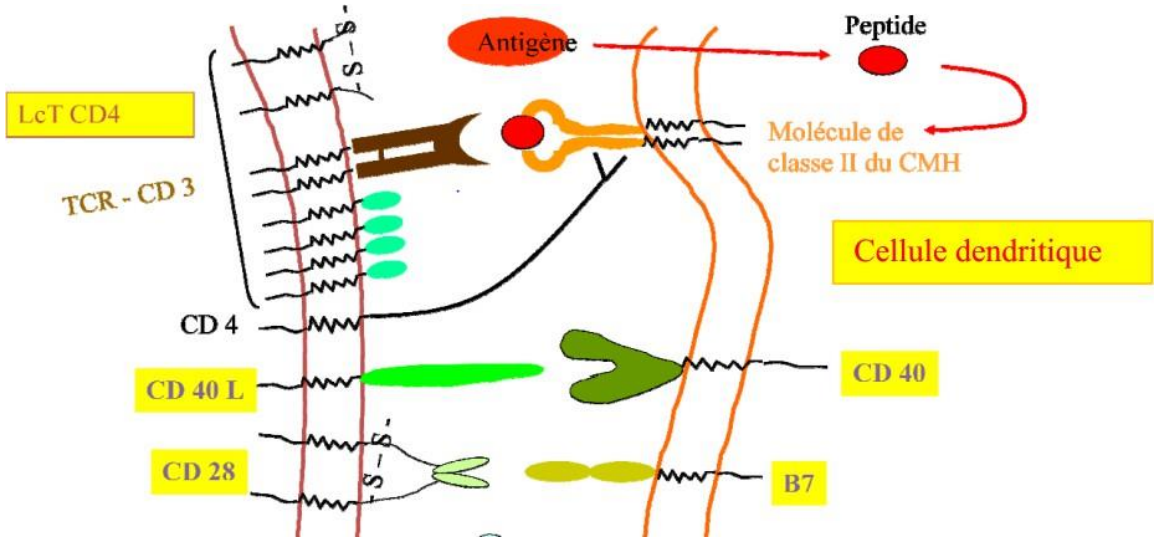

Figure 25: T-cell activation signals

C. The third signal and functional differentiation of T lymphocytes

In the priming of naive T lymphocytes, a "**third signal**" intervenes: it is given by cytokines present in the microenvironment of the lymph nodes. These cytokines are produced by dendritic cells. These cytokines will participate in the functional differentiation of CD4 T lymphocytes. Thus, after recognition of the antigen and activation, CD4+ T lymphocytes proliferate, and some of the activated clones become **effector or helper lymphocytes (*T helper*, Th)** or under certain conditions **T lymphocytes with regulatory activity (*T induced regulators*, iTreg)**.

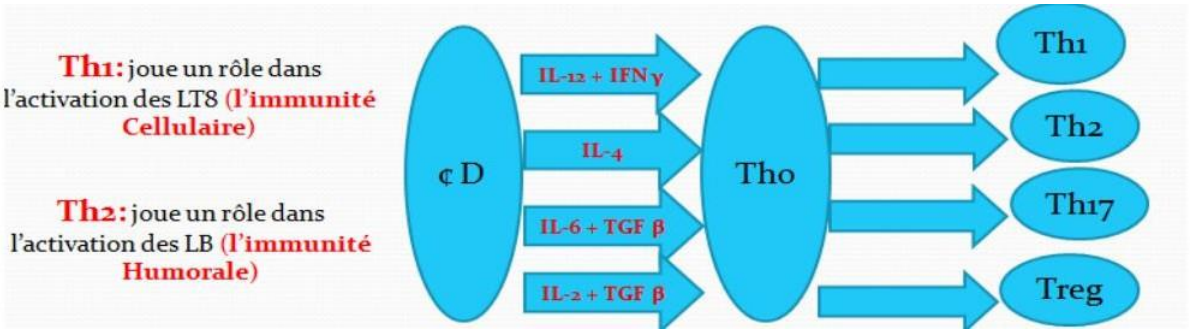

Figure 26: Functional differentiation of T cells

V.3.2. B-cell activation

To be activated by a protein antigen, a naive B lymphocyte must receive at least the following signals:

- The first signal is delivered by the binding of **the antigen to the BCR**.
- The other signals are delivered by the LTh2 **fixed to the LB** which presents it with a peptide associated with an MHC-II.

There are 2 types of activation

A. Thymo-dependent activation: requires activation by LTh2 following 3 steps:

1) LBs capture Ag

2) LB present Ag at LTh2 by MHC II

Un 1er Signal d'activation: liaison entre
CMH II + Ag (LB) **(LTh2) TCR + CD4**

Un 2eme signal de Co stimulation : liaison entre
B7 (LB) **(LTh2) CD28**
CD40 (LB) **(LTh2) CD40L**

3) Isotypic switching: cytokines secreted by LTh2 control AC released by Plasmocytes (active LB)

Table 2: Isotypic switching

Cytokine reçue par LB	Ac
IL-2	IgM
IL-4, IL-5, IL-10	IgG
TGF β	IgA
IL-13	IgE

The result of this activation is the proliferation and differentiation of B lymphocytes into **Plasmocytes** and **memory B lymphocytes**

B. Thymo-independent activation: for **memory LBs** and in this activation LTh2 have no role.

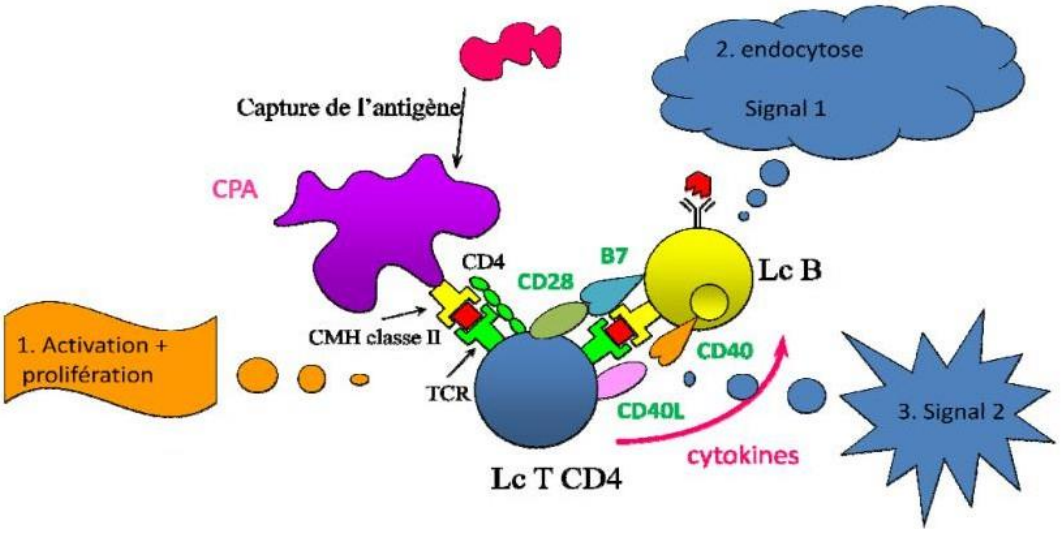

Figure 27: B-cell activation

V.3.3. Role of some cytokines of adaptive immunity

➢ **Interleukin-2 (IL-2):** This is a major factor in lymphocyte growth. In its absence they cannot proliferate or differentiate properly.

➢ **Interferon gamma (IFNγ):** Produced by T4 and T8 lymphocytes, IFN-γ activates macrophages and increases the expression of MHC molecules on the cell surface, which improves the presentation of the antigen to T cells and the recognition of infected cells.

➢ Certain interleukins (e.g. **IL-4 and IL-5**) act on B lymphocytes to make them produce certain types of Ac.

➢ Others contribute to inflammatory reactions (e.g. IL-17). Finally, some promote a return to calm (e.g. IL-21)