Chapter 4 : Lymphocytes, Immunity MPS, Complements

SOME TERMS

Self, Non-self, Antigen

Within my body, there are cells/ tissues/ organs/ chemicals, all of which are part of my *self*. Whereas microorganism (e.g. bacteria, virus, etc.), tissues or organs from other persons/ animals, even cancers which may be present in my body are, for me, *non-selfs*. A normal body tries to remove these non-selfs from the body. These non-selfs, rather, a specific protein (or sometimes a polysaccharide) of the non-self is called an **antigen**. Thus, an antigen may be defined (somewhat crudely) as a substance which elicits an immune response. That is, an **immune response** is a process that removes the antigen from the body.

Common examples of antigen include, protein molecules or rarely polysaccharide molecules of microbes, allergen, foreign tissue graft, blood group antigens and so on. [How the lymphocyte learns to differentiate between self and non-self will be discussed later].

Immunity, Innate Immunity and Acquired Immunity

In short, the ability of human or animal body to remove (pathogenic) microorganisms or their toxins is called immunity. There are two kinds of immunity :

(a) **Innate** (b) **Acquired** (also called **adaptive**).

Innate immunity

Innate immunity is also called, *non-specific neutrophil-macrophage-mediated immunity.*

This type of immunity is mediated chiefly by *neutrophil-macrophage, opsonin, NK cells and large lymphocytes which are cytotoxic but not T cells.*

It is characterized by phagocytosis and digestion of the microbe. This type of immunity described in detail under the heading of *acute inflammation* in Chap. 3 Sec. IV, (i) *starts immediately after the microbial infection,* (ii) *is non-specific* (i.e. same types of neutrophils-macrophages can attack different varieties of infection).

Because, this variety of defensive reaction starts soon after the microbial invasion, it is also called *first line of defence.*

Acquired immunity or adaptive immunity

It is also called, *specific lymphocyte-mediated immunity.*

After the first attack of microbes, if the innate immunity fails to remove the invading microbes, acquired immunity begins to develop within a few weeks. In this variety of immunity, the key role is played by lymphocytes (also macrophages). This type of immunity is **highly specific**, that is, for individual species of microbes, highly selective clone of lymphocytes develop. That is, a clone of lymphocytes developed to fight against the virus of smallpox will not attack the virus of chickenpox.

In acquired immunity, after the antigens have been removed, the efficacy of immune system declines slowly, the clone of lymphocytes, after the cure has been achieved, begins to disappear, but a few lymphocytes of the clone survive as **memory cells**. If a reinfection by the same microbe occurs, these memory cells proliferate vigorously and the specific clone of lymphocytes begin to grow rapidly. That is, the defence against the reinfection is tackled very efficiently and quickly.

Therefore, the special features of acquired immunity include :

(i) **Specificity** : Individual species of antigens elicit specific clone of lymphocytes.

(ii) **Memory** : Re-exposure to antigen elicits quicker and more effective defence.

Subclasses of acquired immunity

(1) One class is called **cell-mediated immunity** and is achieved through T lymphocytes.

(2) Another class of acquired immunity is called **humoral immunity** and is achieved through B lymphocytes and complements.

For details, see below.

T cell lymphocytes

There are several types of T cell lymphocytes :

(i) **Helper T cells**, (ii) **cytotoxic T cells**, (3) **suppressor T cells**, and (4) **memory T cells** (incidentally, the letter T comes from the word, *thymus* - see later).

Helper T cells : There are two varieties of helper T cells (also called **CD4 + T cells**) : (a) T_H^1 and (b) T_H^2 cells.

In short, functions of helper T cells include helping the growth and proper functioning of :

(i) Cytotoxic T cells (ii) Suppressor T cells

(iii) B cell lymphocytes (iv) Macrophages.

In absence of helper T cells, all the varieties of T cells and B cells become virtually useless. In **AIDS** (*acquired immunodeficiency syndrome*), the helper T cells are destroyed by a virus (HIV—human immuno-deficiency virus) and acquired immunity collapses so that trivial infection can lead to fatalities.

These helper T cells produce many chemicals (e.g. IL-3, TNF-α, granulocyte colony stimulating factor and several others). By the help of these chemicals, they achieve their purpose.

Cytotoxic T cells : These cells kill the microbes, cancer cells, reject tissues transplanted from different persons and so on. They kill the antigens by means of **perforins**. Perforins are produced by the cytotoxic T lymphocytes and they perforate the membrane of the antigen → resulting in free communication between ICF and ECF of the antigen → the antigen dies.

Suppressor T cells : If the acquired immunity is excessive, there will be death of many host (innocent) cells. Suppressor T cells ensure that the immune response is regulated (hence they are also called **regulatory** T cells).

Memory T cells : After the removal of antigens, the specific acquired immune mechanism declines→ but a few T lymphocytes persist in the lymph nodes for years (may be life long) and are called memory T cells. When reinfection by the same microbe occurs in later part of life, these memory T cells proliferate vigorously→the microbes are speedily removed.

B lymphocytes-humoral immunity

B lymphocytes, ultimately speaking, produce **antibodies or immunoglobulins**. The two fundamental mechanisms, by which humoral immunity is achieved, are : (i) **B lymphocytes** and (ii) **complement system**.

After an **antigenic challenge**, the specific clone of B lymphocytes are converted into **lymphoblasts** → these lymphoblasts subsequently become **plasmablasts** → plasmablasts then become **plasma cells**. Plasma cells produce the antibodies. The antibodies act in either of the two ways : (i) it (the antibody) directly attacks the antigen (e.g. microbe) and kill it or (ii) it activates the complement system.

The complement system : These are proenzymes, present normally in the plasma. When there is no antigenic challenge, these proenzymes (altogether 30 in number) are inactive. But when there is an antigenic challenge, the complement system is activated. There are three mechanisms to activate the complement system. One major mechanism is that the antibodies activate the complement system. The activated complement system kills the antigen by various methods.

Cytokines-Lymphokines. ILs

The cytokines are protein-like structures behaving like hormones. They are produced by various cells, notably T_H^1 (IL-2, tumor necrosis factor β), T_H^2 (IL-4, IL-5, IL-6), **macrophages** (several ILs, TNF α, granulocyte-monocyte colony-stimulating factor), **virally infected cells** (INF β), **NK cells** (INF γ) and so on.

[**NB** : IL=interleukin; TNF = tumor necrosis factor, NK=natural killer cells, a type of T lymphocyte. For T_H^1 and T_H^2, see above].

When the amino acid sequence of the cytokines are known, then the structure is called **interleukin** (IL). There are several ILs known. They activate T lymphocytes, help the chemotactic process of neutrophils and many others.

TNF causes promotion of inflammation.

Lymphokines are cytokines that are secreted by lymphocytes (e.g. T_H^1, T_H^2, etc.).

Chemokines are also cytokines. There are many members of the family of chemokine. Their main function is to promote chemotaxis.

Clones

An activated lymphocyte is a highly specific cell. It can act only against a highly selective single type of antigen. As stated previously, a lymphocyte which acts against the virus of smallpox is useless for fighting against the virus of chickenpox.

All the members of specific lymphocytes, which act against a highly specific antigen, belong to a **single clone**. All the members of the given clone of lymphocytes have developed from a single committed lymphocyte.

As there are millions of varieties of antigens, so there are millions of varieties of clones. Each clone of lymphocyte, consists of very large number of identical lymphocytes.

ACQUIRED IMMUNITY—A BRIEF ACCOUNT

Invasion by a microbe occurs for the first time in life. As there is **no previous experience** of this antigenic challenge, in the beginning, there is no response by acquired immunity and the body defends itself only by innate immunity.

♦ The innate immunity may be enough to drive out the microbes or within a few weeks the acquired immunity against this particular type of antigen begins to grow so that a specific clone of lymphocytes (both T and B) begin to develop.

♦ Then the microbes are removed and the number of lymphocytes in the clone begin to fall but some lymphocytes (of both T and B) persist as memory cells.

♦ When a second infection by the same species of microbes develop, **the specific clone of the lymphocytes recognize them** and immediately attack them. Also the memory cells proliferate vigorously and the number of lymphocytes of this specific clone swell greatly. The invading antigen is speedily removed.

♦ *This follows, that for the development of acquired immunity, there shall have to be a previous experience of exposure to the very same antigen. One exception, where no experience of previous exposure is necessary, is cancer. Cancer cells are killed by NK cells (see later).*

ACQUIRED IMMUNITY—DETAILS

With this background some details are given below :

The Lymphocytes

In the peripheral blood, lymphocytes account for about 25% of WBC (Table 4.3.1). Under hematoxylin stains, all lymphocytes look alike but by special procedure, it can be shown that there are two kinds of lymphocytes : (1) T and B lymphocytes.

In the peripheral blood, about 80% of the lymphocytes are T lymphocytes. T lymphocytes are of several kinds : (i) helper T cells (which have two subclasses T_H1 and T_H2) (2) cytotoxic T lymphocytes (3) suppressor T lymphocytes (4) memory T cells. NK (natural killer) cells **which are cytotoxic**, however are not T cells.

Development of lymphocytes

In the late stages of fetal life, all leukocytes, granulocytes—monocytes and lymphocytes are developed in the bone marrow. In the postnatal life, the granulocytes and monocytes continue to develop in the marrow, but lymphocytes develop in the (i) **thymus**, (ii) **spleen**, and (ii) **lymphoid tissues of the gastrointestinal tract** (e.g. Peyer's patch).

Further details

In the mid stage of fetal life, the stem cells committed to develop lymphocytes, develop in the liver. But afterwards, in the fetus, the committed stem cells, committed to develop lymphocytes, develop in the bone marrow. From the bone marrow, **immunologically incompetent (lymphocyte) cells** are released. They go into one of the two following areas:

(1) **Thymus** : Cells which go to the thymus are "preprocessed" there (thymus) and become T cells. The letter T comes from the word thymus.

(2) **Bone marrow** : Another kind of lymphocytes of bone marrow go to the bone marrow in mammals (including man) or to the **bursa of Favricius*** in the birds for preprocessing. They are called B cells. The letter B comes from the word bursa (B cells were first discovered in the birds).

T LYMPHOCYTES

In short, the lymphocytes, which are destined to become T cells are released in the fetal life from bone marrow→ go to the thymus where they proliferate very vigorously→ in the thymus not only very large number of lymphocytes thus develop but the lymphocytes develop extreme diversity, each cell capable of tackling only one variety of antigen; as there are millions of varieties of antigen, so there are millions of varieties of T lymphocytes in the thymus and **they all go to the lymph nodes**.

In a lymph node, in course of time, an antigen arrives → this antigen **activates** a specific lymphocyte lodged

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* Favricius was *Guru* of the great William Harvey. Favricius discovered the existence of valves in the veins.

* Tackling one and only one antigen; as there are millions of antigens so the diversity is tremendous.

in this lymph node → now this lymphocyte proliferates vigorously and forms a clone. Now from this lymph node, this clone of lymphocytes is discharged.

Important : In the thymus, by an unknown mechanism, the T lymphocytes are screened. Many lymphocytes reach thymus, but many of them cannot distinguish between "self" and "non-self". Cells who cannot distinguish between self and non-self are called **self-reactive** cells. If these self-reactive cells are allowed to live they will destroy the body's self tissue. By a not clear process, they commit **apoptosis** (cell suicide) and thus removed—the process is called **clonal deletion**. In spite of clonal deletion, some self-reactive cells still manage to survive but in the body they are forced to remain idle—a process called **clonal anergy**. **Note** : clonal deletion can remove self-reactive T cells only, but clonal anergy can remove self-reactive T and B both types of cells.

B LYMPHOCYTES

In the late fetal life, lymphocytes are developed from the committed stem cells, committed to develop lymphocytes as usual. From the bone marrow, lymphocytes destined to become B lymphocytes are preprocessed in the bone marrow (or in the liver in mid fetal life) itself (therefore, bone marrow and liver are called the **bursal equivalents** in man because they behave like bursa of Favricius) → then these lymphocytes go to the lymph nodes where they wait for exposure to antigens. When the exposure occurs a clone of active lymphocytes belonging to the B variety appears.

ANTIGEN RECOGNITION AND CLONAL SELECTION

Antigen recognition and clonal selection are two different processes as explained below :

Stem cells from the bone marrow differentiate into a very large number of T lymphocytes or B lymphocytes and at this stage, i.e. before they migrate to the lymph node, they have the innate (intrinsic) ability to recognize antigen.

In the lymph node, the antigen is presented to the T or B cell as follows :

For **T cells**, the antigen is phagocytosed by a cell, called *antigen presenting cell (APC)*→ the antigen is digested and a particular fraction of protein protrudes from the APC→this fraction of protein, of this particular antigen, combines with the receptor of a very particular T lymphocyte→now this T cell is activated and proliferate profusely to produce a clone—this is clonal selection for T lymphocyte.

For **B lymphocyte**, the B lymphocyte can combine directly with an antigen, of course with the help of a helper T cell. No APC is required→a clone of B lymphocyte produced.

Antigen Presenting Cell (APC)

A **macrophage** is an APC. **Dendritic cells** of lymph node or spleen are also APCs.

An APC contain on their membrane a material called **MHC product**. MHC is **major histocompatibility complex** and is a gene. Product of the MHC is called MHC product (more popularly called **HLA-human leukocyte antigen**, because it was first discovered in leukocyte membrane).

The APC digests the antigen and a particular protein now combines with the MHC product. The MHC product + the protein of antigen now combines with a very particular T lymphocyte → the T lymphocyte is activated.

T CELL RECEPTOR (TCR)

On their cell membrane, T cells contain receptors called TCR. This TCR combines with a complex consisting of MHC protein and antigen, presented by an APC.

TCR consists of two parallel polypeptide chains protruding from the T cells. In about 90% of T cells, the two chains are α and β chains and such T cells are called **α β T cells**. In the rest 10% of T cells, the chains are γ and δ and the cells are called **γ δ T cells**.

Adjacent to TCR, there is another protein on the cell membrane of T cell, called **Cluster of differentiation** or **CD**. CDs are glycoprotein and help the TCR to bind with the MHC protein- antigen complex.

On the helper T cells, the CD is called CD 4. Hence helper T cells are also called CD4+ T cells. Cytotoxic cells are CD 8 + T cells.

HOW THE LYMPHOCYTES KILL THE ANTIGENS

T Cells

This has been, in short, already stated.

In short :

(1) **Helper (CD 4 +) T cells** : They are of two kinds. Both the varieties secrete various cytokines and by the

help of them, promote the activities of (i) *cytotoxic T cells*, (ii) macrophages, (iii) *B lymphocyte*, and (iv) *natural killer (NK) cells*.

(2) **Cytotoxic (CD 8+) T cells** : They, by the help of cytotoxins (**perforin and fragmentin**) which they produce, kill (i) *virus infected cells*, (ii) *cancer cells* and (iii) *various bacteria*. Mode of action of perforin has already been stated. In addition, they induce **apoptosis** in the target cells.

B Cells

B cells can directly bind with their specific antigens and become activated. For this, they require the help of helper T cells.

Once activated, B cells are converted into **plasma cells** and the plasma cells produce **antibodies**. The antibodies are of several types (see below).

Antibodies destroy the antigen by several methods :

(i) By directly neutralizing the microbe (for details, see below).

(ii) By activating the complement system.

(iii) By facilitating phagocytosis.

ANTIBODIES

All antibodies are **immunoglobulins**, but some immunoglobulins are not antibodies. For example, myeloma cells produce immunoglobulins which do not react with any antigen and hence cannot be called antibodies. Antibodies react with their specific antigens. However, ordinarily, often, many persons use the two terms antibodies and immunoglobulins as interchangeable terms.

Classification of Immunoglobulins (Igs)

There are five classes of immunoglobulins (Igs) in a normal person. They are: (i) *IgG* (quantitatively most abundant, accounting for about 70% of plasma Igs in normal persons), (ii) *IgA*, (iii) *IgM*, (iv) *IgD*, and (v) *IgE*.

How the Igs Act

They act by (i) **agglutination** (clumping of microbes which lead to their death), (ii) **neutralization** (toxin producing areas of the microbes are covered), (iii) **precipitation** (e.g. clumped toxin molecules are precipitated), (iv) **lysis** (microbes are directly killed). Antibodies, (v) also attach with the microbes and make them tasty to the **neutrophils** so that phagocytosis is enhanced—this is called **opsonization**. Finally, the antibodies (vi) activate the complement system—**this is a major mechanism**. For details of complement system, see below.

Chemistry of Immunoglobulins

Immunoglobulins are proteins. In the plasma, Igs are found in the γ globulin fraction.

Most Igs consist of 4 polypeptide chains, two of which are **light chains** and the other two are **heavy chains**. Each light chain is parallel to a heavy chain (Fig. 4.4.1).

Antigen binding site is shown in the Figure 4.4.1.

THE COMPLEMENT SYSTEM

The complement system is a family of enzymes. The number of members of the family is 30. They are normally present in the plasma and tissue fluid. Normally, they are in inactive state.

The complement system, when activated, help both : (i) **innate immunity** (e.g. in phagocytosis and digestion of bacteria by neutrophil and monocytes) as well as (ii) **acquired immunity**.

There are three pathways for activating complement system of enzymes (details of the pathway are usually learnt in senior classes) :

(i) The classical pathway

(ii) The mannose binding lectin pathway

(iii) The alternative pathway.

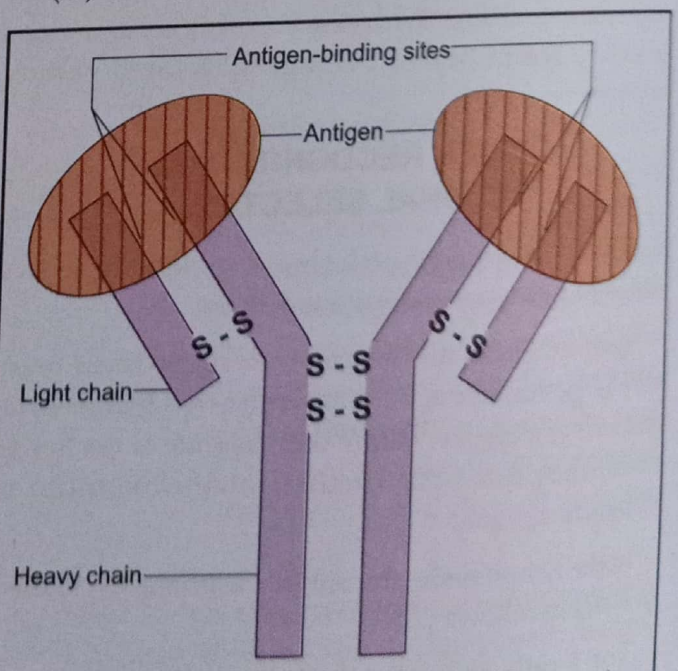

Fig. 4.4.1. Structure of the typical IgG antibody, showing it to be composed of two heavy polypeptide chains and two light polypeptide chains. The antigen binds at two different sites on the variable portions of the chains.