

# IMMUNOLOGY

## An Overview of Immunity: Innate And Adaptive Immunity

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### Keywords

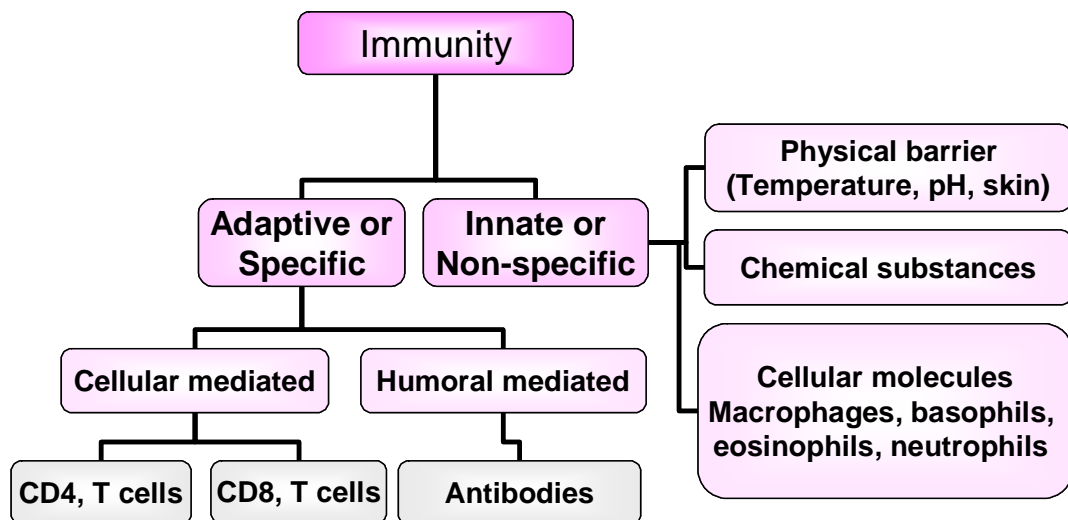
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## Concept of Immunity and its Classification

Immunity is a state of having sufficient biological defenses to avoid infection, disease, or other unwanted biological invasion. The body either already possesses these defense mechanisms (non-specific or innate immunity) or may acquire it over a period of time due to exposure to harmful/ harmless organisms or substance (specific immunity). The response of the body's defence mechanism to recognize self and non-self and store it as 'immunological memory' is related to the functions of the immune system of the body.

The study of the molecular and cellular components that comprise the immune system, including their function and interaction, is the central science of immunology. The immune system is divided into a more primitive innate immune system, and acquired or adaptive immune system of vertebrates, the latter of which is further divided into humoral and cellular components (Fig.1).

A diagrammatic representation of classification of immunity is given in Fig. 1.



**Fig.1: A diagrammatic representation of classification of immunity**

### Innate or Non-Specific Immunity

The **innate immune system** comprises the cells and mechanisms that defend the host from infection by other organisms, in a non-specific manner. This means that the cells of the innate system recognize, and respond to, pathogens in a generic way, but unlike the adaptive immune system, it does not confer long-lasting or protective immunity to the host. Innate immune systems provide immediate defense against infection, and are found in all classes of plant and animal life. Innate immunity is the first line of defense in the body.

### ***Function of innate immunity***

These non-specific defense mechanisms are very diverse. Broadly they include:

- Physical barriers to invasion, e.g. skin and mucous membranes; effects of body temperature; mechanical reflexes such as coughing and sneezing and watering of the eyes;
- Chemical effects of substances such as gastric acid, oxygen and lysozyme.
- Recruiting immune cells to sites of infection and inflammation, through the production of chemical factors, including specialized chemical mediators, called cytokines.
- Activation of the complement cascade to identify bacteria, activate cells and to promote clearance of dead cells or antibody complexes.
- The identification and removal of foreign substances present in organs, tissues, the blood and lymph, by specialized white blood cells.
- Activation of the adaptive immune system through a process known as antigen presentation.

### **Adaptive or Specific Immunity**

The adaptive immune system is composed of highly specialized, systemic cells and processes that eliminate pathogenic challenges. The adaptive immune response provides the vertebrate immune system with the ability to recognize and remember specific pathogens (to generate immunity), and to mount stronger attacks each time the pathogen is encountered. It is adaptive immunity because the body's immune system prepares itself for future challenges. This highly adaptable system utilizes inherent phenomenon such as somatic hypermutation (a process of accelerated somatic mutations), and V(D)J recombination (an irreversible genetic recombination of antigen receptor gene segments) to allow a small number of genes to generate a vast number of different antigen receptors, These receptors are then uniquely expressed on each individual lymphocyte. Because the gene rearrangement leads to an irreversible change in the DNA of each cell, all of the progeny of that cell will then inherit genes encoding the same receptor specificity, including the Memory B cells and Memory T cells that are the keys to long-lived specific immunity.

### ***Functions of adaptive immunity***

Adaptive immunity is triggered when a pathogen evades the innate immune system and generates a certain threshold level of antigen. The major functions of the adaptive immune system then come into play and these include:

- The recognition of specific “non-self” antigens in the presence of “self”, during the process of antigen presentation.
- The generation of responses that are tailored to maximally eliminate specific pathogens or pathogen infected cells.
- The development of immunological memory, in which each pathogen is “remembered” by a signature antigen. These memory cells can be called upon to quickly eliminate a pathogen should subsequent infections occur.

## **Lymphocytes: The Effector Cells of Adaptive Immune System**

Lymphocytes are a type of leucocytes. B cells and T cells are the major types of lymphocytes. The human body has about 2 trillion lymphocytes, constituting 20–40% of the body's white blood cells (WBCs). The peripheral blood contains 20–50% of circulating lymphocytes; the rest move within the lymphatic system.

B cells and T cells are derived from the same pluripotential hemopoietic stem cells, and are indistinguishable from one another until after they are activated. B cells play a large role in the humoral immune response, whereas T-cells are intimately involved in cell-mediated immune responses. B-cells may be named for the bursa of Fabricius, an organ unique to birds, where the cells were first found to develop. However, in nearly all other vertebrates, B cells (and T-cells) are produced by stem cells in the bone marrow. T-cells travel to and develop in the thymus, from which they derive their name. In humans, approximately 1-2% of the lymphocyte pool recirculates each hour to optimize the opportunities for antigen-specific lymphocytes to find their specific antigen within the secondary lymphoid tissues.

In an adult animal, the peripheral lymphoid organs contain a mixture of B- and T cells in at least three stages of differentiation:

- naive cells that have matured, left the bone marrow or thymus, have entered the lymphatic system, but that have yet to encounter their cognate antigen,
- effector cells that have been activated by their cognate antigen, and are actively involved in eliminating a pathogen and,
- memory cells – the long-lived survivors of past infections.

## **Humoral Immunity**

### ***Overview of humoral immunity***

Humoral immunity is the aspect of immunity that is mediated by secreted antibodies, produced in the cells of the B lymphocyte lineage (B cell). B cells express a unique B cell receptor (BCR), in this case, an immobilized antibody molecule. The BCR recognizes and binds to only one particular antigen. A critical difference between B cells and T cells is how each cell "sees" an antigen. T cells recognize their cognate antigen in a processed form - as a peptide in the context of an MHC molecule, while B cells recognize antigens in their native form. Once a B cell encounters its cognate (or specific) antigen (and receives additional signals from a helper T cell (predominately Th2 type), it further differentiates into an effector cell, known as a plasma cell (Fig 2).

Plasma cells are short lived cells (2-3 days) which secrete antibodies. These antibodies bind to antigens, making them easier targets for phagocytes, and trigger the complement cascade. About 10% of plasma cells will survive to become long-lived antigen specific memory B cells. Already primed to produce specific antibodies, these cells can be called upon to respond quickly if the same pathogen re-infects the host; while the host experiences few, if any, symptoms.

Secreted antibodies bind to antigens on the surfaces of invading microbes (such as viruses or bacteria), which flags them for destruction. Humoral immunity is called as such, because it involves substances found in the humours, or body fluids.

Humoral immunity in its totality, refers to antibody production, and the accessory processes that accompany it, including: T helper activation and cytokine production, germinal center formation and isotype switching, affinity maturation and memory cell generation. It also refers to the effector functions of antibody, which include pathogen and toxin neutralization, classical complement activation, and opsonin promotion of phagocytosis and pathogen elimination.

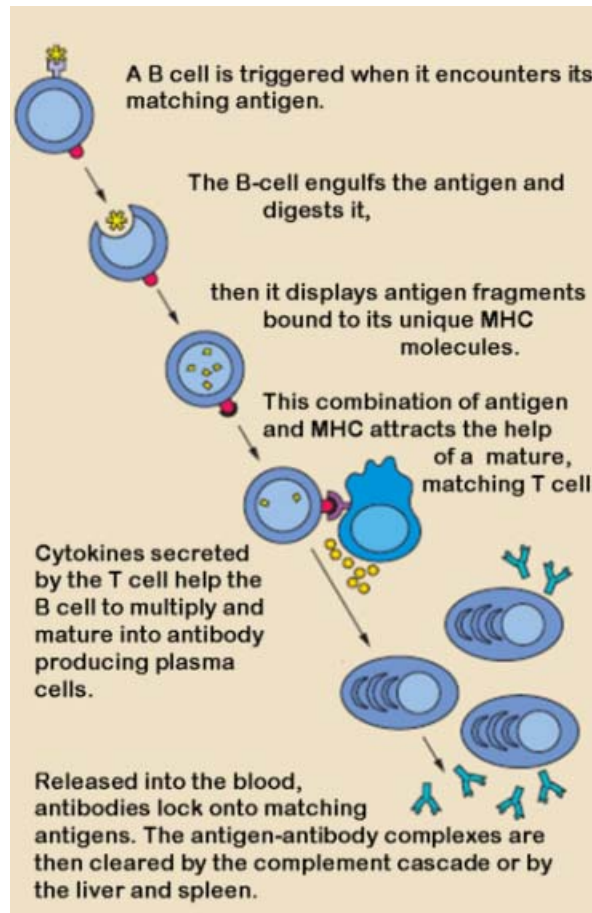


Fig 2

Antibodies or Immunoglobulins are glycoproteins in the immunoglobulin superfamily that function as antibodies. They are found in the blood and tissue fluids, as well as many secretions. In structure, they are large Y-shaped globular proteins. In mammals there are five types of antibody: IgA, IgD, IgE, IgG, and IgM. Each immunoglobulin class differs in its biological properties and has evolved to deal with different antigens. Antibodies are synthesized and secreted by plasma cells that are derived from the B cells of the immune system.

### ***Broad functions of humoral immunity***

- identifying and neutralizing foreign objects like bacteria and viruses. Each antibody recognizes a specific antigen unique to its target.

- On binding, antibodies can cause agglutination and precipitation of antibody-antigen products, prime for phagocytosis by macrophages and other cells, block viral receptors, and stimulate other immune responses, such as the complement pathway.
- If an incompatible blood transfusion has been done, causes a transfusion reaction, which is mediated by the humoral immune response. This type of reaction, called an acute hemolytic reaction, results in the rapid destruction (hemolysis) of the donor red blood cells by host antibodies. The major complication is that hemoglobin released by the destruction of red blood cells can cause acute renal failure.

## Cell Mediated Immunity

### *Overview of cell-mediated immunity*

Cell-mediated immunity is an immune response that does not involve antibodies but rather involves the activation of macrophages, natural killer cells (NK), antigen-specific cytotoxic T-lymphocytes, and the release of various cytokines in response to an antigen. Historically, the immune system was separated into two branches: humoral immunity, for which the protective function of immunization could be found in the humor (cell-free bodily fluid or serum) and cellular immunity, for which the protective function of immunization was associated with cells.

### *Broad functions of cellular immunity*

1. activating antigen-specific cytotoxic T-lymphocytes that are able to induce apoptosis in body cells displaying epitopes of foreign antigen on their surface, such as virus-infected cells, cells with intracellular bacteria, and cancer cells displaying tumor antigens;
2. activating macrophages and natural killer cells, enabling them to destroy intracellular pathogens; and
3. stimulating cells to secrete a variety of cytokines that influence the function of other cells involved in adaptive immune responses and innate immune responses.

Cell-mediated immunity is directed primarily at microbes that survive in phagocytes and microbes that infect non-phagocytic cells. It is most effective in removing virus-infected cells, but also participates in defending against fungi, protozoans, cancers, and intracellular bacteria. It also plays a major role in transplant rejection.

T cells play a central role in cell-mediated immunity (Fig 3). They can be distinguished from other lymphocyte types, such as B cells and NK cells by the presence of a special receptor on their cell surface that is called the *T cell receptor* (TCR). The abbreviation "T", in T cell, stands for thymus since it is the principal organ for their development.

Several different subsets of T cells have been described, each with a distinct function.

- Helper T cells ( $T_H$  cells) are the "middlemen" of the adaptive immune system. Once activated, they divide rapidly and secrete small proteins called cytokines that regulate or "help" the immune response. Depending on the cytokine signals received, these cells differentiate into  $T_{H1}$ ,  $T_{H2}$ ,  $T_{H17}$  or other subsets, which secrete different cytokines.
- Cytotoxic T cells ( $T_C$  cells, or CTLs) destroy virally infected cells and tumor cells, and are also implicated in transplant rejection. These cells are also known as  $CD8^+$  T cells,

since they express the CD8 glycoprotein at their surface. Through interaction with helper T cells, these cells can be transformed into regulatory T cells which prevent autoimmune.

- Memory T cells are a subset of antigen-specific T cells that persist long-term after an infection has resolved. They quickly expand to large numbers of effector T cells upon re-exposure to their cognate antigen, thus providing the immune system with "memory" against past infections. Memory T cells comprise two subtypes: central memory T cells ( $T_{CM}$  cells) and effector memory T cells ( $T_{EM}$  cells). Memory cells may be either  $CD4^+$  or  $CD8^+$ .

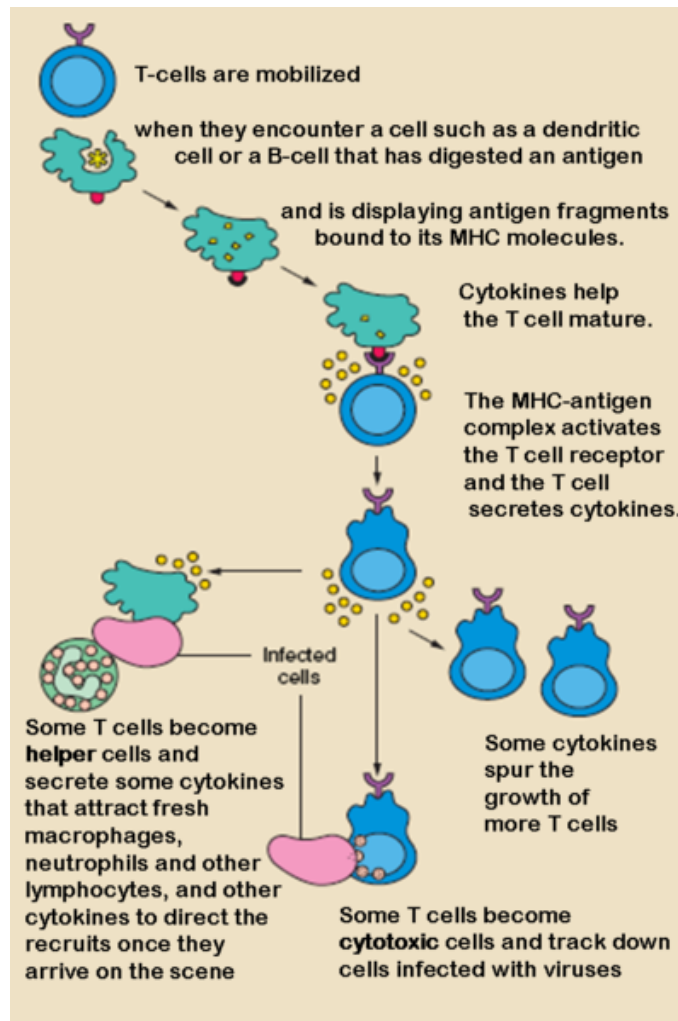


Fig 3

- Regulatory T cells ( $T_{reg}$  cells), formerly known as suppressor T cells, are crucial for the maintenance of immunological tolerance. Their major role is to shut down T cell mediated immunity towards the end of an immune reaction and to suppress auto-reactive T cells that escaped the process of negative selection in the thymus.
- Natural Killer T cells (NKT cells) are a special kind of lymphocyte that bridges the adaptive immune system with the innate immune system. Unlike conventional T cells that recognize peptide antigen presented by major histocompatibility complex (MHC)

molecules, NKT cells recognize glycolipid antigen presented by a molecule called CD1d. Once activated, these cells can perform functions ascribed to both T<sub>h</sub> and T<sub>c</sub> cells (i.e. cytokine production and release of cytolytic/cell killing molecules).

Although the specific mechanisms of activation vary slightly between different types of T cells, the "two-signal model" in CD4+ T cells holds true for most. Activation of CD4+ T cells occurs through the engagement of both the T cell receptor and CD28 on the T cell by the Major histocompatibility complex peptide and B7 family members on the antigen presenting cells (APC) respectively. Both are required for production of an effective immune response; in the absence of CD28 co-stimulation, T cell receptor signalling alone results in anergy. The signalling pathways downstream from both CD28 and the T cell receptor involve many proteins

All T cells originate from hematopoietic stem cells in the bone marrow. Hematopoietic progenitors derived from hematopoietic stem cells populate the thymus and expand by cell division to generate a large population of immature thymocytes. The earliest thymocytes express neither CD4 nor CD8, and are therefore classed as *double-negative* (CD4<sup>-</sup>CD8<sup>-</sup>) cells. As they progress through their development they become *double-positive* thymocytes (CD4<sup>+</sup>CD8<sup>+</sup>), and finally mature to *single-positive* (CD4<sup>+</sup>CD8<sup>-</sup> or CD4<sup>-</sup>CD8<sup>+</sup>) thymocytes that are then released from the thymus to peripheral tissues.

## **Immunological Memory**

When B cells and T cells are activated some will become *memory cells*. Throughout the lifetime of an animal these memory cells form a database of effective B and T lymphocytes, for which upon interaction with a previously encountered antigen the appropriate memory cells are selected and activated, in this manner a stronger immune response can be produced quicker on the second and proceeding exposures to an antigen. This is "adaptive" because the body's immune system prepares itself for future challenges. Immunological memory can either be in the form of *passive* short-term memory or *active* long-term memory.

### ***Passive memory***

Passive memory is usually short-term, lasting between a few days and several months. Newborn infants have had no prior exposure to microbes and are particularly vulnerable to infection. Several layers of passive protection are provided by the mother. *In utero*, maternal IgG is transported directly across the placenta, so that at birth, human babies have high levels of antibodies, with the same range of antigen specificities as their mother. Breast milk contains antibodies that are transferred to the gut of the infant, protecting against bacterial infections, until the newborn can synthesize its own antibodies.

This is passive immunity because the fetus does not actually make any memory cells or antibodies, it only borrows them. Short-term passive immunity can also be transferred artificially from one individual to another via antibody-rich serum.



### ***Active Memory***

Active immunity is generally long-term and can be acquired by infection followed by B cells and T cells activation, or artificially acquired by vaccines, in a process called immunization.

### **Immunization**

Historically, infectious disease has been the leading cause of death in the human population. Over the last century, two important factors have been developed to combat their spread; sanitation and immunization. Immunization (commonly referred to as vaccination) is the deliberate induction of an immune response, and represents the single most effective manipulation of the immune system mankind has developed. Immunizations are successful because they utilize the immune system's natural specificity as well as its inducibility.

The principle behind immunization is to introduce an antigen, derived from a disease causing organism, that stimulates the immune system to develop protective immunity against that organism, but which does not itself cause the pathogenic effects of that organism. An antigen (short for *antibody generator*), is defined as any substance that binds to a specific antibody and elicits an adaptive immune response.

Most viral vaccines are based on live attenuated viruses, while many bacterial vaccines are based on acellular components of micro-organisms, including harmless toxin components. Many antigens derived from acellular vaccines do not strongly induce an adaptive response, and most bacterial vaccines require the addition of *adjuvants* that activate the antigen presenting cells of the innate immune system to enhance immunogenicity. Adjuvants, can be best described as substances that can enhance the immune response to an immunogen. The use of adjuvants, however, is often hampered by undesirable side effects such as fever and inflammation.