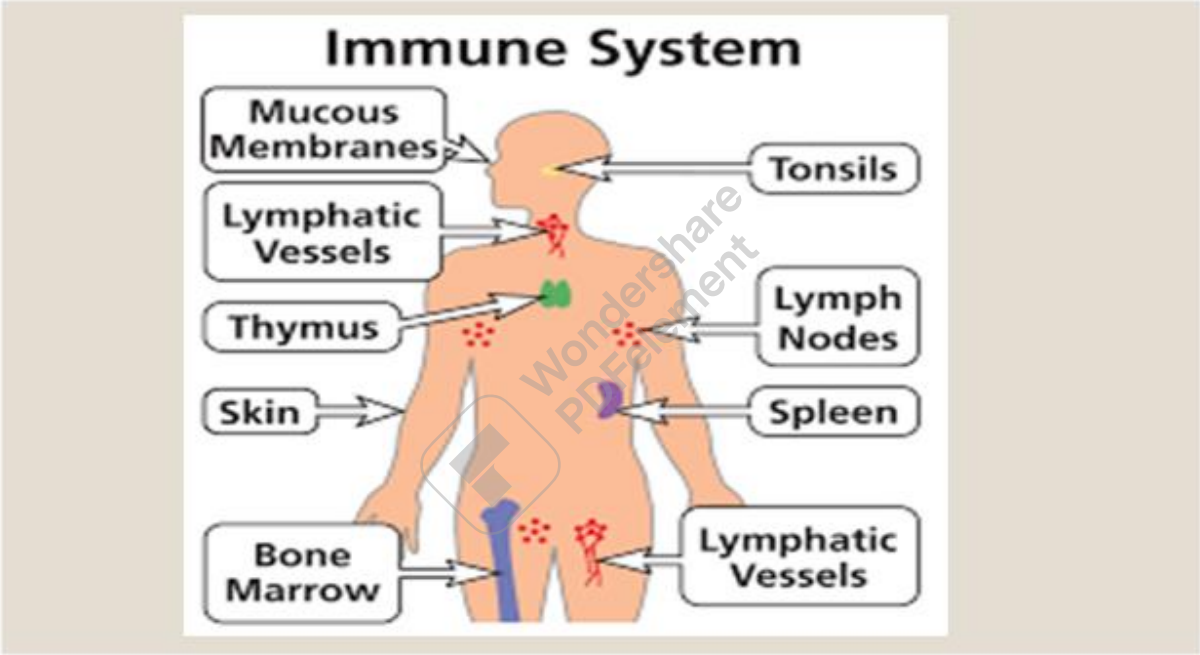
Lec3

The immune system: general considerations

Immunology is the branch of biology concerned with the body's defence reactions. The word 'immunity' is derived from the Latin word immunis, meaning 'free of burden'. In essence, the immune system exists to maintain the integrity of the body by excluding or removing the myriad of potentially burdensome or threatening microorganisms, which could invade from the environment. Internally derived threats, mutant cells with malignant potential, may also be attacked by the immune system.

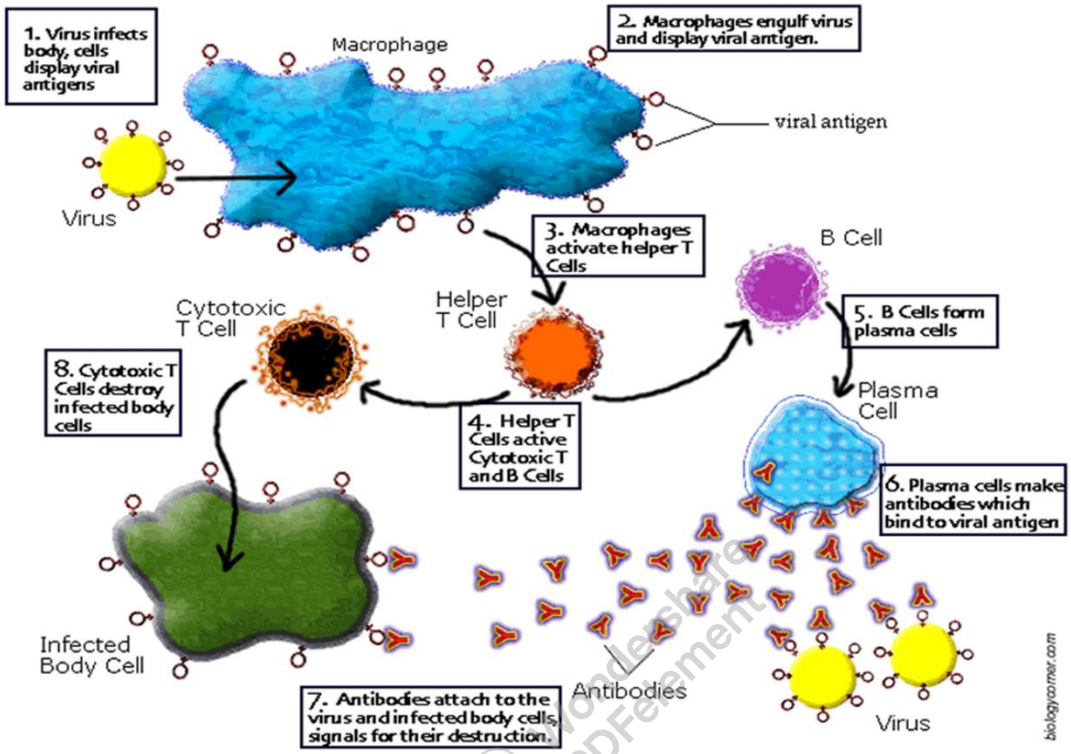


There are two kinds of immunological defence:

1. natural or innate immunity, comprising mainly pre-existing antigen-non-specific defences

2. adaptive or acquired immunity, during which the immune system responds in an antigen-specific manner to neutralize the threat efficiently, and retains a memory of the threat so that any future encounter with the same threat will result in an accelerated and heightened protective response.

During its development, the immune system must be educated specifically to avoid reacting against all normal components of the body (tolerance). Immunology can be considered ‘the science of self-non-self discrimination’.



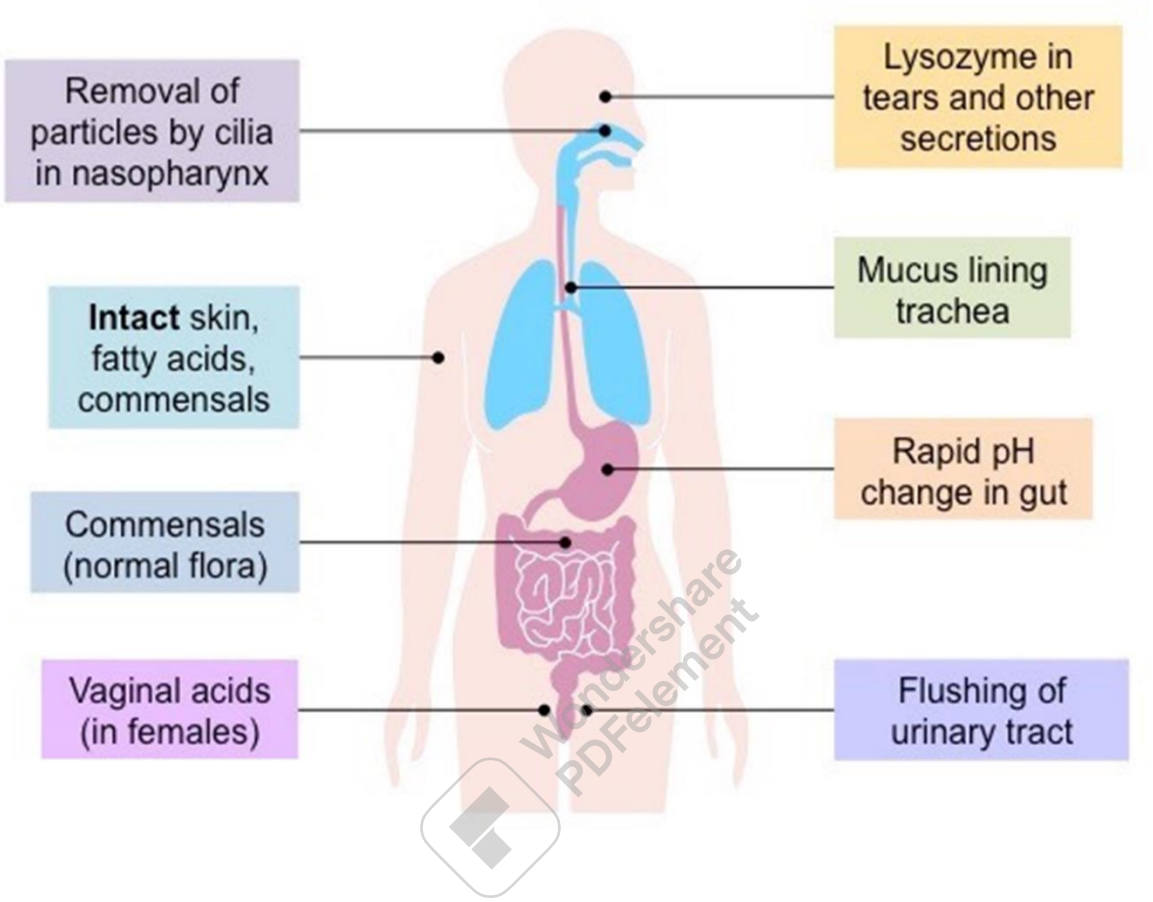
The innate immune system

These intrinsic defence mechanisms are present at birth prior to exposure to pathogens or other foreign macromolecules. They are not enhanced by such exposures and are not specific to a particular pathogen.

Mechanical and chemical barriers

Intact skin is usually impenetrable to microorganisms. Membranous linings of the body tracts are protected by mucus, acid secretions and enzymes such as lysozyme, which breaks down bacterial cell wall proteoglycan. In the lower respiratory tract, the mucous membrane is covered by hair-like protrusions of the epithelial cell membrane called cilia. The movement of cilia can propel mucus-entrapped microorganisms from the tract (mucociliary escalator). Although most pathogens enter the body by binding to and penetrating mucous membranes, several defence mechanisms, including saliva, tears and mucous secretions, are involved in

preventing this entry. Apart from acting to wash away potential invaders, these secretions also contain antibacterial or antiviral substances.

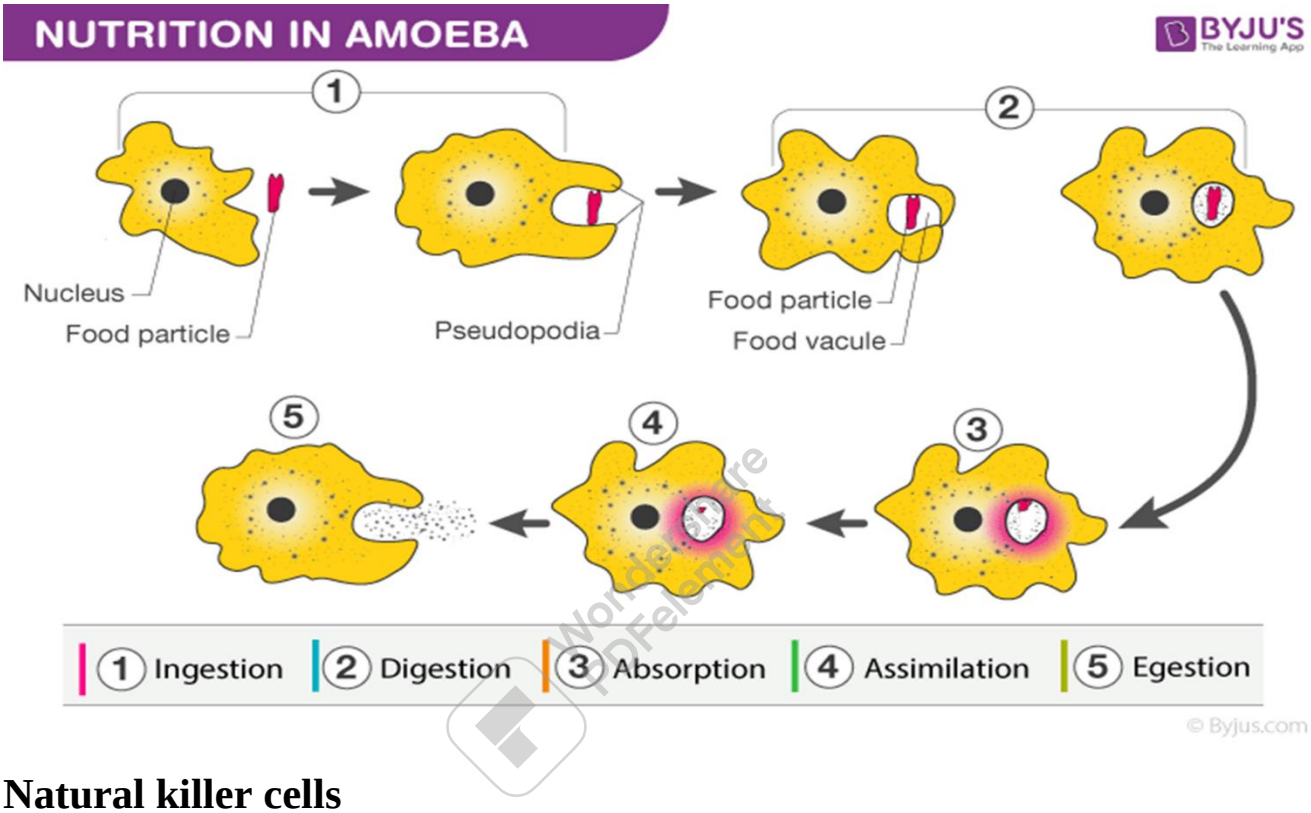


Phagocytosis

Phagocytosis is a process by which phagocytic cells ingest extracellular particulate material, including whole pathogenic microorganisms. If the mechanical defences are breached, the phagocytic cells become the next barrier. These include polymorphonuclear leukocytes (polymorphs) and macrophages. The former are short-lived circulating cells, which can invade the tissues, while the latter are the mature, tissue-resident stage of circulating monocytes.

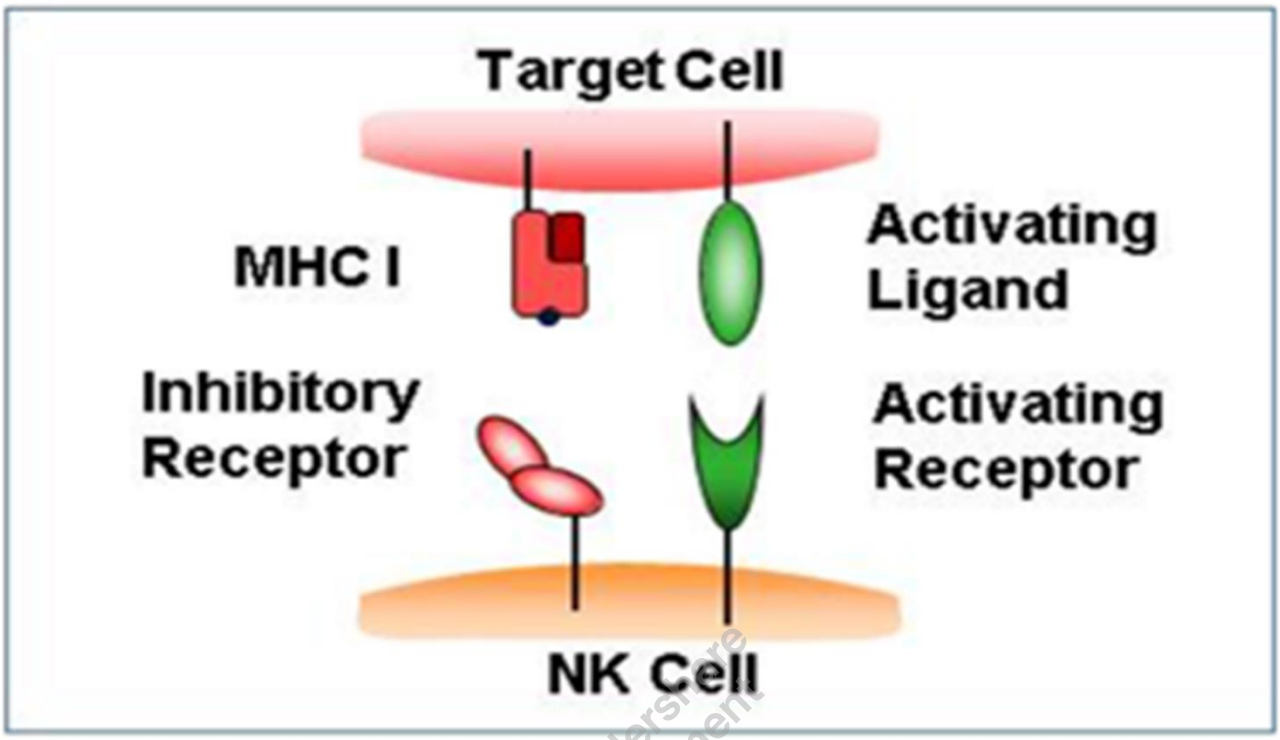
Macrophages are found in areas of blood filtration where they are most likely to encounter foreign particles, e.g. liver sinusoids, kidney mesangium, alveoli, lymph nodes and spleen. Phagocytes attach to microorganisms by non-specific cell membrane ‘threat’ receptors, after which pseudopodia extend around the particle and internalize it into a phagosome. Lysosomal vesicles containing proteolytic

enzymes fuse with the phagosome, and oxygen and nitrogen radicals are generated, which kill the microbe. The phagocytes have several ways of dealing with the phagocytosed material. For example, macrophages reduce molecular oxygen to form microbicidal-reactive oxygen intermediates that are secreted into the phagosome.



Natural killer cells

Natural killer (NK) cells are non-phagocytic lymphocytes that account for up to 15% of blood lymphocytes and have a special role in the killing of virus-infected and malignant cells (Fig. 8.3). These cells have two kinds of receptors with opposing action: antigen receptors able to recognize specific molecules on target cells, through which activation signals are transmitted, and receptors that recognize self major histocompatibility complex I (MHC I) antigens (see below) through which inactivation signals are transmitted. Activation of NK cells can only occur when there is no inactivation signal, so virus-infected and tumour cells with downregulated MHC I antigens are susceptible to NK cytotoxicity, but normal MHC I-positive cells are protected. The killing mechanism is activated by cytokines released by virus-infected cells, tissue cells, lymphocytes and NK cells themselves. The NK cells are also important in the adaptive immune response, being the effector cells for killing antibody-coated microorganisms.



Acute-phase proteins

Acute-phase proteins are serum proteins produced by the liver in response to tissue-damaging infections and other inflammatory stimuli such as cytokines (e.g. interleukins-1 and -6). Although the physiological role of the acute-phase proteins is not fully understood, it has been recognized to enhance the efficiency of innate immunity. Positive acute-phase proteins increase in plasma concentration in the acute-phase response to inhibit or kill microbes through opsonization, coagulation, antiprotease activity and/or complement activation. Negative acute-phase proteins including human serum albumin and transferrin are reduced in concentration in the acute-phase response and act to limit inflammation. Together acute-phase proteins provide immediate defence and enable the body to recognize and react to foreign substances prior to more extensive activation of the immune response. The concentration of the following positive acute-phase proteins in body fluids increases rapidly during tissue injury or infection:

• **C-reactive protein** functions as a soluble PRR and can bind to bacteria to promote their removal by phagocytosis. It is a major acute-phase protein, so named as it binds to the C-polysaccharide cell wall component on a variety of bacteria and fungi. This binding activates the classical complement system, resulting in increased clearance of the pathogen.

• **α1-Antitrypsin** neutralizes proteases released by bacteria, activated polymorphonuclear leukocytes or damaged tissue to limit damage caused by excessive enzyme activity.

• **Mannose-binding protein** functions as a soluble PRR and activates the lectin complement pathway to promote inflammation and attract phagocytes.

Interferon, produced by virus-infected cells, comprises a group of cytokines that mediate innate immunity and includes those that protect against viral infection and those that initiate inflammatory reactions that protect against bacterial pathogens.

The complement system is very much involved in the inflammatory response and is one of the key effector mechanisms of the immune system. It consists of at least 30 components – enzymes, regulators and membrane receptors – which interact in an ordered and tightly regulated manner to bring about phagocytosis or lysis of target cells.Complement components are normally present in body fluids as inactive precursors. The alternative pathway of complement activation can be stimulated directly by microorganisms and is important in the early stages of the infection before the production of antibody. It is part of the innate immune system. The classical pathway requires antibody, which may take weeks to develop. Both pathways can lead to the lytic or membrane attack pathway. During the course of complement activation, numerous split products of complement components, with important biological effects, are produced.

The adaptive immune system

The defence mechanisms in adaptive immunity can specifically recognize and selectively eliminate pathogens and foreign macromolecules. In contrast to innate immunity, adaptive immune responses are reactions to specific antigenic challenge and display four cardinal features: specificity, diversity, immunological memory and discrimination of self and non-self.

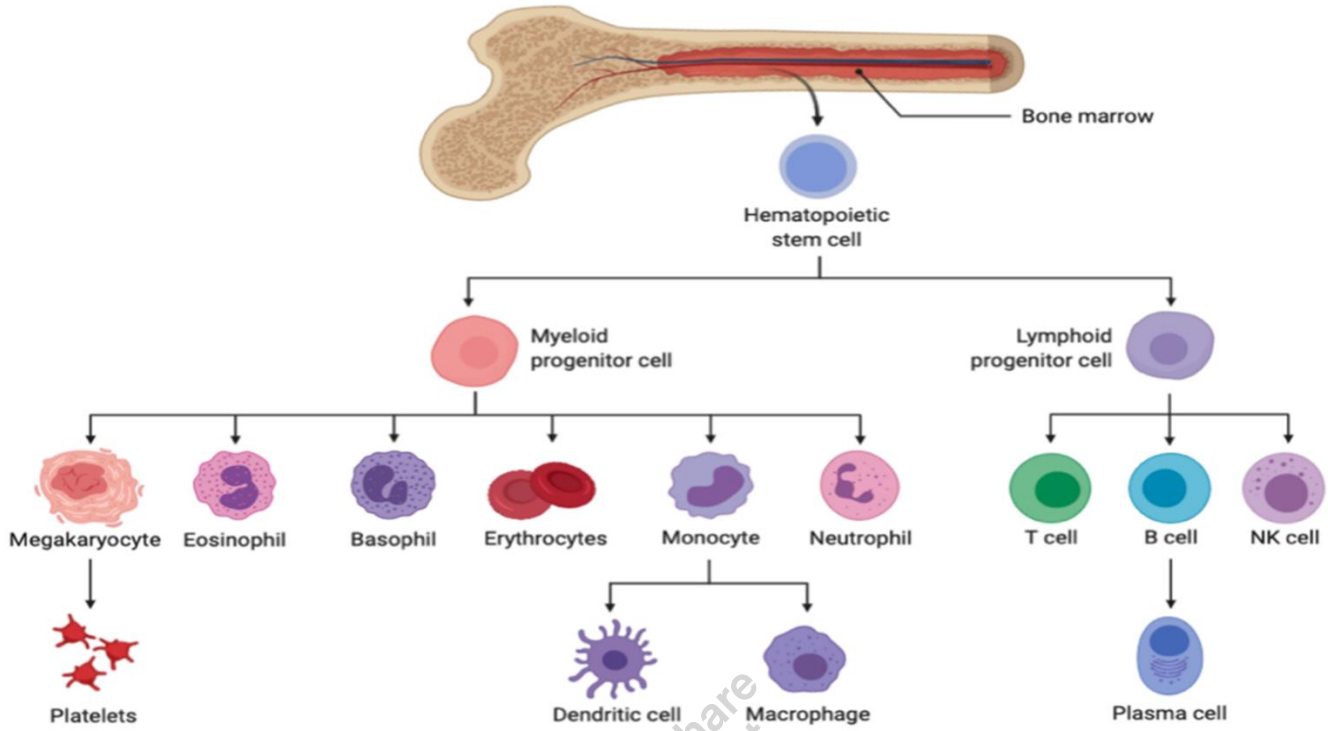
Adaptive immune responses are specific for distinct antigens. This unique specificity exists because B and T lymphocytes express membrane receptors that specifically recognize different antigens. Importantly, adaptive immunity is not dependent on innate immunity. Through delicately modulated interactions, the two types of defence mechanisms work synergistically to produce more effective immunity.

Cells of the immune system

All the cells of the immune system (Fig. 8.8) are derived from self-regenerating haematopoietic stem cells present in bone marrow and foetal liver. These differentiate along either the myeloid or the lymphoid pathway. Myeloid precursor cells give rise to mast cells, erythrocytes, platelets, dendritic cells, polymorphs (eosinophils, basophils, neutrophils) and mononuclear phagocytes (monocytes in the blood, macrophages in the tissues). Lymphoid precursor differentiation gives rise to T (thymus-dependent) lymphocytes, B (bone marrow-derived) lymphocytes and NK lymphocytes.

During post-natal life, B cell genesis takes place in the bone marrow. Each newly formed B cell expresses a unique B cell receptor (BCR) on its membrane for antigen-binding. Although T lymphocytes also arise in the bone marrow, they migrate to the thymus to mature. During its maturation, the T lymphocyte expresses a specific antigen-binding molecule known as the T cell receptor (TCR) on its membrane.

The B lymphocytes are responsible for secreting Ig antibodies and can also function as highly efficient antigen-presenting cells (APCs) for T lymphocytes. The latter are divided into two major subsets: T-helper cells, which usually bear the ‘cluster of differentiation’ marker CD4, and T-cytotoxic cells, which usually carry CD8. The T-helper cells are required for activating the effector function of B cells, other T cells, NK cells and macrophages. They do this by transmitting signals via cell-to-cell contact interactions and/or via soluble hormone-like factors called lymphokines. The T-cytotoxic cells kill target cells such as virus-infected host cells. Another functional property of some T lymphocytes is to downregulate immune responses. These T-suppressor cells are usually CD8-positive. Dendritic cells and monocytes/macrophages play key roles in the immune system as APCs.



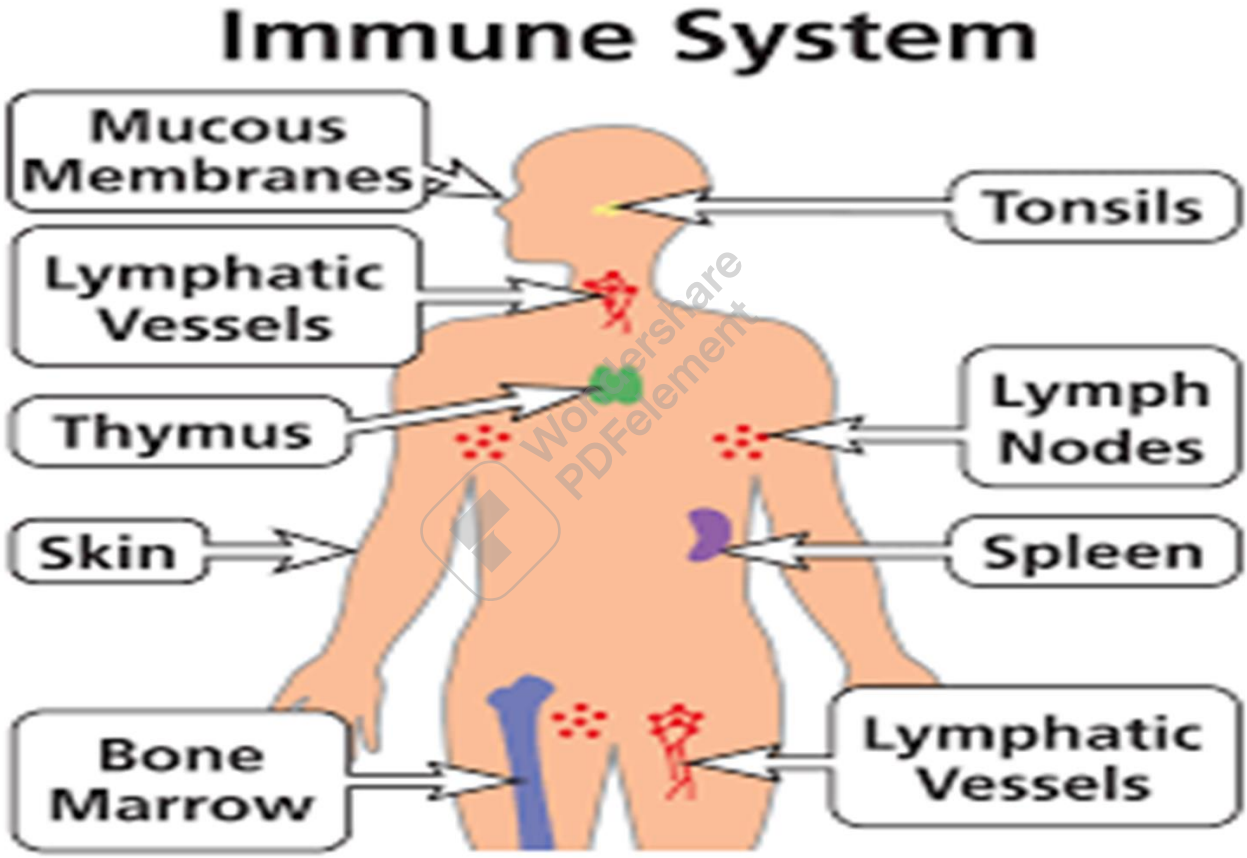
The lymphoid organs

The primary sites of lymphocyte production are the bone marrow and thymus. Immature lymphocytes produced from stem cells in the bone marrow may continue their development within the bone marrow (B lymphocytes, NK cells) or migrate to the thymus and develop into T lymphocytes. ‘Education’ within the primary lymphoid organs ensures that emerging lymphocytes can discriminate self from non-self. They migrate through the blood and lymphatic systems to the secondary lymphoid organs – spleen, lymph nodes and mucosa-associated lymphoid tissue (MALT) of the alimentary, respiratory and urogenital tracts. Here, lymphocytes encounter foreign antigens and become activated effector cells of the immune response.

The spleen acts as a filter for blood and is the major site for clearance of opsonized particles. It is an important site for production of antibodies against intravenous antigens. The lymph nodes form a network of strategically placed filters, which drain fluids from the tissues and concentrate foreign antigen on to APCs and subsequently to lymphocytes. Spleen and lymph nodes are encapsulated organs, whereas MALT is non-encapsulated dispersed aggregates of lymphoid cells

positioned to protect the main passages by which microorganisms gain entry into the body. Gut-associated lymphoid tissue (GALT) includes Peyer's patches of the lower ileum, accumulations of lymphoid tissue in the lamina propria of the intestinal wall and the tonsils.

Mature lymphoid cells continuously circulate between the blood, lymph, lymphoid organs and tissues until they encounter an antigen, which will cause them to become activated .

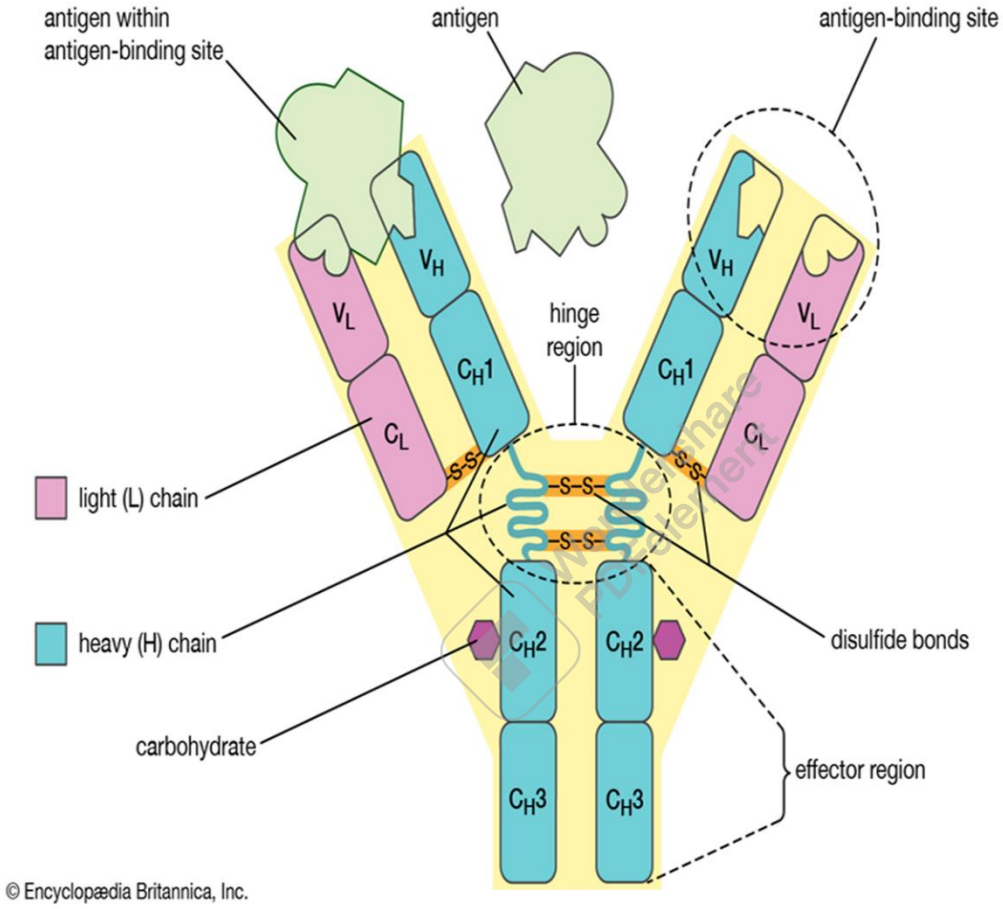


Antigen recognition

The T and B lymphocytes are responsible for specificity in the immune response. They have cell surface receptors whose purpose is to recognize foreign antigens. Each receptor usually binds only to a single antigen, though there may be a degree of cross-reactivity with other antigens of very similar structure. Since all antigen receptors on a given lymphocyte are identical, each B or T cell can usually

recognize only one antigen. A single cell, on encountering its specific antigen, must proliferate to form a clone of identical cells able to deal with the offending antigen (clonal selection).

The TCR recognizes linear peptides bound to MHC molecules on the surface of APCs. The BCR binds directly to often non-linear antigenic determinants (epitopes) and does not require MHC presentation.



Major histocompatibility complex

In humans, products of the highly polymorphic MHC genetic loci on chromosome 6 are known as histocompatibility locus antigens (HLAs). Their function is to bind APC-processed short antigenic peptides and present them on the APC surface to T cells. HLA phenotype is responsible for tissue transplant rejection when the recipient and donor are not HLA-matched.

There are two classes of HLA molecules:

1. HLA-A, -B and -C (class I) are found on all nucleated cells in the body.

2. HLA-DQ, -DR and/>