BASIC IMMUNOLOGY

Introduction

Immunology is a branch of biomedical science that deals with the study of all aspects of the immune systems. It deals with the physiological functioning of the immune system in states of both health and diseases, malfunctioning of the immune system in immunological disorders (autoimmune diseases, hypersensitivities, immune deficiency, transplant rejection) and the physical, chemical and physiological characteristics of the components of the immune system in vitro, in situ and in vivo. Immunology is probably one of the most rapidly developing areas of biomedical research and has great promises with regard to prevention and treatment of wide range of disorders.

HISTORY OF IMMUNOLOGY

Immunology is a science that examines the structure and function of the immune system. It originates from medicine and early studies on the causes of immunity to disease. The earliest known reference to immunity was during the plague of Athens in 430 BC. Then, Thucydides noted that people who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time. In the 18th century, Pierre-Louis Moreau de Maupertuis made experiments with scorpion venom and observed that certain dogs and mice were immune to this venom. This and other observations of acquired immunity were later exploited by Louis Pasteur in his development of vaccination and his proposed germ theory of disease. In 1891, Robert Koch proved, that microorganisms were confirmed as the cause of infectious disease, for which he was awarded a Nobel Prize in 1905. Viruses were confirmed as human pathogens in 1901, with the discovery of the yellow fever virus by Walter Reed.

Immunology made a great advance towards the end of the 19th century, through rapid developments, in the study of humoral immunity and cellular immunity. Particularly important was the work of Paul Ehrlich, who proposed the side-chain theory to explain the specificity of the antigen-antibody reaction; his contributions to the understanding of

humoral immunity were recognized by the award of a Nobel Prize in 1908, which was jointly awarded to the founder of cellular immunology, Elie Metchnikoff.

The immune system is therefore a system of biological structures and processes within the body which helps to protect it against a wide variety of pathogens. To function properly, an immune system must detect a wide variety of agents, from viruses to parasitic worms and distinguish them from the body's own healthy tissue. It should then mount a counter attack against these pathogens to ward off their deleterious effect. The human body has a series of defense mechanisms to protect it from foreign objects and other substances that can invade and injure the body. Common invaders include bacteria, viruses, fungi and various parasites including worms, amoeba and other single-celled protozoans. The body also defends itself from internal threats such as cancer cells, and it often recognizes transplanted organs and tissues as foreign invaders, as well. Sometimes food particles and pollen can also be harmful to the human body and cause an immune response. Collectively, these various invaders are called antigens. An antigen (antibody generator) is therefore a foreign molecule which triggers the generation of immune response by the body.

Each structure of the immune system has a relatively fixed architecture of specialized organs, lymphoid tissues, cells, and chemicals that has the ability to respond to these various invaders that are recognized as non-self or antigen. Infections therefore lead to disease only when the interaction between the host and the causative agent results in damage sufficient to disrupt homeostasis.

Organs of the immune system

These are organs in the body where cells and molecules of the immune system are recognized and localized. These organs are broadly classified into two- the central (primary) and peripheral (secondary) lymphoid tissues. The bone marrow and the thymus are the central lymphatic organs as these are the sites where new "naive" B and T cells originate and rearrange their receptors. The peripheral tissues comprise mainly the lymph node and spleen. They are spaces where antigens, antigen presenting cells, B cells and T cells are brought together to launch an adaptive immune response.

Bone marrow is a semi-solid tissue which may be found within the spongy portions of bones. In birds and mammals, bone marrow is the primary site of new blood cell production or hematopoiesis. All types of hematopoietic cells, including both myeloid and lymphoid lineages, are created in the bone marrow. Some lymphoid cells differentiate in the bone marrow and are termed B cells while some migrate to other lymphoid organs to continue their maturation. The bone marrow is where B cells, natural killer cells, granulocytes and immature thymocytes, in addition to red blood cells and platelets mature.

Thymus

The thymus is a primary lymphoid tissue known as a dedicated organ for T cell development. It is a bilobed structure, located in the thorax. Each lobe contains lymphoid cells (thymocytes) that form a tightly packed outer cortex and an inner medulla. The cortex contains the immature and proliferating cells while the medulla contains more of mature cells indicating existence of a maturation gradient from the cortex to the medulla. The major function of the thymus is in the maturation and selection of an antigen specific T- lymphocytes from bone marrow derived precursor cells.

Lymph node

Lymph nodes are small nodular aggregates of secondary lymphoid tissue that are interconnected by a system of lymphatic vessels, which drain extracellular fluid from tissues, through the lymph nodes, and back into the blood. Lymph nodes have several inlets and an outlet. Afferent lymphatic vessels reaching the most peripheral lymph nodes transport the interstitial fluid filtered from blood capillaries. The lymph flow transports macrophages and dendritic cells loaded with ingested material to the lymph nodes. Lymph flow dramatically increases during an infection carrying with it pathogens and their antigenic molecules, outside and inside of activated macrophages and dendritic cells. Thus, a lymph node is a local command center with continuous real-time information on the antigenic situation in the periphery. From the blood, lymphocytes

constantly enter the lymph node via specialized high endothelial venules. Each lymph node has an efferent vessel connecting to the next lymph node and eventually, via the thoracic duct to the blood. **They are designed to initiate immune responses to tissue-borne antigens.**

Spleen

The spleen is the largest lymphoid organ in the body. It is a secondary lymphoid organ **designed to initiate immune responses to blood-borne antigens**. The spleen monitors antigens in the blood and might be regarded as a huge lymph node in charge of "blood tissue. It can be thought of as an “immunologic conference center” as it consists of lymphocytes, dendritic cells, natural killer cells, red blood cells and macrophages. About half of total body volume will pass through the spleen to filter pathogens using macrophages filtration system. Besides, capturing of antigens from the blood that passes through the spleen, migratory macrophages and dendritic cells bring antigens to the spleen via the blood stream. This initiates an immune response by the production of antibodies by the B cells present. Spleen also acts as a reservoir of blood. When blood is needed in emergency situation such as hemorrhage, the muscles of the spleen contract forcing the stored blood out and back into the general circulation. Spleen also destroys old blood cells as well as plays important role in erythropoiesis before birth. The role of spleen in immune response is linked to diet. Studies have shown that low fat diet and folate supplement help to boost immune system.

Cells of the immune system

All the cellular elements of blood, including the RBC that transport oxygen, the platelets that trigger blood clothing in damaged tissues and the white blood cells of the immune system are derived from the pluripotent stem cells of the bone marrow during haematopoeisis. Differentiation of the pluripotent stem cells arising from the bone marrow gives rise to RBC, platelets and the main categories of WBCs- the lymphoid and myeloid lineages.

The **myeloid lineage** comprises mostly of cells that perform relatively stereotyped responses and are thus considered members of the innate arm of the immune system. The common myeloid progenitor is the precursor of macrophages, granulocytes, mast cells, and dendritic cells of the innate immune system. **The lymphoid lineage** comprises of cells that perform finely tuned antigen-specific roles in immunity and are therefore seen as members of the adaptive immune system. The common lymphoid progenitor in the bone marrow gives rise to the two antigen – specific lymphocytes (B and T lymphocytes) of the adaptive immune system. B lymphocytes are so called because they complete their development in the bone marrow while T lympocytes migrate from their origin in the bone marrow into the thymus where they complete their development. Both B and T cells have surface membrane receptors designed to bind specific antigens. The 3rd type of lymphocyte, the natural killer (NK) cell, is a large, granular lymphocyte that recognizes certain virus and tumor cells.

Cells of the myeloid lineage.

Macrophages have horse-shaped nucleus and are large and versatile cells that are resident in almost all tissues. They are the mature form of monocytes which circulate in the blood and continually migrate into tissues where they differentiate. Macrophages, unlike neutrophils are relatively long-lived cells and are thus seen in chronic inflammation. They Perform several different functions throughout the innate and subsequent adaptive immune response. One is phagocytosis where they engulf and kill invading microorganism intracellularly and then present their antigen to other cells of the immune system such as T and B cells (antigen presentation). Another additional and crucial role of macrophages is to orchestrate immune responses by inducing inflammation which is a prerequisite to a successful immune response. They also secrete a wide array of chemicals including enzymes, signaling proteins that activate other immune system cells and recruit them into an immune response. In their normal resting state, they are the janitors of the body. They spend their time roaming about and cleaning up body tissues and ridding the body of debris and remains of worn out cells that died in the normal course of their life cycle.

Granulocytes are so called because they have densely staining granules in their cytoplasm; they are also called polymorphonucear leukocytes because of their oddly shaped nuclei. There are three types of granulocytes – neutrophils, eosinophils and basophils which are distinguished by the different staining properties of the granules. Unlike macrophages, they are all relatively short-lived, surviving for only a few days and are produced in increased numbers during immune responses, when they leave the blood to migrate to sites of infection or inflammation.

i. Neutrophils

Neutrophils are the most numerous and most important phagocytic cells in innate immune responses representing about 50% - 60% of total circulating leucocytes. Microscopically, these cells possess a multilobular nucleus and are therefore referred to as polymorphonuclear leucocytes (PMNs). They take up a variety of microorganisms by phagocytosis. Neutrophils have a pivotal role to play in the development of acute inflammation.

During the acute phase of inflamation, particularly as a result of bacterial infection, neutrophils migrate toward of site of inflammation in a process called chemotasis and are usually the first to arrive at the scene. Their granules contain acidic and alkaline phosphatases, defensins and peroxidases, all of which represent requisite molecules required for successful elimination of unwanted microbes. Unlike some other phagocytes, neutrophils cannot recharge the enzymes used to kill pathogens. After ingesting a certain number of pathogens, neutrophils die forming major component of pus in an inflamed injury.

ii Eosinophils and Basophils:

They are less abundant than neutrophils, but like neutrophils, they have granules containing a variety of enzymes and toxic proteins which are released when the cells are activated. These cells are chiefly important in defense against parasites which are large to be ingested by macrophages or neutrophils. They can also contribute to allergic inflammatory reactions in which their effects are damaging rather than protective.

They are the 3rd type of phagocytic cells of the immune system. Most dendritic cells have long finger-like process like the dendrites of nerve cells which give them their name. They are produced in the bone marrow and are phagocytes in contact with the external environment. They are located mainly in the skin, nose, lung, stomach and intestines. They are also found in the thymus, lymph nodes and spleen. Immature dendritic cells migrate through the blood stream from the bone marrow to enter tissues. They take up particulate matter by phagocytosis and also continually ingest large amounts of the extra-cellular fluid and its contents by a process known is micropinocytosis. They degrade the pathogens they take up (like the macrophages and neutrophils) but their main role in the immune system is not clearance of microorganisms but presentation of antigens to the other cells of the immune system. When dendritic cells encounter a pathogen, they are stimulated to mature into cells that can activate a particular class of lymphocytes – the T lymphocytes. They do this by displaying antigens derived from the ingested pathogen on their surface in a way that activates the antigen recepter of a T cell. They also provide other signals (molecules that are necessary to activate T lymphocytes that are
encountering their specific antigen for the first time (naïve T lymphocytes). For this reason, dendritic cells are also called antigen presenting cells (APCs). Dendritic cells therefore form a crucial link between the innate and the adaptive immune responses as they present antigens to T cells, one of the key cell types of the adaptive immune system.

Phagocytic cells therefore include, the neutrophils, monocytes and dendrites.

Mast cells

Mast cells reside in connective tissues and mucous membranes. They are known for their role in orchestrating allergic and anaphylactic responses and are believed to play a part in protecting the internal surfaces of the body against pathogens and are also involved in the response to parasitic worms. (Murphy *et al*, 2012). They have large granules in their cytoplasm that released their contents when the mast cell is activated, these help to induce inflammation.

Cells of the lymphoid lineage.

The common lymphoid progenitor in the bone marrow gives rise to the two antigen-specific lymphocytes (B and T cells) of the adaptive immune system and also the natural killer cells (NK cells) which are not antigen-specific and are therefore considered members of the innate system. Lymphocytes are so named because fewer than 1% are present in the circulating blood, the rest reside in the lymph nodes, spleen and other lymphoid organs.

T cells/ lymphocytes

Immature lymphocytes destined to the T cell lineage leave the bone marrow and proceed to the thymus where they develop and mature. As the developing thymocytes begin to express their T cell receptors (TCRs), they are subjected to a rigorous two-step selection process. This process is necessary to remove those cells that would bind to normal self-antigens and cause autoimmunity as well as those that have no attraction whatsoever for the surfaces of APCs. This is accomplished by the exposure of these thymocytes to major histocompactibility complex (MHC) antigens on the thymic stromal cells. Those that have TCRs capable of binding with low affinity will receive positive selection signal to divide and establish clones that will eventually mature. Those that fail to recognize self-MHC at all will not be encouraged to mature (failure of positive selection) while those that bind too strongly to self MHC molecules will be induced to undergo apoptosis (negative selection) because these cells would have potential to cause autoimmune disease. This means that only TCRs that can protect the host from foreign invaders will be permitted to leave the thymus to the periphery (lymph node, spleen and mucosal associated lymphoid tissues) to maximize the chances of encounter with foreign antigens and initiate specific immune responses. T cells are divided into two major subsets that are functionally and phenotypically (identifiably) different. The **T helper (Th) subset, also called the CD4+ T cell**, is a pertinent coordinator of immune regulation. The main function of the Th cell is to augment or potentiate immune responses by the secretion of specialized factors that activate other white blood cells to fight off infection. They are identified by the presence of CD4 marker

on their surface and they recognize antigen only when it is presented along with class II MHC molecules. Based on the cytokines produced Th cells are further divided into Th1 and Th2 subsets. Another important type of T cell is the **T killer/suppressor subset or CD8+ T cel**l. These cells are important in directly killing certain tumor cells, viral-infected cells and sometimes parasites. They lyse cells bearing foreign antigens and are identified by the presence of CD8 marker on their surface. They recognize antigen only when it is presented along with class I MHC molecules (Jacqueline and Bryony, 2001). The CD8+ T cells are also important in down-regulation of immune responses. Both types of T cells can be found throughout the body.

B cells/lymphocytes

B lymphocytes unlike the T cells complete their development and maturation in the bone marrow. B cell development begins in the liver and continues in the bone marrow throughout life. They account for 5-15% of lymphocytes in circulation, 80-90% in bone marrow, 20 -30% in lymph node and 50 -60% in the spleen. The most important surface marker of mature B cell is the surface immunoglobulin of IgM and IgD type. As in T cell development, the developing B cells are also subjected to tests as they begin to express their surface receptors in order to select those that would preferentially bind foreign antigens. When activated by binding to foreign antigens, B cells divide; some of its progeny become memory cells and the remainder becomes antibodies/immunoglobulin- secreting plasma cells. The major function of the B lymphocytes is the production of antibodies in response to foreign proteins of bacteria, viruses and tumor cells. Antibodies are specialized proteins that specifically recognize and bind one particular protein. Antibody production and binding to a foreign substance is often a critical means of signaling other cells to engulf, kill or remove that substance from the body.

Non-specific killer cells.

Natural killer (NK) cells are similar in appearance and function to cytotoxic T lymphocytes. They however, lack the antigen specific receptor that T cells use to identify virus-infected cells and so are counted among the innate lymphoid cells. (Arno, 2017). NK cells can be identified by the presence of CD56 and CD16 and a lack of CD3 cell surface markers. They exhibit the capacity to kill virus-infected and tumor cells via

the same mechanism of inducing apotosis observed with cytotoxic T lymphocyte (grandzyme and perforin). Unlike the lymphocytes, their recognition of target is not MHC-restricted and they do not generate immunologic memory. One mechanism by which NK cells distinguish infected from uninfected cells is by recognizing alterations in MHC class I expression. NK cells are able to sense changes in the expression of MHC class I molecules by integrating the signals from two types of receptors they express on their surface, which together control the NK cell's cytotoxic activity and cytokine production. The receptors are killer activating (**KAR**) and killer inhibiting (**KIR**) receptors. The inhibiting receptors **(KIR**) sense the presence of normal MHC-I molecules on cells probed by the NK cell. A cell with normal MHC-I will be left alone while cell lacking normal MHC-I or expressing altered MHC-I is only recognized by the killer activating (**KAR**) NK receptors and will be killed by induction of apoptosis. Thus, NK cells selectively kill virus infected and malignant cells while sparing normal cells.

TYPES OF THE IMMUNE SYSTEM

There are basically two types; the innate and the adaptive systems

a. Innate immune system

The first line of the innate system aims to **keep invaders out** so they don't enter the body while the second line works to **Kill the invaders** if they escape the first protection and enter the body. They work together to keep us well and healthy.

The physical barriers / the 1st line of defense

In the everyday war against disease causing germs including bacteria, viruses, fungi and protozoa, the body's physical barriers are the first line of defense. These include mechanical, chemical and biological barriers.

The **mechanical barriers** include the skin which is impervious to pathogens. The expose surfaces inside the body in the digestive (intestines), respiratory (lungs) and genitourinary tracts are also protected. In the lungs, coughing and sneezing mechanically expels pathogens and other irritants from the respiratory tract. The

flushing action of tears and urine also mechanically expels pathogens while mucous secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms. The mucous membranes in the trachea and nasal passages also contain cilia and tiny hairs that filter out dust and other particles.

Chemical barriers to infection include the skin and the respiratory tract that secrete antimicrobial peptides such as defensins. Enzymes such as lysozymes and phospholipase A2 found in saliva, tears, nasal secretions, earwax and breastmilk are also antibacterials. Vaginal secretions serve as chemical barrier following menarche when they become slightly acidic, while semen contain defensins and zinc that kill pathogens. In the stomach, gastric acid and proteases serve as powerful chemical defenses against ingested pathogens.

Biological barriers involve the commensal flora within the genitourinary and gastrointestinal tract by competing with the pathogenic bacteria for food and space and in some cases by changing the conditions in their environment such as pH or available iron. These barriers work together to prevent antigens from getting inside the body. Occasionally, however, the physical barriers can be compromised for example through a cut, burn or injury to the skin and antigens can enter the body. When that happens, these antigens then trigger the second line of defense.

Second line of defense

When a pathogen succeeds in breaching one of the host's anatomic barriers, some innate immune mechanisms start acting immediately. These first defenses include several classes of preformed **soluble molecules** present in blood, extracellular fluid, and epithelial secretions that can either kill the pathogen or weaken its effect. They include, antimicrobial enzymes such as lysozyme which begin to digest bacterial cell walls and antimicrobial peptides such as the defensins lyse bacterial cell membranes directly. A system of plasma proteins known as the **complement system** target pathogens both for lysis and for phagocytosis by cells of the innate immune system such as macrophages.

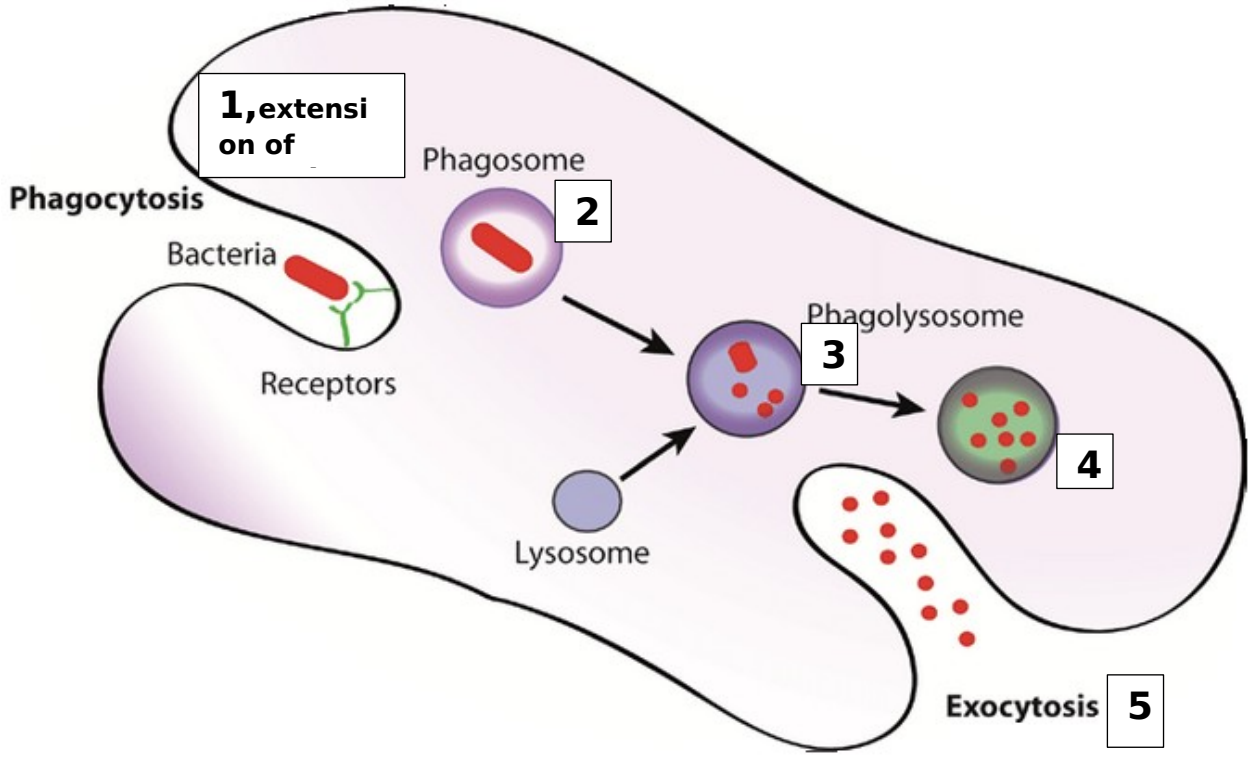
Infammation; In the second phase of the response, the presence of a pathogen triggers off inflammatory responses by the body. The blood vessels begin to dilate resulting in swelling, redness, pain at the affected area. This process brings in phagocytic cells (fighters) to the focus of infection.

Phagocytosis and intracellular killing:

This is the process by which the phagocytic cells in the body engulf any foreign substances that have invaded the body and kill them intracellularly. Phagocytes are usually attracted to the site of infection by the danger signals generated at the site. Neutrophils are usually the first to arrive the scene. Once in the tissue, neutrophils release chemoattractive factors that call in other phagocytes (monocytes, macrophages and even eosinophils) to join in the fight. The innate immune cells (phagocytes) sense the presence of a pathogen by recognizing molecules that are present on the pathogen but not present in host cells using their cell surface receptors. These molecules on the pathogens are termed **pathogen-associated molecular patterns (PAMPs)** while the receptors on the surface of the phagocytes that recognized them before attacking them are termed **pattern recognition receptors (PRR).** Some of these molecular patterns on the surface of pathogens which phagocytes receptors (PRR) can recognize and become activated include; bacterial lipopolysaccharide, bacterial lipopeptides, peptidoglycan, flagellin, bacterial DNA (which contains methylation patterns different from that of human DNA), double-stranded RNA typical of viruses etc. Upon recognizing these molecules, the phagocytes become activated, setting in motion several different effector mechanisms to eliminate the infection. The phagocyte must attach to the microbe by means of its numerous receptors. Phagocytes also have receptors for complement proteins and Fc region of antibody among other receptors. Sometimes complement proteins and antibodies coat the surfaces of microbes to enhance their recognition by phagocytes' receptors. By so doing, they are called **opsonins (**the coating complement proteins and coating antibodies**)** and the process of coating microbes by them is called **opsonization**. After attaching to a bacterium, the phagocyte begins to extend pseudopods around the bacterium. The pseudopods eventually surround the bacterium and internalise it, and the bacterium is enclosed in a

phagosome. During phagocytosis, the granules or lysosomes of the phagocyte fuse with the phagosome and empty their contents. The microbe is subsequently destroyed. Summarily, the process of phagocytosis involves:

1.Extension of pseudopodia to engulf attached material
2.Fusion of pseudopodia to trap the material in a phagosome
3.Fusion of the phagosome with a lysosome to create phagolysosome
4.Digestion
5.Extocytosis of digested contents.



Stages in phagocytosis 1-5 shown

The innate immune system reacts to all threats immediately and in many cases can completely vanquish microorganism or other threats without any further involvement of

other parts of the immune system. However, some antigens particularly viruses replicate so quickly within the body that it can overwhelm the innate system. In those cases, elements of the innate immune system will attempt to keep the invaders at bay while the adaptive immune system ramps up to deal with the threat specifically.

b. Adaptive immune system/ third line of defense

The body's 3rd line of defense is the adaptive immune system also called acquired immune system. It is acquired through contact with specific pathogens during the life time. It is triggered in vertebrates when a pathogen evades the innate immune system and generates a threshold level of antigen and danger signals activating dendritic cells. Adaptive immune system plays three primary roles. First, because the response by the innate immune system is not specific, if it goes on for too long it can also damage healthy cells in the process. Adaptive system, recognizes specific "non self" antigens in the presence of "self" during the process of antigen presentation and generates responses that are tailored to maximally eliminate specific pathogens or pathogen-infected cells. Second, because microbes like bacteria and viruses continually mutate, over time they become resistant to the effects of the immune system. To counter this, the adaptive immune system as the name implies, can adapt itself to target very specific mutations of antigens as they are encountered. Third, the adaptive immune system, protects against re-infection. It creates immunological memory after an initial response to specific pathogen and the pathogen is subsequently remembered through memory B and T cells and can easily be eliminated if it invades the body again. This process of acquired immunity is the basis of **vaccination**. Adaptive immunity can provide long-lasting protection. For example, someone who recovers from measles is now protected against measles for a life time but in some other cases it does not provide lifetime protection as seen in chicken pox disease. Adaptive immune system response destroys invading pathogens and any toxic molecules they produce.

Two types of adaptive immunity include cell-mediated immunity offered by T cells/lymphocytes and Humoral/antibody mediated immunity offered by B cells.

Cell-mediated (cellular) adaptive immunity:

The pathogens targeted by **cellular immunity** are protected/hidden from **antibody and complement binding** by their intracellular locations i.e these pathogens are inside the cells and cannot be reached by antibodies and complement proteins but T cells can attack them. T cells recognize a "non-self" target, such as a pathogen, only after antigens (small fragments of the pathogen) have been processed and presented in combination with a "self" receptor called a major histocompatibility complex (MHC) molecule. There are two major subtypes of T cells: **the Cytotoxic T cells (Killer T cell) and the helper T cell**. Killer T cells only recognize antigens coupled to/presented by the Class I MHC molecules, while helper T cells only recognize antigens coupled to/presented by the Class II MHC molecules. These two mechanisms of antigen presentation reflect the different roles of the two major types of T cell.

With the exception of non-nucleated cells (including erythrocytes), all cells are capable of presenting antigens through the function of MHC molecules. However, some cells are specially equipped to present antigen, and to prime naive T cells. They are termed **professional antigen-presenting cells (APCs) cells and include dendritic cells, B-cells, and macrophages**. They possess special "co-stimulatory" ligands recognized by co-stimulatory receptors on T cells. Each type of T cell is specially equipped to deal with each unique toxin or microbial pathogen.

Helper T-cells

$CD4^+$ lymphocytes, also called "helper" or "regulatory" T cells, are immune response mediators that help to regulate both the innate and adaptive immune responses and help determine which immune responses the body makes to a particular pathogen. These cells have no cytotoxic activity and do not kill infected cells or clear pathogens directly. They instead control the immune response by directing other cells to perform these tasks.

APCs engulf exogenous pathogens such as bacteria, parasites or toxins and migrate to the T cell-enriched lymph nodes. They use enzymes to chop the pathogen into smaller pieces, called antigens. In the lymph node, the APCs display these non-self antigens on its surface by coupling them to **MHC class II** molecules. This MHC: antigen complex is recognized by a specific **$CD4^+$T helper cells** (**clonal selection**) in the lymph node and are activated. They activated T cells make clones (multiply) of itself (**clonal expansion**). The activation of a resting helper T cell causes it to release chemicals called cytokines that influence the activity of many cell types. Cytokine signals produced by helper T cells enhance the microbicidal function of macrophages and the activity of killer T cells. In addition, helper T cell activation provide extra stimulatory signals typically required to activate antibody-producing B cells. Some of the T cells differentiate into memory cells that lived for a long time to initiate more rapid immune response if same antigen invades the body again in the future.

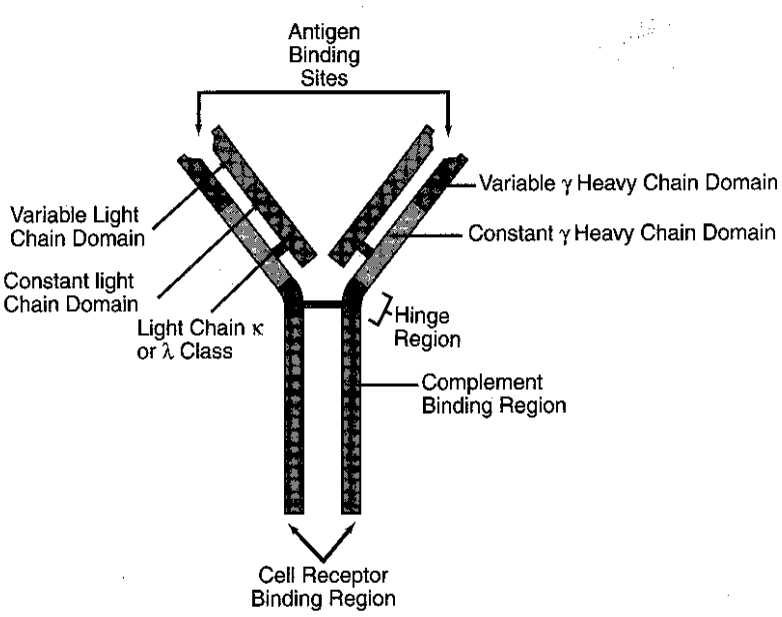
CD8+ T lymphocytes and cytotoxicity

This is also known as killer T cells or cytotoxic T-lymphocyte (CTL). Killer T cells are a sub-group of T cells that kill cells that are infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional. Each type of T cell recognizes a different antigen. **Endogenous antigens** are produced by intracellular bacteria and viruses replicating inside a host cell. The host cell uses enzymes to digest virally associated proteins, and displays these pieces on its surface to T-cells by coupling them to MHC class I molecules. Killer T cells are activated when their T cell receptor (TCR) binds to this specific antigen in a complex with the **MHC Class I** receptor of the infected host cell. Recognition of this MHC:antigen complex is aided by a co-receptor on the T cell, called **CD8.** The T cell then travels throughout the body in search of cells where the MHC I receptors bear this antigen. When an activated T cell contacts such cells, it releases cytotoxins, such as **perforin,** which form pores in the target cell's plasma membrane, allowing ions, water and toxins to enter. The entry of another toxin called **granulysin** (a protease) induces the target cell to undergo apoptosis (death). On resolution of the infection, most effector cells die and phagocytes clear them away but a few of these cells remain as memory cells. On a later encounter with the same antigen,

these memory cells quickly differentiate into effector cells, dramatically shortening the time required to mount an effective response. With the exception of non-nucleated cells (including erythrocytes), MHC class I unlike MHC class II is expressed by not only APCs but all host cells.

Humoral (antibody mediated) adaptive immunity

This is the immunity mediated by antibodies. This arm of the immune response is directed towards the defense against **microbes or toxins in extracellular spaces of the body and may lead to extracellular degradation of such materials or enhancement of their destruction via phagocytosis**. B Cells are the cells involved in the creation of antibodies that circulate in blood plasma and lymph. A B cell identifies pathogens when antibodies on its membrane (B cell receptor-BCR) bind to a specific foreign antigen. This antigen/antibody complex is taken up by the B cell. It processes /breaks down the antigen by proteolysis into peptides. The B cell then displays these antigenic peptides on its surface MHC class II molecules. This MHC: antigen complex attracts a **matching helper T cell**, which releases cytokines that activate the B cell. As the activated B cell begins to divide (clonal expansion), they differentiate into effector/plasma and memory cells. The offspring (plasma cells) secrete millions of copies of the antibody that can recognize this antigen. Each activated B cells can make and secrete up to 2000 antibodies per second. The secreted antibodies travel with the circulating blood throughout the body, seeking for and binding/coating this particular antigen (i.e opsonisation) making it easier for phagocytes to recognized the antibody-opsonized pathogens for subsequent phagocytosis and elimination. The memory B cells hang around to be activated later in case of future attack by the same antigen.



The basic structure of an antibody/Immunogloblin

Each antibody molecule has a two -fold axis of symmetry and is composed of two identical heavy chains and two identical light chains. Heavy and light chains each have variable and constant regions; the variable regions of a heavy chain and a light chain combine to form an antigen-binding site, so that both chains contribute to the antigen-binding specificity of the antibody molecule.

Table 1: Comparisms of innate and Adaptive immune system

Characteristics	Innate	Adaptive
Specificity	For structures shared by groups of microbes	For specific antigens of microbial and nonmicrobial agents
Diversity	Limited	High
Memory	No	Yes
Self-reactivity	No	No
Components		
Anatomic and chemical barriers	Skin, mucosa, chemicals (lysozyme, interferons α and β), temperature, pH	Lymph nodes, spleen, mucosal-associated lymphoid tissues
Blood proteins	Complement	Antibodies
Cells	Phagocytes and natural killer (NK) cells	Lymphocytes (other than NK cells)

DISORDERS OF THE IMMUNE SYSTEM

An **immune disorder** is a dysfunction of the immune system. These disorders can be characterized in several different ways: by the component(s) of the immune system affected, by whether the immune system is overactive or underactive and by whether the condition is congenital or acquired.

However, failures of host defense fall into three broad categories: immunodeficiencies, autoimmunity, and hypersensitivities others include immune complex disorders and host-graft reaction.

Immunodeficiency

This occurs when one or more of the components of the immune system are either inactive, do not operate properly, or the system is absent altogether. The ability of the immune system to respond to pathogens can be diminished in both the young and the

elderly, with immune responses beginning to decline at around 50 years of age due to immunosenescence. Immune deficiency can be primary/congenital or secondary.

A primary immune deficiency occurs when the abnormalities of the immune system develop from an inborn defect in the cells. This may result from an inherited genetic or developmental defect in the immune system. So, the defect is present at birth but may not manifest until later in life. These diseases can be caused by defects in virtually any gene involved in immune development or function, innate or adaptive, humoral or cell mediated, plus genes not previously associated with immunity. The nature of the component(s) that fail(s) determines the degree and type of the immune defect, some immunodeficiency disorders are relatively minor, requiring little or no treatment, although others can be life threatening and necessitate major intervention. Affected cells include T-cells, B-cells, phagocytic cells or the complement system.

In general, defects in the T-cell components of the immune system tend to have a greater overall impact on the immune response than genetic mutations that affect only B cells or innate responses. This is due to the pivotal role of T cells in directing downstream immune events, and occurs because defects in this cell type often affect both humoral and cell-mediated responses.

The nature of the immune defect will determine which groups of pathogens are most challenging to individuals who inherit these immunodeficiency disorders. **Inherited defects that impair B cells, resulting in depressed expression of one or more of the antibody classes, are typically characterized by recurring bacterial infections.** These symptoms are similar to those exhibited by some of the individuals who inherit mutations in genes that encode **complement components**. Phagocytes are so important for the removal of fungi and bacteria that individuals with disruptions of phagocytic function suffer from more of these types of infections. Finally, the pivotal role of the T cell in orchestrating the direction of the immune response means that disruptions in the performance of this cell type can have wide-ranging effects, including depressed antibody production, dysregulation of cytokine expression, and impaired cellular cytotoxicity.

Secondary/acquired immune deficiencies occur when damage is caused by environmental factors. Radiation, chemotherapy, burns, infections and malnutrition contribute to the many causes of secondary immune deficiencies. Acquired Immune Deficiency Syndrome (AIDS) is a secondary immune deficiency caused by the Human Immunodeficiency Virus (HIV) infection that destroys CD4+T cells. AIDS infections are known as "opportunistic" because they are produced by "commonplace" organisms that are harmless in people with healthy immune system, but which take advantage of the "opportunity" provided by immunocompromised condition. The most common infection is an unusual and life-threatening form of pneumonia caused by Pneumocystis carinii (a protozoan infection).

Diets lacking sufficient protein are associated with impaired cell-mediated immunity, complement activity, phagocytes function, antibody concentrations, and cytokine production. Deficiency of single nutrients such as zinc; selenium; iron; copper; vitamins A, C, E, and **Bs;** and folic acid (vitamin **B9)** also reduces immune responses.

HYPERSENSITIVITY

Hypersensitivity (also called **hypersensitivity reaction** or **intolerance**) is a set of undesirable reactions produced by the normal immune system. They are usually referred to as an over- reaction of the immune system to harmless materials and these reactions may be damaging, uncomfortable, or occasionally fatal. Examples include; atopy, anaphylaxis, asthma and Churg-Strauss Syndrome.

There are four types of hypersensitivity reactions;

Immunoglobulin E (IgE) released from mast cells and basophils mediates **Type I hypersensitivity**. Here, harmless substances can sometimes elicit inappropriate immune responses, for example most common type of allergic reactions- **hives, some type of asthma and hay fever** are produced when the immune system respond to a false alarm. **Type II hypersensitivities** also known as antibody–dependent hypersensitivity is mediated by **IgG and IgM** antibodies. Examples include, autoimmune hemolytic anemia, rheumatic heart disease, thrombocytopenia, erythroblastosis fetalis, Graves' disease, myasthenia gravis. Here, the antibodies

perceive the host cell as foreign and binds to antigen on its surface to leading to cellular destruction.

Type III hypersensitivity is also known as immune complex diseases. The mediators are **Immunoglobulin G (**IgG) antibody, Complement and Neutrophils. The antibody (IgG) binds to soluble antigen, forming a circulating immune complex (aggregations of antigens, complement proteins, and IgG and IgM antibodies). The diseases associated with Type III includes, Arthus reaction, post streptococcal glomerulonephritis, membranous nephropathy, reactive arthritis, systemic lupus erythematosus.

The following disorders are associated with **Type IV hypersensitivity**; Contact dermatitis, Chronic transplant rejection, Rheumatoid arthritis, Multiple sclerosis, Hashimoto's thyroiditis. Type IV is not mediated by any antibody and it is termed antibody-independent reactions or cell-mediated responses.

Autoimmunity.

Autoimmunity results from some failure of the host's immune system to distinguish self from non-self, causing destruction of self cells and organs. In other words, the immune system's recognition apparatus breaks down, and the body begins to manufacture antibodies and T cells directed against the body's own constituents cells, like cell components, or specific organs. Such antibodies are known as auto antibodies and the diseases they cause are known as autoimmune diseases. These diseases result from the destruction of self proteins, cells, and organs by auto-antibodies or self-reactive T cells. For example, autoantibodies to thyroid-specific antigens are the major offender in Hashimoto's thyroiditis, autoantibodies to red blood cells can cause anaemia, autoantibodies to pancreatic cells contribute to Type 1 diabetes, and autoantibodies to nerve and muscle cells are found in patients with myasthenia gravis. Autoantibody known as rheumatoid factor is common in persons with rheumatoid arthritis

Graft versus host diseases

Transplantation of tissues and organs can cause life-threatening reactions in recipients when the body sees the tissue as foreign and mounts immune responses to reject it. Graft rejection reaction is immunologic, it shows specificity and memory. It has been

shown to be mediated by lymphocytes**.** The antigens that serve as the principal targets of rejection are proteins encoded in the **major histocompatibility complex (MHC).** In clinical practice, **immunosuppressants** administration is the mainstay in preventing and treating rejection of transplanted organs. This approach is designed mainly to inhibit T cell activation and effector functions.