IMMUNOLOGY

DEFINITION:

The branch of biomedical science concerned with the response of the organism to **antigenic challenge**, the recognition of self from non-self, and all of the biological (in vivo), serological (in vitro), and physical chemical aspects of immune phenomena **defence mechanisms** include all physical, chemical and biological properties of the organism which reduce it's susceptibility to foreign organisms, material, etc. functionally these may be divided into those which are static, or **innate** to the organism, and those which are responsive, or **adaptive** to a potential pathogen or foreign substance.

LYMPHATIC SYSTEM

The **lymphatic system**, or **lymphoid system**, is an organ system in vertebrates that is part of the circulatory system and the immune system. It is made up of a large network of lymphatic vessels, lymphatic or lymphoid organs, and lymphoid tissues.

The vessels carry a clear fluid called lymph (the Latin word *lympha* refers to the deity of fresh water, "Lympha" towards the heart.

Unlike the cardiovascular system, the lymphatic system is not a closed system. The human circulatory system processes an average of 20 litres of blood per day through capillary filtration, which removes plasma from the blood. Roughly 17 litres of the filtered plasma is reabsorbed directly into the blood vessels, while the remaining three litres remain in the interstitial fluid. One of the main functions of the lymphatic system is to provide an accessory return route to the blood for the surplus three litres.

The other main function is that of immune defense. Lymph is very similar to blood plasma, in that it contains waste products and cellular debris, together with bacteria and proteins. The cells of the lymph are mostly lymphocytes. Associated lymphoid organs are composed of lymphoid tissue, and are the sites either of lymphocyte production or of lymphocyte activation. These include the lymph nodes (where the highest lymphocyte concentration is found), the spleen, the thymus, and the tonsils.

Lymphocytes are initially generated in the bone marrow. The lymphoid organs also contain other types of cells such as stromal cells for support. Lymphoid tissue is also associated with mucosas such as mucosa-associated lymphoid tissue (MALT).Fluid from circulating blood leaks into the tissues of the body by capillary action, carrying nutrients to the cells. The fluid bathes the tissues as interstitial fluid, collecting waste products, bacteria, and damaged cells, and then drains as lymph into the lymphatic capillaries and lymphatic vessels. These vessels carry the lymph throughout the body, passing through numerous lymph nodes which filter out unwanted materials such as bacteria and damaged cells. Lymph then passes into much larger lymph vessels known as lymph ducts. The right lymphatic duct drains the right side of the region and the much larger left lymphatic duct, known as the thoracic duct, drains the left side of the body. The ducts empty into the subclavian veins to return to the blood circulation. Lymph is moved through the system by muscle contractions. In some vertebrates, a lymph heart is present that pumps the lymph to the veins.

The lymphatic system was first described in the 17th century independently by Olaus Rudbeck and Thomas Bartholin.

The lymphatic system consists of a conducting network of lymphatic vessels, lymphoid organs, lymphoid tissues, and the circulating lymph.

Primary lymphoid organs

The primary (or central) lymphoid organs generate lymphocytes from immature progenitor cells. The thymus and the bone marrow constitute the primary lymphoid organs involved in the production and early clonal selection of lymphocyte tissues.

1.Bone marrow

Bone marrow is responsible for both the creation of T cells and the production and maturation of B cells, which are important cell types of the immune system. From the bone marrow, B cells immediately join the circulatory system and travel to secondary lymphoid organs in search of pathogens. T cells, on the other hand, travel from the bone marrow to the thymus, where they develop further and mature. Mature T cells then join B cells in search of pathogens. The other 95% of T cells begin a process of apoptosis, a form of programmed cell death.

2.Thymus

The thymus increases in size from birth in response to postnatal antigen stimulation. It is most active during the neonatal and pre-adolescent periods. At puberty, by the early teens, the thymus begins to atrophy and regress, with adipose tissue mostly replacing the thymic stroma. However, residual T lymphopoiesis continues throughout adult life. The loss or lack of the thymus results in severe immunodeficiency and subsequent high susceptibility to infection. In most species, the thymus consists of lobules divided by septa which are made up of epithelium; it is therefore often considered an epithelial organ. T cells mature from thymocytes, proliferate, and undergo a selection process in the thymic cortex before entering the medulla to interact with epithelial cells.

The thymus provides an inductive environment for the development of T cells from hematopoietic progenitor cells. In addition, thymic stromal cells allow for the selection of a functional and self-tolerant T cell repertoire. Therefore, one of the most important roles of the thymus is the induction of central tolerance.

Secondary lymphoid organs

The secondary (or peripheral) lymphoid organs (SLO), which include lymph nodes and the spleen, maintain mature naive lymphocytes and initiate an adaptive immune response. The peripheral lymphoid organs are the sites of lymphocyte activation by antigens. Activation leads to clonal expansion and affinity maturation. Mature lymphocytes recirculate between the blood and the peripheral lymphoid organs until they encounter their specific antigen.

1.Spleen

The main functions of the spleen are:

1. to produce immune cells to fight antigens

2. to remove particulate matter and aged blood cells, mainly red blood cells
3. to produce blood cells during fetal life.

The spleen synthesizes antibodies in its white pulp and removes antibody-coated bacteria and antibody-coated blood cells by way of blood and lymph node circulation.
in its reserve, half of the body's monocytes within the red pulp.These monocytes, upon moving to injured tissue (such as the heart), turn into dendritic cells and macrophages while promoting tissue healing. The spleen is a center of activity of the mononuclear phagocyte system and can be considered analogous to a large lymph node, as its absence causes a predisposition to certain infections. Like the thymus, the spleen has only efferent lymphatic vessels. Both the short gastric arteries and the splenic artery supply it with blood. The germinal centers are supplied by arterioles called *penicilliary radicles*.Until the fifth month of prenatal development, the spleen creates red blood cells; after birth, the bone marrow is solely responsible for hematopoiesis. As a major lymphoid organ and a central player in the reticuloendothelial system, the spleen retains the ability to produce lymphocytes. The spleen stores red blood cells and lymphocytes. It can store enough blood cells to help in an emergency. Up to 25% of lymphocytes can be stored at any one time

Lymph nodes

A lymph node is an organized collection of lymphoid tissue, through which the lymph passes on its way back to the blood. Lymph nodes are located at intervals along the lymphatic system.
Several afferent lymph vessels bring in lymph, which percolates through the substance of the lymph node, and is then drained out by an efferent lymph vessel. Of the nearly 800 lymph nodes in the human body, about 300 are located in the head and neck.[17] Many are grouped in clusters in different regions, as in the underarm and abdominal areas. Lymph node clusters are commonly found at the proximal ends of limbs (groin, armpits) and in the neck, where lymph is collected from regions of the body likely to sustain pathogen contamination from injuries. Lymph nodes are particularly numerous in the mediastinum in the chest, neck, pelvis, axilla, inguinal region, and in association with the blood vessels of the intestines.
The substance of a lymph node consists of lymphoid follicles in an outer portion called the cortex. The inner portion of the node is called the medulla, which is surrounded by the cortex on all sides except for a portion known as the hilum. The hilum presents as a depression on the surface of the lymph node, causing the otherwise spherical lymph node to be bean-shaped or ovoid.

The efferent lymph vessel directly emerges from the lymph node at the hilum. The arteries and veins supplying the lymph node with blood enter and exit through the hilum. The region of the lymph node called the paracortex immediately surrounds the medulla. Unlike the cortex, which has mostly immature T cells, or thymocytes, the paracortex has a mixture of immature and mature T cells. Lymphocytes enter the lymph nodes through specialised high endothelial venules found in the paracortex.

A lymph follicle is a dense collection of lymphocytes, the number, size, and configuration of which change in accordance with the functional state of the lymph node. For

example, the follicles expand significantly when encountering a foreign antigen. The selection of B cells, or *B lymphocytes*, occurs in the germinal centre of the lymph nodes.

Secondary lymphoid tissue provides the environment for the foreign or altered native molecules (antigens) to interact with the lymphocytes. It is exemplified by the lymph nodes, and the lymphoid follicles in tonsils, Peyer's patches, spleen, adenoids, skin, etc. that are associated with the mucosa-associated lymphoid tissue (MALT). In the gastrointestinal wall, the appendix has mucosa resembling that of the colon, but here it is heavily infiltrated with lymphocytes.

Tertiary lymphoid organs

Tertiary lymphoid organs (TLOs) are abnormal lymph node-like structures that form in peripheral tissues at sites of chronic inflammation, such as chronic infection, transplanted organs undergoing graft rejection, some cancers, and autoimmune and autoimmune-related diseases.TLOs are regulated differently from the normal process whereby lymphoid tissues are formed during ontogeny, being dependent on cytokines and hematopoietic cells, but still drain interstitial fluid and transport lymphocytes in response to the same chemical messengers and gradients. TLOs typically contain far fewer lymphocytes, and assume an immune role only when challenged with antigens that result in inflammation. They achieve this by importing the lymphocytes from blood and lymph. TLOs often have an active germinal center. TLOs play an important role in the immune response to cancer. Patients with TLOs in the vicinity of their tumors tend to have a better prognosis, although the opposite is true for certain cancers. TLOs that contain an active germinal center tend to have a better prognosis than those with TLOs without a germinal center. The reason that these patients tend to live longer
is thought to be the immune response against the tumor, which is mediated by the TLOs. TLOs may also promote an anti-tumor response when patients are treated with immunotherapy.
TLOs have been referred to in many different ways, including as tertiary lymphoid structures (TLS) and ectopic lymphoid structures (ELS). When associated with colorectal cancer, they are often referred to as a Crohn's-like lymphoid reaction..

Other lymphoid tissue

Lymphoid tissue associated with the lymphatic system is concerned with immune functions in defending the body against infections and the spread of tumours. It consists of connective tissue formed of reticular fibers, with various types of leukocytes (white blood cells), mostly lymphocytes enmeshed in it, through which the lymph passes. Regions of the lymphoid tissue that are densely packed with lymphocytes are known as *lymphoid follicles*. Lymphoid tissue can either be structurally well organized as lymph nodes or may consist of loosely organized
lymphoid follicles known as the mucosa-associated lymphoid tissue (MALT). The central nervous system also has lymphatic vessels. The search for T cell gateways into and out of the meninges uncovered functional meningeal lymphatic vessels lining the dural sinuses, anatomically integrated into the membrane surrounding the brain.

Lymphatic vessels

The lymphatic vessels, also called lymph vessels, are thin-walled vessels that conduct lymph between different parts of the body. They include the tubular vessels of the lymph capillaries, and the larger collecting vessels–the right lymphatic duct and the thoracic duct (the left lymphatic duct). The lymph capillaries are mainly responsible for the absorption of interstitial fluid from the tissues, while lymph vessels propel the absorbed fluid forward into the larger collecting ducts, where it ultimately returns to the bloodstream via one of the subclavian veins.

The tissues of the lymphatic system are responsible for maintaining the balance of the body fluids. Its network of capillaries and collecting lymphatic vessels work to efficiently drain and transport extravasated fluid, along with proteins and antigens, back to the circulatory system. Numerous intraluminal valves in the vessels ensure a unidirectional flow of lymph without reflux. Two valve systems, a primary and a secondary valve system, are used to achieve this unidirectional flow. The capillaries are blind-ended, and the valves at the ends of capillaries use specialised junctions together with anchoring filaments to allow a unidirectional flow to the primary vessels. The collecting lymphatics, however, act to propel the lymph by the combined actions of the intraluminal valves and lymphatic muscle cells.

Lymphatic tissues begin to develop by the end of the fifth week of embryonic development. Lymphatic vessels develop from lymph sacs that arise from developing veins, which are derived from mesoderm.

The first lymph sacs to appear are the paired jugular lymph sacs at the junction of the internal jugular and subclavian veins.From the jugular lymph sacs, lymphatic capillary plexuses

spread to the thorax, upper limbs, neck, and head. Some of the plexuses enlarge and form lymphatic vessels in their respective regions. Each jugular lymph sac retains at least one

connection with its jugular vein, the left one developing into the superior portion of the thoracic duct.

The next lymph sac to appear is the unpaired retroperitoneal lymph sac at the root of the mesentery of the intestine. It develops from the primitive vena cava and mesonephric veins. Capillary plexuses and lymphatic vessels spread from the retroperitoneal lymph sac to the abdominal viscera and diaphragm. The sac establishes connections with the cisterna chyli but loses its connections with neighbouring veins.

The last of the lymph sacs, the paired posterior lymph sacs, develop from the iliac veins. The posterior lymph sacs produce capillary plexuses and lymphatic vessels of the abdominal wall,

pelvic region, and lower limbs. The posterior lymph sacs join the cisterna chyli and lose their connections with adjacent veins.

With the exception of the anterior part of the sac from which the cisterna chyli develops, all lymph sacs become invaded by mesenchymal cells and are converted into groups of lymph nodes.

The spleen develops from mesenchymal cells between layers of the dorsal mesentery of the stomach

The thymus arises as an outgrowth of the third pharyngeal pouch.

Function

The lymphatic system has multiple interrelated functions:

It is responsible for the removal of interstitial fluid from tissues

It absorbs and transports fatty acids and fats as chyle from the digestive system

It transports white blood cells to and from the lymph nodes into the bones

The lymph transports antigen-presenting cells, such as dendritic cells, to the lymph nodes where an immune response is stimulated.

Immune function

The lymphatic system plays a major role in the body's immune system, as the primary site for cells relating to adaptive immune system including T-cells and B-cells. Cells in the lymphatic system react to antigens presented or found by the cells directly or by other dendritic cells. When an antigen is recognized, an immunological cascade begins involving the activation and recruitment of more and more cells, the production of antibodies and cytokines and the recruitment of other immunological cells such as macrophages.

ANTIGEN

An **antigen** (**Ag**) is a molecule or molecular structure, such as may be present at the outside of a pathogen, that can be bound to by an antigen-specific antibody (Ab) or B cell antigen receptor (BCR). The presence of antigens in the body normally triggers an immune response. The term "antigen" originally described a structural molecule that binds specifically to an antibody only in the form of native antigen. It was expanded later to refer to any molecule or a linear molecular fragment after processing the native antigen that can be recognized by T-cell receptor (TCR). BCR and TCR are both highly variable antigen receptors diversified by somatic V(D)J recombination. Both T cells and B cells are cellular components of adaptive immunity. The Ag abbreviation stands for an *antibody generator*.

Antigens are "targeted" by antibodies. Each antibody is specifically produced by the immune system to match an antigen after cells in the immune system come into *contact* with it; this allows a precise identification or matching of the antigen and the initiation of a tailored response. The antibody is said to "match" the antigen in the sense that it can bind to it due to an adaptation in a region of the antibody; because of this, many different antibodies are produced, each able to bind a different antigen while sharing the same basic structure. In most cases, an adapted antibody can only react to and bind one specific

Also, an antigen is a molecule that binds to Ag-specific receptors, but cannot necessarily induce an immune response in the body by itself. Antigens are usually proteins, peptides (amino acid chains) and polysaccharides (chains of monosaccharides/simple sugars) but lipids and nucleic acids become antigens only when combined with proteins and polysaccharides. In general, saccharides and lipids (as opposed to peptides) qualify as antigens but not as immunogens since they cannot elicit an immune response on their own. Furthermore, for a peptide to induce an immune response (activation of T-cells by antigen-presenting cells) it must be a large enough size, since peptides too small will also not elicit an immune response.

The antigen may originate from within the body ("self-antigen") or from the external environment ("non-self"). The immune system is supposed to identify and attack "non-self"

invaders from the outside world or modified/harmful substances present in the body and usually does not react to self-antigens under normal homeostatic conditions due to negative selection of T cells in the thymus.

Vaccines are examples of antigens in an immunogenic form, which are intentionally administered to a recipient to induce the memory function of adaptive immune system toward the antigens of the pathogen invading that recipient

HAPTENS

Haptens are small molecules that elicit an immune response only when attached to a large carrier such as a protein; the carrier may be one that also does not elicit an immune response by itself (in general, only large molecules, infectious agents, or insoluble foreign matter can elicit an immune response in the body). Once the body has generated antibodies to a hapten-carrier adduct, the small-molecule hapten may also be able to bind to the antibody, but it will usually not initiate an immune response; usually only the haptencarrier adduct can do this. Sometimes the small-molecule hapten can even block immune response to the hapten-carrier adduct by preventing the adduct from binding to the antibody, a process called *hapten inhibition*. The mechanisms of absence of immune response may vary and involve complex immunological mechanisms, but can include absent or insufficient co-stimulatory signals from antigen-presenting cells.

Haptens have been used to study allergic contact dermatitis (ACD) and the mechanisms of inflammatory bowel disease (IBD) to induce autoimmune-like responses.
The concept of haptens emerged from the work of Karl Landsteiner who also pioneered the use of synthetic haptens to study immunochemical phenomena.
The first researched haptens were aniline and its carboxyl derivatives (o-, m-, and paminobenzoic acid).

A well-known example of a hapten is urushiol, which is the toxin found in poison ivy. When absorbed through the skin from a poison ivy plant, urushiol undergoes oxidation in the skin cells to generate the actual hapten, a reactive quinone-type molecule, which then reacts with skin proteins to form hapten adducts. Usually, the first exposure causes only

Examples of haptens sensitization, in which there is a proliferation of effector T-cells. After a subsequent, second exposure, the proliferated T-cells can become activated, generating an immune reaction that produces typical blisters of a poison ivy exposure.

Some haptens can induce autoimmune disease. An example is hydralazine, a blood pressure-lowering drug that occasionally can produce drug-induced lupus erythematosus in certain individuals. This also appears to be the mechanism by which the anaesthetic gas halothane can cause a life-threatening hepatitis, as well as the mechanism by which penicillin-class drugs cause autoimmune hemolytic anemia.

Other haptens that are commonly used in molecular biology applications include fluorescein, biotin, digoxigenin, and dinitrophenol.

Lastly, nickel allergy is caused by nickel metal ions penetrating the skin and binding to skin proteins.

ADJUVANTS

An **adjuvant** (from Latin, "adjuvare", meaning "to help") is a pharmacological or immunological agent that improves the immune response of a vaccine. Adjuvants may be added to a vaccine to boost the immune response to produce more antibodies and longerlasting immunity, thus minimizing the dose of antigen needed. Adjuvants may also be used to enhance the efficacy of a vaccine by helping to modify the immune response to particular types of immune system cells: for example, by activating T cells instead of antibody-secreting B cells depending on the purpose of the vaccine. Adjuvants are also used in the production of antibodies from immunized animals. There are different classes of adjuvants that can affect the immune response in different ways, but the most commonly used adjuvants include aluminium hydroxide and paraffin oil.

Immunologic adjuvants are added to vaccines to stimulate the immune system's response to the target antigen, but do not provide immunity themselves. Adjuvants can act in various ways in presenting an antigen to the immune system. Adjuvants can act as a depot for the antigen, presenting the antigen over a longer period of time, thus maximizing the immune response before the body clears the antigen. Examples of depot type adjuvants are oil emulsions. An adjuvant can also act as an irritant, which engages and amplifies the body's immune response A tetanus, diphtheria, and pertussis (DPT) vaccine, for example, contains small quantities of inactivated toxins produced by each of the target bacteria, but also contains some aluminium hydroxide.Such aluminium salts are common adjuvants in vaccines sold in the United States and have been used in vaccines for more than 70 years.

Immunologic adjuvants

Mechanism

Adjuvants are needed to improve routing and adaptive immune responses to antigens. This reaction is mediated by two main types of lymphocytes, B and T lymphocytes. Adjuvants apply their effects through different mechanisms. Some adjuvants, such as alum, function as delivery systems by generating depots that trap antigens at the injection site, providing a slow release that continues to stimulate the immune system. This is now under debate, as studies have shown that surgical removal of these depots had no impact on the magnitude of IgG1 response.

As stabilizing agents

Although immunological adjuvants have traditionally been viewed as substances that aid the immune response to the antigen, adjuvants have also evolved as substances that can aid in stabilizing formulations of antigens, especially for vaccines administered for animal health.

Mechanism of immune stimulation

Adjuvants can enhance the immune response to the antigen in different ways:

1. Extend the presence of antigen in the blood
2. Help the antigen presenting cells absorb antigen
3. Activate macrophages and lymphocytes
4. Support the production of cytokines

ANTIGENIC DETERMINANTS AND PROCESSING PATHWAYS

Antigen epitopes make it possible for the immune system to recognize pathogens.

An epitope (also known as an antigenic determinant) is part of an antigen that is recognized by the immune system, specifically by antibodies and B and T cells. Other immune cells like APCs cannot recognize epitopes (only PAMPS and DAMPS).
Antigenic determinants (epitopes) are divided into conformational epitopes and linear epitopes.

Antigen processing occurs within a cell and results in fragmentation of proteins, association of the fragments with MHC molecules, and expression of the peptide -MHC molecules at the cell surface where they can be recognized by the T cell receptor on a T cell.

Antigen processing may be done through either the endogenous pathway (viral proteins from within an infected cell) or through the exogenous pathway (engulfing a pathogen and isolating its antigen from within the APC).

The endogenous pathway uses MHC class I and binds to cytotoxic T cells, while the exogenous pathway uses MHC class II and binds to helper T cells.

Some viruses can prevent antigen processing by disrupting movement of MHC within the cell.

Linear epitopes: These consist of the primary amino acid structure of a protein that makes up the larger antigen.

The Exogenous Pathway:

Phagocytized pathogens are broken down from within the cell and their broken-down antigens bind with MHC II, which then is expressed on the surface of the antigen-presenting cell.

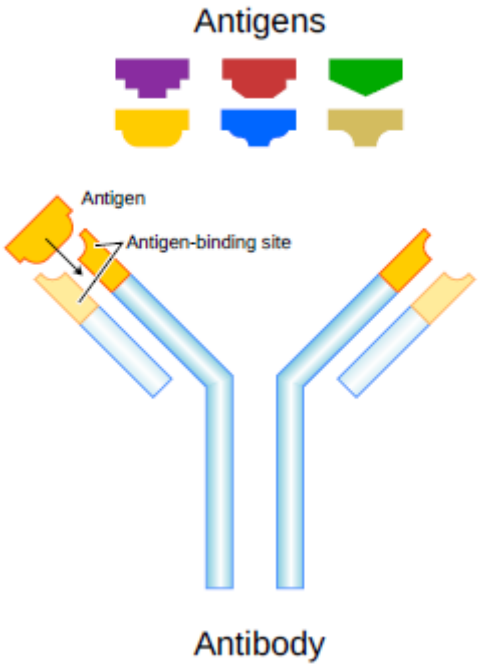
An epitope, also known as an antigenic determinant, is the part of an antigen that is recognized by the immune system, specifically by antibodies, B cells, and T cells. The latter can use epitopes to distinguish between different antigens, and only binds to their specific antigen. In antibodies, the binding site for an epitope is called a paratope. Although epitopes are usually derived from non-self proteins, sequences derived from the host that can be recognized are also classified as epitopes. Epitopes determine how antigen binding and antigen presentation occur.

Types of Antigenic Determinants

The epitopes of protein antigens are divided into two categories based on their structures and interaction with the paratope.
A conformational epitope is composed of discontinuous sections of the antigen's amino acid sequence. These epitopes interact with the paratope based on the 3-D surface features and tertiary structure (overall shape) of the antigen. Most epitopes are conformational.
Linear epitopes interact with the paratope based on their primary structure (shape of the protein's components). A linear epitope is formed by a continuous sequence of amino acids from the antigen, which creates a "line" of sorts that builds the protein structure.

Antigenic determinants recognized by B cells and the antibodies secreted by B cells can be either conformational or linear epitopes. Antigenic determinants recognized by T cells are typically linear epitopes. T cells do not recognize polysaccharide or nucleic acid antigens. This is why polysaccharides are generally T-independent antigens and proteins are generally Tdependent antigens. The determinants need not be located on the exposed surface of the antigen in its original form, since recognition of the determinant by T cells requires that the antigen be first processed by antigen presenting cells. Free peptides flowing through the body are not recognized by T cells, but the peptides associate with molecules coded for by the major histocompatibility complex (MHC). This combination of MHC molecules and peptide is recognized by T cells.

Antigen-Binding Site of an Antibody:



Antigen-binding sites can recognize different epitopes on an antigen.

In order for an antigen-presenting cell (APC) to present an antigen to a naive T cell, it must first be processed so it can be recognized by the T cell receptor. This occurs within an APC that phagocytizes an antigen and then digests it through fragmentation (proteolysis) of the antigen protein, association of the fragments with MHC molecules, and expression of the peptide-MHC molecules at the cell surface. There, they are recognized by the T cell receptor on a T cell during antigen presentation. MHC molecules must move between the cell membrane and cytoplasm in order for antigen processing to occur properly. However, the pathway leading to the association of protein fragments with MHC molecules differs between class I and class II MHC, which are presented to cytotoxic or helper T cells respectively.

There are two different pathways for antigen processing:

1.**The endogenous pathway** occurs when MHC class I molecules present antigens derived from intracellular (endogenous) proteins in the cytoplasm, such as the proteins produced within virus-infected cells. Generally, proteosomes are used to break up the viral proteins and combine them with MHC I.

2.The exogenous pathway occurs when MHC class II molecules present fragments derived from extracellular (exogenous) proteins that are located within the cell. First, pathogens are phagocytized, then endosomes within the cell break down antigens with proteases, which then combine with MHC II.

Some viral pathogens have developed ways to evade antigen processing. For example, cytomegalovirus and HIV-infected cells sometimes disrupt MHC movement through the cytoplasm, which may prevent them from binding to antigens or from moving back to the cell membrane after binding with an antigen.

IMMUNOGLOBULINS - STRUCTURE AND FUNCTION

I. DEFINITION

Immunoglobulin (Ig)

Immunoglobulins are glycoprotein molecules that are produced by plasma cells in response to an immunogen and which function as antibodies. The immunoglobulins derive their name from the finding that they migrate with globular proteins when antibody-containing serum is placed in an electrical field.

II. GENERAL FUNCTIONS OF IMMUNOGLOBULINS

A. Antigen binding

Immunoglobulins bind specifically to one or a few closely related antigens. Each immunoglobulin actually binds to a specific antigenic determinant. Antigen binding by antibodies is the primary function of antibodies and can result in protection of the host. The valency of antibody refers to the number of antigenic determinants that an individual antibody molecule can bind. The valency of all antibodies is at least two and in some instances more.

B. Effector Functions

Frequently the binding of an antibody to an antigen has no direct biological effect. Rather, the significant biological effects are a consequence of secondary "effector functions" of antibodies. The immunoglobulins mediate a variety of these effector functions. Usually the ability to carry out a particular effector function requires that the antibody bind to its antigen.
Not every immunoglobulin will mediate all effector functions. Such effector functions include:

1. Fixation of complement - This results in lysis of cells and release of biologically active molecules.

2. Binding to various cell types - Phagocytic cells, lymphocytes, platelets, mast cells, and basophils have receptors that bind immunoglobulins. This binding can activate the cells to perform some function. Some immunoglobulins also bind to receptors on placental trophoblasts, which results in transfer of the immunoglobulin across the placenta.
As a result, the transferred maternal antibodies provide immunity to the fetus and newborn

III. BASIC STRUCTURE OF IMMUNOGLOBULINS

The basic structure of the immunoglobulins is Although different immunoglobulins can differ structurally, they all are built from the same basic units.

A. Heavy and Light Chains

All immunoglobulins have a four chain structure as their basic unit. They are composed of two identical light chains (23kD) and two identical heavy chains (50-70kD)

B. Disulfide bonds

1. Inter-chain disulfide bonds - The heavy and light chains and the two heavy chains are held together by inter-chain disulfide bonds and by non-covalent interactions The number of inter-chain disulfide bonds varies among different immunoglobulin molecules.

2. Intra-chain disulfide binds - Within each of the polypeptide chains there are also intra-chain disulfide bonds.

C. Variable (V) and Constant (C) Regions

When the amino acid sequences of many different heavy chains and light chains were compared, it became clear that both the heavy and light chain could be divided into two regions based on variability in the amino acid sequences.

These are the:

1. Light Chain - VL (110 amino acids) and CL (110 amino acids)

2. Heavy Chain - VH (110 amino acids) and CH (330-440 amino acids)

D. Hinge Region

This is the region at which the arms of the antibody molecule forms a Y. It is called the hinge region because there is some flexibility in the molecule at this point.

E. Domains

Three dimensional images of the immunoglobulin molecule show that it is not straight as depicted in figure 2A. Rather, it is folded into globular regions each of which contains an intrachain disulfide bond (figure 2B-D). These regions are called domains.

1. Light Chain Domains - VL and CL

2. Heavy Chain Domains - VH, CH1 - CH3 (or CH4)

F. Oligosaccharides

Carbohydrates are attached to the CH2 domain in most immunoglobulins. However, in some cases carbohydrates may also be attached at other locations.

Immunoglobulin classes

The immunoglobulins can be divided into five different classes, based on differences in the amino acid sequences in the constant region of the heavy chains. All immunoglobulins within a given class will have very similar heavy chain constant regions. These differences can be detected by sequence studies or more commonly by serological means (i.e. by the use of antibodies directed to these differences).

1. IgG - Gamma heavy chains
2. IgM - Mu heavy chains
3. IgA - Alpha heavy chains
4. IgD - Delta heavy chains
5. IgE - Epsilon heavy chains

STRUCTURE AND SOME PROPERTIES OF IG CLASSES AND SUBCLASSES

A. IgG

1. Structure

The structures of the IgG subclasses are presented in figure 7. All IgG's are monomers (7S immunoglobulin). The subclasses differ in the number of disulfide bonds and length of the hinge region.

2. Properties

IgG is the most versatile immunoglobulin because it is capable of carrying out all of the functions of immunoglobulin molecules.

a) IgG is the major Ig in serum - 75% of serum Ig is IgG

b) IgG is the major Ig in extra vascular spaces

c) Placental transfer - IgG is the only class of Ig that crosses the placenta. Transfer is mediated by a receptor on placental cells for the Fc region of IgG. Not all subclasses cross equally well; IgG2 does not cross well.

d) Fixes complement - Not all subclasses fix equally well; IgG4 does not fix complement

e) Binding to cells - Macrophages, monocytes, PMNs and some lymphocytes have Fc receptors for the Fc region of IgG. Not all subclasses bind equally well; IgG2 and IgG4 do not bind to Fc receptors. A consequence of binding to the Fc receptors on PMNs, monocytes and macrophages is that the cell can now internalize the antigen better.

The antibody has prepared the antigen for eating by the phagocytic cells. The term opsonin is used to describe substances that enhance phagocytosis. IgG is a good opsonin. Binding of IgG to Fc receptors on other types of cells results in the activation of other functions.

B. IgM

1. Structure

The structure of IgM is presented in figure 8. IgM normally exists as a pentamer (19S immunoglobulin) but it can also exist as a monomer. In the pentameric form all heavy chains are identical and all light chains are identical. Thus, the valence is theoretically 10. IgM has an extra domain on the mu chain (CH4) and it has another protein covalently bound via a S-S bond called the J chain. This chain functions in polymerization of the molecule into a pentamer.

2. Properties

a) IgM is the third most common serum Ig.

b) IgM is the first Ig to be made by the fetus and the first Ig to be made by a virgin B cells when it is stimulated by antigen.

c) As a consequence of its pentameric structure, IgM is a good complement fixing Ig. Thus, IgM antibodies are very efficient in leading to the lysis of microorganisms.

d) As a consequence of its structure, IgM is also a good agglutinating Ig . Thus, IgM antibodies are very good in clumping microorganisms for eventual elimination from the body.

e) IgM binds to some cells via Fc receptors.

f) B cell surface Ig

Surface IgM exists as a monomer and lacks J chain but it has an extra 20 amino acids at the C-terminus to anchor it into the membrane (figure 9). Cell surface IgM

functions as a receptor for antigen on B cells. Surface IgM is noncovalently associated with two additional proteins in the membrane of the B cell called Ig-alpha and Ig-beta as indicated in figure 10. These additional proteins act as signal transducing molecules since the cytoplasmic tail of the Ig molecule itself is too short to transduce a signal. Contact between surface immunoglobulin and an antigen is required before a signal can be transduced by the Ig-alpha and Ig-beta chains. In the case of T-independent antigens, contact between the antigen and surface immunoglobulin is sufficient to activate B cells to differentiate into antibody secreting plasma cells. However, for T-dependent antigens, a second signal provided by helper T cells is required before B cells are activated.

C. IgA

1. Structure

Serum IgA is a monomer but IgA found in secretions is a dimer as presented in Figure 11. When IgA exits as a dimer, a J chain is associated with it.

When IgA is found in secretions is also has another protein associated with it called the secretory piece or T piece; sIgA is sometimes referred to as 11S immunoglobulin. Unlike the remainder of the IgA which is made in the plasma cell, the secretory piece is made in epithelial cells and is added to the IgA as it passes into the secretions

The secretory piece helps IgA to be transported across mucosa and also protects it from degradation in the secretions.

2. Properties

a) IgA is the 2nd most common serum Ig.

b) IgA is the major class of Ig in secretions - tears, saliva, colostrum, mucus. Since it is found in secretions secretory IgA is important in local (mucosal) immunity.

c) Normally IgA does not fix complement, unless aggregated.

d) IgA can binding to some cells - PMN's and some lymphocytes.

D. IgD

1. Structure

The structure of IgD is presented in the Figure 13. IgD exists only as a monomer.

2. Properties

a) IgD is found in low levels in serum; its role in serum uncertain.

b) IgD is primarily found on B cell surfaces where it functions as a receptor for antigen. IgD on the surface of B cells has extra amino acids at C-terminal end for anchoring to the membrane. It also associates with the Ig-alpha and Ig-beta chains.

c) IgD does not bind complement.

E. IgE

1. Structure

The structure of IgE is presented in Figure 14. IgE exists as a monomer and has an extra domain in the constant region.

2. Properties

a) IgE is the least common serum Ig since it binds very tightly to Fc receptors on basophils and mast cells even before interacting with antigen.

b) Involved in allergic reactions - As a consequence of its binding to basophils an mast cells, IgE is involved in allergic reactions. Binding of the allergen to the IgE on the cells
results in the release of various pharmacological mediators that result in allergic symptoms.
c) IgE also plays a role in parasitic helminth diseases. Since serum IgE levels rise in parasitic diseases, measuring IgE levels is helpful in diagnosing parasitic infections.
Eosinophils have Fc receptors for IgE and binding of eosinophils to IgE-coated helminths results in killing of the parasite.
d) IgE does not fix complement.

CLINICAL IMPLICATIONS OF HUMAN IMMUNOGLOBULIN CLASSES

Adapted from:F.T. Fischbach in "A Manual of Laboratory Diagnostic Tests," 2nd Ed., J.B. Lippincott Co., Philadelphia, PA, 1984.

IgG

1. Increases in:

a) Chronic granulomatous infections
b) Infections of all types
c) Hyperimmunization
d) Liver disease
e) Malnutrition (severe)
f) Dysproteinemia
g) Disease associated with hypersensitivity granulomas, dermatologic disorders, and IgG myeloma
h) Rheumatoid arthritis

2. Decreases in:

a) Agammaglobulinemia
b) Lymphoid aplasia
c) Selective IgG, IgA deficiency
d) IgA myeloma
e) Bence Jones proteinemia
f) Chronic lymphoblastic leukemia

IgM

1. Increases (in adults) in:

a) Waldenström's macroglobulinemia
b) Trypanosomiasis
c) Actinomycosis
d) Carrión's disease (bartonellosis)
e) Malaria
f) Infectious mononucleosis
g) Lupus erythematosus
h) Rheumatoid arthritis
I) Dysgammaglobulinemia (certain cases)

Note: In the newborn, a level of IgM above 20 ng./dl is an indication of in utero stimulation of the immune system and stimulation by the rubella virus, the cytomegalovirus, syphilis, or toxoplasmosis.

2. Decreases in:
a) Agammaglobulinemia
b) Lymphoproliferative disorders (certain cases)
c) Lymphoid aplasia
d) IgG and IgA myeloma
e) Dysgammaglobulinemia
f) Chronic lymphoblastic leukemia

IgA

1. Increases in:
a) Wiskott-Aldrich syndrome
b) Cirrhosis of the liver (most cases)
c) Certain stages of collagen and other autoimmune disorders such as rheumatoid arthritis and lupus erythematosus
d) Chronic infections not based on immunologic deficiencies
e) IgA myeloma

2. Decreases in:
a) Hereditary ataxia telangiectasia
b) Immunologic deficiency states (e.g., dysgammaglobulinemia, congenital and acquired agammaglobulinemia, and hypogammaglobulinemia)
c) Malabsorption syndromes
d) Lymphoid aplasia
e) IgG myeloma
f) Acute lymphoblastic leukemia
g) Chronic lymphoblastic leukemia

IgD

1. Increases in:
a) Chronic infections
b) IgD myelomas

IgE

1. Increases in:
a) Atopic skin diseases such as eczema
b) Hay fever
c) Asthma
d) Anaphylactic shock
e) IgE-myeloma

2. Decreases in:
a) Congenital agammaglobulinemia
b) Hypogammaglobulinemia due to faulty metabolism or synthesis of immunoglobulins

REFERENCES:

1.Immunology By P.Lydyard
2.Wikipedia Websource
3.Shodhganga Websource