Immune System

Much progress has been made over the last several decades in unraveling the complex nature of our immune system. The ability of our immune system to protect us is dependent upon the ability of immune cells to communicate with one another in order to coordinate activities. Cells are able to communicate with one another through cell-to-cell contact or by secreting small signaling proteins called cytokines. Cell-to-cell contact and/or reaction to cytokines is mediated through a diverse variety of membrane bound receptors and ligands that are expressed on the surface of the cell at the right moment. Ligands are molecules that bind to receptors initiating a signal. Literally hundreds of these receptors and ligands have been identified by immunologists all over the world. Today each receptor is referenced using an international language called the "Cluster of Differentiation" or CD. A number identifying the order in which the receptor was discovered follows the letters CD. For example, all T lymphocytes express the receptor CD3. However, a special type of T lymphocyte called a "Helper" T Cell, also expresses the receptor referred to as CD4.

Key Elements of Immunity

Before examining the specifics of oral infections and the host response, several key elements involved in immunity will be summarized. In higher animals, resistance to a pathogen includes a non-adaptive, non-specific or innate response (natural immunity) and an adaptive or acquired response, which act in concert to protect the host. A simple way to remember this is to consider innate immunity as what you are born with. The innate response occurs in the same way and to the same extent regardless of how many times a pathogen is encountered. In contrast, an adaptive or acquired response occurs after a pathogen comes into contact with the host and a "specific response" to that pathogen is developed and stored in a memory bank for any future contact. On second contact with the pathogen, a more rapid and heightened immune response ensues to eliminate it.

Innate immunity includes the following component parts:

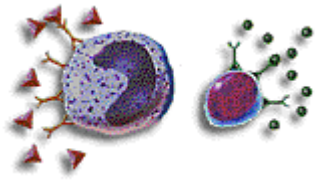
- External barriers such as skin, oral mucosa, body secretions and even endogenous (normal) microbial inhabitants
- Physiological factors as body pH and temperature
- Blood and tissue leukocytes (neutrophils, monocytes, macrophages, mast cells, basophils, eosinophils and natural killer cells)
- Dendritic cells for immune surveillance and antigen presentation
- Primary and secondary lymphoid tissue
- Soluble mediators of inflammation including acute phase proteins, complement and cytokines

The adaptive or acquired immune response system is mediated by T and B lymphocytes which are commonly referred to as T Cells and B Cells. There are three important characteristics to adaptive immunity:

- Self-recognition (or recognition of non-self)
- Specificity
- Memory

Three Important Characteristics to Adaptive Immunity

Self-Recognition



In healthy, immune competent individuals, immune responses are not produced against "*self*"-components. In vertebrates, Major Histocompatibility Complexes (MHC) exist that allow for differentiation between self and non-self antigens. In humans it is called the Human Leukocyte Antigen System (HLA) and it is responsible for genetically encoding our cells for recognition by the Immune System as either self or non-self.

Nucleated cells express MHC Class I genes, whereas a subgroup of immune cells called antigen presenting cells (APCs) express MHC Class II genes. In a healthy cell, a MHC Class I molecule coupled with one of the cell's peptides is expressed at the cell surface. This complex acts as a signal to circulating Natural Killer lymphocytes or cytotoxic T cells not to attack. However, if that cell is invaded by a pathogen, the MHC Class I molecule couples to a non-self peptide of the pathogen which then signals the cytotoxic lymphocytes to attack and destroy the cell. Tissue cells that undergo malignant transformation may also express peptides with the MHC Class I molecules that are no longer recognized as self; thus promoting the destruction of these cancerous cells.

Specificity

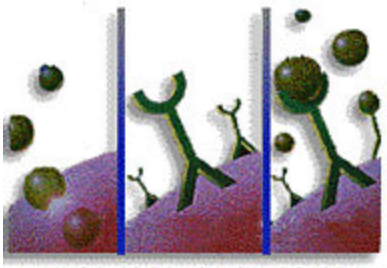
This property refers to the ability of the immune system to recognize non-self antigens and respond in a specific manner to them, rather than responding in a random manner. Specificity is initiated by Antigen Presenting Cells such as activated T Cells, B Cells, macrophages, dendritic cells and thymic epithelial cells. The APCs express MHC Class II molecules at their surface, which are coupled to antigenic peptides. When this antigenic peptide is presented to a T cell, the T cell becomes activated and in turn helps stimulate B cells to proliferate and differentiate into Plasma Cells which make antibodies "specific" to that antigen only. When the body encounters the measles virus, for example, and responds to it, it does not respond against all other viruses.

Response to one organism does not give protection against another unrelated organism.

Memory

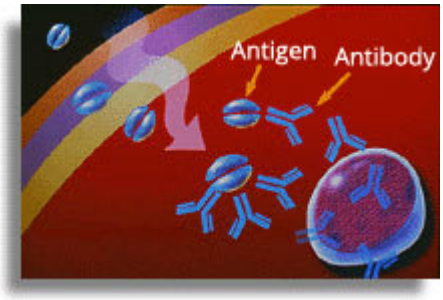
The initial contact with a molecule eliciting an immune response (antigen) leaves an imprint of information. With the help of the activated T cell, B cells also produce memory cells with antigen-specific antibodies expressed on their surface as B cell Receptors. These memory cells live for a longer period of time and, on second contact with an antigen, can respond more robustly and more quickly to eliminate it. We rarely suffer twice from measles, mumps, etc. The first contact imprints "*memory*" so that the body repels the next invasion.

Vaccines are synthetic forms or processed natural antigens used to stimulate the production of antibodies. Every time that antigen invades the body, the body remembers (memory), and an appropriate and specific response is produced by the host immune cells and antibodies.



Cells are imprinted with memory from previous contact with antigen (e.g. infectious agent)

Immunogens and Antigens



Foreign material, including microorganisms, can contain chemical groups recognizable by the body as foreign. In general terms, molecules of any chemical group that elicit an immune response are termed immunogens. More specifically, a molecule that is capable of ***gen***erating an ***anti***body is termed an ***antigen***. Antigenicity is determined by areas on the molecule termed antigenic determinants or epitopes. If a microorganism bypasses the body's other defenses, the immune system will produce a specific response that is directed against a particular antigenic epitope of this microorganism.

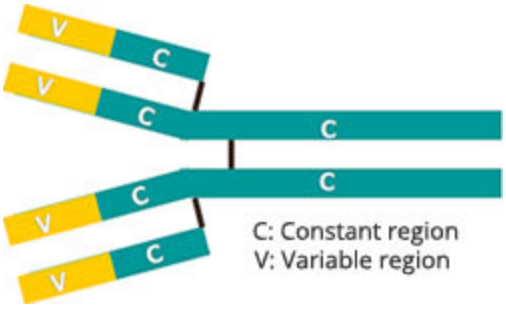
Most antigens are pure proteins, glycoproteins or lipoproteins. T Cells recognize the small peptides of proteins but not polysaccharides or nucleic acids. An Antigen Presenting Cell (APC) can present one of these antigenic peptides to the T Cell, thereby activating it. The activated T cell will in turn join to a B Cell stimulating it to differentiate into a Plasma Cell, which will produce specific antibodies to that particular antigen. This type of antigen that requires a T Cell to B Cell interaction for antibody production to occur is referred to as a T-dependent antigen. On the other hand, B Cells can express antibodies on their surface membrane, which are called B Cell Receptors (BCR). These receptors recognize not only proteins, but also polysaccharides and nucleic acids. These latter molecules are large and contain several different antigenic epitopes each of which can cross-link the membrane bound cell receptors (antibodies) on different clones of B Cells stimulating each cell to produce an antibody to one of the epitopes. This pathway is referred to Polyclonal B Cell stimulation. Since these antigens do not require a T Cell to B Cell interaction in order to produce antibodies, they are referred to as T-independent antigens. Examples include bacterial polysaccharides such as Lipopolysaccharide (LPS), a virulent product of many gram-negative bacteria.

Immunoglobulins

Immunoglobulins (Ig) are gamma globulin proteins present in bodily fluids (e.g. blood serum) and mucosal secretions (e.g., saliva, tears, vaginal secretions), and may also be found at the site of inflammation within the tissue. They are produced by plasma cells, which are differentiated B lymphocytes or B cells. Based on structure and protein composition, immunoglobulins are divided into five classes, two of which are further sub classified. Each has its own distinct chemical structure and specific biological function.

Typical Immunoglobulin Structure

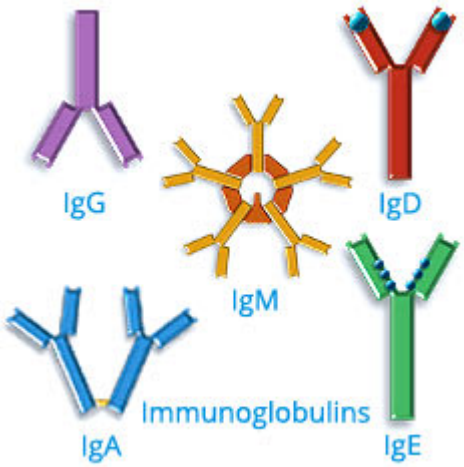
The immunoglobulin molecule is composed of a Constant region and Variable regions.

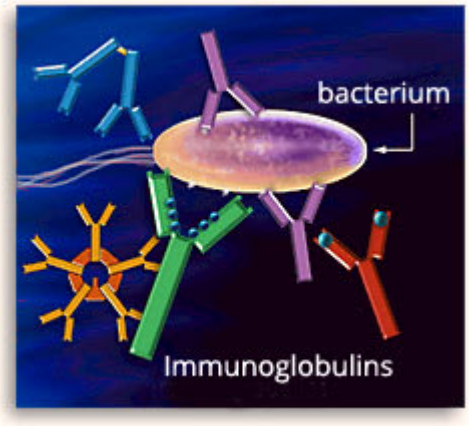


The Constant region generally is unique to the Ig Class or Ig Subclass and confers its biologic activity. The Variable regions form a complex, conformational molecular arrangement for the attachment of each specific antigen.

Five Classes [subclasses] of Immunoglobulins

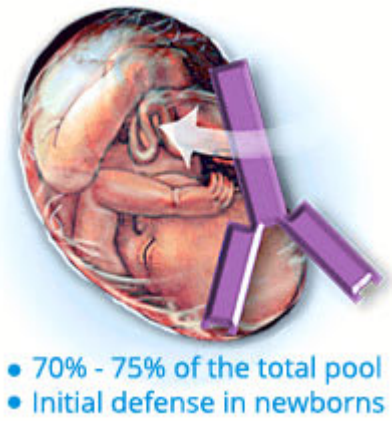
- Immunoglobulin G (IgG) [subclass IgG1, IgG2, IgG3, IgG4]
- Immunoglobulin A (IgA) [subclass IgA1, IgA2]
- Immunoglobulin M (IgM)
- Immunoglobulin D (IgD)
- Immunoglobulin E (IgE)





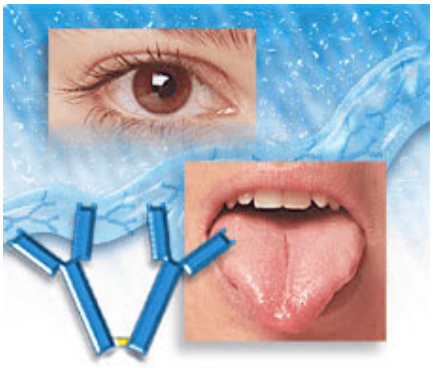
The five classes [subclasses] of immunoglobulins include:

IgA



Immunoglobulin G is the main immunoglobulin present in the blood and represents 70% to 75% of the total immunoglobulin pool. Several forms (subclasses) of IgG cross the placental barrier and are responsible for defense against infection in the first few months of a baby's life.

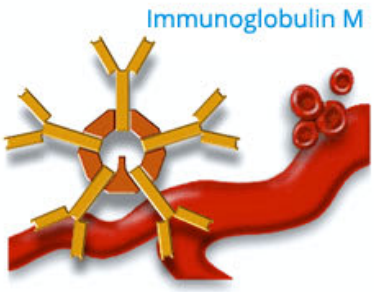
IgA



Immunoglobulin A (secretory)

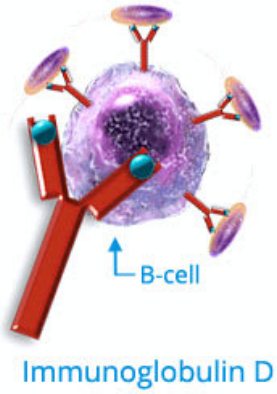
Immunoglobulin A provides localized antibody protection on mucosal surfaces. It is found in mucosal secretions such as saliva, tears, sweat, nasal fluids, fluids of the lung and colostrum, genito-urinary tract, and gastro-intestinal tract. It is a primary defense against microorganisms attacking exposed mucosal surfaces. IgA functions by preventing the microorganism from adhering to, and penetrating, the mucosal epithelial lining.

IgM



Immunoglobulin M is the major immunoglobulin present on the surface of immature B cells and is effective against microbes by binding with complement and causing agglutination and bacteriolysis. It is the first immunoglobulin to take part in the immune response and plays an important role in controlling bacteria that find their way into the blood stream (bacteremia).

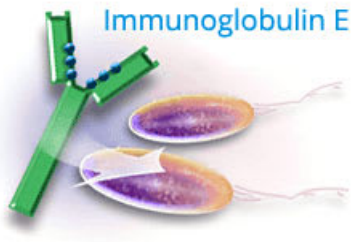
IgD



Immunoglobulin D

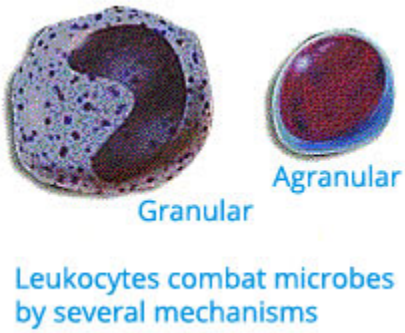
Immunoglobulin D is a trace antibody in the serum and is present on the surface of B cells. It may be involved in stimulating and suppressing these antibody producing cells in the manufacture of antibodies.

IgE



Immunoglobulin E is found in very low concentration in human serum, but it increases during allergic reactions and some parasitic infections. IgE is bound to high affinity membrane receptors (FceRI) on mast cells in the tissue and basophils in the blood. Cross-linking of cell bound IgE by an allergen elicits the release of inflammatory mediators like histamine and several cytokines. IgE is also the main immunoglobulin responding to infection caused by certain parasites.

Blood Leukocytes



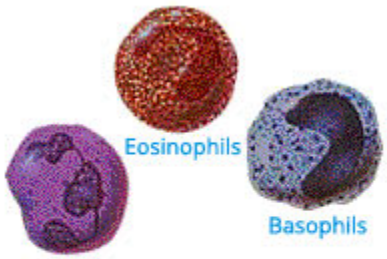
Leukocytes combat microbes by several mechanisms

White blood cells, or leukocytes, can be classified into five major categories based on morphological and functional characteristics. They may also be classified as granular or agranular based on the presence or lack of granules (small particles) within the cell cytoplasm. Leukocytes defend against invading microorganisms either by stimulating specific cellular or humoral (antibody production) immune responses, or by phagocytosis.

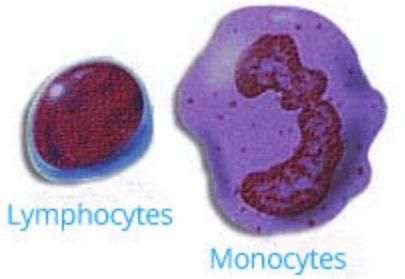
There are three types of granular leukocytes (granulocytes):

1. Neutrophils or polymorphonuclear leukocytes (PMNs)
2. Eosinophils
3. Basophils

Their names reflect the staining characteristics of the granules present in their cytoplasm. The name polymorphonuclear leukocyte also refers to the number of lobes comprising the nucleus of that cell type.



Neutrophils or polymorphonuclear (PMNs) leukocytes



Monocytes, the fourth group of leukocytes, have few granules and a typically kidney-shaped nucleus. In tissue, monocytes become macrophages. Macrophages are capable of surviving months to years thereby providing important immune surveillance within the tissue of the various organ systems.

The last major group of leukocytes includes the lymphocytes. They are agranular round cells, with a proportionally large nucleus. Lymphocytes are primarily responsible for adaptive or acquired immunity.

Granulocytes

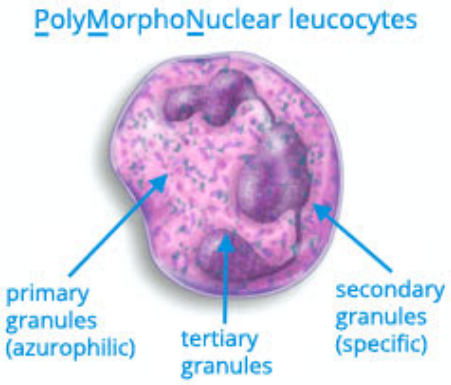
Neutrophils or PMNs are generally the first cells to migrate to the site of an invading microorganism or the site of trauma. This directed migration (chemotaxis) is caused by the release of signaling molecules called chemokines which can be released by several different cell types at the site of inflammation. The PMNs eliminate invaders by phagocytosis and other mechanisms. PMNs comprise 50-70% of the circulating leukocytes and more than 90% of the circulating granulocytes.

PMN's have three types of granules:

1. The primary or azurophilic granules are lysosomes that contain powerful digestive enzymes including acid hydrolases, elastase, myeloperoxidase and other proteins such as lysozyme and defensins.

2. Secondary or specific granules contain lactoferrin, lysozyme, collagenase and other proteins.

3. Tertiary granules contain gelatinase and other enzymes.



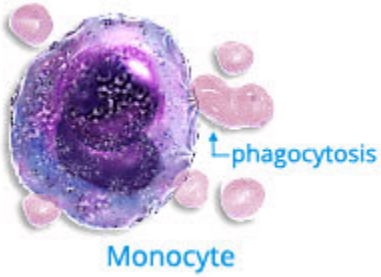
Eosinophils are involved in defense against parasitic infections and in control of allergic (hypersensitivity) reactions. Eosinophils comprise 1% to 3% of blood leukocytes.

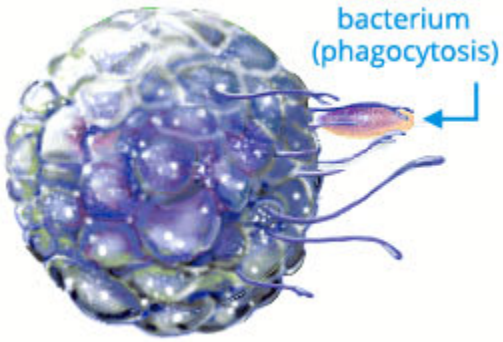
Circulating basophils comprise less than 1% of leukocytes. Granules in basophils contain heparin, histamine, and serotonin. When these (and other) chemicals are released from the cell, they cause an acute inflammatory response, which is why they are collectively called mediators of inflammation. Basophils are related to mast cells, which are found in the tissues only. Mast cells and basophils are the cells involved in immediate hypersensitivity (Type I) reactions (anaphylaxis).

Monocytes - Macrophages

Monocytes, which constitute 3-7% of leukocytes, are usually the second cell type to move to the site of injury or inflammation. Monocytes, like PMNs, can eliminate pathogens and debris by phagocytosis. After leaving the circulation, monocytes develop into tissue macrophages.

Macrophages are active against infectious agents by phagocytosis. They are also important antigen presenting cells that take up antigen and, after processing, present the antigen to lymphocytes. Thus, macrophages can help orchestrate the immune response.





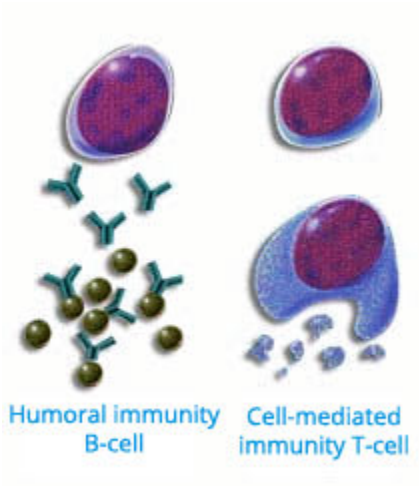
Lymphocytes

Lymphocytes comprise about 30% of the circulating leukocytes. Lymphocytes are involved in the development of adaptive or acquired immune responses. There are two major types of lymphocytes: T-cells and B-cells, both having surface receptors for antigen.

The Antigen-Antibody Reaction

When an antigen enters the body, two types of adaptive immune responses can occur:

- The synthesis and release of free antibody into the blood and other body fluids, called Humoral Immunity, is provided by B-cells.
- The production of sensitized lymphocytes called T-cells that are effectors of Cell-mediated Immunity.



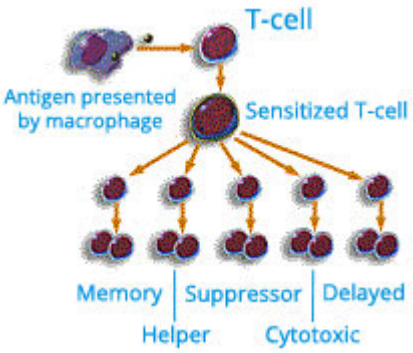
Cellular Immunity involving T-cells is effective against fungi, many parasites, intracellular bacteria, most viruses, cancer cells, and surgically transplanted or transfused foreign tissues. This is the type of response associated with graft rejection in transplant cases, and also with transfusion incompatibility.

Humoral Immunity, through circulating antibodies, is effective against extracellular organisms, including bacteria, some parasites, and some viruses.

Lymphocytes are produced in bone marrow from stem cells. A portion of the lymphocytic precursor cell population migrates to the thymus to mature into T-cells, while others are processed in the bone marrow to become B-cells. It should be mentioned that at 8-9 weeks of fetal development, B cells form in the liver but, soon after, the bone marrow becomes the primary site of production. The thymus gland and bone marrow are considered primary lymphoid organs while peripheral lymph nodes, mucous associated lymphoid tissue and the spleen are considered secondary lymphoid organs.

Maturity of T and B Cells

The T Cell:
T-cells mature in the thymus gland or in the lymph nodes. Since the thymus is only 10-15% functional in the adult, the lymph nodes take on greater importance in the maturation process.



Thymus Gland: T Cells migrating to the Thymus gland from the bone marrow will undergo a process of selection to eliminate not only the weakest cells, but also those so strong that they may attack healthy tissue cells (autoimmunity). Cells educated in the Thymus generally are either Helper (CD4+) or Suppressor/Cytotoxic (CD8+) cells. Other types of T-helper cells include T-helper 17, T regulatory cells, and T follicular helper cells.

Lymph Node: Naïve T cells in the paracortex of the lymph node may be activated by dendritic cells that have internalized and processed pathogenic antigens that made their way to the lymph node via lymphatic drainage from the site of infection or inflammation; or, by dendritic cells that have migrated to the lymph node from the site of infection. Once activated, T cells undergo clonal expansion and differentiate into functional effector cells (short-lived) or memory effector cells (long-lived). Functional effector cells migrate to the site of infection or inflammation where they orchestrate T helper (CD4+) or T cytotoxic/suppressor (CD8+) functions to combat pathogens. Memory cells may enter the circulation or healthy tissue sites, or remain in the lymph node.

The B Cell: B cells mature in the bone marrow or in the lymph node.

Bone Marrow: Mature B cells express antibodies on their surface, which are specific for a particular antigen. The antibodies are expressed on the cell surface and are primarily IgM with some IgD. These cells circulate in the blood or home to sites of infection or inflammation. However, until they are activated by T-cells, they do not proliferate or differentiate to form antibody producing Plasma Cells.

Lymph Node: Antigen-dependent B cells in the cortex of the lymph node may be stimulated by Helper T cells to proliferate and differentiate into Plasma Cells and memory cells. Immunoglobulin (antibody) class switching of the B cell from IgM to IgG, IgA or IgE may also take place as a result of the T cell interaction.

Learning Objectives

Upon completion of this topic, you should be able to:

- Define innate and adaptive or acquired immunity.
- Describe principal components of innate and acquired immunity.
- Compare and contrast the five classes of immunoglobulins.
- Name the major types of leukocytes.
- Discuss the origin, maturation, and function of T-cells and B-cells.