Lec.2

Innate Immunity

Immunology: is the study of our protection from foreign macromolecules or invading organisms and our responses to them. These invaders include viruses, bacteria, protozoa or even larger parasites.

Our first lines of defence against foreign organisms are barrier tissues such as the skin that stop the entry of organism into our bodies. If, however, these barrier layers are penetrated, the body contains cells that respond rapidly to the presence of the invader. These cells include macrophages and neutrophils that engulf foreign organisms and kill them without the need for antibodies. Immediate challenge also comes from soluble molecules that deprive the invading organism of essential nutrients (such as iron) and from certain molecules that are found on the surfaces of epithelia, in secretions (such as tears and saliva) and in the blood stream. This form of immunity is the innate or non-specific immune system that is continually ready to respond to invasion.

A second line of defence is the specific or adaptive immune system which may take days to respond to a primary invasion. In the specific immune system, we see the production of antibodies (soluble proteins that bind to foreign antigens) and cell-mediated responses in which specific cells recognize foreign pathogens and destroy them. In the case of viruses or tumors, this response is also vital to the recognition and destruction of virally-infected or tumorigenic cells.

The response to a second round of infection is often more rapid than to the primary infection because of the activation of memory B and T cells. We shall see how cells of the immune system interact with one another by a variety of signal molecules so that a coordinated response may be mounted. These signals may be proteins such as lymphokines which are produced by cells of the lymphoid system, cytokines and chemokines that are produced by other cells in an immune response, and which stimulate cells of the immune system.

Although the innate and adaptive immune systems both function to protect against invading organisms, they differ in a number of ways. The adaptive immune system requires some time to react to an invading organism, whereas the innate immune system includes defences that, for the most part, are constitutively present and ready to be mobilized upon infection. Second, the adaptive immune system is antigen specific and reacts only with the organism that induced the response. In contrast, the innate system is not antigen specific and reacts equally well to a variety of organisms. Finally, the adaptive immune system demonstrates immunological memory. It

“remembers” that it has encountered an invading organism and reacts more rapidly on subsequent exposure to the same organism. In contrast, the innate immune system does not demonstrate immunological memory

Non-Specific Immune System

The elements of the non-specific (innate) immune system include anatomical barriers, secretory molecules and cellular components. Among the mechanical anatomical barriers are the skin and internal epithelial layers, the movement of the intestines and the oscillation of broncho-pulmonary cilia. Associated with these protective surfaces are chemical and biological agents.

A. Anatomical barriers to infections

1. Mechanical factors

The epithelial surfaces form a physical barrier that is very impermeable to most infectious agents. Thus, the skin acts as our first line of defence against invading organisms. The desquamation of skin epithelium also helps remove bacteria and other infectious agents that have adhered to the epithelial surfaces.

Movement due to cilia or peristalsis helps to keep air passages and the gastrointestinal tract free from microorganisms. The flushing action of tears and saliva helps prevent infection of the eyes and mouth. The trapping affect of mucus that lines the respiratory and gastrointestinal tract helps protect the lungs and digestive systems from infection.

2. Chemical factors

Fatty acids in sweat inhibit the growth of bacteria. Lysozyme and phospholipase found in tears, saliva and nasal secretions can breakdown the cell wall of bacteria and destabilize bacterial membranes. The low pH of sweat and gastric secretions prevents growth of bacteria. Defensins (low molecular weight proteins) found in the lung and gastrointestinal tract have antimicrobial activity. Surfactants in the lung act as opsonins (substances that promote phagocytosis of particles by phagocytic cells).

3. Biologicalfactors

The normal flora of the skin and in the gastrointestinal tract can prevent the colonization of pathogenic bacteria by secreting toxic substances or by competing with pathogenic bacteria for nutrients or attachment to cell surfaces.

B. Humoral barriers to infection

The anatomical barriers are very effective in preventing colonization of tissues by microorganisms. However, when there is damage to tissues the anatomical barriers are breached and infection may occur. Once infectious agents have penetrated tissues, another innate defence mechanism comes into play, namely acute inflammation. Humoral factors play an important role in inflammation, which is characterized by oedema and the recruitment of phagocytic cells.
These humoral factors are found in serum or they are formed at the site of infection.

1. Complement system – The complement system is the major humoral non-specific defence mechanism. Once activated complement can lead to increased vascular permeability, recruitment of phagocytic cells, and lysis and opsonization of bacteria.

2. Coagulation system – Depending on the severity of the tissue injury, the coagulation system may or may not be activated. Some products of the coagulation system can contribute to the non-specific defences because of their ability to increase vascular permeability and act as chemotacic agents for phagocytic cells. In addition, some of the products of the coagulation system are directly antimicrobial. For example, beta-lysin, a protein produced by platelets during coagulation can lyse many Gram positive bacteria.
3. Lactoferrin and transferrin – By binding iron, an essential nutrient for bacteria, and these proteins limit bacterial growth.
4. Interferon – Interferon are proteins that can limit virus replication in cells.
5. Lysozyme – Lysozyme breaks down the cell wall of bacteria.
6. Interleukin-1 – (IL-1) induces fever and the production of acute phase proteins, some of which are antimicrobial because they can opsonize bacteria.

C. Cellular barriers to infection

Part of the inflammatory response is the recruitment of polymorphonuclear eosinophiles and macrophages to sites of infection. These cells are the main line of defence in the non-specific immune system.

1. Neutrophils – Polymorphonuclear cells (PMNs) are recruited to the site of infection where they phagocytose invading organisms and kill them intracellularly. In addition, PMNs contribute to collateral tissue damage that occurs during inflammation.

2. Macrophages – Tissue macrophages and monocytes , which differentiate into macrophages, also function in phagocytosis and intracellular killing of microorganisms. In addition, macrophages are capable of extracellular killing of infected or altered self target cells. Furthermore, macrophages contribute to tissue repair and act as antigen-presenting cells, which are required for the induction of specific immune responses.

3. Natural killer (NK) and lymphokine activated killer (LAK) cells – NK and LAK cells can non-specifically kill virus infected and tumor cells. These cells are not part of the inflammatory response but they are important in nonspecific immunity to viral infections and tumor surveillance.

4. Eosinophils – Eosinophils have proteins in granules that are effective in killing certain parasites.

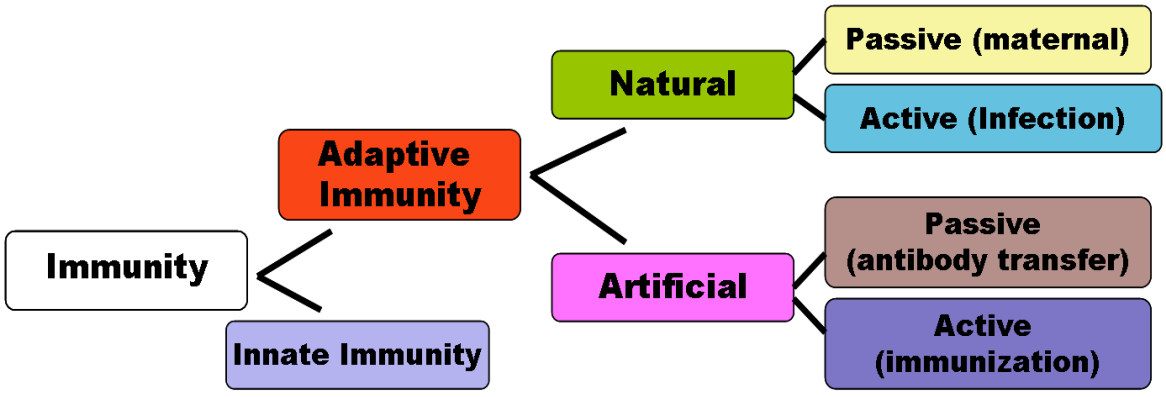
Specific Immune System

Adaptive immunity is often sub-divided into two major types depending on how the immunity was introduced. **Naturally acquired immunity** occurs through contact with a disease causing agent, when the contact was not deliberate, whereas **artificially acquired immunity** develops only through deliberate actions such as vaccination. Both naturally and artificially acquired immunity can be further subdivided depending on whether immunity is induced in the host or passively transferred from an immune host.

Passive immunity is acquired through transfer of antibodies or activated T-cells from an immune host, and is short lived, usually lasts only a few months, whereas **active immunity** is induced in the host itself by antigen, and lasts much longer, sometimes life-long. The diagram below summarizes these divisions of immunity.

A further subdivision of adaptive immunity is characterized by the cells involved; humoral immunity is the aspect of immunity that is mediated by secreted antibodies,

Whereas the protection provided by cell mediated immunity involves T-lymphocytes alone humoral immunity is active when the organism generates its own antibodies and passive when antibodies are transferred between individuals. Similarly, cell mediated immunity is active when the organisms' own T-cells are stimulated and passive when T cells come from another organism.



Passive immunity is the transfer of active immunity, in the form of readymade antibodies, from one individual to another. Passive immunity can occur naturally, when maternal antibodies are transferred to the fetus through the placenta, and can also be induced artificially, when high levels

of human (or horse) antibodies specific for a pathogen or toxin are transferred to non- immune individuals. Passive immunization is used when there is a high risk of infection and insufficient time for the body to develop its own immune response, or to reduce the symptoms of ongoing or immunosuppressive diseases. Passive immunity provides immediate protection, but the body does not develop memory, therefore the patient is at risk of being infected by the same pathogen later.

Naturally acquired passive immunity

Maternal passive immunity is a type of naturally acquired passive immunity, and refers to antibody-mediated immunity conveyed to a fetus by its mother during pregnancy. Maternal antibodies (MatAb) are passed through the placenta to the fetus by an FcRn receptor on placental cells.

This occurs around the third month of gestation. IgG is the only antibody isotype that can pass through the placenta. Passive immunity is also provided through the transfer of IgA antibodies found in breast milk that are transferred to the gut of the infant, protecting against bacterial infections, until the newborn can synthesize its own antibodies.

Artificially acquired passive immunity

Artificially acquired passive immunity is a short-term immunization induced by the transfer of antibodies, which can be administered in several forms; as human or animal blood plasma, as pooled human immunoglobulin for intravenous (IVIG) or intramuscular (IG) use, and in the form of monoclonal antibodies (MAb). Passive transfer is used prophylactically in the case of immunodeficiency diseases, such as hypogammaglobulinemia. It is also used in the treatment of several types of acute infection, and to treat poisoning. Immunity derived from passive immunization lasts for only a short period of time, and there is also a potential risk for hypersensitivity reactions, and serum sickness, especially from gamma globulin of non-human origin.

The artificial induction of passive immunity has been used for over a century to treat infectious disease, and prior to the advent of antibiotics, was often the only specific treatment for certain infections. Immunoglobulin therapy continued to be a first line therapy in the treatment of severe respiratory diseases until the 1930’s, even after sulfonamide antibiotics were introduced.

Passive transfer of cell-mediated immunity

Passive or "adoptive transfer" of cell-mediated immunity, is conferred by the transfer of "sensitized" or activated T-cells from one individual into another. It is rarely used in humans because it requires histocompatible (matched) donors, which are often difficult to find. In unmatched donors this type of transfer carries severe risks of graft versus host disease. It has, however, been used to treat certain diseases including some types of cancer and immunodeficiency. This type of transfer differs from a bone marrow transplant, in which (undifferentiated) hematopoietic stem cells are transferred.

Active immunity

The time course of an immune response. Due to the formation of immunological memory, reinfection at later time points leads to a rapid increase in antibody production and effectors T cell activity. These later infections can be mild or even in apparent.

When Bcells and T cells are activated by a pathogen, memory B-cells and T-cells develop. Throughout the lifetime of an animal these memory cells will “remember” each specific pathogen encountered, and are able to mount a strong response if the pathogen is detected again. This type of immunity is both *active* and *adaptive* because the body's immune system prepares itself for future challenges. Active immunity often involves both the cell-mediated and humoral aspects of immunity as well as input from the innate immune system. The *innate system* is present from birth and protects an individual from pathogens regardless of experiences, whereas adaptive immunity arises only after an infection or immunization and hence is "acquired" during life.

Naturally acquired active immunity

Naturally acquired active immunity occurs when a person is exposed to a live pathogen, and develops a primary immune response, which leads to immunological memory. This type of immunity is “natural” because it is not induced by deliberate exposure. Many disorders of immune system function can affect the formation of active immunity such as immunodeficiency (both acquired and congenital forms) and immunosuppression.

Artificially acquired active immunity

Artificially acquired active immunity can be induced by a vaccine, a substance that contains antigen. A vaccine stimulates a primary response against the antigen without causing symptoms of the disease. The term vaccination was coined by Edward Jenner and adapted by Louis Pasteur for his pioneering work in vaccination. The method Pasteur used entailed treating the infectious agents for those diseases so they lost the ability to cause serious disease. Pasteur adopted the name vaccine as a generic term in honor of Jenner's discovery, which Pasteur's work built upon.