

Unit 4 Lecture 9

Specific Body Defenses

As stated earlier, a non-specific body defense is any defense that protects against a variety of invaders. A specific body defense is defense directed against a single kind of invader of the body. Specific body defense involves the formation of antibodies in response to the presence of a single antigen. Specific body defense is the **third line of defense**. Lymphocytes are exclusively responsible for production of antibodies. Non-specific defenses in turn complete actions that destroy the antigens.

An antigen is defined as a chemical with the potential to stimulate lymphocytes to produce antibodies. Antigens are characterized by usually being foreign or "non-self" molecules, except alloantigens and isoantigens. They are macromolecules with formula weights of 10,000 daltons or more. Smaller molecules are haptens, which become antigens when combined with proper proteins. They may be single molecules (simple antigens). Antigens are usually a protein or protein and a polysaccharide or lipid. Rarely are they a nucleic acid. In bacteria, they can be used to serologically type organisms. The cell wall components form "O" antigen, the capsular components form the "K" antigen, and the flagellar components form the "H" antigens, i.e. *Escherichia coli* O157:H7. Cell membrane components form the ABO or blood typing antigens.

Antibodies are proteins that are produced by lymphocytes in response to the presence of an antigen. Antibodies are macromolecules with formula weights in excess of 150,000 daltons. They are found as gamma globulins (immunoglobulins that circulate in the body) or on cell membranes of basophils & T-lymphocytes. Their basic structure is that of two light chains and two heavy chains. Variation in light chains accounts for "specificity" of antibodies.

Classes of immunoglobulins include IgG, IgM, IgA, IgE, and IgD. IgG antibodies are the most abundant immunoglobulin (80-85% of all immunoglobulins in a healthy individual). They are the only antibody group known to cross placenta. They cause agglutination and initiation of the complement cascade when reacted with antigen. IgM antibodies (5-13%) are the largest immunoglobulin, the first antibody to appear in infections, and cause agglutination and complement cascade when reacted with antigen. They are most effective against Grain-negative cells and are needed for seroconversion. IgA antibodies (10-13%) are the second most abundant immunoglobulin. They are found associated with mucous membranes and are secreted onto membranes when antigens are present. IgE antibodies are found attached to basophils and mast cells after production by lymphocytes. They cause histamine release when reacted with antigen and are present in allergic or helminth infections. IgD immunoglobulins are the least abundant

immunoglobulin class and are found on the surface of competent B-cells to possibly trigger IgG release.

There are two types of lymphocytes, B-lymphocytes and T-lymphocytes. B-lymphocytes are responsible for "humoral immunity" or antibody production and are "thymus independent". They develop from stem cells in fetus and are believed to develop in red bone marrow. They live and reproduce in lymphoid tissue and become "plasma cells" and "memory cells" when functional. Antibodies are released into blood stream circulate freely, attacking mainly prokaryotic or chemical antigens such as bacterial exotoxins, extracellular bacteria, extracellular viruses. They destroy antigens via the complement cascade.

T-lymphocytes are responsible for "cell-mediated" or "thymus dependent" immunity. They develop from stem cells in fetus and specialize in the thymus gland. They live and reproduce in lymphoid tissue and exist in several functional forms. T_H cells, "Helper" T-cells, are needed to present antigen to any lymphocyte before it can manufacture antibodies. T_C cells, cytotoxic or "Killer" T-cells, destroy eukaryotic cells, which have been recognized, directly. T_D cells, "Delayed hypersensitivity" T-cells, have several functions in inflammation, chemotaxis, and phagocytosis. Their response is noted after 72 hours (skin test for TB). T_S cells, "Suppressor" cells, control the intensity of immune response. T_{regs} recently identified function in preventing autoimmune reactions. They also help the body resist repeat infections, protect the "good" bacteria of the gut and aid in sustaining pregnancy. T-lymphocytes attack antigens that are primarily part of eukaryotic cell structure (Protozoans, fungi, large parasites, transplanted tissues, tumors, cells with intracellular bacteria or viruses).

Comparisons/contrasts of forms of immune response.

Humoral immunity	Cell-mediated immunity
<p>Afferent phase</p> <ul style="list-style-type: none"> ▪ Entry of antigen ▪ Entrapment by macrophage ▪ Antigen presented to T_H cell 	<p>Afferent phase</p> <ul style="list-style-type: none"> ▪ Entry of antigen ▪ Entrapment by macrophage ▪ Antigen presented to T_H cell
<p>Central phase</p> <ul style="list-style-type: none"> ▪ B cells sensitized ▪ Clones of B cells form ▪ B cells convert to plasma cells ▪ Retention of B "memory" cells in lymph tissue 	<p>Central phase</p> <ul style="list-style-type: none"> ▪ T cells sensitized ▪ Clones of T cells form ▪ T cells differentiate to $T_C, T_S,$ & T_D ▪ Retention of T "memory" cells in lymph tissue

Effector phase	Effector phase
<ul style="list-style-type: none"> Plasma cells secrete immunoglobulins Immunoglobulins react with antigens anywhere blood or tissue fluid is found Elicit all responses of the classes of immunoglobulins 	<ul style="list-style-type: none"> T cells carrying receptors go via blood to site of antigen Receptors on T cells react with antigens only where activated T-cells are found Elicit all responses of T_C & T_D cells

Types of Immunity

Innate or native immunity means that there is a natural resistance to the microbe. It is genetic in nature and can be species or individual specific. Acquired immunity comes from contact with a microbe or virus either through an infection or by artificial means. The types of acquired immunity are active or passive, natural or artificial. Combining two of the terms demonstrates the different types that can exist. Natural active immunity is acquired by contracting the disease. In most cases it gives lifelong protection. Artificial active immunity is the basis of vaccination. It is acquired through injection or ingestion of an antigen and tries to create lifelong protection. Because of the variation in degree of response, boosters are usually required at some point ([anamnestic response](#)). See your text for the antigenic categories. Natural passive is acquired from mother to the fetus/baby. Artificial passive occurs when antibody/antitoxin is given for immediate protection.

Vaccines help prevent disease and protect the health of the world. Small pox has been eliminated from the world and polio has been eliminated from the Americas. A new measles formulation plans on reducing mortality worldwide. Other efforts are underway against meningococcal meningitis in Africa against *Haemophilus influenzae* Type b, varicella, and hepatitis type A. New generations of vaccines are also being developed against cholera, typhoid, *Shigella*, and *Helicobacter pylori*. Vaccines are made from whole killed cells or inactivated viruses that do not cause disease, live attenuated cells (lost virulence), subcellular (bacteria) or subunit (virus) or through genetic engineering. Herd immunity. What is it? Herd immunity requires that a vast majority of the population be vaccinated against a specific disease. If that happens it is unlikely for a disease to infect an unvaccinated individual. Problems associated with vaccinations vary. These are called side effects and may be short or long term. Other problems are production control and costs and proper storage and administration concerns.

Natural passive immunity is acquired by the fetus or newborn from mother. IgG antibodies cross the placenta and IgA in mother's milk protect the infant for up to six months. Artificial passive immunity is acquired through injection of antiserum. It is short term protection for up to six weeks. Examples

include gamma globulins from humans and lab animals, convalescent serum, hyperimmune serum, or antitoxin.

Immune serum globulin is derived from pool of donors. Specific immune globulins (SIG) are derived from a more defined group of donors and limited in availability and can be quite costly. Examples of SIG are antitoxins to botulism, diphtheria, and tetanus, antivenom, Rhogam, and pooled globulins to a specific agent. Drawbacks to the use of antiserum involve its specificity, side reactions, the accidental acquisition of viral diseases, and the limited time of protection - short term.

Immunological Disease

As good for us as the immune system is, it is not without [problems](#); specifically the development of hypersensitivities or deficiencies in the development of a response at all. For hypersensitivity reactions the host must have capacity to be sensitized. Therefore, genetic make-up, age, and emotional state are all important in the development of hypersensitivity reactions. The sequence of sensitization requires an initial exposure (first exposure to antigen causing immune response, but symptoms usually not present or mild at most). The sensitizing dose sets up the individual for the shocking or provocative dose (a later exposure to antigen that causes serious tissue reaction).

Antigen sources can be exogenous antigens (Allergens) from a non-living source or different species. Examples include food, drug, pollens, insect bites, poison ivy, and vaccine allergies. Homologous antigens (Isoantigens) come from another human. Sources include transfusion reactions (wrong blood type given), transplant rejections, Erythroblastosis fetalis or hemolytic disease of the newborn ([HDN](#)). An Rh- woman gives birth to an Rh+ infant. If measures are not taken to neutralize this reaction, antibodies are formed in the mother against Rh+ antigens. Subsequent Rh+ births are affected because IgG antibodies cross the placenta. The result is massive destruction of red blood cells in the fetus requiring immediate intervention.

Autologous antigens (Autoantigens) come from own body. Some examples include:

- Pernicious anemia - Intrinsic factor
- Hashimoto's thyroiditis - Follicular cells of thyroid
- Rheumatoid arthritis - Hyaluronic acid
- Rheumatic fever - Endocardium
- Systemic lupus erythematosus (SLE) - DNA of connective tissue.
- Thrombocytopenic purpura - Platelets
- Multiple sclerosis - Myelin sheath of nerve
- Guillain-Barré syndrome - Myelin sheath of nerve
- Myasthenia gravis - Neuromuscular junction
- Diabetes (Type I) - Beta cells of pancreas

Hypersensitivities are classified into four types; Types I through IV. Type I hypersensitivity is classical and immediate. IgE antibodies react with exogenous antigens only. Reaction time is 30 minutes or less. The reaction is due to histamine release and subsequent reactions within the body. Type I reactions can be further subdivided into atopic allergies and anaphylaxis. Atopic allergies (localized) depend on portal of entry. Examples include asthma, hay fever, GI distress, and wheal and flare. Anaphylaxis (generalized) requires that antigen be transmitted throughout the body via the bloodstream. In anaphylaxis small arteries dilate, blood pressure decreases, and there is circulatory failure. In the lungs, the bronchioles constrict causing asphyxiation. Symptoms (warning signs) include apprehension, flushed skin, itching, and nausea. Reversal of symptoms is achieved by rapid administration of adrenalin and antihistamines.

Type II (Cytotoxic) hypersensitivity reaction is caused by circulating IgM and/or IgG from B-lymphocytes. The reaction time is variable. The hypersensitivity is due to reaction of complement with antigens on specific cells. Examples include transfusion reactions which happen immediately and graft rejections which take longer. Some autoimmune diseases (longer) fall into this category as well as *Erythroblastosis fetalis* (HDN). Also included are cytotoxic reactions to drugs such as penicillin or sulfa. The reaction causes destruction of cells which results in cell debris that overwhelm the kidney causing damage to that organ. Steroids are used to repress the reaction but do not "cure" the cell damage.

Type III hypersensitivity reactions are immune-complex mediated. That is, an antigen-antibody reaction has occurred initially with circulating IgM and/or IgG from B- lymphocytes forming complexes and these complexes being deposited on basement membranes. As a result, circulating neutrophils release lysosomal granules that destroy tissue. Examples include therapy-related disorders (Arthus reaction which plugs capillary beds resulting in tissue necrosis and Serum sickness which results from too much passive immunity. This, too, plugs vessels resulting in inflammation, fever, joint pain, etc.). Acute glomerulonephritis is another example in which the complex plugs the filtering mechanism of kidney. Always follows a *Streptococcus pyogenes* (group A strep) infection. Steroids repress the reaction but not cell damage. Systemic lupus erythematosus and rheumatoid arthritis are examples of autoimmune diseases that fall into this category.

Type IV reactions are delayed hypersensitivity. Unlike the previous three reactions these are T-lymphocyte dependent. The reaction requires 24-72 hours to occur and there is direct destruction of cells by T-cells. Transplant rejections, beyond Type II, and granuloma formation fall into this category. A granuloma is defined as inflamed tissue with lymphocytes and macrophages. The granuloma walls off and destroy infection often create major tissue damage in the process. Skin demonstrating type IV reactions include TB, Leprosy, fungal diseases (Histoplasmosis and Blastomycosis), and some

protozoan and Helminthes. Steroids repress the reaction at the cost of cell-mediated immunity.

Type V reactions are a relatively new category of hypersensitivity. The concept is that of autoantibodies that bind to hormone receptors, thus mimicking the hormone itself. The result is the stimulation of the target cell.

The above discussion considered what would happen if the immune system over or hyper produced. The immune system can also dysfunction by depressed immunity. This immunodeficiency can be the result of a congenital condition or the result of diseases such as AIDS. Immunosuppression can be drug induced (cortisones inhibit both B- & T-cell reactions, Cyclosporin inhibits T helper cells) or radiation induced.

See Text Table 16.5 Categories of Immunodeficiency Disease

- Primary Immune Deficiencies
- B-cell defects
- Agammaglobulinemia
- hypogammaglobulinemia
- T-cell defects
- Thymic aplasia (DeGeorge syndrome)
- Combined B-cell and T-cell defects
- SCID
- Wiskott-Aldrich Syndrome
- Phagocytic Defects
- Chediak-Higashi Syndrome
- Compliant defects
- Secondary
- From natural causes
- AIDS, Cancer, nutritional deficiency, stress, pregnancy
- From immunosuppressive agents such as irradiation, burns, steroids, drugs, spleen removal

A word on Grafts. An autograft is obtained from ones own self. Examples include skin grafts for burn patients to donating your own blood to be transfused at a later date. An isograft is a graft between identical twins. Allografts (homograft) come from the same species. Most grafts are of this type. A xenograft is a graft between different species.

Immunological Methods

Determination of antibody levels is the basis of serology. One may determine the titer or the level of antibody in blood. Various tests and methods are available:

- Precipitation (of soluble antigens by a precipitin)
- [Agglutination](#) (of particles or cells by an agglutinin)

- Cytolysis (of cells by a cytolyisin)
- Neutralization (of toxins by antitoxins)
- [Complement fixation](#) (tests for loss of complement)