Lecture Notes: Immune System (Part II: Adaptive Immune System)

THIS IS THE FIRST PART OF A LECTURE ON THE ADAPTIVE IMMUNE SYSTEM
ANOTHER PART OF TO THIS LECTURE WILL FOLLOW!

I. Adaptive or Specific Immune System
  A. General Characteristics
    1. Specific so that it can eliminate with equal precision almost any type of pathogen
    2. Functional System
      a. can eliminate specific foreign substances as well as abnormal body cells
      b. can magnify the inflammatory response
        i. responsible for most complement activation
    3. Must be primed by an initial exposure to a specific foreign substance called an antigen
      a. takes time
  B. History
    1. experiments in the late 1800s found that there were protective factors in the blood that defended against future infection by the same pathogen
      a. protective factors are proteins called antibodies
      b. these factors could be transferred to other organisms that were not exposed to the antigen
    2. important findings about the adaptive immune response
      a. antigen-specific
      b. systemic
      c. has “memory”
  C. Two branches of adaptive immunity
    1. Humoral immunity or antibody-mediated immunity consists of antibodies circulating in the fluids of the body
      a. produced by lymphocytes or their offspring
    2. Cellular or cell-mediated immunity – lymphocytes themselves
      a. Targets – virus or parasite-infected tissue cells, cancer cells, foreign graft cells
      b. can act directly by lysing foreign cells or indirectly by releasing chemicals that enhance the inflammatory response or activate other lymphocytes or macrophages.

II. Antigens
  A. Antigens vs. Haptens
    1. Antigens – substances that can mobilize the immune system and provoke an immune response
      a. most large, complex molecules that are NOT normally present in the body
      b. help distinguish “self” from “nonself”
    2. Complete antigens
      a. have immunogenicity – the ability to stimulate formation of specific lymphocytes and antibody production
      b. have reactivity – the ability to react with the lymphocytes and antibodies

c. antigens include nearly all foreign proteins, nucleic acids, lipids, and many large polysaccharides.
    i. proteins are the strongest antigens
d. other antigens can be pollen grains or microorganisms
e. generally small molecules like peptides, nucleotides, and many hormones are NOT immunogenic
f. these small particles can link with other substances though and become immunogenic
    i. allergies

3. Haptens – small molecules that are reactive but not immunogenic unless attached to a protein carrier

B. Antigenic Determinants
1. only certain parts of an antigen is immunogenic. This part is known as the antigenic determinant
2. free antibodies or activated lymphocytes bind to these antigenic determinants
3. a single antigen can have a variety of antigenic determinants and stimulate many different kinds of antibodies
4. large simple molecules that have many regularly repeating units (not chemically complex) are not very immunogenic.

C. Self-antigens: MHC proteins
1. self-antigens – not foreign to us, but is foreign to other individuals
2. MHC proteins (major histocompatibility complex) – group of glycoproteins that marks a cell as self
    a. millions of different combinations of the genes are possible, it is unlikely that anybody except for identical twins will have the same MHC proteins
    b. Class I MHC proteins are found on virtually all body cells
    c. Class II MHC proteins are found only on certain cells that act in the immune response

III. Cells of the Adaptive Immune System
A. Types
1. B-cells - involved in the humoral immunity
2. T-cells – involved in cell-mediated immunity
3. APC (antigen presenting cells) – does not respond to specific antigens, but plays an auxillary role

B. Lymphocytes
1. originate from hematopoietic stem cells in red bone marrow
2. immature lymphocytes are identical when released from bone marrow
    a. determination of which lymphocyte (B or T) depends on where in the body it becomes immunocompetent
        i. immunocompetent - able to recognize a specific antigen by binding to it
3. T cells formed in the thymus (2-3 days) where the T cells are selected for their ability to identify foreign antigens
    a. negative selection – lymphocytes that strongly attack self-antigens are destroyed in the thymic medulla

b. positive selection – weakly anti-self continue to develop and the ones that can best recognize self when attached to antigens are identified. This occurs in the thymic cortex.
c. lymphocytes develop self-tolerance and immunocompetence

4. B cells become immunocompetent and self-tolerant in bone marrow
   a. anergy – self-reactive B cells are inactivated
5. primary lymphoid organs – thymus and bone marrow
6. secondary lymphoid organs – all other lymphoid organs
7. immunocompetent lymphocytes display receptors that bind to specific antigens
   a. cells are committed because all of their 10-100 thousand receptors are identical
8. Lymphocytes become immunocompetent before meeting the antigens they may later attack – genes determine which specific foreign substances our immune system will be able to recognize and resist
9. immature lymphocytes that are immunocompetent go to lymph nodes, spleen, and other secondary lymphoid organs where encounters with antigens occur and they become fully functional B and T cells.

C. Antigen-Presenting Cells (APCs)

1. engulfs particles and presents fragments of these antigens on their own surfaces where they can be recognized by T cells.
   a. major types are: dendritic cells (interstitial cells of connective tissues and Langerhans' cells of the skin epidermis), macrophages, and activated B lymphocytes
2. APCs secrete proteins that activate T cells and activated T cells secrete chemicals that activate macrophages and increase DC maturation.
3. APCs and lymphocytes are found throughout the lymphatic system but T cells are more numerous in paracortical areas of lymph nodes and DC and B cells are more numerous in germinal centers of lymph nodes
4. Macrophages tend to remain fixed in lymphoid organs
5. Lymphocytes circulate continuously throughout the body (especially T cells – 65-85% of bloodborne lymphocytes)

Lecture Notes: Immune System (Part II: Adaptive Immune System)

THIS IS THE SECOND PART OF THE ADAPTIVE IMMUNE SYSTEM LECTURE!

IV. Humoral Immune Response

A. Clonal Selection and differentiation of B Cells

1. antigen challenge – the first encounter between an immunocompetent lymphocyte and an invading antigen.
2. immunocompent B cells are activated by antigen binding to receptors on the B cell surface
   cross-linked adjacent antigen-receptor complexes are internalized by endocytosis

   Clonal selection is triggered
   B cells grow and multiply to form an army of exact replicas called clones
   Clones become either plasma cells or memory B cells
   Plasma cells secrete antibodies
   Memory B cells can mount an almost immediate attack if the same antigen is encountered again
3. Plasma cells can secrete antibodies at a rate of about 2000 molecules/sec and have a life span of 4 to 5 days.
4. Memory cells are long-lived
5. Primary immune response – cellular proliferation and differentiation upon initial exposure to antigen
   a. lasts 3-6 days with peak plasma antibody levels reached at about 10 days
6. Secondary immune response – reexposure to the same antigen
   a. faster and more prolonged than primary immune response
   b. due to the immunological memory of sensitized memory B cells
   c. takes 2-3 days to reach antibody levels that EXCEED those of primary immune response
   d. antibodies bind with greater affinity and blood levels remain high for weeks to months
   e. some memory cells can last a lifetime

B. Active and Passive Humoral Immunity

1. active humoral immunity – when B cells encounter antigens and produce antibodies against them
   a. naturally acquired – obtained by exposure to bacterial and viral infections
   b. artificially acquired – obtained from vaccines
      i. vaccines contain dead or attenuated (living but extremely weakened) pathogens or parts of them
      ii. vaccines can spare us most of the discomfort from a primary response and provide functional antigenic determinants that are immunogenic and reactive
      iii. booster shots – intensify the immune response
      iv. wiped out smallpox and decreased illnesses like whooping cough, polio, and measles as well as hepatitis B, tetanus, and pneumonia

v. vaccines target helper T cells (T_H2 cells) but not T_H1 cells which provide strong cellular responses so lots of antibodies are formed but cellular immunological memory is poorly established
vi. in some cases can cause disease if the antigen isn't weakened enough or cause allergies
vii. "naked DNA" antiviral vaccines and edible vaccines help prevent allergic responses

2. passive humoral immunity – antibodies are harvested from the serum of an immune human or animal donor.
   a. immunological memory does not occur so immunity ends when the "borrowed" antibodies naturally degrade in the body.
   b. passive immunity can be conferred naturally from a mother to a fetus and the mother's antibodies can protect the baby for several months
   c. artificial passive immunity can come from sera such as gamma globulin (administered after hepatitis exposure) or antivenoms or antitoxins

C. Antibodies
1. antibodies are also called immunoglobulins
   a. Igs are gamma globulin part of blood proteins
2. antibody structure
   a. made of 4 looping polypeptide chains linked together by disulfide bonds
   b. 2 chains are identical and are called heavy (H) chains and are made up of about 400 amino acids each
   c. the other 2 are also identical to each other and are called light (L) chains but are only about half the size of the heavy chains
   d. hinge region is at the approximate middle where two disulfide bonds connect the two heavy chains
   e. all four chains together form a molecule called an antibody monomer and is roughly T or Y shaped
   f. variable region are at the ends of the H and L chains and together form the antigen binding site
   g. constant regions form the stem of the monomer and determine the antibody class
   h. constant regions are the effector regions and dictate which cells and chemicals the antibody can bind to and how the antibody class will function in antigen elimination.
      i. E.g. antibodies can fix complement, circulate in the blood, can be found in body secretions, cross the placental barrier, etc.
3. antibody classes
   a. IgD – exists as a monomer and is attached to the external surface of the B cell where it functions as an antigen receptor and is important in B cell activation
   b. IgM – exists in a monomer or pentamer form.
      i. monomer attached to the B cell surface and is an antigen receptor
      ii. pentamer circulates in blood plasma and is released by plasma cells during the primary response. It presence in the blood indicates

current infection and it acts as a potent agglutinating agent and readily fixes and activates complement

c. IgG –exists as a monomer and is the most abundant and diverse antibody in plasma and accounts for 75-85% of circulating antibodies. Can protect against bacteria, viruses, and toxins and can fix complement. It is the main antibody of both primary and secondary responses.

d. IgA – is a dimer in plasma and is also called secretory IgA because it is present in body secretions such as saliva, sweat, intestinal juice, and milk and helps prevent pathogens from gaining access to the body.

e. IgE – a monomer that is secreted by epithelial plasma cells and almost never found in the blood. They bind to mast cells and basophils when activated by antigen and it causes those cells to release histamine and other chemicals that mediate inflammation and allergic reactions. Blood IgE levels rise dramatically during allergic reactions or chronic gastrointestinal tract parasites.

4. antibody diversity
   a. plasma cells can make over a billion types of antibodies due to resuffuling of gene segments in a process called somatic recombination. Gene segments recombine as B cells become immunocompetent and the newly assembled genes become expressed in the surface receptors of B cells and are later released by plasma cells as antibodies.
   b. Random mixes of H and L gene segments plus extremely variable regions of the variable gene segments called hypervariable regions create the huge variability seen in antibodies.
   c. Plasma cells can secrete 2 or more different antibody classes with the same antigen specificity.
      i. Primary response starts with IgM release by a plasma cell followed by secretion of IgG by the same plasma cell.
      ii. Secondary responses consist almost entirely of IgG release.
5. antibody targets and functions
   a. antibodies inactivate antigen-bearing invaders and tag them for destruction
   b. common event is antigen-antibody complexes
   c. defensive mechanisms
      i. complement fixation and activation – chief weapon against cellular antigens. Antibodies bind to cells, change shape on constant regions and allow complement fixation onto the antigenic cell surface causing the cell to lyse. Also starts a positive feedback loop enhancing inflammatory response and promoting phagocytosis via opsonization.
      ii. neutralization – antibodies bind to specific sites on the antigen preventing them from binding to their cellular targets and causing injury.
      iii. agglutination – cross-linking of many antigen-antibody complexes as to cause clumping

iv. precipitation – soluble molecules are cross-linked into large complexes and settle out of solution where they are easily captured and consumed by phagocytes

6. monoclonal antibodies – commercially available pure antibody preparations specific for a single antigenic determinant produced by descendents of a single cell
   a. made from hybridomas which are fusions of tumor cells and B lymphocytes and have good characteristics of each like the ability to proliferate indefinitely in culture and can produce a single type of antibody.
      i. can be used to diagnose pregnancy, some sexually transmitted diseases, some types of cancer, hepatitis, and rabies
      ii. can treat leukemia and lymphomas by specifically delivering anticancer drugs.

V. Cell-Mediated Immune Response

A. Types of T cells
   1. CD4 cells have the glycoprotein CD4 cell surface receptors displayed
      a. also called T4 cells, CD4 cells are primarily helper T cells (T_H)
   2. CD8 cells have the glycoprotein CD8 cell surface receptors displayed
      a. also called T8 cells, CD8 cells are primarily cytotoxic T cells (T_C)
   3. Delayed hypersensitive T cells (T_{DH}) a special type of T_H cell
   4. Suppressor T cells (T_S)
   5. Memory T cells

B. Functions of T cells
   1. T cells can recognize and respond only to processed fragments of protein antigen displayed on the surface of cells
   2. More effective in cell-cell interactions unlike antibodies, which cannot attack microorganisms that can quickly slip inside body cells and multiply like tuberculosis bacillus.
   3. T_H cells binds with specific antigens presented by an APC and stimulates production of other cells like T_C cells and B cells. It can also act directly by secreting cytokines like interleukins 2, 4, and 5.
   4. T_C cells, also called cytolytic (CTL) or killer T cells, are activated by an antigen presented by any body cell and are recruited by T_H cells. T_H cells also enhance the activity of T_C cells. T_C cells specialize in killing virus-invaded body cells and cancer cells and is involved with rejection of foreign tissue graphs. Secretes lymphotoxin, which causes DNA fragmentation and promotes inflammation. Also secretes perforin which causes cell lysis by creating large pores in the membrane of target cells.
   5. T_S cells stops activity of B and T cells once infection has been conquered. Secretes suppressor factors which suppresses the immune response.
   6. T_{DH} promotes nonspecific killing by macrophages and is important in delayed hypersensitivity reactions like allergic contact dermatitis which follows skin contact with poison ivy, heavy metals, etc.
   7. Memory T cells are like the memory B cells in the fact that they are generated during the primary response and may exist in the body for years allowing rapid response to subsequent reinfections of the same antigen.

C. Clonal selection and differentiation of T cells
   1. T cell cloning requires “double recognition” such that immunocompetent T cells must be able to simultaneous recognize the antigen and a MHC protein.
      a. Class I MHC proteins are displayed by all body cells except for red blood cells and are always recognized by CD8 T cells. Class I MHC proteins are made in the
      ER where endogenous antigens, foreign proteins that are synthesized within a body cell as from viral activity or cancerous cells, are transported by special transport proteins called TAPs. The antigen is then loaded onto the Class I MHC protein where the complex (MHC + antigen) is incorporated into the plasma membrane.
      b. Class II MHC proteins are displayed on the surfaces of mature B cells, some T cells, and antigen-presenting cells, where they enable the cells of the immune system to recognize one another. They are synthesized in the ER but unlike MHC proteins they have an invariant chain attached which prevents MHC Class II binding to peptides in the ER. The MHC Class II protein migrates to the phagolysosome where the invariant chain is removed and exogenous antigens, which are foreign antigens that have been phagocytosed and broken down within the phagosome vesicle, are loaded. The loaded MHC Class II proteins are then displayed on the cell surface where CD4 cells can recognize them.
   2. T cell activation
      a. involves two steps: antigen binding and costimulation.
         i. Antigen binding - T cell receptors or TCRs bind to an antigen-MHC protein complex on the surface of the body cell.
            1. MHC restriction – preference for certain classes of MHC proteins
            2. immunologic surveillance – the process in which T cells adhere to and crawl over other cells in search of antigens that they might recognize
         ii. Costimulation – the process of a T cell recognizing a costimulatory signal before it can proliferate to form a clone. The costimulatory signal could be a T cell binding to other surface receptors on an APC like the B7 protein of macrophages binding to the CD_{28} T cell receptor. Other costimulatory signals could be cytokines like interleukin 1 and 2. Costimulation is REQUIRED for T cell cloning.

VI. Organ Transplants and Prevention of Rejection
   A. Types of Grafts
      1. Autografts – tissue grafts transplanted from one body site to another in the same person
      2. isografts – grafts donated by genetically identical individuals
      3. allografts – grafts transplanted from individuals that are not genetically identical but belong to the same species.
      4. Xenografts – grafts taken from another animal species
   B. Procedures

1. to minimize rejection patients receiving grafts are treated with immunosuppressive theraphy involving 1 or more of:
    a. corticosteriod drugs like prednisone to suppress inflammation
    b. cytotoxic drugs
    c. radiation therapy
    d. antilymphocyte globulins
    e. an immunosuppressant drug such as cyclosporin
    f. all have severe side effects

VII. Homeostatic Imbalances of Immunity

A. Immunodeficiencies

1. immunodeficiencies – congenital and acquired conditions in which the production or function of immune cells, phagocytes, or complement is abnormal.
    a. severe combined immunodeficiency (SCID) syndrome results from genetic defects that produce a B and T cell deficiency.
    b. Hodgkin's disease, cancer of the lymph nodes, is an acquired immunodeficiency
    c. AIDS (acquired immune deficiency syndrome) – interferes with the activity of helper T (CD4) cells. Caused by the virus HIV (human immunodeficiency virus) which destroys the helper T cells. After invading the cells with a coat glycoprotein gp120 with the help of gp41, HIV uses the enzyme reverse transcriptase to make DNA from its viral RNA. The DNA copy, called a provirus, then inserts into the host DNA and directs the synthesis of more HIV cells. AIDS is treated by reverse transcriptase inhibitors like AZT and protease inhibitors like saquinavir, etc. Combination therapy seemed to be very effective but as of late it is failing in about half the treated patients.

B. Autoimmune disease

1. autoimmune disease – condition that results when the body produces antibodies and sensitized cytotoxic T cells that destroy its own tissues.
    a. Multiple sclerosis (MS) – destroys the white matter of the brain and spinal cord
    b. Myasthenia gravis – impairs communication between nerves and skeletal muscle
    c. Graves' disease – prompts the thyroid gland to produce excessive amounts of thyroxine
    d. Type I diabetes mellitus – destroys pancreatic beta cells resulting in a deficit of insulin and the inability to use carbohydrates
    e. systemic lupus erythematosus (SLE) – systemic disease that affects the kidneys, heart, lungs, and skin.
    f. Glomerulonephritis – severe impairment of renal function
    g. rheumatoid arthritis (RA) – systematically destroys joints
    h. can be treated by depressing immune response like antibodies to the CD4 receptor on T_H cells and thalidomide, which inhibits production of TNF-α., which is tumor necrosis factor that produced by lymphocytes and in large amounts by macrophages that enhances nonspecific killing, slows tumor

growth, causes selective damage to blood vessels, enhance granulocyte chemotaxis, and help activate T cells, phagocytes, and eosinophils.

2. Possible triggers for autoimmune disorders
    a. lymphocyte programming is ineffective (negative selection ineffective)
    b. new self-antigens appear
    c. foreign antigens resemble self-antigens
        i. antibodies against streptococcal infection can cross-react with heart antigens causing rheumatic fever which causes lasting damage to heart muscle, valves, joints, and kidneys.

C. Hypersensitivities
1. hypersensitivities or allergies – result of immune responses in which the immune system causes tissue damage as it fights off a perceived "threat"
    a. antigens are called allergens; rarely lethal
    b. types of hypersensitivities are determined by their time course and whether T cells are the principal immune elements involved.
    c. antibody-mediated hypersensitivity (immediate, acute, or type I hypersensitivities) begin within seconds of contact and can last ½ hour.
        i. anaphylaxis – most common type of immediate hypersensitivity where allergens trigger release of IL-4 which in turn stimulates production of IgE-secreting plasma cells which attach to mast cells and basophils which release histamine and other inflammatory chemicals upon further exposure to the allergen. Treated with antihistamines
        ii. anaphylactic shock – rare but is basically systemic anaphylaxis where bronchioles constrict, edema occurs, and circulatory shock may occur resulting in death within minutes. Treated with epinephrine.
        iii. atopy – spontaneous development of immediate-type allergies to certain environmental antigens. May result in hives, hay fever, or asthmatic symptoms.
    d. antibody-mediated hypersensitivity (subacute hypersensitivities) – slower onset 1-3 hours and longer duration 10-15 hours
        i. cytotoxic (type II) reactions – antibodies bind to antigens on specific body cells to stimulate phagocytosis and complement-mediated lysis of cellular antigens. E.g. mismatched blood transfusions
        ii. immune complex (type III) reactions – antigen-antibody complexes form that cannot be cleared. Intense inflammatory reactions occur and severe damage to local tissues. E.g. farmer's lung
    e. delayed hypersensitivity (type IV) reactions are cell-mediated and appear 1-3 days after exposure to the allergen.
        i. involves cytotoxic cells and T_{DH} cells. Corticosteroid drugs are used for treatment.
            1. includes allergic contact dermatitis and TB skin tests
            2. provides protective reactions against viruses, bacteria, fungi, protozoa, resistance against cancer, rejection of foreign

grafts or transplanted organs, and protection against facultative intracellular pathogens (FIPs) like salmonella bacteria.