Lecture 27: Immunological Disorders - Hypersensitivities, autoimmunity, immune deficiencies

Hypersensitivities are immune responses that lead to host damage
- Hypersensitivity responses occur in persons who have been "sensitized" to a particular antigen; that is, their immune system has previously encountered the antigen
- In the context of hypersensitivities, the relevant antigen is often referred to as an allergen.
- Hypersensitivity responses are classified into four principal types (Tortora et al., Table 19.1)
  - Types I, II and III involve antibody production and are sometimes called immediate hypersensitivities
  - Type IV involves cell-mediated immune responses, and is sometimes called delayed-type hypersensitivity

Type I hypersensitivities, or anaphylactic reactions are what we usually mean by an "allergic response"
- Anaphylaxis occurs when antigen binds to molecules of IgE antibody that are attached to the surface of mast cells or basophils (Tortora et al., Figure 19.1)
- When antigen binds to IgE attached to a mast cell or basophil, the cell is triggered to undergo degranulation
  - Degranulation involves release of intracellular granules that contain chemical mediators
  - It is the mediators that cause the allergic response in tissues
- The mediators released upon degranulation include histamine, prostaglandins and leukotrienes; collectively, they activate inflammation and smooth muscle contraction
- Systemic anaphylaxis, or "anaphylactic shock" can occur with some antigens, including venoms, that are introduced into circulation
  - In anaphylactic shock, release of mediators leads to dilation of peripheral blood vessels throughout the body, resulting in a potentially fatal drop in blood pressure
  - Epinephrine can be used to counteract the effect of the mediators
- Localized anaphylaxis, in which the anaphylactic response is limited to tissues of the respiratory tract or gastrointestinal tract, is relatively common
  - "Hay fever" and food allergies are examples of localized anaphylaxis
  - Antihistamines, which are used in treatment of localized anaphylaxis, act by competing for histamine receptor sites
  - Asthma is a localized anaphylactic response in the lower respiratory tract; the characteristic symptoms are due to mediator-caused bronchial constriction
- The allergen responsible for a Type I hypersensitivity response can sometimes be identified by skin tests (Tortora et al., Figure 19.3)

Type II hypersensitivities, cytotoxic reactions, result from attachment of antibodies to host cells
- Cells with antibodies bound to them may be destroyed by several mechanisms
  - Complement activation refers to assembly of serum proteins onto the cell, which may lead to cell lysis
  - Neutrophils and eosinophils possess antibody receptors, and may be stimulated to destroy a cell with antibody bound to it
  - As mentioned in the discussion of cell-mediated immunity, K cells also destroy cells with antibody attached
  - Antibodies may also interfere with cell function
- The most familiar example of Type II hypersensitivity is the transfusion reaction that occurs upon transfusion of incompatible blood
  - The ABO blood group system refers to a group of carbohydrate antigens found on the surface of erythrocytes (Tortora et al., Table 19.2)
A person's ABO blood group is determined by which antigen(s) their erythrocytes exhibit
- Erythrocytes of persons with type A blood exhibit the A antigen
- Erythrocytes of persons with type B blood exhibit the B antigen
- Erythrocytes of persons with type AB blood exhibit both the A antigen and the B antigen
- Erythrocytes of persons with type O blood exhibit neither the A antigen nor the B antigen

If your erythrocytes don't have a particular antigen, it is "non-self" and you will produce antigens against it
- Thus, the immune system of a person with type O blood will destroy blood cells exhibiting either the A antigen or the B antigen, and so on
- The immune system of persons with type AB blood "sees" both the A antigen and the B antigen as "self" and thus can tolerate blood of any type

The Rh factor is another erythrocyte antigen associated with hemolytic disease of the newborn (Tortora et al., Figure 19.4)
- Persons whose erythrocytes exhibit the Rh factor are Rh+, while persons whose erythrocytes lack the Rh factor are Rh-
- Hemolytic disease of the newborn can occur in Rh+ children (who have inherited the Rh factor from their father) of Rh- mothers
- At birth, there is limited mixing of neonatal and maternal blood, associated with tearing of the placenta; Rh factor from neonatal blood can thus sensitize the immune system of an Rh- mother, causing her to produce antibodies to Rh factor
- If the fetus in a later pregnancy is also Rh+, maternal anti-Rh antibodies can cross the placenta and attack the erythrocytes of the fetus
- Hemolytic disease of the newborn can prevented by a strategy of artificial passive immunization
  - At the time of the birth of the first Rh+ child, anti-Rh antibodies are administered to the mother
  - These antibodies combine with the Rh+ fetal erythrocytes, preventing sensitization of the mother
  - Neat, huh?

Type II hypersensitivity may also occur when drugs act as haptens, as in thrombocytopenic purpura (Tortora et al., Figure 19.5)

Type III hypersensitivity responses result from formation of immune complexes (Tortora et al., Figure 19.6)
- These complexes can become trapped in tissues, leading to inflammatory reactions
- Glomerulonephritis, inflammatory damage to the kidneys, may result from immune complex precipitation

Type IV hypersensitivities, or delayed-type hypersensitivities, are a consequence of inappropriate cell-mediated immune responses
- In response to recognizing foreign antigen displayed by tissue cells, helper T cells produce inflammatory lymphokines
- Allergic contact dermatitis, such as occurs with poison ivy (Tortora et al., Figure 19.7), results from binding of antigenic molecules to cell surfaces

Hypersensitivity reactions account for the tissue damage that accompanies autoimmune diseases
- Autoimmunity occurs when there is a breakdown in self-tolerance leading to immune reaction to self antigens
- Systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA) involve immune complex deposition, type III hypersensitivity
- The symptoms of Hashimoto's thyroiditis and type 1 insulin-dependent diabetes mellitus involve T cell-mediated destruction of cells, type IV hypersensitivity
Histocompatibility antigens are the cell surface proteins recognized by T cells as "self" - These proteins are encoded by the major histocompatibility complex (MHC) - Clinically, the MHC proteins are referred to as human leukocyte antigens, and can be identified serologically (Tortora et al., Figure 19.9) - HLA antigens are important to the medical community because = they are the main antigens targeted in transplant rejection; matching of HLA antigens of donor and recipient is therefore important = a number of diseases have been shown to occur at higher frequencies in persons whose cells display particular HLA antigens (Tortrora et al., Table 19.3)

Successful tissue transplantation requires knowledge of the part played by the immune system in transplant rejection - Some tissues, such as corneas, do not stimulate an immune response, because antibodies and lymphocytes are not found at these immunologically privileged sites. - Transplants of "privileged" tissue can be classified according to the genetic relationship between donor and recipient = For autografts, the donor and recipient are the same individual. Many skin grafts are autografts, as are autologous blood transfusions. = In isografts, transplants occur between different but genetically identical individuals. Since most of us lack identical twins, isografts are mostly a laboratory phenomenon. = The majority of what we think of as "transplants" are allografts. = There is considerable interest in technologies for allowing xenografts, transplants across species lines. - The major concern in tissue transplantation is a strong immune response by the recipient against the donor tissue = If the donor tissue contains immunologically competent lymphocytes, there is also the potential for graft-versus-host (GVH) reactions = Allograft recipients typically receive treatment to induce immunosuppression; cyclosporine is the drug most commonly used for this purpose.