McCance: Pathophysiology, 6th Edition

Chapter 07: Adaptive Immunity

Key Points – Print

SUMMARY REVIEW

General Characteristics of Adaptive Immunity

1. Compared with the innate inflammatory response, the adaptive immune response is slower, specific rather than nonspecific or general, and has "memory" that makes it much longer lived.
2. The adaptive immune response is most often initiated by cells of the innate system. These cells process and present portions of invading pathogens (i.e., antigens) to lymphocytes in peripheral lymphoid tissue.
3. The adaptive immune response is mediated by two different types of lymphocytes—B lymphocytes and T lymphocytes. Each has distinct functions. B cells are responsible for humoral immunity that is mediated by circulating antibodies, whereas T cells are responsible for cell-mediated immunity, in which they kill targets directly or stimulate the activity of other leukocytes.
4. Adaptive immunity can be either active or passive depending on whether immune response components originated in the host or came from a donor.

Recognition and Response

1. Antigens are the molecules that can react with components of the adaptive immune system, including antibodies and lymphocyte surface receptors. Immunogens are antigens that can initiate the adaptive immune response. To be immunogenic, an antigen must be of the correct type, size, and complexity and be present in sufficient quantities. Haptens are small-molecular-weight antigens that are not themselves immunogenic.
2. Both B and T lymphocytes bind antigen through cognate receptor complexes on their surfaces. These receptor complexes (i.e., the BCR and TCR complexes, respectively) work in conjunction with accessory proteins to produce lymphocyte activation.
3. The antigen-binding molecule of the BCR is antibody. Antibodies are composed of four polypeptide chains—two identical heavy chains and two identical light chains—held together by disulfide bonds. Each heavy chain has a variable region and a large constant region. Each light chain has a variable region and a short constant region. The class of antibody is determined by which constant regions make up their heavy chains, giving each class a slightly different molecular structure. The classes include IgG (the most prevalent), IgA (mostly in secretions), IgE (the most rare), IgD, and IgM (the first and largest immunoglobulin produced). The parts of antibody that bind antigen are called the Fab, and the part that reacts with cells and molecules of the innate system is called the Fc. Antigen binds to hypervariable regions (complementary determining regions, or CDRs) of both the heavy and light chains.

4. For most antigens to elicit an immune response, they must be presented to lymphocytes by molecules on the surface of antigen-presenting cells. Endogenous protein antigens are presented by class I molecules of MHC. Exogenous protein antigens are presented by class II MHC molecules. Lipid antigens are presented by CD1.
5. The MHC is a cluster of genes found on human chromosome 6. The products of these genes are also called *HLA antigens.* The MHC genes are highly polymorphic, having many different possible alleles. An individual will carry only two alleles at each locus, one from each parent. The particular combination of alleles a given individual carries defines his or her MHC haplotype.
6. For an immune response to develop, a variety of cells must interact through surface adhesion molecules.
7. During their interactions, cells must communicate with each other through soluble cytokines. In addition to their roles in the innate immune response, cytokines have multiple functions in the adaptive immune response including both positive and negative regulation of B cell and T cell maturation. In general, it is the precise combination of cytokines influencing a given cell that ultimately determines that cell's response.

Generation of Clonal Diversity

1. The generation of clonal diversity occurs in the primary lymphoid organs (thymus for T cells, bone marrow for B cells) in the fetus.
2. An individual's population of T cells and B cells has the collective ability to respond to virtually any antigen. This ability results from genetic rearrangement of various genes to form the variable regions for the TCR and BCR. Rearrangement of *V* and *J* genes results in the variable regions of the TCR α- chain and the BCR light chain, and rearrangement of *V, D,* and *J* genes result in the variable regions of the TCR β- chain and the BCR heavy chain.
3. Differentiation of B cells and T cells in the primary lymphoid organs results in expression of several characteristic surface markers, such as CD4 on helper T cells, CD8 on cytotoxic T cells, and CD21 and CD40 on B cells.
4. During generation of clonal diversity, B cells and T cells that produce receptors against self-antigens are eliminated by a process of central tolerance.
5. Cells leaving the primary lymphoid organs are immunocompetent (capable of reacting to antigen) and enter the circulation and secondary lymphoid organs.

Induction of an Immune Response: Clonal Selection

1. Clonal selection is the process by which antigen selects lymphocytes with complementary TCRs or BCRs and induces an immune response with the production of specific antibody or cytotoxic T cells, or both.
2. For lymphocyte activation, most antigens must be processed and presented by an APC in the context of the appropriate molecule, either MHC class I, MHC class II, or CD1 molecules.

3. Most immune responses require helper T cells (Th cells). Precursor Th cells interact with APCs through the TCR/CD4 complex, a variety of adhesion molecules, and cytokines, especially IL-1, and develop into either Th1 or Th2 subsets. Th1 cells are responsible for helping to activate macrophages and cytotoxic T cells, whereas Th2 cells are responsible for helping to activate B cells.
4. Another set of Th cells, Th17 cells, provides help in developing inflammation, particularly attraction of neutrophils and macrophages and induction of chemokine and antimicrobial protein production by epithelial cells.
5. B cell activation results from recognition of soluble antigen by the BCR, processing of the antigen, and presentation by MHC class II antigens to Th2 cells. Interactions between the B cells and Th2 cells through adhesion molecules (e.g., CD40 and CD40L) are also required. Depending on the particular combination of cytokines produced by the Th2 cell, the B cells can undergo class-switch from making IgM antibody to making and secreting either IgA, IgE, or IgG.
6. The humoral immune response is divided into two phases, primary and secondary. These differ in the relative amounts of IgG produced—the secondary response having a much higher proportion of IgG relative to IgM. The two responses also differ in the speed with which each occurs after antigen challenge—the secondary response being much more rapid than the primary response because of the presence of memory cells in the secondary phase.
7. B cells become activated upon recognition of a particular antigen to proliferate and differentiate into plasma cells that function as factories for the synthesis of large amounts of antibody that is specific for the recognized antigen or into memory B cells.
8. T cell activation results from recognition by the TCR and CD8 of antigen presented by MHC class I. Appropriate intercellular adhesion molecules and cytokines, such as IL-2 from Th1 cells, are also necessary for efficient differentiation. T cells become CTLs or memory T cells.
9. Superantigens are molecules produced by infectious agents that can bind to the Th cell's TCR outside the normal antigen-binding site and to class II MHC on the APCs, resulting in activation of a large number of Th cells and excessive production of proinflammatory cytokines that may cause shock and death of the patient. Examples of these antigens, called *superantigens,* include the bacterial toxins that can cause toxic shock syndrome and food poisoning.

Effector Mechanisms

1. The antibodies that are produced by B cells affect antigens by several different mechanisms that can be categorized as either direct or indirect. Direct mechanisms are mediated by the antigen-binding portions of antibodies (the Fab portions containing the variable regions). This binding results in neutralization of the biologic activity of antigens and possibly removal of the antigen by agglutination or precipitation. Indirect mechanisms depend on both the Fab and the nonantigen-binding portion of antibodies (the Fc portions containing the constant regions), which interact with components of innate immunity.

2. Antibodies of the systemic immune system function throughout the body, whereas antibodies of the secretory (mucosal) immune system—primarily immunoglobulins of the IgA class—are associated with bodily secretions and function to prevent pathogenic infection on epithelial surfaces.
3. Cytotoxic T cells (Tc cells) adhere directly to antigen presented by MHC class I on target cells (virus-infected cells or cancer cells) through the TCR, CD8, and a variety of adhesion proteins. This contact results in killing of the target by apoptosis through the release of perforin and granzymes and/or direct stimulation of apoptotic receptors on the target (e.g., Fas).
4. NK cells kill targets in a fashion similar to that of Tc cells. However, NK cells recognize target cells that do not express MHC class I.
5. With infections that are resistant to cells of innate immunity, some Th1 cells produce cytokines that activate macrophages to become more efficient phagocytes.
6. Treg cells control (suppress) immune responses and prevent overreaction against foreign and self-antigens.

Fetal and Neonatal Immune Function

1. The human neonate has a poorly developed immune response, particularly in the production of IgG. The fetus and neonate are protected in utero and during the first few postnatal months by maternal antibody that was actively transported across the placenta.
2. The maternal antibodies are slowly catabolized after birth until they disappear altogether by about 10 months of age. The neonate begins producing IgG at birth, and the child's antibodies reach protective levels after about 6 months of age.

Aging and Immune Function

1. T-cell activity is deficient in older adults, and a shift in the balance of T cell subsets is observed. These changes may result in increased susceptibility to infection.
2. Antibody production to specific antigens is inferior, although older adults tend to have increased levels of circulating autoantibodies.