TOPIC: Immune Cells and Ag Recognition Lecture #10

TEACHING OBJECTIVES:

1. To review the role of immune cells in protection from different types of pathogens
2. To discuss the types of cells involved in immune responses
3. To describe the nature of specificity in adaptive immune responses
4. To understand the role of lymphocyte recirculation in immune responses

REQUIRED READING:

Male, *et al*. Immunology, 7th Ed., Cpt 1 and 2.

CELLS OF THE IMMUNE SYSTEM AND ANTIGEN RECOGNITION

1) Overview

a) The immune system has developed to protect the host from pathogens and other foreign substances. Self/non-self discrimination is one of the hallmarks of the immune system. There are two mains sites where pathogens may reside: extracellularly in tissue spaces or intracellularly within a host cell; and the immune system has different ways of dealing with pathogens at these sites. Although immune responses are tailored to the pathogen and to where the pathogen resides, most pathogens can elicit both an antibody and a cell-mediated response, both of which may contribute to ridding the host of the pathogen. However, for any particular pathogen an antibody or a cell-mediated response may be more important for defense against the pathogen

b) Extracellular pathogens: antibodies are the primary defense against extracellular pathogens and they function in three major ways:

i) Neutralization - by binding to the pathogen or foreign substance antibodies can block the association of the pathogen with their targets. For example, antibodies to bacterial toxins can prevent the binding of the toxin to host cells thereby rendering the toxin ineffective. Similarly, antibody binding to a virus or bacterial pathogen can

block the attachment of the pathogen to its target cell thereby preventing infection or colonization.

ii) Opsonization - Antibody binding to a pathogen or foreign substance can opsonize the material and facilitate its uptake and destruction by phagocytic cells. The Fc region of the antibody interacts with Fc receptors on phagocytic cells rendering the pathogen more readily phagocytosed.

iii) Complement activation - Activation of the complement cascade by antibody can result in lysis of certain bacteria and viruses. In addition, some components of the complement cascade (*e.g.* C3b) opsonize pathogens and facilitate their uptake via complement receptors on phagocytic cells.

c) Intracellular pathogens: Because antibodies do not get into host cells, they are ineffective against intracellular pathogens. The immune system uses a different approach to deal with these kinds of pathogens. Cell-mediated responses are the primary defense against intracellular pathogens and the approach is different depending upon where the pathogen resides in the host cell (*i.e.*, in the cytosol or within vesicles). For example, most viruses and some bacteria reside in the cytoplasm of the host cell, however, some bacteria and parasites actually live within endosomes in the infected host cell. The primary defense against pathogens in the cytosol is the cytotoxic T lymphocyte (Tc or CTL). In contrast, the primary defense against a pathogen within vesicles is a subset of helper T lymphocytes (Th1).

i) Cytotoxic T cells (CTL) - CTLs are a subset of T lymphocytes that express a unique antigen on their surface called CD8. These cells recognize antigens from the pathogen that are displayed on the surface of the infected cell and kill the cell thereby preventing the spread of the infection to neighboring cells. CTLs kill by inducing apoptosis in the infected cell.

ii) Th1 helper T cells - Th cells are a subset of T cells that express a unique antigen on their surface called CD4. A subpopulation of Th cells, Th1 cells, is the primary defense against intracellular pathogens that live within vesicles. Th1 cells recognize antigen from the pathogen that are expressed on the surface of infected cells and release cytokines that activate the infected cell. Once activated, the infected cell can then kill the pathogen. For example, *Mycobacterium tuberculosis*, the causative agent of tuberculosis, infects macrophages but is not killed because it blocks the fusion of lysosomes with the endosomes in which it resides. Th1 cells that recognize *M. tuberculosis* antigens on the surface of an infected macrophage can secrete cytokines that activate macrophages. Once activated the lysosomes fuse with endosomes and the *M. tuberculosis* bacteria are killed.

2) Cells of the immune system

a) All cells of the immune system originate from a hematopoietic stem cell in the bone marrow, which gives rise to two major lineages, a myeloid progenitor cell and a lymphoid progenitor cell (Figure 1). These two progenitors give rise to the myeloid cells (monocytes, macrophages, dendritic cells, mast cells, and granulocytes) and lymphoid

cells (T cells, B cells and NK cells), respectively. These cells make up the cellular components of the innate (non-specific) and adaptive (specific) immune systems.

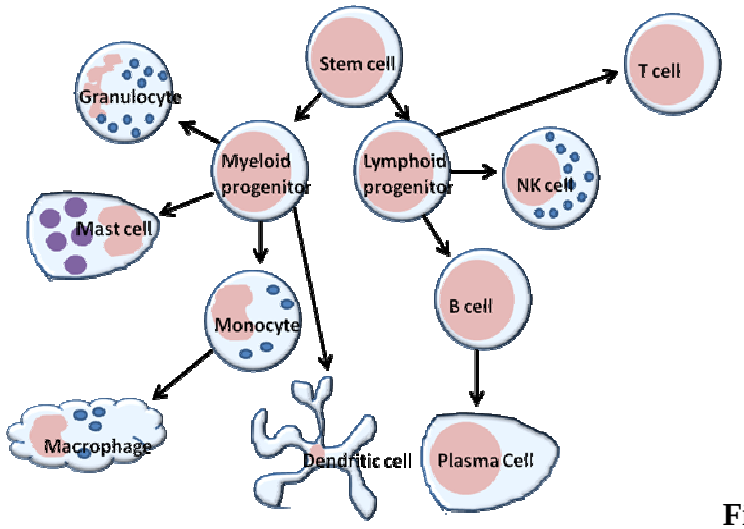

Figure 1.

b) Cells of the innate immune system – Cells of the innate immune system include phagocytic cells (monocyte/macrophages and PMNs), NK cells, basophils, mast cells, eosinophils and platelets. The roles of these cells have been discussed previously (see nonspecific immunity, lecture 1). The receptors of these cells are pattern recognition receptors (PRRs) that recognize broad molecular patterns found on pathogens (pathogen associated molecular patterns, PAMPS).

c) Cells that link the innate and adaptive immune systems – A specialized subset of cells called antigen presenting cells (APCs) are a heterogeneous population of leukocytes that play an important role in innate immunity and also act as a link to the adaptive immune system by participating in the activation of helper T cells (Th cells). These cells include dendritic cells and macrophages. A characteristic feature of APCs is the expression of a cell surface molecule encoded by genes in the major histocompatibility complex, referred to as class II MHC molecules. B lymphocytes also express class II MHC molecules and they also function as APCs, although they are not considered as part of the innate immune system. In addition, certain other cells (*e.g.*, thymic epithelial cells) can express class II MHC molecules and can function as APCs.

d) Cells of the adaptive immune system – Cells that make up the adaptive (specific) immune system include the B and T lymphocytes. After exposure to antigen, B cells differentiate into plasma cells whose primary function is the production of antibodies. Similarly, T cells can differentiate into either cytotoxic (CTL) or T helper (Th) cells of which there are two types Th1 and Th2 cells. There are a number of cell surface markers that are used in clinical laboratories to distinguish B cells, T cells and their subpopulations. These are summarized in Table 1.

Table 1.

Marker	B cell	CTL	T-helper
Antigen R	BCR (surface Ig)	TCR	TCR
CD3	--	+	+
CD4	--	--	+
CD8	--	+	--
CD19/ CD20	+	--	--
CD40	+	--	--

3) Specificity of the adaptive immune response

a) Specificity of the adaptive immune response resides in the Ag receptors on T and B cells, the TCR and BCR, respectively. The TCR and BCR are similar in that each receptor is specific for one antigenic determinant but they differ in that BCRs are divalent while TCRs are monovalent (Figure 2). A consequence of this difference is that while B cells can have their antigen receptors cross-linked by antigen, TCRs cannot. This has implications as to how B and T cells can become activated.

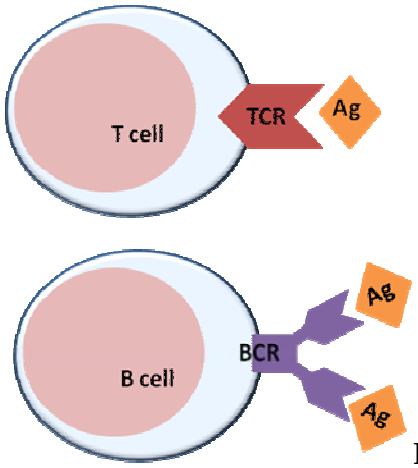

Figure 2.

b) Each B and T cell has a receptor that is unique for a particular antigenic determinant and there are a vast array of different antigen receptors on both B and T cells (discussed in more detail in lecture 11). The question of how these receptors are generated was the major focus of immunologists for many years. Two basic hypotheses were proposed to explain the generation of the receptors: the instructionist (template) hypothesis and the clonal selection hypothesis.

i) Instructionist hypothesis – The instructionist hypothesis states that there is only one common receptor encoded in the germline and that different receptors are generated using the Ag as a template. Each Ag would cause the one common receptor to be folded to fit the Ag. While this hypothesis was simple and very appealing, it was not

consistent with what was known about protein folding (*i.e.* protein folding is dictated by the sequence of amino acids in the protein). In addition this hypothesis did not account for self/non-self discrimination in the immune system. It could not explain why the one common receptor did not fold around self Ag.

ii) Clonal selection hypothesis – The clonal selection hypothesis states that the germline encodes many different Ag receptors - one for each antigenic determinant to which an individual will be capable of mounting an immune response. Ag selects those clones of cells that have the appropriate receptor. The four basic principles of the clonal selection hypothesis are:

(1) Each lymphocyte has a SINGLE type of Ag receptor with a unique specificity.

(2) Interaction between the foreign molecule and Ag receptor capable of binding that molecule with a high affinity leads to lymphocyte activation.

(3) The differentiated effector cell derived from an activated lymphocyte will have the same Ag receptor as the parental lymphocyte; thus they are clones.

(4) Lymphocytes bearing Ag receptors for self molecules are deleted early in lymphoid development and are absent from the repertoire of mature lymphocytes.

c) The clonal selection hypothesis is now generally accepted as the correct hypothesis to explain how the adaptive immune system operates. It explains many of the features of the immune response: 1) the specificity of the response; 2) the signal required for activation of the response (*i.e.* Ag); 3) the lag in the adaptive immune response (time is required to activate cells and to expand the clones of cells); and 4) self/non-self discrimination.

4) Development of the immune system

a) All immune cells arise from the hematopoietic stem cell. PMNs pass from the circulation into the tissues. Mast cells are identifiable and thought to be "resident" in most tissues. B cells mature in the fetal liver and bone marrow. T cells mature in the thymus. NK cells likely originate in the bone marrow. Lymphocytes recirculate through secondary lymphoid tissues such as the spleen where cells such as dendritic cells act as APCs.

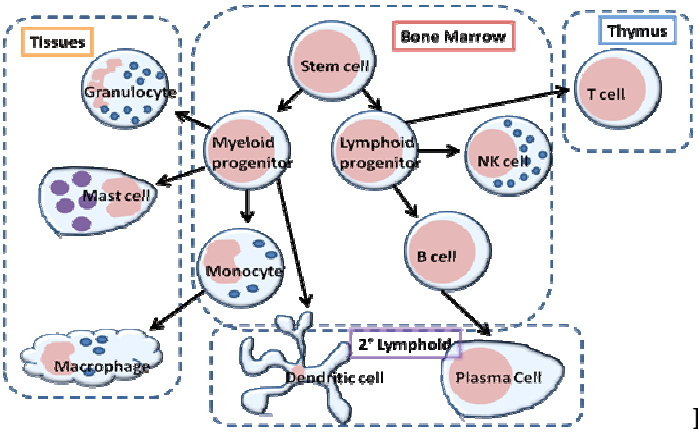

Figure 3.

5) Lymphocyte recirculation

a) There are relatively few T or B lymphocytes with a receptor for any particular antigen (1/10,000 – 1/100,000), the chances for a successful encounter between an antigen and the appropriate lymphocyte are slim. However, the chances for a successful encounter are greatly enhanced by the recirculation of lymphocytes through the secondary lymphoid organs. Lymphocytes in the blood enter the lymph nodes and percolate through the lymph nodes (Figure 4). If they do not encounter an antigen in the lymph node, they leave via the lymphatics and return to the blood via the thoracic duct. It is estimated that 1-2% of lymphocytes recirculate every hour. If the lymphocytes in the lymph nodes encounter an antigen, which has been transported to the lymph node via the lymphatics, the cells become activated, divide and differentiate to become a plasma cell, Th or CTL cell. After several days the effector cells can leave the lymph nodes via the lymphatics and return to the blood via the thoracic duct and then make their way to the infected tissue site.

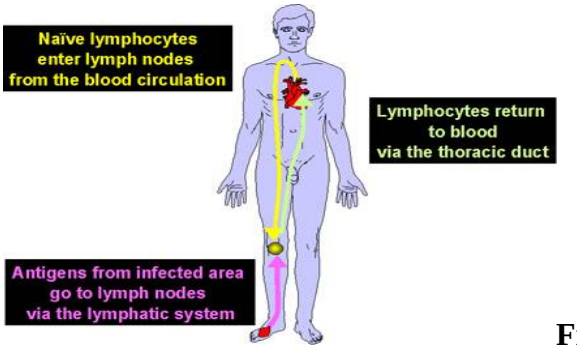

Figure 4.

b) Naïve (virgin) lymphocytes enter the lymph nodes from the blood via High Endothelial Venules (HEVs). Homing receptors on the lymphocytes direct the cells to the HEVs. In the lymph nodes, lymphocytes with the appropriate Ag receptor encounter Ag, which has been transported to the lymph nodes by dendritic cells or macrophages. After activation the lymphocytes express new receptors that allow the cells to leave the lymph node and reenter the circulation. Receptors on the activated lymphocytes recognize cell adhesion molecules expressed on endothelial cells near the site of an infection and chemokines produced at the infection site help attract the activated cells (Figure 5).

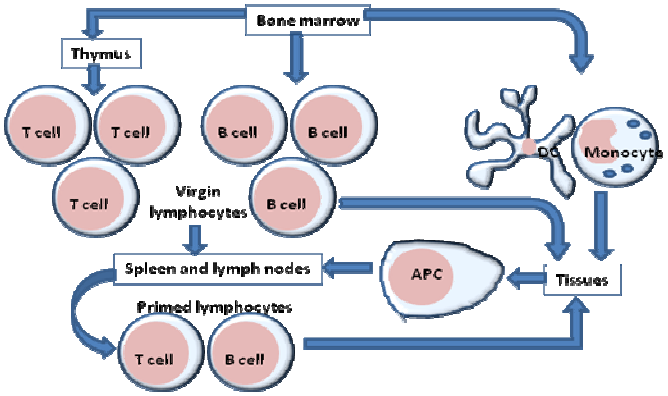

Figure 5.