

TOPIC: Cells Involved in Immune Responses

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TEACHING OBJECTIVES: To provide an overview of the types of cell interactions and molecules required for specific immunity

To describe specific immunity and the cells involved

SUGGESTED READING: Roitt, Brostoff, Male, 6th Edition, Mosby, 2001 Chapter 1; Chapter 2, pp. 15-30, 42-44; Chapter 5, pp 87-97; Chapter 6, pp. 112-115



White blood cell (lymphocyte) in capillary (TEM x16,210) ©© Dr Dennis Kunkel, University of Hawaii. Used with permission

OVERVIEW

Immunology is the study of the mechanisms that a host has evolved to rid itself of pathogens and other foreign substances.

There are two sites at which pathogens may be located:

1. **Extracellular sites**
2. **Intracellular sites**

Antibodies are effective against extracellular pathogens and function in three major ways:

1. **Neutralization**
 - a. Antibodies may bind to bacterial toxins
 - b. Antibodies may bind to molecules that viruses and bacteria use to attach to cells to gain entry for infection
2. **Opsonization**
 - a. An antibody facilitates uptake by phagocytes

3. Complement activation

- a. Antibodies facilitate uptake by phagocytes and lyse certain bacteria. It should be noted that antibodies in each class can have different sites of action and are not equally effective in neutralization, **opsonization**, and complement activation.

Antibodies are not particularly effective against pathogens that reside intracellularly.

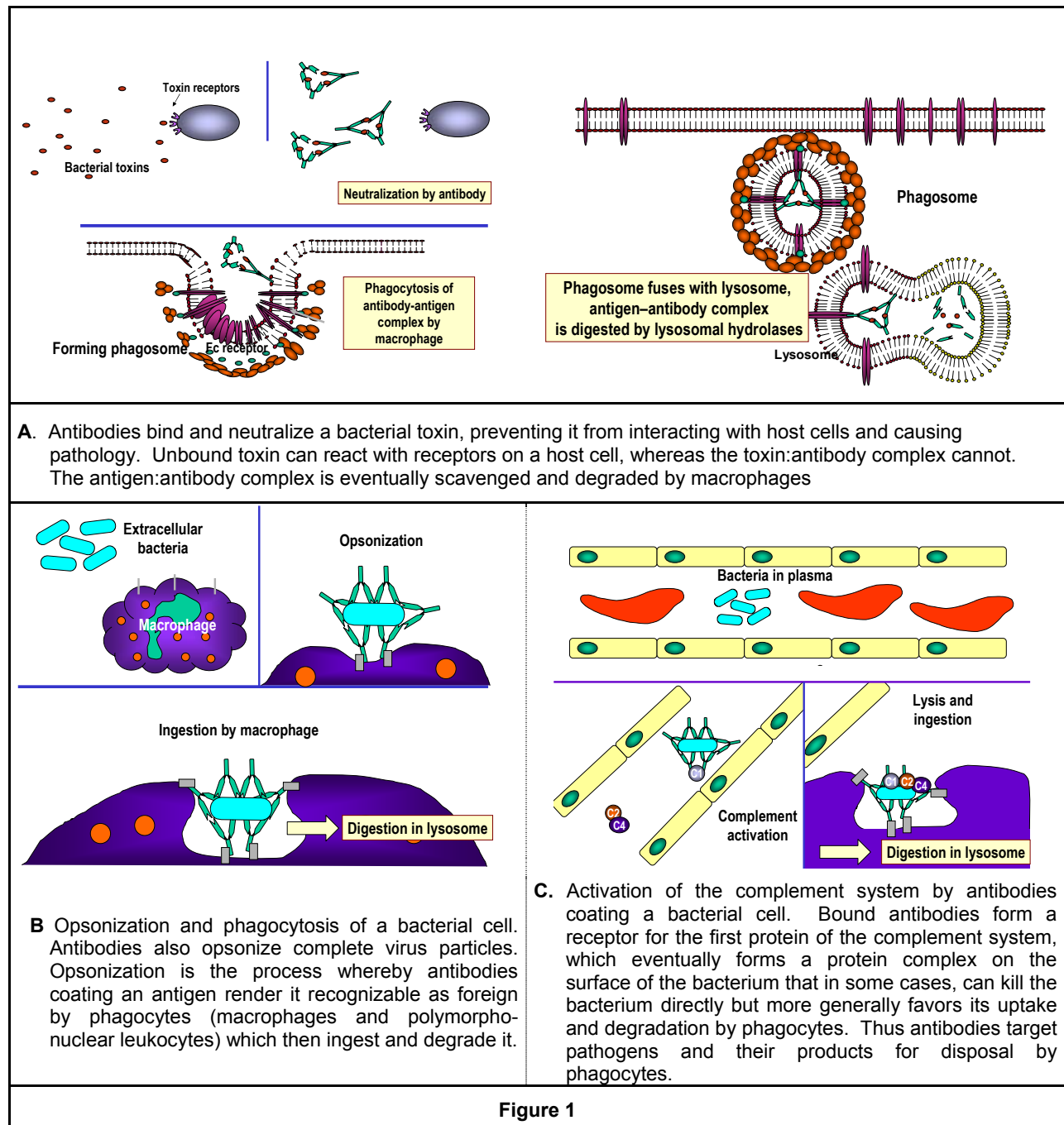


Figure 1

Intracellular Sites

T cell-mediated responses are effective against intracellular pathogens, which reside in one of two major intracellular compartments:

1. **cytosol** - continuous with nucleus via nuclear pores - site of all viruses and some bacteria
2. **vesicular system** - comprises endoplasmic reticulum, Golgi apparatus, endosomes, lysosomes, and other intracellular vesicles - site of some bacteria and some parasites

Location of pathogen largely determines which T cell population responds:

Cytotoxic (cytolytic) T cells (Tc)

These cells express **CD8** molecules and when activated can kill target cells that harbor pathogens in the **cytosol**. (Figure 2). Also abbreviated as CTL (cytotoxic or cytolytic T lymphocytes)

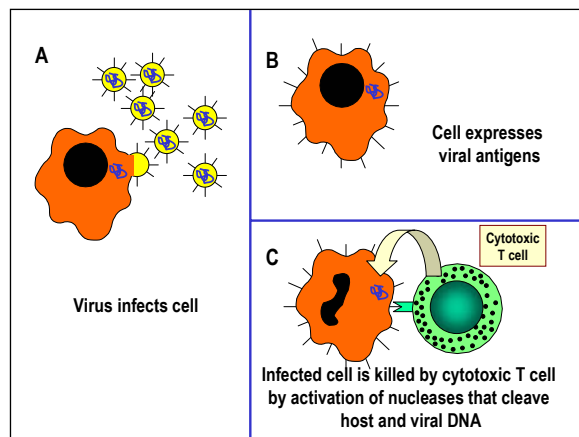


Figure 2: Mechanism of host defense against intracellular infection by viruses. Cells infected by viruses are recognized by specialized T cells called Tc or cytotoxic T lymphocytes (CTLs), which kill the infected cells directly. The killing mechanism involves the activation of nucleases in the infected cell, which cleave host and viral DNA.

Helper T Cells (Th)

These cells express **CD4** molecules and can differentiate into:

- a) **Inflammatory Th1 cells** that can eliminate pathogens residing intracellularly in **vesicular** compartments. (Figure 3)
- b) “True” **helper Th2 cells** required for antibody production by B cells against T-dependent antigens on pathogens residing **extracellularly**.

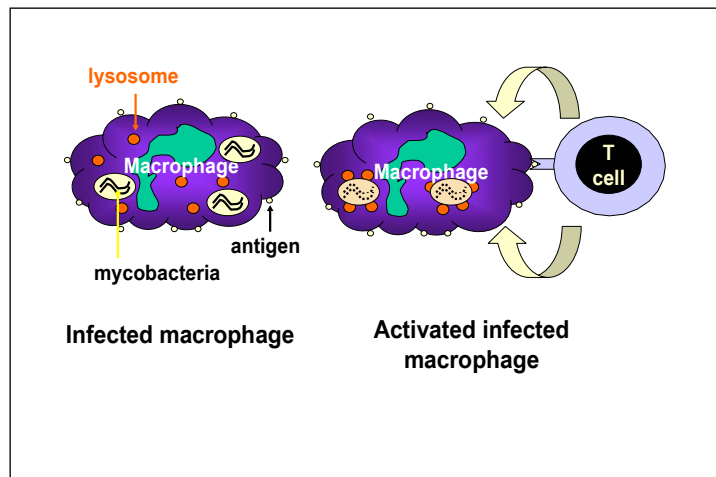


Figure 3: Mechanism of host defense against intracellular infection by mycobacteria. Mycobacteria infecting macrophages live in cytoplasmic vesicles that resist fusion with lysosomes and consequent destruction of the bacteria by macrophage bacteriocidal activity. However, when the appropriate Th1 cell recognizes an infected macrophage it releases macrophage-activating molecules that induce lysosomal fusion and the activation of macrophage bacteriocidal activities.

Pathogens may elicit both an antibody (humoral) and cell-mediated response, each of which contributes to ridding the host of the pathogen.

For example: cells with intracellular viruses can be killed by cytotoxic T cells; viruses that are free extracellularly can be neutralized and opsonized by antibody.

A humoral or cell-mediated response may by itself be insufficient to eliminate the pathogen.

For example: *Mycobacterium leprae*, an intracellular bacterium that can cause leprosy. There are two main classes of patients: 1) In some, the major response is Ig production and *M. Leprae* grows abundantly in macrophages leading to gross tissue destruction and development of lepromatous leprosy which is usually fatal 2) In others, little Ig is produced, but there are few live intracellular *M. leprae* because a cell-mediated response has also occurred. Thus, disease progression is slow with a good outcome.

Specificity of Immune Responses

The specificity for these immune responses resides in the T cell receptor (TCR) which recognizes pathogen (antigen)-derived peptides bound to major histocompatibility complex (MHC) molecules expressed on the surface of nucleated cells. Every TCR on an individual T cell has one specificity. (**REMEMBER:** the B cell receptor that binds antigen is a membrane-bound immunoglobulin, and every Ig on an individual B cell has one specificity.)

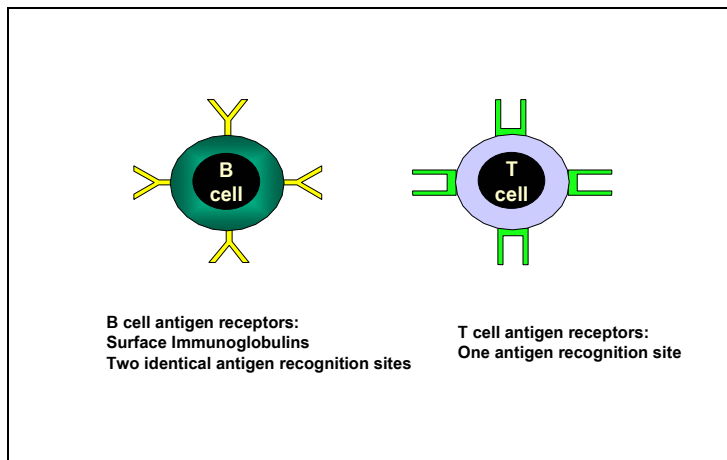


Figure 4: The antigen receptors of B cells have two antigen-recognition sites whereas those of T cells have only one.

Diversity of Receptor Specificity

What accounts for the vast array of receptor specificities?

This is frequently referred to as the **repertoire**.

Historical note: The discovery and elucidation of the T cell receptor (TCR) is recent. Antibodies and their ability to bind many different antigens have been known for a long time, and two major hypotheses were advanced to explain how antibodies could be formed that bind to many antigens:

- a) Instructionist (template) hypothesis
- b) Clonal selection hypothesis

The instructionist hypothesis did not account for recognition of self vs. non-self antigens. Because of this and increasing scientific evidence, the clonal selection hypothesis has been accepted.

Clonal Selection

The Four Basic Principles of the Clonal Selection Hypothesis

Each lymphocyte bears a single type of receptor of a unique specificity

Interaction between a foreign molecule and a lymphocyte receptor capable of binding that molecule with high affinity leads to lymphocyte activation

The differentiated effector cells derived from an activated lymphocyte will bear receptors of an identical specificity to those of the parental cell from which that lymphocyte was derived

Lymphocytes bearing receptors specific for self molecules are deleted at an early stage in lymphoid cell development and are therefore absent from the repertoire of mature lymphocytes

This hypothesis accounts for the specificity of an immune response, signals required for specific activation, lag in specific (adaptive) immune responses, and lack of an immune response against self antigens.

Self-reactive T cells are eliminated mainly in the thymus.

Classes of Major Histocompatibility Complex (MHC) Molecules Recognized by the TCR of T Cells

The TCR recognizes peptide bound to a MHC molecule expressed on the cell surface. There are two classes of MHC molecules, called MHC class I and MHC class II.

1. MHC class I

Expressed on the surface of all nucleated cell types
Recognized by the TCR of CD8 cytotoxic T cells (Tc cells)
CD8 binds to the class I MHC-peptide complex
Source of peptides is the cytosol

2. MHC class II

Expressed on the surface of a small number of nucleated cell types, referred to as antigen presenting cells (APC), the most important ones being macrophages, B cells, and dendritic cells (Langerhans cells)
Recognized by the TCR of CD4 helper T cells (Th cells)
CD4 binds to class II MHC-peptide complexes
Source of peptides is the vesicular compartment

NOTE: The fragmentation of proteins and association of peptides with each of the two classes of MHC molecules undergo different pathways that are referred to collectively as **antigen processing and presentation**.

Immunity: Contrasts between non-specific and specific

A. Non-specific (natural, native, innate)

1. System in place prior to exposure to antigen
2. Lacks discrimination among antigens
3. Can be enhanced after exposure to antigen through effects of cytokines

B. Specific (acquired, adaptive)

1. Induced by antigen
2. Enhanced by antigen
3. Shows fine discrimination

The hallmarks of the specific immune system are memory and specificity.

1. The specific immune system "remembers" each encounter with a microbe or foreign antigen, so that subsequent encounters stimulate increasingly effective defense mechanisms.
2. The specific immune response amplifies the protective mechanisms of non-specific immunity, directs or focuses these mechanisms to the site of antigen entry, and thus makes them better able to eliminate foreign antigens.

Cells of the Immune System

There are two main lineages that derive from the hemopoietic stem cell:

1. the lymphoid lineage

T lymphocytes (T cells)
B lymphocytes (B cells)
Natural killer cells (NK cells)

2. the myeloid lineage

Monocytes, macrophages
Langerhans cells, dendritic cells
Megakaryocytes
Granulocytes (eosinophils, neutrophils, basophils)

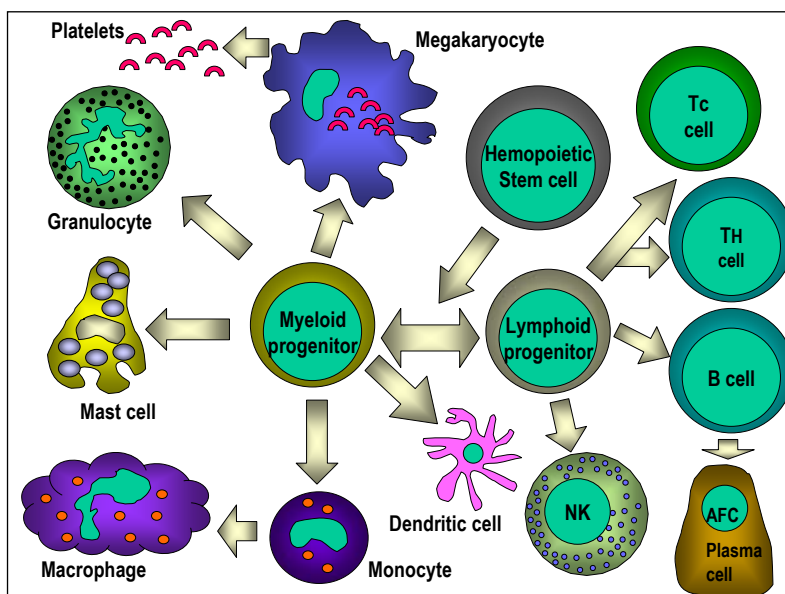


Figure 5: All hematopoietic cells are derived from pluripotent stem cells which give rise to two main lineages: one for lymphoid cells and one for myeloid cells. The common lymphoid progenitor has the capacity to differentiate into either T cells or B cells depending on the microenvironment to which it homes. In mammals, T cells develop in the thymus while B cells develop in the fetal liver and bone marrow. An AFC is an antibody-forming cell, the plasma cell being the most differentiated AFC. NK cells also derive from the common lymphoid progenitor cell. The myeloid cells differentiate into the committed cells on the left. The collective name "granulocyte" is used for eosinophils, neutrophils and basophils

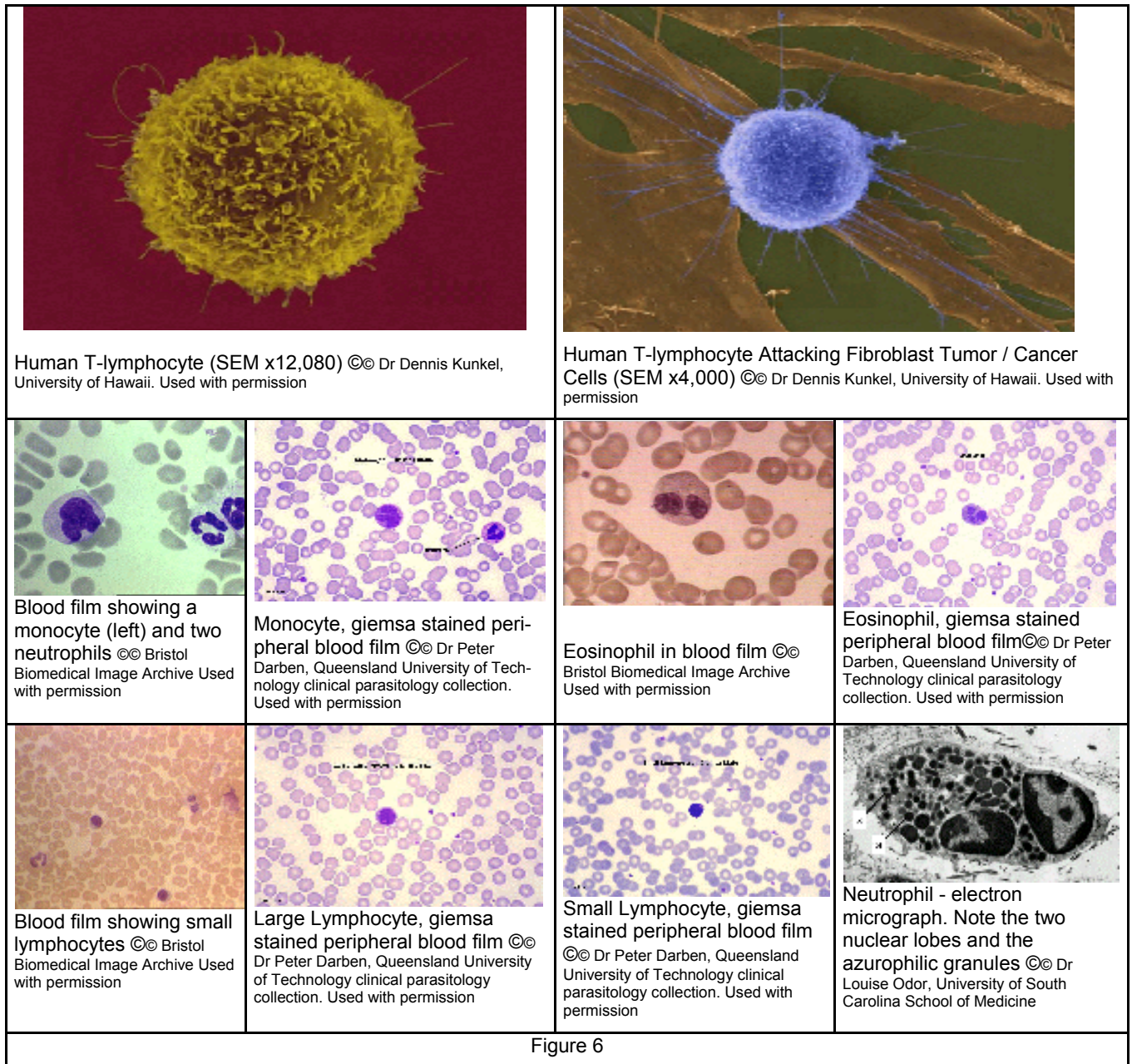


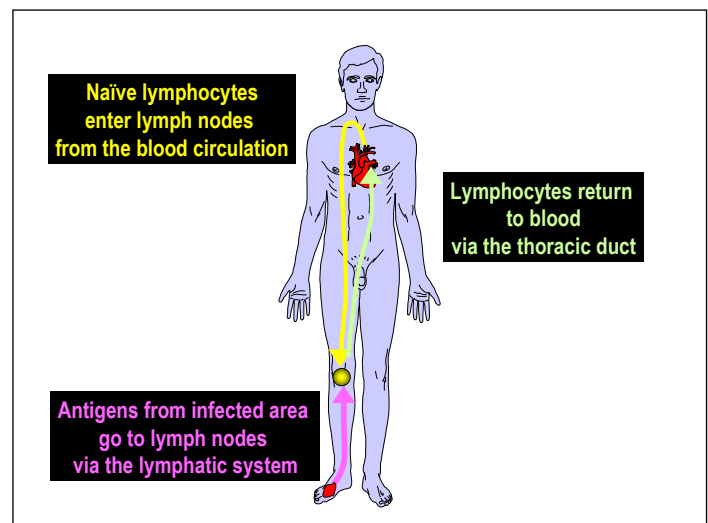
Figure 6

Lymphocyte recirculation

Lymphocytes recirculate and encounter antigen in peripheral lymphoid tissues.

Since so few lymphocytes possess a receptor that can bind a given antigen (1/10,000 to 1/100,000), chances for a successful encounter with an antigen presenting cell are optimized by circulating lymphocytes through lymphoid tissues.

Figure 7: Circulating lymphocytes encounter antigen in peripheral lymphoid tissues.



Leukocyte Migration and Localization

Productive cell interactions leading to specific immune responses occur mainly in lymph nodes and spleen. (The lymph node and spleen are referred to as **secondary lymphoid tissues**; **bone marrow and thymus** are termed **primary lymphoid tissues**.)

Figure 8 shows the various kinds of leukocyte migration:

1. T cells exiting the thymus and B cells leaving the bone marrow (naive lymphocytes, also called virgin lymphocytes) migrate from primary lymphoid tissues to the blood and thence into secondary lymphoid tissues. From there they return to the circulation and ultimately back to the secondary lymphoid tissues. This is known as lymphocyte recirculation. Approximately 1-2% of the lymphocyte pool recirculates each hour and optimizes the opportunities for antigen-specific lymphocytes to come into contact with antigen in the secondary lymphoid tissues.
2. Lymphocytes activated by an encounter with antigen move from the spleen or lymph node and travel to other tissues. For example, activated T cells express new cell surface molecules that enable them to bind to peripheral vascular endothelium and thence to egress to extravascular spaces. Primed and activated are synonymous terms.
3. Antigen presenting cells may pick up antigen and migrate to the secondary lymphoid tissues. The Langerhans cell of the skin is a classic example.

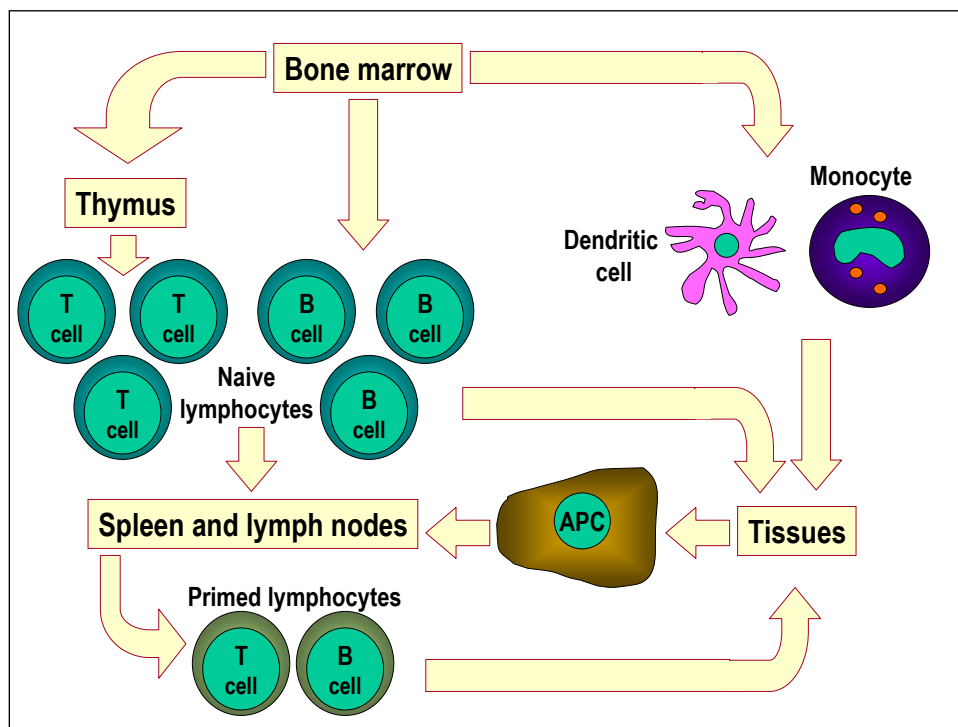


Figure 8: Naive lymphocytes from the primary lymphoid tissues such as bone marrow migrate to secondary lymphoid tissues, i.e. the spleen and lymph nodes. Antigen-presenting cells (APCs), including dendritic cells and mononuclear phagocytes (monocytes), also derive from bone marrow stem cells. These APCs enter tissues, take up antigen and transport it to the lymphoid tissues to be presented to T cells and B cells. Primed lymphocytes then migrate from the lymphoid tissues and accumulate preferentially at sites of infection and inflammation.