Erythroid Cells

- Cells of the erythroid lineage—**erythrocytes**, or red blood cells—also arise from a common myeloid precursor (sometimes referred to as a common myeloid-erythroid precursor).
- They contain high concentrations of hemoglobin, and circulate through blood vessels and capillaries delivering oxygen to surrounding cells and tissues.
- Damaged red blood cells can also release signals (free radicals) that induce innate immune activity.
- In mammals, erythrocytes are a nuclear; their nucleated precursors (erythroblasts) extrude their nuclei in the bone marrow. However, the erythrocytes of almost all non mammalian vertebrates (birds, fish, amphibians, and reptiles) retain their nuclei.

FOURTH LECTURE

Cells of the Lymphoid Lineage Regulate the Adaptive Immune Response

- **Lymphocytes** are the principal cell players in the adaptive immune response. They represent 20% to 40% of circulating white blood cells and 99% of cells in the lymph.
- Lymphocytes can be broadly subdivided into three major populations on the basis of functional and phenotypic differences:
- B lymphocytes (B cells), T lymphocytes (T cells), and natural killer (NK) cells.
- In humans, approximately a trillion (1012) lymphocytes circulate continuously through the blood and lymph and migrate into the tissue spaces and lymphoid organs.

Megakaryocytes

Megakaryocytes are large myeloid cells that reside in the bone marrow and give rise to thousands of **platelets**, very small cells (or cell fragments) that circulate in the blood and participate in the formation of blood clots. Although platelets have some of the properties of independent cells, they do not have their own nuclei.

TABLE 2-3 Common CD markers used to distinguish functional lymphocyte subpopulations

CD designation	Function	B cell	T_H	T_C	NK cell
CD2	Adhesion molecule; signal transduction	–	+	+	+
CD3	Signal transduction element of T-cell receptor	–	+	+	–
CD4	Adhesion molecule that binds to class II MHC molecules; signal transduction	–	+ (usually)	– (usually)	–
CD5	Unknown	+ (subset)	+	+	+
CD8	Adhesion molecule that binds to class I MHC molecules; signal transduction	–	– (usually)	+ (usually)	(variable)
CD16 (FcγRIII)	Low-affinity receptor for Fc region of IgG	–	–	–	+
CD19	Signal transduction; CD21 co-receptor	+	–	–	–
CD21 (CR2)	Receptor for complement (C3d and Epstein-Barr virus)	+	–	–	–
CD28	Receptor for costimulatory B7 molecule on antigen-presenting cells	–	+	+	–
CD32 (FcγRII)	Receptor for Fc region of IgG	+	–	–	–
CD35 (CR1)	Receptor for complement (C3b)	+	–	–	–
CD40	Signal transduction	+	–	–	–
CD45	Signal transduction	+	+	+	+
CD56	Adhesion molecule	–	–	–	+

Synonyms are shown in parentheses.

- Lymphocytes are very difficult to distinguish morphologically
- T and B cells, in particular, appear identical under a microscope.
- We therefore rely heavily on the signature of surface proteins they express to differentiate among lymphocyte subpopulations.
- Surface proteins expressed by immune cells are often referred to by the **cluster of differentiation (CD** or *cluster of designation*) nomenclature.
- This nomenclature was established in 1982 by an international group of investigators who recognized that many of the new antibodies produced by laboratories all over the world (largely in response to the advent of monoclonal antibody technology) were seeing the same proteins.
- They therefore defined clusters of antibodies that appeared to be seeing the same protein and assigned a name— a cluster of differentiation or CD—to each group.
- Although originally designed to categorize the multiple antibodies, the CD nomenclature is now firmly associated with specific surface proteins found on cells of many types.

- Mature B cells and T cells are ready to encounter antigen, but they are considered **naïve** until they do so.
- Contact with antigen induces naïve lymphocytes to proliferate and differentiate into both effector cells and memory cells.
- **Effector cells** carry out specific functions to combat the pathogen, while the **memory cells** persist in the host, and upon re challenge with the same antigen mediate a response that is both quicker and greater in magnitude.
- The first encounter with antigen is termed a **primary response**, and the re-encounter a **secondary response**.

- In addition to their CD surface signatures, each B or T cell also expresses an antigen-specific receptor (the **B cell receptor (BCR)** or the **T cell receptor (TCR)**, respectively) on its surface.
- Although the populations of B cells and T cells express a remarkable diversity of antigen receptors (more than a billion),
- all receptors on an individual cell's surface have identical structures and therefore have identical specificities for antigen.
- If a given lymphocyte divides to form two daughter cells, both daughters bear antigen receptors with antigen specificities identical to each other and to the parental cell from which they arose, and so will any descendants they produce.
- The resulting population of lymphocytes, all arising from the same founding lymphocyte, is a **clone**.

B Lymphocytes

- The **B lymphocyte (B cell)** derived its letter designation from its site of maturation, in the *b*ursa of Fabricius in birds; the name turned out to be apt, as *b*one marrow is its major site of maturation in humans, mice, and many other mammals.
- Mature B cells are definitively distinguished from other lymphocytes and all other cells by their synthesis and display of the B-cell receptor (BCR), a membrane-bound immunoglobulin (antibody) molecule that binds to antigen, each B cell expresses 50,000-150,000 the immunoglobulin receptors (Ig receptor) on its surface , although the membrane Igs may consist more than one class of Ig (usually IgM and IgD on naïve B cells).
- Igs can directly recognize protein, polysaccharide, glycolipid , or nucleic acid antigens in their undigested or natural state .

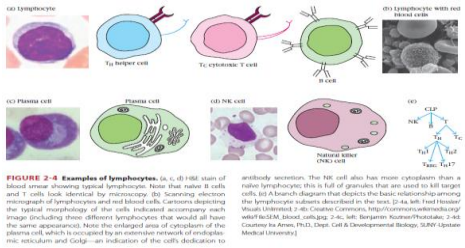
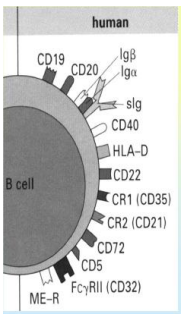


FIGURE 2-4 Examples of lymphocytes. (a, c, d) H&E stain of blood smear showing typical lymphocyte. Note that naïve B cells and T cells look identical by microscopy. (b) Scanning electron micrograph of lymphocytes and red blood cells. Cartoons depicting the typical morphology of the cells indicated accompany each image (including three different lymphocytes that would all have the same appearance). Note the enlarged area of cytoplasm of the plasma cell, which is occupied by an extensive network of endoplasmic reticulum and Golgi—an indication of the cell's dedication to antibody secretion. The NK cell also has more cytoplasm than a naïve lymphocyte; this is full of granules that are used to kill target cells. (e) A branch diagram that depicts the basic relationship among the lymphocyte subsets described in the text. [2-4a, left: Fred Hossler/Visuals Unlimited; 2-4b Creative Commons, http://commons.wikimedia.org/wiki/File:SEM_blood_cells.jpg; 2-4c, left: Benjamin Kozlner/Photolabs; 2-4d: Courtesy Ira Ames, Ph.D., Dept. Cell & Developmental Biology, SUNY Upstate Medical University.]

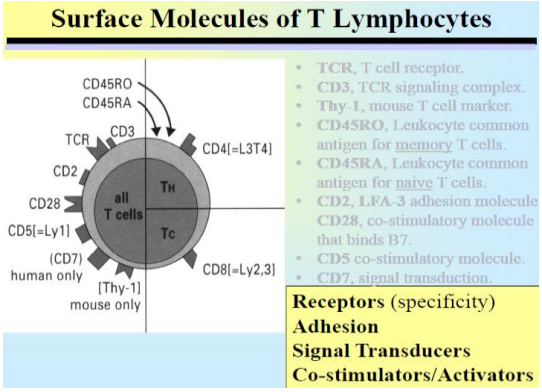
- Each B cell expresses a surface antibody with a unique specificity, and each of the approximately 1.5–3 _ 105 molecules of surface antibody has identical binding sites for antigen.
- B lymphocytes also can improve their ability to bind antigen through a process known as somatic hypermutation and can generate antibodies of several different functional classes through a process known as class switching.
- Ultimately, activated B cells differentiate into effector cells known as **plasma cells**.
- Plasma cells lose expression of surface immunoglobulin and become highly specialized for secretion of antibody.
- A single cell is capable of secreting from a few hundred to more than a thousand molecules of antibody per second.
- Plasma cells do not divide and, although some long-lived populations **memory cells** of plasma cells are found in bone marrow.

Surface Molecules of B Lymphocytes



Ig H+L, B cell receptor for antigen.
Ig α/β, signal transduction molecules.
HLA-D, class II restricted major histocompatibility marker.
CR21 and **CD35**, complement receptors.
CD19, B-cell co-receptor subunit.
CD20, **CD5**, signal transduction molecules.
CD40, co-stimulatory.
CD5, co-stimulator-activator.
CD32, FcγRII.
CD45, leukocyte common antigen.

Receptors (specificity)
Signal Transducers
Co-stimulators/Activators



T lymphocytes

- **(T cells)** derive their letter designation from their site of maturation in the thymus.
- Like the B cell, the T cell expresses a unique antigen-binding receptor called the T-cell receptor (TCR) which either αβ or γδ .
- However, unlike membrane-bound antibodies on B cells, which can recognize soluble or particulate antigen, T-cell receptors only recognize processed pieces of antigen (typically peptides) bound to cell membrane proteins called **major histocompatibility complex (MHC) molecules**.
- MHC molecules are genetically diverse glycoproteins found on cell membranes. The ability of MHC molecules to form complexes with antigen allows cells to decorate their surfaces with internal (foreign and self) proteins, exposing them to browsing T cells. MHC comes in two versions: **class I MHC molecules**, which are expressed by nearly all nucleated cells of vertebrate species, and **class II MHC molecules**, which are expressed by professional antigen-presenting cells and a few other cell types during inflammation.

- Naïve CD8_ T cells browse the surfaces of antigen presenting cells with their T-cell receptors. If and when they bind to an MHC-peptide complex, they become activated, proliferate, and differentiate into an effector cell called a **cytotoxic T lymphocyte (CTL)**.
- The CTL has a vital function in monitoring the cells of the body and eliminating any cells that display foreign antigen complexed with class I MHC, such as virus-infected cells, tumor cells, and cells of a foreign tissue graft . To proliferate and differentiate optimally, naïveCD8_ T cells also need help from mature CD4_ T cells.

- T lymphocytes are divided into two major cell types—**T helper (TH) cells** and **T cytotoxic (TC) cells**—that can be distinguished from one another by the presence of either **CD4** or **CD8** membrane glycoproteins on their surfaces.
- *T cells displaying CD4 generally function as TH cells and recognize antigen in complex with MHC class II, whereas those displaying CD8 generally function as TC cells and recognize antigen in complex with MHC class I.*
- The ratio of CD4_ to CD8_ T cells is approximately 2:1 in normal mouse and human peripheral blood. A change in this ratio is often an indicator of immunodeficiency disease (e.g., HIV), autoimmune diseases, and other disorders.

- Another type of CD4_ T cell, the **regulatory T cell (TREG)**,has the unique capacity to inhibit an immune response. These cells can arise during maturation in the thymus from autoreactive cells (natural TREG), but also can be induced at the site of an immune response in an antigen-dependent manner (induced TREG).
- They are identified by the presence of CD4 and CD25 on their surfaces, as well as the expression of the internal transcription factor FoxP3.
- TREG cells are critical in helping us to quell autoreactive responses that have not been avoided via other mechanisms.

Naïve CD4_ T cells also browse the surfaces of antigen presenting cells with their T-cell receptors. If and when they recognize an MHC-peptide complex, they can become activated and proliferate and differentiate into one of a variety of effector T cell subsets.

- **T helper type 1 (TH1) cells** regulate the immune response to intracellular pathogens, and
- **T helper type 2 (TH2) cells** regulate the response to many extracellular pathogens.

T helper type 17 cells (TH17), so named because they secrete IL-17, play an important role in cell-mediated immunity and may help the defense against fungi.

- **T follicular helper cells (TFH)** play an important role in humoral immunity and regulate B-cell development in germinal centers. Which helper subtype dominates a response depends largely on what type of pathogen (intracellular versus extracellular, viral, bacterial, fungal, helminth) has infected an animal.
- Each of these CD4_ T-cell subtypes produces a different set of cytokines that enable or "help" the activation of B cells, TC cells, macrophages, and various other cells that participate in the immune response.

How can cells recognize an absence? NK cells express a variety of receptors for self MHC class I that, when engaged, inhibit their ability to kill other cells. When NK cells encounter cells that have lost their MHC class I, these receptors are no longer engaged and `1can no longer inhibit the potent cytotoxic tendencies of the NK cell, which then releases its cytolytic granules and kills the abnormal target cell.

NK cells also express receptors for immunoglobulins and can therefore decorate themselves with antibodies that bind pathogens or proteins from pathogens on the surface of infected cells. This allows an NK cell to make a connection with a variety of target cells (independently of their MHC class I expression).

Once the antibodies bring the NK cell in contact with target cells, the NK cell releases its granules and induces cell death.

Natural Killer Cells

Natural killer (NK) cells are lymphoid cells that are closely related to B and T cells.

- However, they do not express antigen specific receptors and are considered part of the innate immune system. They are distinguished by the expression of a surface marker known as NK1.1, as well as the presence of cytotoxic granules.
- Once referred to as "large granular lymphocytes" because of their appearance under a microscope,
- NK cells constitute 5% to 10% of lymphocytes in human peripheral blood. They are efficient cell killers and attack a variety of abnormal cells, including some tumor cells and some cells infected with virus.
- They distinguish cells that should be killed from normal cells in a very clever way: by"recognizing" the absence of MHC class I, which is expressed by almost all normal cells, but is specifically down-regulated by some tumors and in response to some viral infections.

NKT Cells

- Another type of cell in the lymphoid lineage,
- **NKT cells** Like T cells, NKT cells have T-cell receptors (TCRs), and some express CD4.
- Unlike most T cells, however, the TCRs of NKT cells are not very diverse and recognize specific lipids and glycolipids presented by a molecule related to MHC proteins known as CD1.,
- NK cells, NKT cells have antibody receptors, as well as other receptors classically associated with NK cells.
- Activated NKT cells can release cytotoxic granules that kill target cells, but they can also release large quantities of cytokines that can both enhance and suppress the immune response.
- They appear to be involved in human asthma, but also may inhibit the development of autoimmunity and cancer. Understanding the exact role of NKT cells in immunity is one research priority.