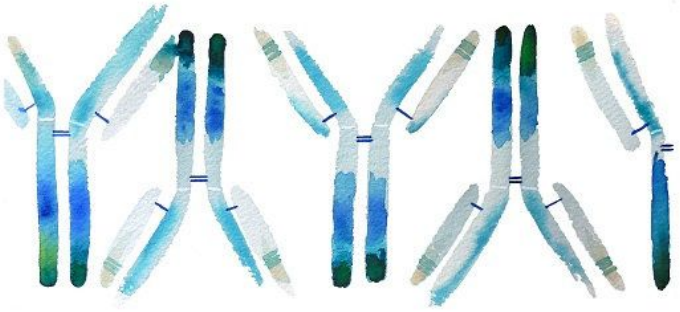
Medical Immunology



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Lecture 3

TABLE 2–1 Normal Blood Cell Counts

	Mean Number per Microliter	Normal Range
White blood cells (leukocytes)	7400	4500-11,000
Neutrophils	4400	1800-7700
Eosinophils	200	0-450
Basophils	40	0-200
Lymphocytes	2500	1000-4800
Monocytes	300	0-800

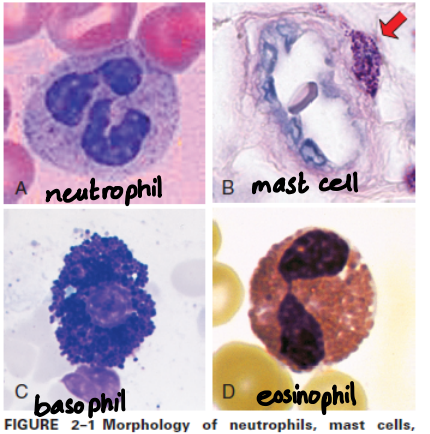
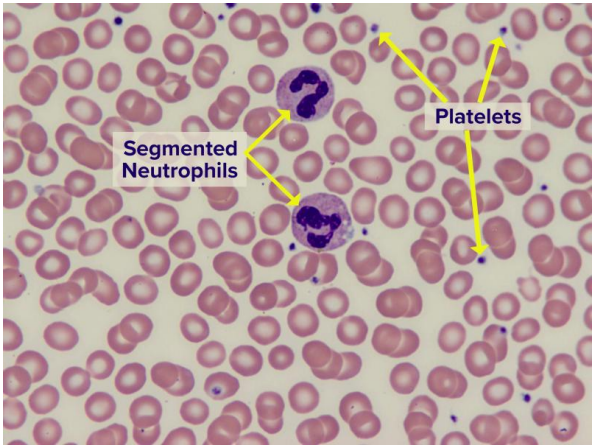
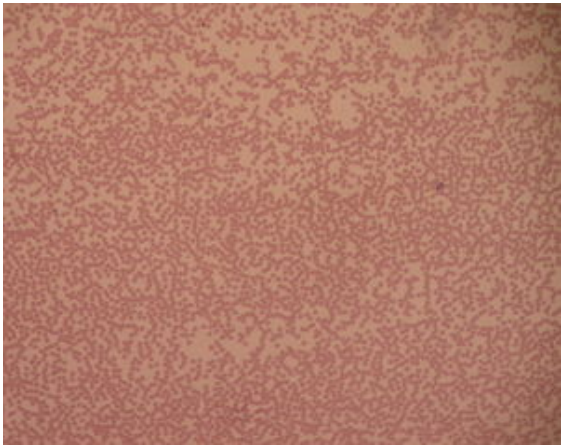


FIGURE 2–1 Morphology of neutrophils, mast cells, basophils, and eosinophils. A, The light micrograph of a Wright-Giemsa–stained blood neutrophil shows the multilobed nucleus, because of which these cells are also called polymorphonuclear leukocytes, and the faint cytoplasmic granules. **B,** The light micrograph of a Wright-Giemsa–stained section of skin shows a mast cell *(arrow)* adjacent to a small blood vessel, identifiable by the red blood cell in the lumen. The cytoplasmic granules in the mast cell, which are stained purple, are filled with histamine and other mediators that act on adjacent blood vessels to promote increased blood flow and delivery of plasma proteins and leukocytes into the tissue. *(Courtesy of Dr. George Murphy, Department of Pathology, Brigham and Women's Hospital, Boston, Massachusetts.)* **C,** The light micrograph of a Wright-Giemsa–stained blood basophil shows the characteristic blue-staining cytoplasmic granules. *(Courtesy of Dr. Jonathan Hecht, Department of Pathology, Brigham and Women's Hospital, Boston, Masssachusetts.)* **D,** The light micrograph of a Wright-Giemsa–stained blood eosinophil shows the characteristic segmented nucleus and red staining of the cytoplasmic granules.

Although most of these cells are found in the blood, their responses to microbes are usually **localized to tissues** and are generally **not reflected** in changes in the **total** numbers of circulating leukocytes





Blood film with a striking absence of neutrophils, leaving only red blood cells and platelets

People with neutropenia are more susceptible for infections than normal people

Neutropenia is an abnormally low concentration of neutrophils in the blood. Neutropenia has many causes and can be *congenital* and *acquired (e.g. cancer treatment, autoimmune diseases)*.

Affect on rapidly dividing cells including bone marrow

Clinical History

Patient: 22-year-old African-American male

Chief Complaint: Episodic fevers

History of Present Illness: The patient has experienced episodic fevers regularly for the past 6 months. Initially, the fevers occurred 4-6 weeks apart but have been increasing in frequency in the past 2 months. Each episode reportedly lasts about 3 days, with the fever peaking around 103°F. The fever is accompanied by muscle pain and occasionally sore throat, chills, and night sweats. There is no associated nausea, vomiting, or lymphadenopathy. During the previous 3 weeks, the patient reported a decreased appetite and an unintended weight loss of 10-20 pounds. The fevers typically resolved with acetaminophen, and the patient recently completed several courses of amoxicillin.

Past Medical History: The patient was hospitalized approximately 3 weeks prior to this presentation for similar symptoms. At that time, he was noted to have a significantly reduced absolute neutrophil count, which recovered with supportive care. Since his discharge, he has had weekly complete blood counts, all of which have been normal.

Social History: The patient is a smoker and drinks rarely. He denies substance abuse issues or recreational drug use.

Family History: Non-contributory.

Physical Exam

Vital Signs: Temperature, 99°F; heart rate, 82 beats per minute; respiratory rate, 16 per minute; blood pressure, 160/80 mmHg.
Skin: No rash.
Lymph Nodes: No significant submandibular, cervical, or supraclavicular lymphadenopathy.
Pulmonary: Clear to auscultation.

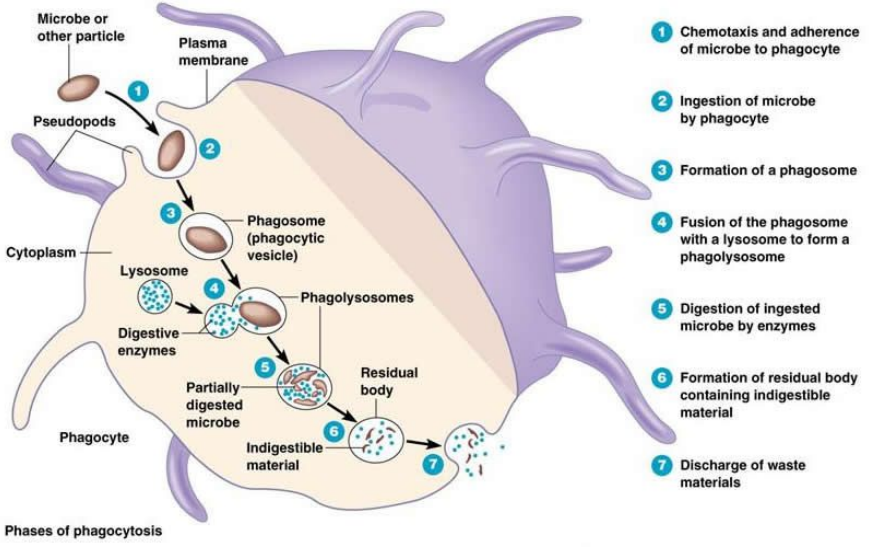
Principal Laboratory Findings: See **Table 1** and **Image 1**.

Keywords: Genetics, Hematology, Hematopathology, Clinical Pathology, Chemistry

Cells of the immune system / Phagocytes

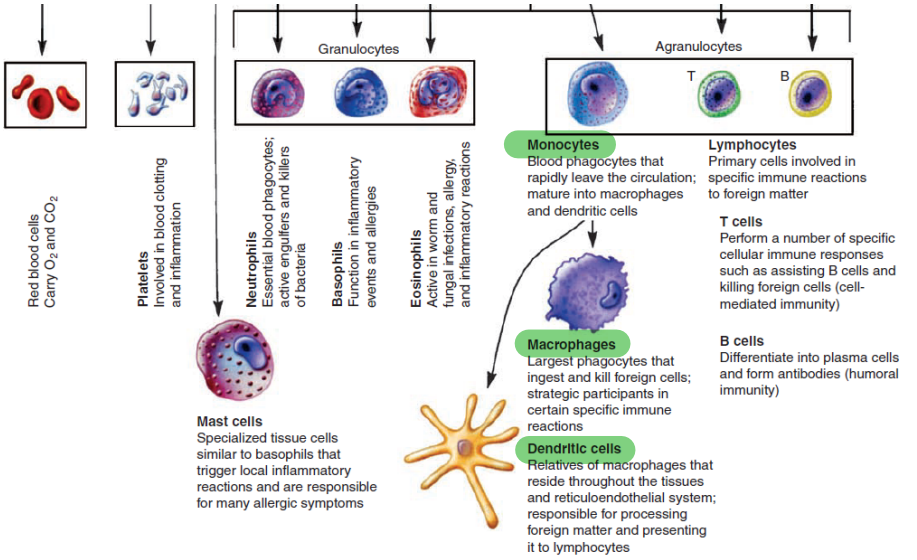
- Phagocytes, including **neutrophils** and **macrophages**, are cells whose primary function is to identify, ingest, and destroy microbes.

- Phagocytes also communicate with other cells in ways that promote or regulate immune responses.



Cells of the immune system

- **Phagocytes**
- **Mast Cells, Basophils, Eosinophils**
- **Antigen-Presenting Cells**
- **Lymphocytes**



Cells of the immune system / Antigen presenting cells

حلقة وصل بين innate immunity و adaptive immunity لأنهم بجيبو ال specific antigen لخلايا B & T

Mainly T cells

Antigen-presenting cells (APCs) are cell populations that are specialized to **capture** microbial and other **antigens**, **display** them to **lymphocytes**, and provide signals that **stimulate** the **proliferation** and **differentiation** of the **lymphocytes**.

The major type of APC that is involved in initiating T cell responses is the **dendritic cell**.

Macrophages and **B cells** as well present antigens to T lymphocytes in different types of immune responses.

APCs **link responses of the innate immune system to responses of the adaptive immune** system, and therefore they may be considered components of both systems.

Cells of the immune system / Antigen presenting cells/ Dendritic Cells

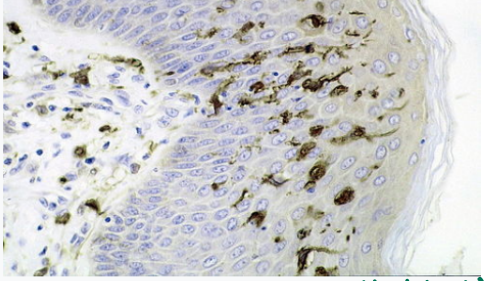
* These dendritic cells were called as such because they've dendrites to occupy larger area in the tissue

- Dendritic cells are the most important APCs for **activating naive T cells**, and they play major roles in innate responses to infections and in linking innate and adaptive immune responses.

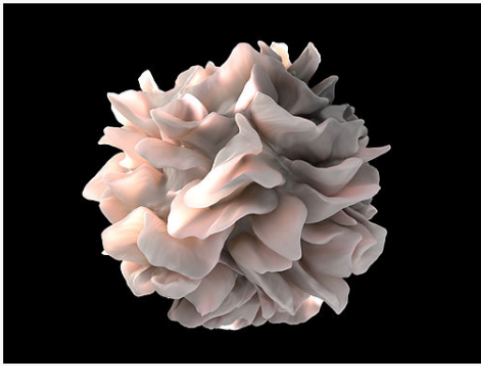
* It is a tissue-resident cell mainly waiting to the presence of an antigen

- They have long **membranous projections** and **phagocytic capabilities** and are widely distributed in lymphoid tissues, mucosal epithelium, and organ parenchyma.

- In response to activation by microbes, conventional dendritic cells in skin, mucosa, and organ parenchyma become mobile, migrate to lymph nodes, and display microbial antigens to T lymphocytes.



Dendritic cells in skin (in black)



Artistic rendering of the surface of a human dendritic cell illustrating sheet-like processes that fold back onto the membrane surface.

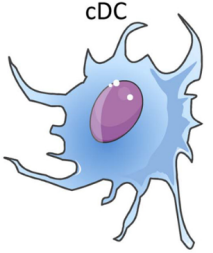
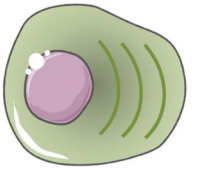
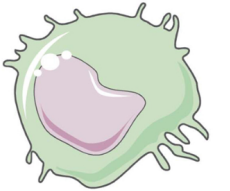
* **Mechanism of the dendritic cell function :**

1) **Hold the antigen with its dendrites**
2) **Phagocyte the antigen**
3) **Process the antigen and display it on its surface on molecule called MHC**
4) **Presenting it to lymphocytes (T & B cells which are mainly exist in lymph nodes and spleen or in other mucusal lymphoid aggregation , Not in the tissue itself**

- **Note : dendritic cell migrate to the lymph nodes to reach T cells .**

- **The previous cell isn't the only type of dendritic cells , however it's the conventional or classical dendritic cell .**

Innate immunity/ Dendritic cells

	cDC	pDC	Monocyte / Macrophage
APC type			
Primary functions	T cell priming and functional polarization, Induction of Immunity vs Tolerance	Interferon-α/β production Innate defenses against viruses	Tissue homeostasis Trophic and scavenger functions Microbicidal compound production

- it's called such this because it looks like plasma cell (differentiated B cell that produces antibodies)
- Both produce a certain sort of proteins that being produced continuously:-
  - Plasma cell → Antibodies
  - Plasmacytoid DC → Cytokines (mainly interferons)

DC include two main cell types, the **plasmacytoid DC (pDC**) that are **expert in type I interferon synthesis** upon viral stimulation and the **conventional DC (cDC)** that are specialized in **antigen capture**, **processing**, and **presentation for T-cell priming.**

- Both have a prominent ER that produces lots of proteins

Cells of the immune system / Antigen-Presenting Cells/ Follicular Dendritic Cells

* Doctor said that this cell isn't really a dendritic cell ,but it looks like a dendritic cell (has long membranous projections)

- **Follicular dendritic cells (FDCs)** are cells with membranous projections that are found intermingled in specialized collections of activated B cells, called **germinal centers**, in the lymphoid follicles of the lymph nodes, spleen, and mucosal lymphoid tissues.
  * It usually exist in one type of tissues (the lymphoid tissue)
    ex1 lymph nodes particularly in a structure called follicles. ex2 spleen
  * Don't exist in the infected tissue usually
- FDCs are not derived from precursors in the bone marrow and are of mesenchymal origin, they are **non migratory**(not mobile)
- FDCs trap antigens complexed to antibodies or complement products and display these antigens on their surfaces for recognition by B lymphocytes.

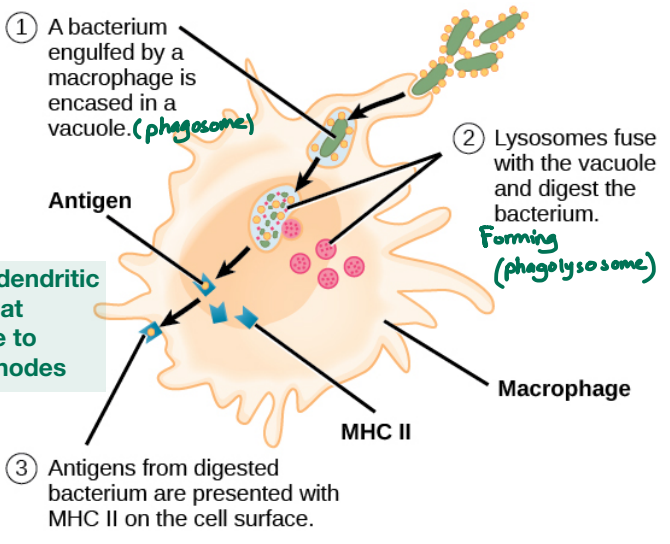
* their function is just to capture the antigen and make it close enough to B cells

* (Conventional dendritic cells , macrophages and B cells) their role in antigen-presenting is to interact with T cells because T cells can only recognise a processed antigen on MHC molecule
  but, in case of B cells the antigen doesn't have to be processed , they don't need the processing of antigen because they have receptors that hold the antigen as it (before processing & linking to MHC)

* T cells are 2 types : helper & killer (cytotoxins)

2 **Macrophages present** antigen **to helper T lymphocytes** at the sites of infection, which leads to **helper T cell activation and production of molecules** that further **activate** the **macrophages**. This process is important for the eradication of microbes that are ingested by the phagocytes but resist killing.

not as dendritic cells that migrate to lymph nodes



3 **B cells present** antigens to helper T cells in lymph nodes and spleen, which is a key step in the cooperation of helper T cells with B cells in humoral immune responses to protein antigens.

Major histocompitability complex I

Random continuous process

Their function is **to display peptide fragments of proteins from within the cell** to cytotoxic T cells; this will trigger an immediate response from the immune system against a particular non-self antigen displayed with the help of an MHC class I protein.

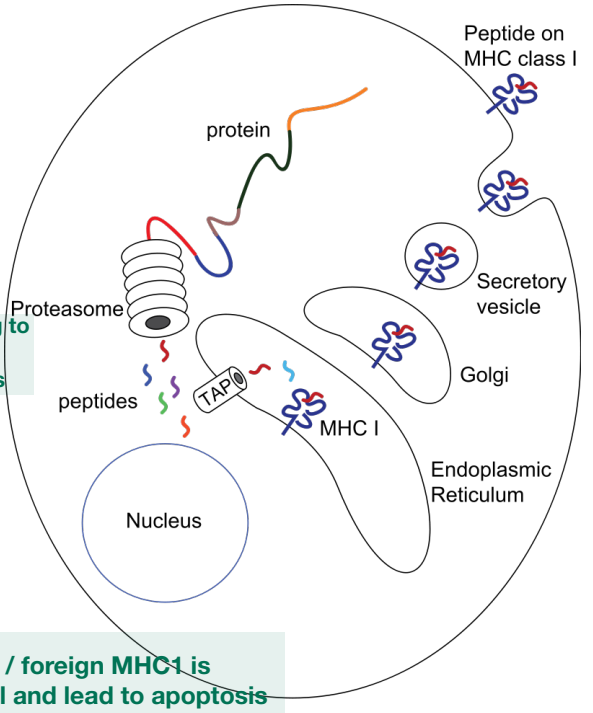
then these peptides will go into ER , linking to MHC1, then this complex will be presented on cell's surface through secretory vesicles

The **proteasome** is a macromolecule that consists of 28 subunits, of which half affect proteolytic activity.

* why this process ? to distinguish if the cell is infected or not

Cells constantly break down proteins and present them on MHC I.

* The cell that interact with the infected cell that contain the new / foreign MHC1 is cytotoxic T cells which release molecules that perforate the cell and lead to apoptosis



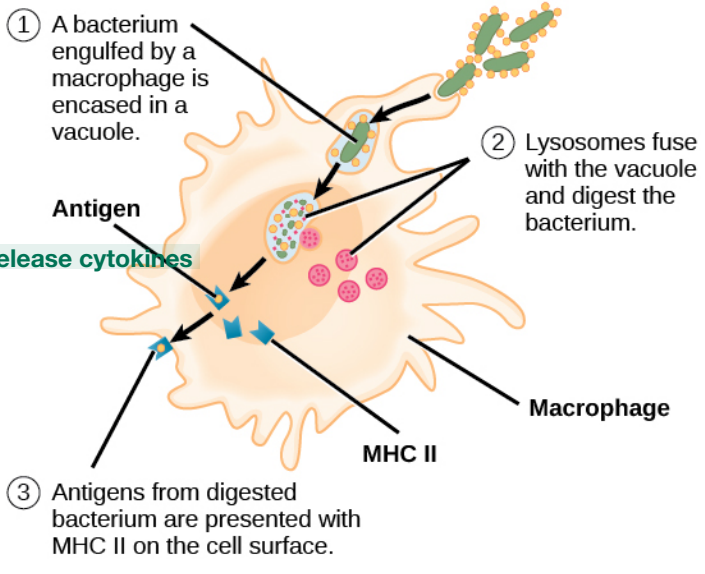
Major histocompitability complex II

* In general, T-cells should tell if this is a self antigen & not interact with it OR if it is a foreign antigen & interact with it

Normally found only on professional antigen-presenting cells such as **dendritic cells**, **Macrophages**, **B cells** and some **endothelial cells.**

* MHC2 is recognised by T helper cells, then T helpers release cytokines

The antigens presented by class II peptides are derived from **extracellular proteins** (not cytosolic as in MHC class I).



(the virus attack the cell) T-Cytotoxin recognise this foreign antigen then release perforin ,making pores in the membrane, then an enzyme called granzymes enter the cell leading to activate the apoptosis .

(ingested in purpose) to be presented on MHC2 to interact with helper T cells

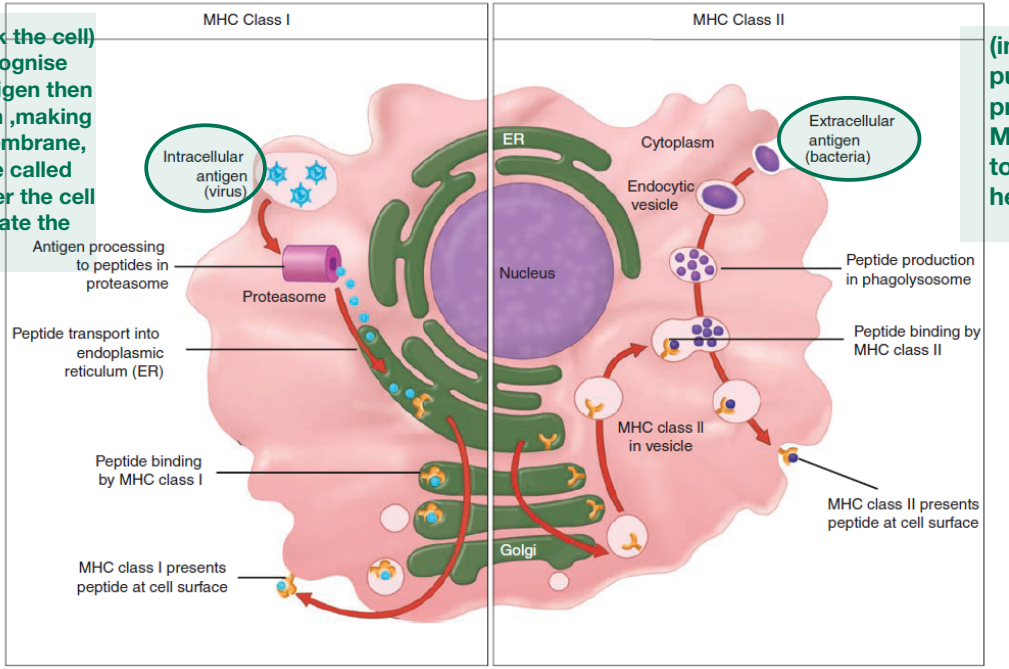
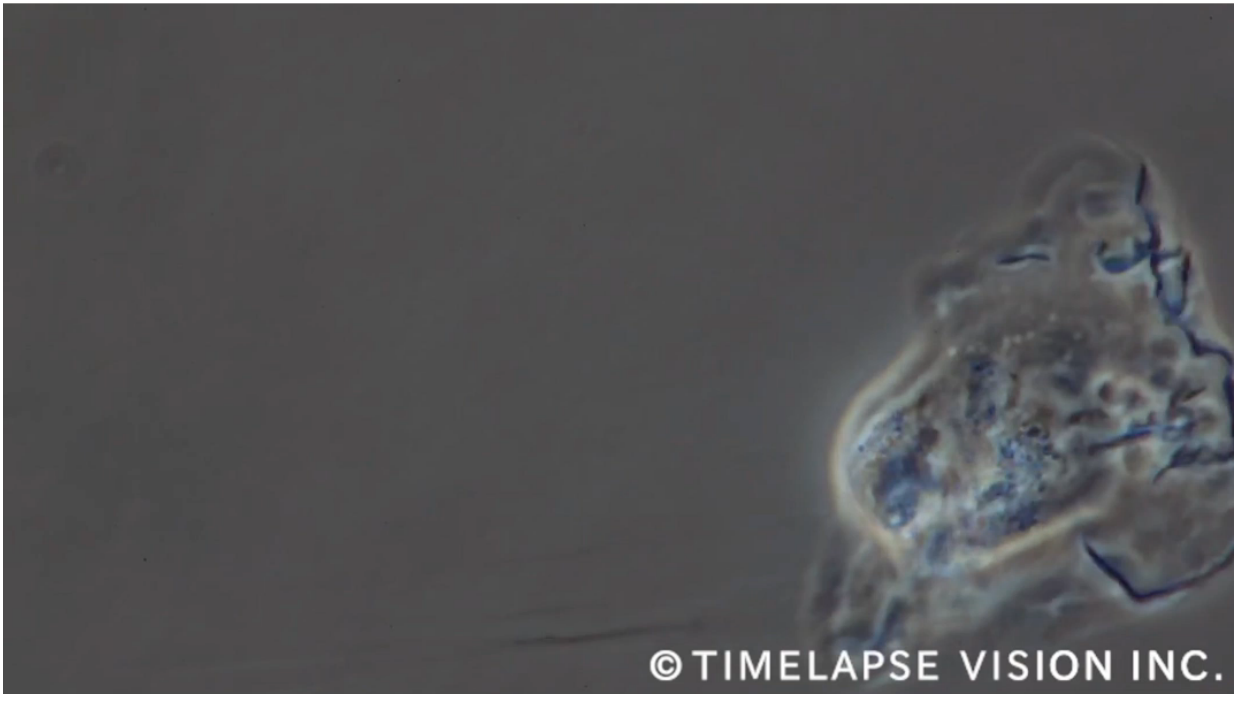


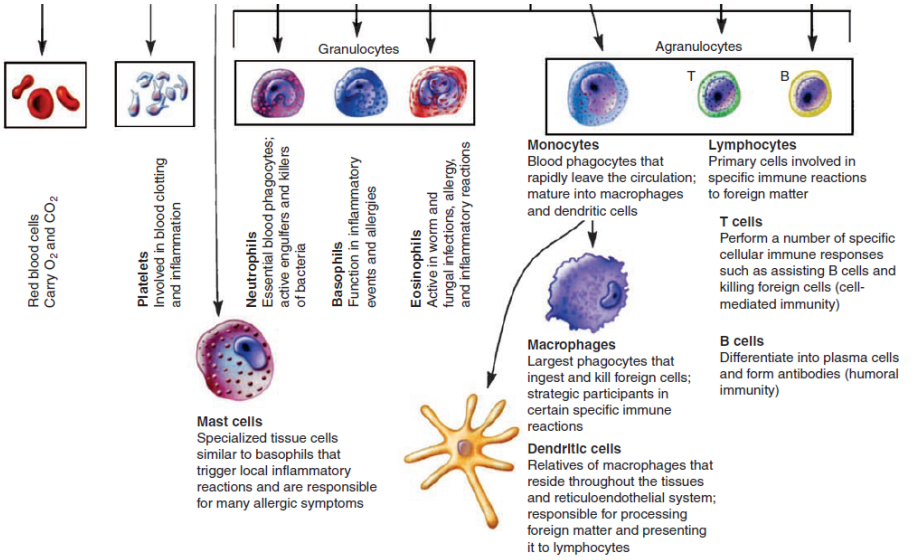
FIGURE 2–11. Antigen processing and presentation. A. Antigens originating in the cytoplasm are digested by the proteasome to peptides. The peptides are bound to the MHC class I molecules in the endoplasmic reticulum (ER) and transported to the surface for presentation. **B.** Antigens originating outside the cell are endocytosed and digested in the phagolysosome. The digested peptides are bound to MHC class II molecules in the ER and transported to the surface for presentation. MHC, major histocompatibility complex.



Dendritic cell presents antigens to **lymphocytes**

Cells of the immune system

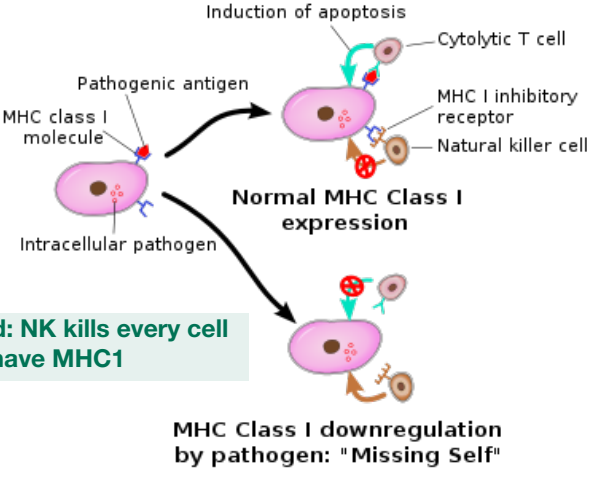
- **Phagocytes**
- **Mast Cells, Basophils, Eosinophils**
- **Antigen-Presenting Cells**
- **Lymphocytes**



- Natural killer (NK) cells are **lymphocytes** distinct from T and B cells that play important roles in innate immune responses **mainly against intracellular viruses and bacteria.**

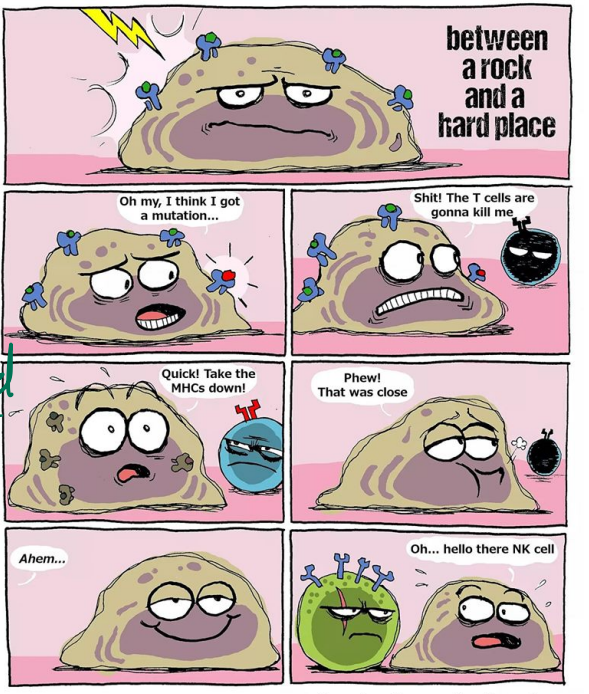
- The term natural killer derives from the fact that these cells are capable of performing their killing function **without** a need for **clonal expansion** and **differentiation.**

- Most NK cells express inhibitory receptors that recognize **class I major histocompatibility complex (MHC)** molecules, which are cell surface proteins normally expressed on almost all healthy cells in the body



⁎ **Doctor said: NK kills every cell that don't have MHC1**

Good Story to understand



- The most abundant cell within the circulation : Neutrophils
  Then : lymphocytes

- Lymphocytes consist of distinct subsets that are **different in their functions** and protein products, but are **morphologically similar**. (large nucleus , small cytoplasm)

- **B** (**B**ursa of Fabricius) lymphocytes originate in the **b**one marrow and **early maturation** occurs there. Also, **T** (**T**hymus) lymphocytes originate in the bone marrow, but **mature** in the **thymus**.

- Membrane proteins are used as **phenotypic markers** to **distinguish distinct populations of lymphocytes**

* We can't distinguish between B & T cells under the microscope
* After activation you can differentiate between them

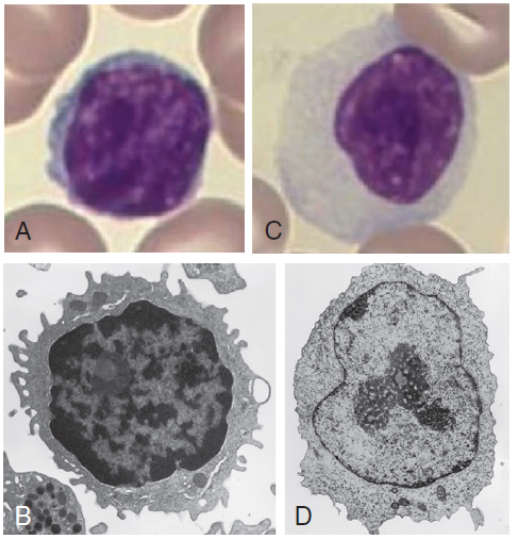


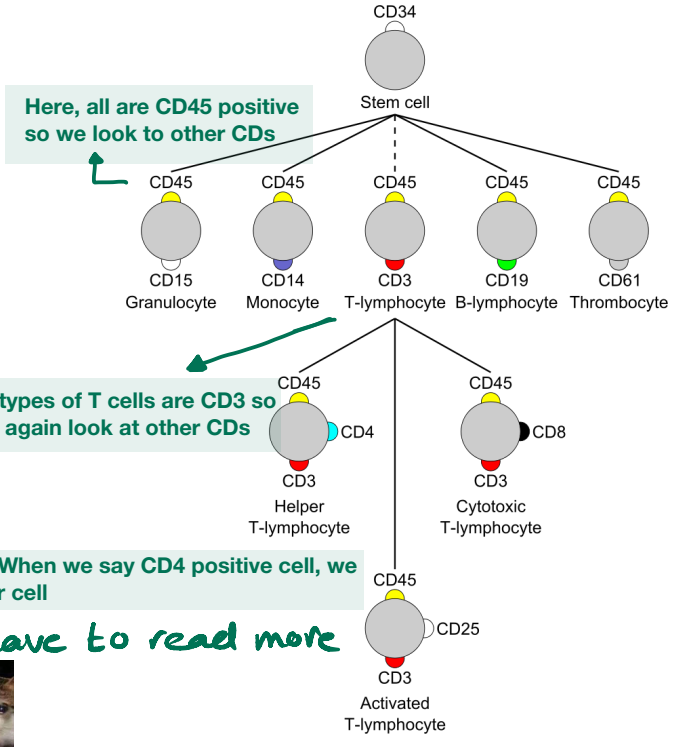
FIGURE 2–7 Morphology of lymphocytes. **A,** Light micrograph of a lymphocyte in a peripheral blood smear. *(Courtesy of Jean Shafer, Department of Pathology, University of California, San Diego. Copyright 1995-2008, Carden Jennings Publishing Co., Ltd.)* **B,** Electron micrograph of a small lymphocyte. *(Courtesy of Dr. Noel Weidner, Department of Pathology, University of California, San Diego.)* **C,** Light micrograph of a large lymphocyte (lymphoblast). *(Courtesy of Jean Shafer, Department of Pathology, University of California, San Diego. Copyright 1995-2008, Carden Jennings Publishing Co., Ltd.)* **D,** Electron micrograph of a large lymphocyte (lymphoblast). *(From Fawcett DW. Bloom and Fawcett: A Textbook of Histology, 12th ed. Chapman & Hall, New York, 1994. With kind permission of Springer Science and Business Media.)*

Cells of the immune system / Cluster of differentiation

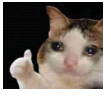
*** How can we differentiate between them ?**

- The cluster of differentiation (CD) is a protocol used for the **identification** and **investigation** of **cell surface molecules** providing targets for immunophenotyping of cells.

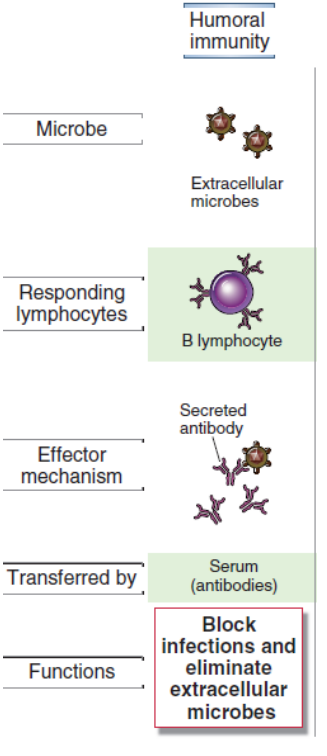
- In terms of physiology, CD molecules can act in numerous ways, often acting as **receptors** or **ligands** important to the cell and some function as **adhesion** molecules.



H.W : doctor said that we have to read more about T & B cells

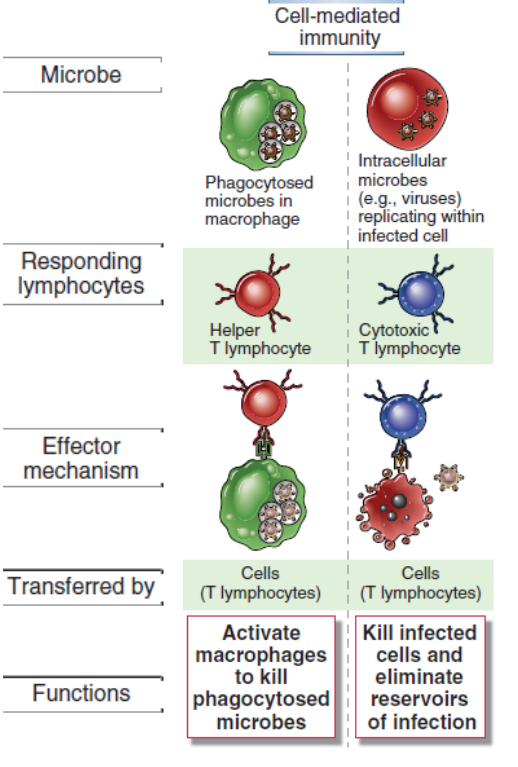


- B-lymphocytes are the **only cells capable of producing antibodies**.
- They recognize **extracellular (including cell surface) antigens** and differentiate into antibody-secreting **plasma cells**, thus functioning as the mediators of humoral immunity.



Cells of the immune system / Lymphocytes/ T-lymphocytes

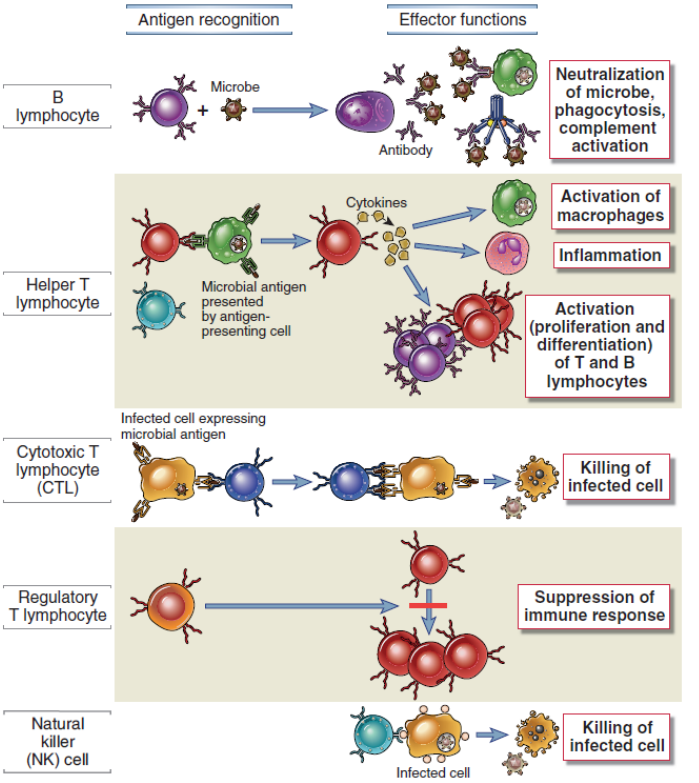
- T lymphocytes, the cells of cell-mediated immunity, **recognize the antigens of intracellular microbes** and either **help** phagocytes to **destroy these microbes** or **directly kill the infected cells**.
- **T cells do not produce antibody molecules**.
- Their antigen receptors are membrane molecules distinct from but structurally related to antibodies.



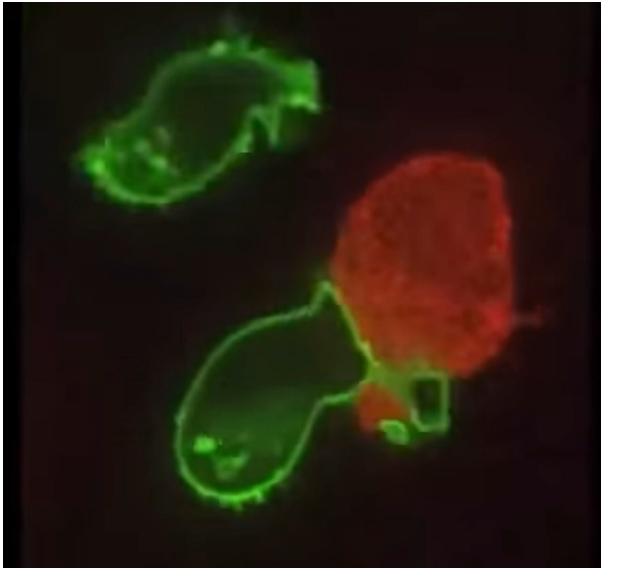
Humoral immunity is mediated by molecules in the blood and mucosal secretions, called antibodies, which are produced by cells called B lymphocytes.

Cell-mediated immunity is mediated by T lymphocytes.

viruses and some bacteria, survive and proliferate inside phagocytes and other host cells, where they are inaccessible to circulating antibodies. Defense against such infections is a function of cell mediated immunity, which promotes the destruction of microbes residing in phagocytes or the killing of infected cells to eliminate reservoirs of infection.



Through the action of **perforin**, **granzymes** enter the cytoplasm of the target cell and their serine protease function triggers the **caspase** cascade, which eventually lead to **apoptosis** (programmed cell death).



Cells of the immune system / Lymphocytes

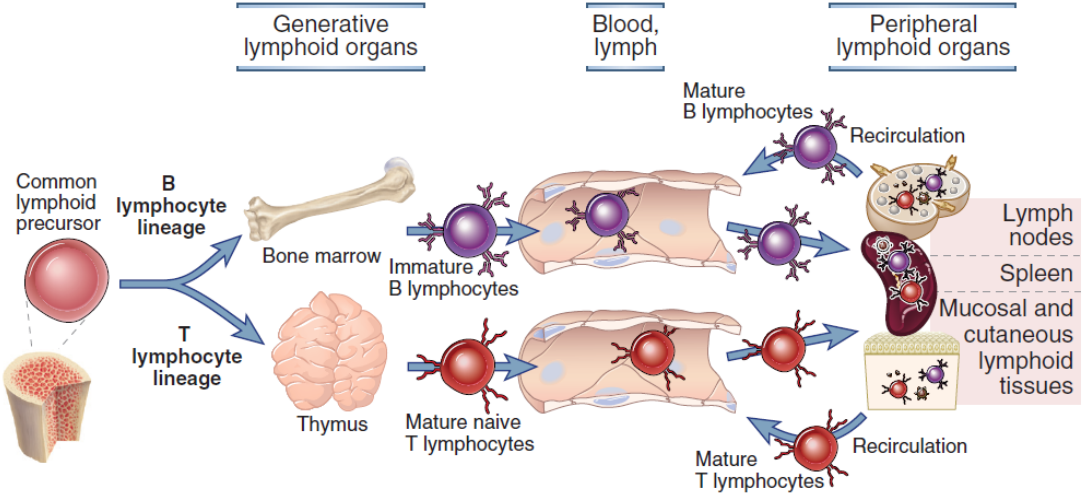
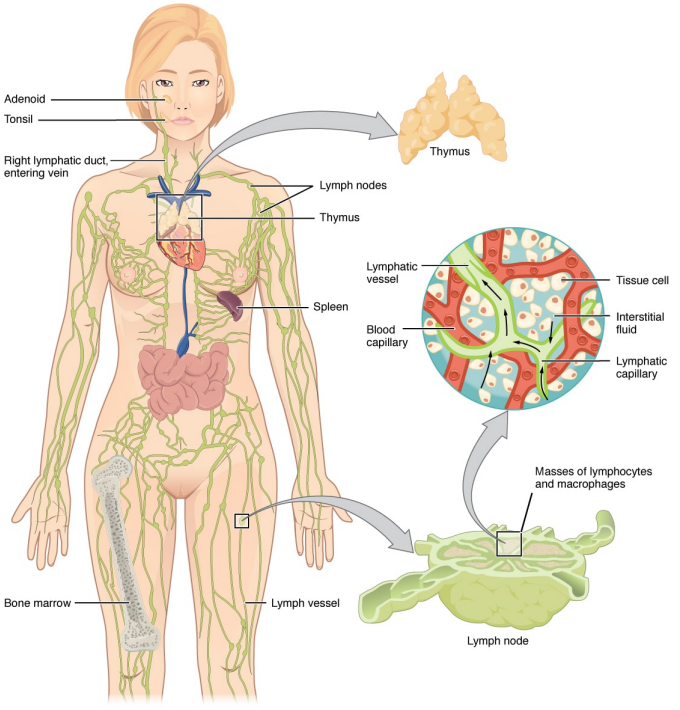


FIGURE 2–5 Maturation of lymphocytes. Lymphocytes develop from bone marrow stem cells and mature in the generative lymphoid organs (bone marrow and thymus for B and T cells, respectively) and then circulate through the blood to secondary lymphoid organs (lymph nodes, spleen, regional lymphoid tissues such as mucosa-associated lymphoid tissues). Fully mature T cells leave the thymus, but immature B cells leave the bone marrow and complete their maturation in secondary lymphoid organs. Naive lymphocytes may respond to foreign antigens in these secondary lymphoid tissues or return by lymphatic drainage to the blood and recirculate through other secondary lymphoid organs.

Cells of the immune system / Lymphocytes

The total number of lymphocytes in a healthy adults about 5 × 1011. Of these:

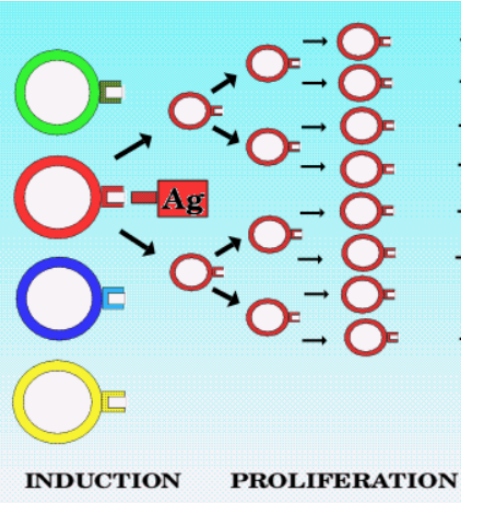
- ~2% are in the blood,
- ~10% in the bone marrow,
- ~15% in the mucosal lymphoid tissues of the gastrointestinal and respiratory tracts, and
- ~65% in lymphoid organs (mainly the lymph nodes and spleen)



- **Lymphocytes**, the unique cells of **adaptive** immunity, are the only cells in the body that express **clonally** distributed **antigen receptors**, each with a fine **specificity** for a different antigenic determinant.

- Each **clone** of lymphocytes consists of the **progeny of one cell** and expresses antigen receptors with a **single specificity**.

- There are **millions** of **lymphocyte clones** in the body, enabling the organism to **recognize** and respond to **millions** of foreign **antigens**.



- How the enormously diverse repertoire of antigen receptors (millions), and therefore specificities, is generated from a small number of genes for these receptors in the germline*?

- Genes encoding the **antigen receptors** of lymphocytes are formed by **recombination of DNA segments during the maturation of these cells**. There is a random aspect to these somatic recombination events that results in the generation of millions of different receptor genes and a highly diverse repertoire of antigen specificities among different clones of lymphocytes.

- The **antigen receptors** are basically **antibodies** bound to the cell surface.

*Germline DNA: The DNA in germ cells (egg and sperm cells that join to form an embryo). Germline DNA is the source of DNA for all other cells in the body. Also called constitutional DNA.

- In contrast with most organs, such as the heart, which does the same job throughout life, the immune system **needs to adapt to an environment that is always changing**. This problem is solved by investing in strategies that **exploit the power of random change itself**.

- **Using randomness in this way creates waste, but preserves responsiveness.**

Tonegawa's Nobel Prize work elucidated the genetic mechanism of the adaptive immune system, which had been the central question of immunology for over 100 years. Prior to Tonegawa's discovery, one early idea to explain the adaptive immune system suggested that each gene produces one protein; however, there are under 19,000 genes in the human body which nonetheless can produce millions of antibodies.

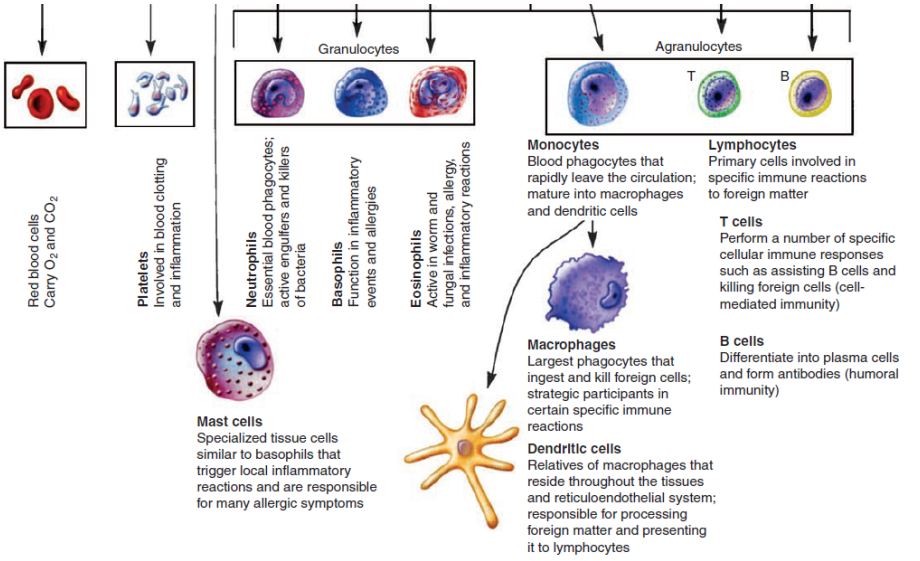
TABLE 2–2 Lymphocyte Classes

Class	Functions	Antigen Receptor and Specificity	Selected Phenotype Markers	Percentage of Total Lymphocytes (Human)		
				Blood	Lymph Node	Spleen
αβ T lymphocytes						
$CD4^+$ helper T lymphocytes	B cell differentiation (humoral immunity) Macrophage activation (cell-mediated immunity) Stimulation of inflammation	αβ heterodimers Diverse specificities for peptide–class II MHC complexes	$CD3^+$, $CD4^+$, $CD8^-$	50-60*	50-60	50-60
$CD8^+$ cytotoxic T lymphocytes	Killing of cells infected with viruses or intracellular bacteria; rejection of allografts	αβ heterodimers Diverse specificities for peptide–class I MHC complexes	$CD3^+$, $CD4^+$, $CD8^-$	20-25	15-20	10-15
Regulatory T cells	Suppress function of other T cells (regulation of immune responses, maintenance of self-tolerance)	αβ heterodimers Unresolved	$CD3^+$, $CD4^+$, $CD25^+$ (most common, but other phenotypes as well)	Rare	10	10
γδ T lymphocytes	Helper and cytotoxic functions (innate immunity)	γδ heterodimers Limited specificities for peptide and nonpeptide antigens	$CD3^+$, $CD4^+$, and CD8 variable			
B lymphocytes	Antibody production (humoral immunity)	Surface antibody Diverse specificities for all types of molecules	Fc receptors; class II MHC; CD19, CD21	10-15	20-25	40-45
Natural killer cells	Cytotoxic killing of virus-infected or damaged cells (innate immunity)	Various activating and inhibitory receptors Limited specificities for MHC or MHC-like molecules	CD16 (Fc receptor for IgG)	10	Rare	10
NKT cells	Suppress or activate innate and adaptive immune responses	αβ heterodimers Limited specificity for glycolipid-CD1 complexes	CD16 (Fc receptor for IgG); CD3	10	Rare	10

*In most cases, the ratio of $CD4^+CD8^-$ to $CD8^+CD4^-$ is about 2:1.
IgG, immunoglobulin G; MHC, major histocompatibility complex.

Cells of the immune system

- **Phagocytes**
- **Mast Cells, Basophils, Eosinophils**
- **Antigen-Presenting Cells**
- **Lymphocytes**



Further reading:

Cellular and Molecular Immunology. 7th Edition..
Chapter 2. Cells and tissues of the immune system