All armies are divided into officers and enlisted ranks. The human immune system is no different.

Think of the myeloid cells as enlisted troops. Their main job is to follow orders, not think for themselves.

Myeloid cells react the same way whenever they encounter foreign antigens. Hence they are categorized as cells of the innate immune system.

Lymphoid cells (with the exception of NK cells) act as the officers. They receive reports, make decisions, and issue orders to other white blood cells.

B and T lymphocytes can differentiate into memory cells after encountering antigens. If they run into the same antigen in the future, they respond much faster and more efficiently. B and T cells are the core of the specific or adaptive immune system.
If you remember nothing else...

- **Neutrophils** – a.k.a. Polymorphonuclear cells or PMNs - the immune system's shock troops. Comprise 50-65% of all white blood cells. Contain pale staining granules with preformed mediators; capable of phagocytosis.

- **Monocytes** – have a distinctive horseshoe shaped nucleus. They differentiate into tissue macrophages (literally means big eaters) and comprise approximately 12% of white blood cells. Main job of macrophages is to engulf pathogens and clean up debris. Also present antigens to T_{H1} cells.

- **Eosinophils** - contain red staining granules and a double lobed nucleus. Make up 2-5% of WBCs. These cells play an important role in asthma and the immune response to parasites, e.g. worms.

- **Basophils** – contain numerous purple staining granules packed with histamine and other inflammatory mediators. Usually make up no more than 1% of WBCs. Play a prominent role in allergic reactions and anaphylaxis. **Mast cells** are located in the tissues and are thought to have functions similar to basophils. Both basophils and mast cells have IgE on their surfaces.

- **B-Lymphocytes** – mature in the Bone marrow. Produce immunoglobulins, a.k.a. antibodies, the hallmark of humoral immunity. Act as antigen presenting cells to T_{H2} cells.

- **T-Lymphocytes** – mature in the Thymus gland, where they undergo two rounds of selection. T helper cells (CD4+) interact with antigen presenting cells and basically call the shots in a specific immune response. Cytotoxic T Lymphocytes (CD8+) are responsible for cell mediated immunity. I like to think of them as highly trained ninjas who prefer hand to hand combat.

- **NK cells** – sometimes called large granular lymphocytes – Natural killer cells patrol the body for virally infected cells as well as transformed cells/tumor cells. Analogous to a special forces unit, they're born already knowing who the enemy is, and they take no prisoners.
Cytokines and Fever

White blood cells communicate using signals that can have autocrine, paracrine, and/or endocrine effects.

Cytokines act as protein messengers that, with certain exceptions, promote inflammation and fever. They also recruit granulocytes, lymphocytes, and macrophages to the site of an infection.

Type I Interferons - these proteins help contain a viral infection by decreasing protein synthesis in infected cells. They help neighboring cells resist the virus via antiviral proteins (AVPs). IFNα and IFNβ fall into this category.

IFNα is used to treat viral infections, esp. Hepatitis C, whereas IFNβ is used to treat autoimmune disorders, esp. multiple sclerosis.

Type II Interferon – this refers to IFNγ. T-cells are a major source of gamma IFN; its main effect is to activate macrophages.

Chemokines - think of them as chemotactic cytokines that tell WBCs to “come quick, it's an emergency.” They are released by WBCs and endothelial cells during inflammation.

### Table: Interleukin Main function(s)

<table>
<thead>
<tr>
<th>Interleukin</th>
<th>Main function(s)</th>
</tr>
</thead>
<tbody>
<tr>
<td>IL-1</td>
<td>Inflammation and fever</td>
</tr>
<tr>
<td>IL-2</td>
<td>T cell activation &amp; proliferation Cell mediated immunity</td>
</tr>
<tr>
<td>IL-4</td>
<td>IgE production, allergic response</td>
</tr>
<tr>
<td>IL-5</td>
<td>Eosinophil survival</td>
</tr>
<tr>
<td>IL-6</td>
<td>Humoral immunity B cells _ plasma cells</td>
</tr>
<tr>
<td>IL-8</td>
<td>Neutrophil chemotaxis</td>
</tr>
<tr>
<td>IL-10</td>
<td>Inhibitory effect; suppresses inflammation</td>
</tr>
<tr>
<td>IL-12</td>
<td>Similar effects to IL-2 NK activation; IFN _ production</td>
</tr>
<tr>
<td>IL-15</td>
<td>NK cell maturation</td>
</tr>
<tr>
<td>IL-17</td>
<td>Neutrophil maturation</td>
</tr>
</tbody>
</table>

Many mediators, e.g. TNFα and LPS from gram negative bacteria, induce IL-1 production. IL-1 stimulates prostaglandin synthesis in the hypothalamus, which resets the body's thermostat and results in
The Complement Cascade

If you remember nothing else:

- The classical, lectin, and alternative pathways all converge at C3.
- C3a and C5a attract WBCs to the site of infection. Their purpose is to yell “Intruder alert!!” non-stop.
- C3b opsonizes antigens/microbes so that phagocytes will engulf them more readily. Think of it as adding cheese to broccoli so a young child will swallow it.
- C3b is essential in activating C5. C5b along with C6-C9 forms a pore called the membrane attack complex (MAC). Several MACs punch holes in a bacterium's cell walls, lysing the cell.
- Inhibitory proteins, including C1 Inh and DAF (Decay Accelerating Factor), prevent the complement system from spiraling out of control. Deficiencies in these proteins may play a role in various autoimmune diseases, e.g. SLE, probably by allowing complement and Ag-Ab complexes to deposit in the kidneys and other organs. This sets the stage for chronic inflammation.

Complement proteins act as an elaborate burglar alarm system. When it comes to triggering inflammation, these proteins get the ball rolling.

The classical pathway (so named because it was discovered first) is activated when C1 binds to an antigen-antibody complex. C1 activates C2 and C4, which in turn activate C3.

The lectin and alternative pathways are activated directly by microbial membranes and also result in the activation of C3.
T Cells in a Nutshell

- T-cell precursors migrate from the bone marrow to the thymus gland, where they mature into T lymphocytes.
- T-cells undergo positive and negative selection in the thymus. In this way, both unresponsive and hyperresponsive T cells are eliminated, probably by apoptosis.
- Fewer than 5% of T cells survive the selection process. As the saying goes, many are called, but few are chosen.
- By the end of puberty, humans have most of the T cell subsets they are going to have for the rest of their lives. After puberty, the thymus progressively atrophies.
- Mature T cells take up residence throughout the body, esp. in the spleen, lymph nodes, and patches of mucosal lymphoid tissue in the respiratory tract and intestinal mucosa (Peyer's patches/MALT).
- CD4+ T cells are known as T helper (T<sub>H</sub>) cells.
- CD8+ T cells, a.k.a. Cytotoxic T Lymphocytes or CTL, zap virally infected cells. They kill their targets by a process called ADCC as well as by triggering apoptosis.
- T cells and B cells are the only two human cell types known to undergo gene rearrangements. This process generates a huge variety of T cell receptors (TCR) in addition to immunoglobulins (Ig)/BCR in B cells.
- Unlike Ig, which may be surface bound or soluble, the TCR remains bound to the T cell surface. Its job is to recognize foreign antigens presented in the context of MHC (Major Histocompatibility) proteins.
- Type I MHC is found on the surface of all nucleated cells. It is a key way infected cells tell CD8+ T cells “I'm hit. Put me out of my misery. The needs of the many outweigh the needs of the few.”
- Type II MHC is found mainly on the surfaces of antigen presenting cells, esp. B cells, macrophages, and dendritic cells. These “professional APCs” interact directly with T helper cells.
- Macrophages report to T<sub>H</sub>1 cells and induce a cell mediated response, (characterized by the release of IL-2 and IFNγ). This favors the activation of CTL, NK cells and macrophages.
- B cells report to T<sub>H</sub>2 cells inducing a humoral response, characterized by the release of IL-4 and IL-6. This favors the activation of granulocytes and B cells.
NK Cells

• Mercifully, this lecture was short.

• NK cells, a.k.a. Large Granular Lymphocytes, function as part of the innate immune response but also interact with B and T cells (mainly via cytokines).

• Their surface protein profile is: CD16+ (they express the FcγIII Receptor), CD56+, CD3-.

• The main cytokines that activate NK cells are IL-2, IL-12, and IFNγ.

• NK cells serve two main functions: 1) to kill target cells coated with antibodies, esp. IgG, and 2) to act as tumor surveillance cells. This includes detecting cells transformed by potentially oncogenic viruses like EBV, CMV, etc.

• NK cells patrol the body, scanning the surface proteins on tissues they encounter. Since tumor cells often have altered surface antigens (depending upon the tumor's degree of differentiation), this tips off the NK cell that the cell is potentially dangerous and needs to be eliminated.

• As with CTL cells, NK cells kill their targets in a variety of ways, including the release of perforin and other toxins from their granules, ADCC (Antibody Dependent Cell mediated Cytotoxicity), and the induction of apoptosis.
B Cells at a Glance (Will be covered on Exam #2)

- B cells mature in the bone marrow where they undergo gene rearrangements to produce a huge repertoire of immunoglobulins/ B cell receptors.

- B cells get 2 chances to rearrange their Ig heavy chain genes and up to 6 chances to rearrange their Ig light chain genes. If they fail, they die by apoptosis.

- Primary Ab response – occurs after initial exposure of naïve B cell to antigen; takes 7-14 days to peak; consists of low affinity IgM and IgG antibodies.

- Secondary Ab response – happens in 24-48 hrs. Almost exclusively IgG. Titers remain high for months to years afterward.

- Affinity maturation (via somatic hypermutation). In the wake of the 1° Ab response, B cells that responded most strongly to a foreign antigen are whisked away to the spleen and other safe, undisclosed locations. There they undergo top secret medical experiments and emerge as ultra-tough B cell warriors, sort of like that guy in the Captain America movie.

- Memory B cells/clonal expansion: Some B cells “remember” their encounter with an antigen. If their paths cross again, these specific B cell clones proliferate as plasma cells and release large amounts of soluble antibodies.

- Basic Ab structure: symmetrical Y shaped protein consisting of 2 heavy chains and 2 light chains. Antibodies contain 2 identical Fab regions (stands for fragment antigen binding) and one Fc (fragment crystallizable) region that binds to receptors on various white blood cells.

- Immunoglobulin Isotypes:
  - IgG – roughly 2/3 of human antibodies. They circulate as gamma globulin, fix complement, enter breast milk, and cross the placenta.
  - IgA – found on mucosal surfaces and is the major Ab component of barrier/mucosal immunity. Major Ab in breast milk.
  - IgM – forms pentameric structures. The most effective Ig at fixing complement. Does not cross the placenta.
  - IgE – mediates allergic responses and anaphylaxis. When two IgE molecules get crosslinked, basophils and mast cells degranulate and release histamine, sort of like miniature hand grenades.
  - IgD – found on the surface of immature B cells; function unknown.