Unit 5: Where are we heading?

Unit 1: Why should we care about infectious diseases?
Unit 2: What does it mean to have an infectious disease?
Unit 3: When does a microbe become a pathogen?
Unit 4: How do pathogens make us sick?

Unit 5: How do we get better?

In earlier units, we discussed how the immune system provides different ‘layers’ of protection. Now, we will turn our attention to the mechanisms of innate and adaptive immunity. We will study the processes by breaking them down into two stages, recognition and response. After learning about innate and adaptive immunity, we will then focus on how vaccines work.
LESSON 5.1 WORKBOOK

Our body’s barriers — the innate immune system

Up until now we have focused on how pathogens make us sick. In Unit 5, we are going to explore how the body responds to infection, and how we get better. In this lesson we will review the structures/barriers of the immune system that we learned in Unit 1. Then, we will learn more about the first cellular responses that fight infection after microbes enter the sterile areas of the host. This is called innate immunity and we will see how innate immune cells recognize and respond to pathogens.

Review the physical, chemical, molecular, and cellular barriers of the immune system.

Before learning more about how immune responses work, you might want to review the immune barriers we discussed in Lesson 1.5. These include:

- Physical barriers such as epithelial cells that separate the sterile inside of the body from the environment (e.g., skin and mucous membranes)
- Chemical barriers on epithelial surfaces that restrict colonization (e.g., mucus and stomach acid)
- Molecular barriers on epithelial surfaces that restrict colonization by microbial invaders (e.g., lysozyme in tears and defensins)

1. Cellular responses are generally broken into two classes:
   a. innate and adaptive response
   b. innate and responsive response
   c. intrusive and adaptive response
   d. intrusive and responsive response
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- Molecular defenses in the blood (e.g., complement)
- Cellular defenses in the blood. These are separated into two major groups:
  - Innate cells (phagocytes and other cells we will learn about today)
  - Adaptive cells (B and T cells)
- The special barrier: our commensal flora (the microbiota)

**DEFINITIONS OF TERMS**

**Cell differentiation** — is the process of a cell changing to become another cell type or subtype. For example, a stem cell can turn into a lymphocyte.

**Stem cell** — is a cell that has not been differentiated yet and can divide to produce more stem cells or can differentiate.

**Bone marrow** — the soft tissues inside the bones, producing our blood cells.

**Hematopoiesis** — the production of blood cells.

For a complete list of defined terms, see the **Glossary**.

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**Workbook**

**Lesson 5.1**

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2. All cells in the blood, including immune cells, are made in the _____ in a process called _____.
   a. phagocytosis, hematopoiesis
   b. blood, hematopoiesis
   c. bone marrow, hematopoiesis
   d. heart, hematopoiesis
e. all of the above

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All cells in the blood, including immune cells, are made in the bone marrow through a process called hematopoiesis

Like most cells in the body, blood cells are constantly dying and being replaced (this is called turning over). All cells in the blood are generated from stem cells in the bone marrow. The stem cells can either divide, which keeps the number of stem cells constant, or they can specialize to become one of the cell types in the blood: this is called differentiation. The processes of differentiation gives rise to our platelets, red, and many different types of white blood cells. Keep in mind that it is not important to understand the details of hematopoiesis. It is more important to realize that our body constantly adjusts this process based on our needs. For example, when we have a bad infection, this process accelerates to make more cells, more specifically white blood cells, to fight the infection. This process uses a considerable amount of energy and requires additional input. In fact, when a person is fighting an infection, their white blood cell count needs to go up, and they may need an extra 1,000 calories a day to make these additional white blood cells!

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**Figure 1:** Hematopoiesis: all types of blood cells originate from stem cells in the bone marrow.
What is the function of each cell type?

Platelets are small cells that clot our blood. Blood clotting is an important process, and too little clotting can lead to uncontrolled bleeding, while too much can cause heart attacks. For example, people with hemophilia don’t form blood clots, so even small cuts can lead to uncontrolled bleeding. On the contrary, uncontrolled clotting can lead to formation of blood clots inside blood vessels. These clots can block the blood supply to the heart causing heart attack or the blood supply to the brain causing stroke.

Red blood cells pick up oxygen in the lungs and transport it to the cells in all organs. Oxygen is needed in the cells to produce energy. In addition, when energy is produced, carbon dioxide is released. The red blood cells will release the oxygen, then bind carbon dioxide, and carry it back to our lungs for disposal.

When we don’t have enough red blood cells, a condition called anemia develops. If you are anemic, even simple tasks can be difficult to perform since your cells cannot produce enough energy to function efficiently.

The rest of the cells in the blood are white blood cells — the innate and adaptive immune cells. As we learned in Lesson 1.5, there are a number of types of innate cells, and only two types of adaptive immune cells (B and T cells). We will learn more about B and T cells in the next few lessons. Here we will focus on innate cells because they are the first cellular responders after a microbe enters the sterile area of the body.

How do innate immune cells respond to an infection?

Innate cells have three main functions: kill pathogens by phagocytosis, kill pathogens with chemicals, and signal for more help from other immune cells. Innate cells can typically perform more than one function but some of them are better than others in a specific task. For example, the best phagocytes are macrophages, dendritic cells (DC), and neutrophils. These are professional eating machines that gobble up pathogens. The best killers with chemicals are Natural Killer (NK) cells and eosinophils. These cells release toxic molecules...
**LESSON READINGS**

that kill virus-infected host cells, as well as cancer cells (NK cells), and bacterial and protozoa pathogens (eosinophils). **Basophils** and **mast cells** are the best at secreting molecules that trigger inflammation and summon more immune cells where needed, to fight an invader.

*Note: please don’t try to remember the cell names and what each cell type does best. Rather, focus only on types of functions that innate cells perform in general.*

Innate cells are in the blood and tissues of the body, constantly patrolling for foreign invaders. And if they recognize something as non-self (foreign) they spring into action. But how do they recognize self from non-self?

**How innate cells ‘see’ pathogens?**

To fight infection, immune cells need to be able to distinguish between a pathogen and a self-cell. This ability to distinguish between self and non-self is the foundation of the immune response, and requires a special set of receptors on the surface of your immune cells that can recognize non-self microbial molecules. After all, if immune cells can’t ‘see’ the pathogen they won’t respond. The receptors your innate cells use to recognize pathogens are genetically inherited from your parents. This means that they can’t just adapt to a pathogen, so instead they need to recognize parts of pathogens that are highly *conserved*. These highly conserved targets of recognition are called **Pathogen Associated Molecular Patterns (PAMPs)**. Most PAMPs are structures that are required for a pathogen’s life cycle, so mutating the PAMP to try to avoid immune recognition is likely to put the pathogen at a huge selective disadvantage.

However, as we saw in Unit 4, pathogenic microbes do find ways to mutate, and adapt to camouflage themselves from immune cells. Fortunately, the receptors on innate cells are not accurate enough to ‘see’ most of the changes. In fact, they only recognize general

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**Workbook**

**Lesson 5.1**

**DEFINITIONS OF TERMS**

**Conserved parts** — structures or sequences that are identical or similar across species.

For a complete list of defined terms, see the **Glossary**.

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**Workbook**

**Lesson 5.1**

4. Which of the following statements about innate cells is NOT true?
   a. The three most important are macrophages, dendritic cells, and neutrophils.
   b. They call for help by releasing cytokines, which can stimulate or inhibit cells.
   c. If they are not able to control an infection, they will activate adaptive immune cells.
   d. none of the above

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**Figure 4:** Examples of common PAMPs: flagellin that makes bacterial flagella, LPS in Gram-negative cell wall, and double-stranded (ds) RNA in viral genomes.

**Figure 5:** Innate cells can ‘see’ pathogens as well as you can see these buildings, but not clearly enough to distinguish details.
LESSON READINGS

structures, or patterns. This is like having poor vision and no glasses — innate cells can tell a person from a dog but not one person from another. So, if a pathogen changes its face, innate cells will still 'see' the pathogen as non-self. Because of this, the innate immune system can clear almost all infections. However, if the pathogen does mutate in just the right way, innate cells may become blind to the pathogen!

After innate cells recognize a PAMP, they neutralize the threat in three main ways:

Phagocytosis

Phagocytosis: When some innate cells recognize a pathogen, they will engulf it. Once inside, the innate cell digests (kills) the pathogen using the enzymes in its lysosome that act like the stomach enzymes and acids of an innate cell. This process is also the same one used to clear the dead cells from our bodies. Most microbes can’t survive after being engulfed by a phagocyte, but some virulent pathogens have figured out a way to disable the enzymes by releasing factors that inactivate the enzymes. The TB bacterium (M. tuberculosis) is an example of such a pathogen.

Chemotaxis

Chemotaxis: Imagine that some bacteria of Clostridium tetani, the bacteria that causes tetanus, get through the skin on a rusty nail. Innate cells will be waiting in the tissue for just this opportunity to phagocytosis the bacteria. They will also sound the alarm by releasing molecules called cytokines and chemokines that recruit other immune cells. This is a way to make sure that there are enough innate cells to clear the infection. But getting immune cells to the site of an infection presents a few challenges:

- Cells in a tissue are usually tightly packed, so there is no empty space for immune cells to travel through.
- Immune cells in the blood are flying by fast, like a car on a highway with no exits.
So, the cytokines and chemokines do something else that is remarkable: they increase the flow of blood at the site of the infection. This causes swelling but also allows cells from the blood to enter an infected tissue. This also creates off ramps for immune cells flying by in the blood. This process allows innate and adaptive cells to accumulate at the site of the infection to clear the *C. tetani*.

However, this process does lead to some painful symptoms that we call **inflammation**. Inflammation is swelling, heat, redness, pain and more. For example, if a mosquito takes a blood meal and injects malaria, the site of the bite will become red and hot as innate cells move to the site to clean up the mess! Immune cells also move in to clean up the mess when host cells are damaged, and this is how inflammation happens in the absence of an infection. We will learn more about inflammation in lesson 5.4.

**Innate cells will clear most pathogens, and will activate B and T cells for the rest**

The last key function of innate immune cells is activating adaptive responses. We will learn more about how this works in the next few lessons.
PAMPs that innate cells recognize are generally conserved structures. Why might this be the case?

_____________________________________________________________________________________________________

_____________________________________________________________________________________________________

_____________________________________________________________________________________________________

Predict the effect of a severely altered PAMP structure on a) the survival of the microbe and b) the ability of our innate cells to recognize this microbe.

_____________________________________________________________________________________________________

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What happens when a PAMP is recognized by an innate cell?

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Based on what you know about the immune system, draw a model to show the different components and how they interact.
<table>
<thead>
<tr>
<th>TERM</th>
<th>DEFINITION</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anemia</td>
<td>A decrease in the red blood cells count or hemoglobin levels in the blood.</td>
</tr>
<tr>
<td>Bone marrow</td>
<td>The soft tissues inside the bones, producing our blood cells.</td>
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<td>Cell differentiation</td>
<td>The process of a cell changing to become another cell type or subtype. For example, a stem cell can turn into a lymphocyte.</td>
</tr>
<tr>
<td>Chemokines</td>
<td>Type of cytokines that induce chemotaxis of nearby cells.</td>
</tr>
<tr>
<td>Conserved parts</td>
<td>Structures or sequences that are identical or similar across species, or cells in an organism.</td>
</tr>
<tr>
<td>Cytokines</td>
<td>Small proteins that are used as signal molecules to convey messages between different cells.</td>
</tr>
<tr>
<td>Heart attack</td>
<td>A blockage of normal blood flow to the heart muscle.</td>
</tr>
<tr>
<td>Hematopoiesis</td>
<td>The production of blood cells.</td>
</tr>
<tr>
<td>Hemophilia</td>
<td>Genetic disorders that inhibit the normal process of blood clotting.</td>
</tr>
<tr>
<td>Lysosome</td>
<td>Membrane vesicle found in most animal cells. It contains enzymes that can digest down all kind of biomolecules such as proteins and sugars.</td>
</tr>
<tr>
<td>Stem cell</td>
<td>A cell that has not been differentiated yet and can divide to produce more stem cells or can become differentiated.</td>
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