13.1: First Line defense- Physical, Mechanical and Chemical Defenses

Learning Objectives

- Describe the various physical barriers and mechanical defenses that protect the human body against infection and disease
- Describe how enzymes in body fluids provide protection against infection or disease
- Describe the role of microbiota as a first-line defense against infection and disease

Nonspecific innate immunity can be characterized as a multifaceted system of defenses that targets invading pathogens in a nonspecific manner. In this chapter, we have divided the numerous defenses that make up this system into three categories: physical defenses, chemical defenses, and cellular defenses. However, it is important to keep in mind that these defenses do not function independently, and the categories often overlap. Table 1 provides an overview of the nonspecific defenses discussed in this chapter.

**Table 1: Overview of Nonspecific Innate Immune Defenses**

<table>
<thead>
<tr>
<th>Physical barriers</th>
</tr>
</thead>
<tbody>
<tr>
<td>Physical defenses</td>
</tr>
<tr>
<td>Mechanical defenses</td>
</tr>
<tr>
<td>Microbiome</td>
</tr>
<tr>
<td>Chemical defenses</td>
</tr>
<tr>
<td>Chemicals and enzymes in body fluids</td>
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<tr>
<td>Antimicrobial peptides</td>
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</table>
Overview of Nonspecific Innate Immune Defenses

Plasma protein mediators

Cytokines

Inflammation-eliciting mediators

Granulocytes

Agranulocytes

Clinical Focus: part 1

Angela, a 25-year-old female patient in the emergency department, is having some trouble communicating verbally because of shortness of breath. A nurse observes constriction and swelling of the airway and labored breathing. The nurse asks Angela if she has a history of asthma or allergies. Angela shakes her head no, but there is fear in her eyes. With some difficulty, she explains that her father died suddenly at age 27, when she was just a little girl, of a similar respiratory attack. The underlying cause had never been identified.

Exercise \(\PageIndex{1}\)

1. What are some possible causes of constriction and swelling of the airway?
2. What causes swelling of body tissues in general?

Physical defenses provide the body’s most basic form of nonspecific defense. They include physical barriers to microbes, such as the skin and mucous membranes, as well as mechanical defenses that physically remove microbes and debris from areas of the body where they might cause harm or infection. In addition, the microbiome provides a measure of physical protection against disease, as microbes of the normal microbiota compete with pathogens for nutrients and cellular binding sites necessary to cause infection.

Physical Barriers

Physical barriers play an important role in preventing microbes from reaching tissues that are susceptible to infection. At the cellular level, barriers consist of cells that are tightly joined to prevent invaders from crossing through to deeper tissue. For example, the endothelial cells that line blood vessels have very tight cell-to-cell junctions, blocking microbes from gaining access to the bloodstream. Cell junctions are generally composed of cell membrane proteins that may connect with the extracellular matrix or with complementary proteins from neighboring cells. Tissues in various parts of the body have different types of cell junctions. These include tight junctions, desmosomes, and gap junctions, as illustrated in Figure \(\PageIndex{1}\)). Invading microorganisms may attempt to break down these substances chemically, using enzymes such as proteases that can cause structural damage to create a point of entry for pathogens.
The Skin Barrier

One of the body’s most important physical barriers is the skin barrier, which is composed of three layers of closely packed cells. The thin upper layer is called the epidermis. A second, thicker layer, called the dermis, contains hair follicles, sweat glands, nerves, and blood vessels. A layer of fatty tissue called the hypodermis lies beneath the dermis and contains blood and lymph vessels (Figure 1).

The topmost layer of skin, the epidermis, consists of cells that are packed with keratin. These dead cells remain as a tightly connected, dense layer of protein-filled cell husks on the surface of the skin. The keratin makes the skin’s surface mechanically tough and resistant to degradation by bacterial enzymes. Keratin also helps to make the outer surface of the skin relatively waterproof, this helps keep the surface of the skin dry, which reduces microbial growth. Fatty acids on the skin’s surface create a dry, salty, and acidic environment that inhibits the growth of some microbes and is highly...

Figure 1: There are multiple types of cell junctions in human tissue, three of which are shown here. Tight junctions rivet two adjacent cells together, preventing or limiting material exchange through the spaces between them. Desmosomes have intermediate fibers that act like shoelaces, tying two cells together, allowing small materials to pass through the resulting spaces. Gap junctions are channels between two cells that permit their communication via signals. (credit: modification of work by Mariana Ruiz Villareal)
resistant to breakdown by bacterial enzymes. Sebum from the oil glands in hair follicles is an endogenous mediator, providing an additional layer of defense by helping seal off the pore of the hair follicle, preventing bacteria on the skin’s surface from invading sweat glands and surrounding tissue. Certain members of the microbiome, can use lipase enzymes to degrade sebum, using it as a food source. This produces oleic acid, which creates a mildly acidic environment on the surface of the skin that is inhospitable to many pathogenic microbes. Oleic acid is an example of an exogenously produced mediator because it is produced by resident microbes and not directly by body cells. In addition, the dead cells of the epidermis are frequently shed, along with any microbes that may be clinging to them (desquamation). Shed skin cells are continually replaced with new cells from below, providing a new barrier that will soon be shed in the same way.

Perspiration (sweat) provides some moisture to the epidermis, which can increase the potential for microbial growth. For this reason, more microbes are found on the regions of the skin that produce the most sweat, such as the skin of the underarms and groin. However, in addition to water, sweat also contains substances that inhibit microbial growth, such as salts, lysozyme, and antimicrobial peptides. Sebum also serves to protect the skin and reduce water loss. Although some of the lipids and fatty acids in sebum inhibit microbial growth, sebum contains compounds that provide nutrition for certain microbes. In the ears, cerumen (earwax) exhibits antimicrobial properties due to the presence of fatty acids, which lower the pH to between 3 and 5.

Infections can occur when the skin barrier is compromised or broken. A wound can serve as a point of entry for opportunistic pathogens, which can infect the skin tissue surrounding the wound and possibly spread to deeper tissues.

Every Rose has its Thorn

Mike, a gardener from southern California, recently noticed a small red bump on his left forearm. Initially, he did not think much of it, but soon it grew larger and then ulcerated (opened up), becoming a painful lesion that extended across a large part of his forearm (Figure \(\PageIndex{3}\)). He went to an urgent care facility, where a physician asked about his occupation. When he said he was a landscaper, the physician immediately suspected a case of sporotrichosis, a type of fungal infection known as rose gardener’s disease because it often afflicts landscapers and gardening enthusiasts.

Under most conditions, fungi cannot produce skin infections in healthy individuals. Fungi grow filaments known as hyphae, which are not particularly invasive and can be easily kept at bay by the physical barriers of the skin and mucous membranes. However, small wounds in the skin, such as those caused by thorns, can provide an opening for opportunistic pathogens like *Sporothrix schenckii*, a soil-dwelling fungus and the causative agent of rose gardener’s disease. Once it breaches the skin barrier, *S. schenckii* can infect the skin and underlying tissues, producing ulcerated lesions like Mike’s. Compounding matters, other pathogens may enter the infected tissue, causing secondary bacterial infections.

Luckily, rose gardener’s disease is treatable. Mike’s physician wrote him a prescription for some antifungal drugs as well as a course of antibiotics to combat secondary bacterial infections. His lesions eventually healed, and Mike returned to work with a new appreciation for gloves and protective clothing.
Barriers in the Eye

Although the eye and skin have distinct anatomy, they are both in direct contact with the external environment. An important component of the eye is the nasolacrimal drainage system, which serves as a conduit for the fluid of the eye, called tears. Tears flow from the external eye to the nasal cavity by the lacrimal apparatus, which is composed of the structures involved in tear production (Figure 4). The lacrimal gland, above the eye, secretes tears to keep the eye moist. There are two small openings, one on the inside edge of the upper eyelid and one on the inside edge of the lower eyelid, near the nose. Each of these openings is called a lacrimal punctum. Together, these lacrimal puncta collect tears from the eye that are then conveyed through lacrimal ducts to a reservoir for tears called the lacrimal sac, also known as the dacrocyst or tear sac.

From the sac, tear fluid flows via a nasolacrimal duct to the inner nose. Each nasolacrimal duct is located underneath the skin and passes through the bones of the face into the nose. Chemicals in tears, such as defensins, lactoferrin, and lysozyme, help to prevent colonization by pathogens. Lysozyme cleaves the bond between NAG and NAM in peptidoglycan, a component of the cell wall in bacteria. It is more effective against gram-positive bacteria, which lack the protective outer membrane associated with gram-negative bacteria. Lactoferrin inhibits microbial growth by chemically binding and sequestering iron. This effectually starves many microbes that require iron for growth. In addition, mucins facilitate removal of microbes from the surface of the eye.

Mucous Membranes

The mucous membranes lining the nose, mouth, lungs, and urinary and digestive tracts provide another nonspecific barrier against potential pathogens. Mucous membranes consist of a layer of epithelial cells bound by tight junctions.
The epithelial cells secrete a moist, sticky substance called mucus, which covers and protects the more fragile cell layers beneath it and traps debris and particulate matter, including microbes. Mucus secretions also contain antimicrobial peptides.

In many regions of the body, mechanical actions serve to flush mucus (along with trapped or dead microbes) out of the body or away from potential sites of infection. For example, in the respiratory system, inhalation can bring microbes, dust, mold spores, and other small airborne debris into the body. The nasal cavity is lined with hairs that trap large particles, like dust and pollen, and prevent their access to deeper tissues. The nasal cavity is also lined with a mucous membrane and Bowman’s glands that produce mucus to help trap particles and microorganisms for removal, a layer known as the mucociliary blanket. The viscosity and acidity of this secretion inhibits microbial attachment to the underlying cells. The upper respiratory system is under constant surveillance by mucosa-associated lymphoid tissue (MALT), including the adenoids and tonsils. Other mucosal defenses include secreted antibodies (IgA), lysozyme, surfactant, and antimicrobial peptides called defensins. The epithelial cells lining the upper parts of the respiratory tract are called ciliated epithelial cells because they have hair-like appendages known as cilia. Movement of the cilia propels debris-laden mucus out and away from the lungs. The expelled mucus is then swallowed and destroyed in the stomach, or coughed up, or sneezed out (Figure \(\PageIndex{5}\)). This system of removal is often called the mucociliary escalator.

![Ciliated and nonciliated epithelial cells from the human trachea](https://bio.libretexts.org/Courses/Manchester_Community_College_(MCC)/Remix_of_Openstax%3AMicrobiology_by_Parker...)

**Figure \(\PageIndex{5}\):** This scanning electron micrograph shows ciliated and nonciliated epithelial cells from the human trachea. The mucociliary escalator pushes mucus away from the lungs, along with any debris or microorganisms that may be trapped in the sticky mucus, and the mucus moves up to the esophagus where it can be removed by swallowing.

The mucociliary escalator is such an effective barrier to microbes that the lungs, the lowermost (and most sensitive)
portion of the respiratory tract, were long considered to be a sterile environment in healthy individuals. Only recently has research suggested that healthy lungs may have a small normal microbiota. Disruption of the mucociliary escalator by the damaging effects of smoking or diseases such as cystic fibrosis can lead to increased colonization of bacteria in the lower respiratory tract and frequent infections, which highlights the importance of this physical barrier to host defenses. Lastly, the outer surface of the lungs is protected with a double-layered pleural membrane, which protects the lungs and provides lubrication to permit the lungs to move easily during respiration. They also are protected by alveolar macrophages. These phagocytes efficiently kill any microbes that manage to evade the other defenses.

Like the respiratory tract, the digestive tract is a portal of entry through which microbes enter the body, and the mucous membranes lining the digestive tract provide a nonspecific physical barrier against ingested microbes. Several factors appear to work against making the mouth hospitable to certain microbes. For example, chewing allows microbes to mix better with saliva so they can be swallowed or spit out more easily. In the oral cavity, saliva contains mediators such as lactoperoxidase enzymes, and lysozyme, which can damage microbial cells. Lysozyme is part of the first line of defense in the innate immune system and cleaves linkages between N-acetylglucosamine (NAG) and N-acetylmuramic acid (NAM) in bacterial peptidoglycan. Additionally, fluids containing immunoglobulins and phagocytic cells are produced in the gingival spaces. The stomach is an extremely acidic environment (pH 1.5–3.5) due to the gastric juices that break down food and kill many ingested microbes; this helps prevent infection from pathogens. Further down, the intestinal tract is lined with epithelial cells, interspersed with mucus-secreting goblet cells (Figure \(\PageIndex{6}\)). This mucus mixes with material received from the stomach, trapping foodborne microbes and debris.

Goblet cells, which are modified simple columnar epithelial cells, also line the GI tract (Figure \(\PageIndex{6}\)). Goblet cells secrete a gel-forming mucin, which is the major component of mucus. The production of a protective layer of mucus helps reduce the risk of pathogens reaching deeper tissues. Small aggregates of underlying lymphoid tissue in the ileum, called Peyer’s patches, detect pathogens in the intestines via microfold (M) cells, which transfer antigens from the lumen of the intestine to the lymphocytes on Peyer’s patches to induce an immune response. The Peyer’s patches then secrete IgA and other pathogen-specific antibodies into the intestinal lumen to help keep intestinal microbes at safe levels.

The mechanical action of peristalsis, a series of muscular contractions in the digestive tract, moves the sloughed mucus...
and other material through the intestines, rectum, and anus, excreting the material in feces. In fact, feces are composed of approximately 25% microbes, 25% sloughed epithelial cells, 25% mucus, and 25% digested or undigested food. Finally, the normal microbiota provides an additional barrier to infection via a variety of mechanisms. For example, these organisms outcompete potential pathogens for space and nutrients within the intestine. This is known as competitive exclusion. Members of the microbiota may also secrete protein toxins known as bacteriocins that are able to bind to specific receptors on the surface of susceptible bacteria.

### Endothelia

The epithelial cells lining the urogenital tract, blood vessels, lymphatic vessels, and certain other tissues are known as endothelia. These tightly packed cells provide a particularly effective frontline barrier against invaders. The endothelia of the blood-brain barrier, for example, protect the central nervous system (CNS), which consists of the brain and the spinal cord. The CNS is one of the most sensitive and important areas of the body, as microbial infection of the CNS can quickly lead to serious and often fatal inflammation. The cell junctions in the blood vessels traveling through the CNS are some of the tightest and toughest in the body, preventing any transient microbes in the bloodstream from entering the CNS. This keeps the cerebrospinal fluid that surrounds and bathes the brain and spinal cord sterile under normal conditions.

In both men and women, however, the kidneys are sterile. Although urine does contain some antibacterial components, bacteria will grow in urine left out at room temperature. Therefore, it is primarily the flushing action that keeps the ureters and bladder free of microbes. The female reproductive system employs lactate, an exogenously produced chemical mediator, to inhibit microbial growth. The cells and tissue layers composing the vagina also produce glycogen, a branched and more complex polymer of glucose.

Exercise \(PageIndex(2)\)

1. Describe how the mucociliary escalator functions.
2. What other defenses do each of the body sites have in common?
3. Name two places you would find endothelia.

### Antimicrobial Peptides

The antimicrobial peptides (AMPs) are a special class of nonspecific cell-derived mediators with broad-spectrum antimicrobial properties. Some AMPs are produced routinely by the body, whereas others are primarily produced (or produced in greater quantities) in response to the presence of an invading pathogen. Research has begun exploring how AMPs can be used in the diagnosis and treatment of disease.

AMPs may induce cell damage in microorganisms in a variety of ways, including by inflicting damage to membranes, destroying DNA and RNA, or interfering with cell-wall synthesis. Depending on the specific antimicrobial mechanism, a particular AMP may inhibit only certain groups of microbes (e.g., gram-positive or gram-negative bacteria) or it may be more broadly effective against bacteria, fungi, protozoa, and viruses. Many AMPs are found on the skin, but they can also be found in other regions of the body.
A family of AMPs called defensins can be produced by epithelial cells throughout the body as well as by cellular defenses such as macrophages and neutrophils. Defensins may be secreted or act inside host cells; they combat microorganisms by damaging their plasma membranes. AMPs called bacteriocins are produced exogenously by certain members of the resident microbiota within the gastrointestinal tract. The genes coding for these types of AMPs are often carried on plasmids and can be passed between different species within the resident microbiota through lateral or horizontal gene transfer. There are numerous other AMPs throughout the body. The characteristics of a few of the more significant AMPs are summarized in Table \( \PageIndex{2} \).

<table>
<thead>
<tr>
<th>AMP</th>
<th>Secreted by</th>
<th>Body site</th>
<th>Pathogens inhibited</th>
<th>Mode of action</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bacteriocins</td>
<td>Resident microbiota</td>
<td>Gastrointestinal tract</td>
<td>Bacteria</td>
<td>Disrupt membrane</td>
</tr>
<tr>
<td>Cathelicidin</td>
<td>Epithelial cells, macrophages, and other cell types</td>
<td>Skin</td>
<td>Bacteria and fungi</td>
<td>Disrupts membrane</td>
</tr>
<tr>
<td>Defensins</td>
<td>Epithelial cells, macrophages, neutrophils</td>
<td>Throughout the body</td>
<td>Fungi, bacteria, and many viruses</td>
<td>Disrupt membrane</td>
</tr>
<tr>
<td>Dermicidin</td>
<td>Sweat glands</td>
<td>Skin</td>
<td>Bacteria and fungi</td>
<td>Disrupts membrane integrity and ion channels</td>
</tr>
<tr>
<td>Histatins</td>
<td>Salivary glands</td>
<td>Oral cavity</td>
<td>Fungi</td>
<td>Disrupt intracellular function</td>
</tr>
</tbody>
</table>

Exercise \( \PageIndex{3} \)

Why are antimicrobial peptides (AMPs) considered nonspecific defenses?

**Mechanical Defenses**

In addition to physical barriers that keep microbes out, the body has a number of mechanical defenses that physically remove pathogens from the body, preventing them from taking up residence. We have already discussed several examples of mechanical defenses, including the shedding of skin cells, the expulsion of mucus via the mucociliary escalator, and the excretion of feces through intestinal peristalsis. Other important examples of mechanical defenses include the flushing action of urine and tears, which both serve to carry microbes away from the body. The flushing action of urine is largely responsible for the normally sterile environment of the urinary tract, which includes the kidneys, ureters, and urinary bladder. Urine passing out of the body washes out transient microorganisms, preventing them from taking up residence. The eyes also have physical barriers and mechanical mechanisms for preventing infections. The eyelashes and eyelids prevent dust and airborne microorganisms from reaching the surface of the eye. Any microbes or debris that make it past these physical barriers may be flushed out by the mechanical action of blinking, which bathes the eye in tears, washing debris away (Figure \( \PageIndex{7} \)).
Figure \(\PageIndex{7}\): Tears flush microbes away from the surface of the eye. Urine washes microbes out of the urinary tract as it passes through; as a result, the urinary system is normally sterile.

Exercise \(\PageIndex{4}\)

Name two mechanical defenses that protect the eyes.

**Microbiome**

In various regions of the body, resident microbiota serve as an important first-line defense against invading pathogens. Through their occupation of cellular binding sites and competition for available nutrients, the resident microbiota prevent the critical early steps of pathogen attachment and proliferation required for the establishment of an infection. For example, in the vagina, members of the resident microbiota compete with opportunistic pathogens like the yeast *Candida*. This competition prevents infections by limiting the availability of nutrients, thus inhibiting the growth of *Candida*, keeping its population in check. Similar competitions occur between the microbiota and potential pathogens on the skin, in the upper respiratory tract, and in the gastrointestinal tract. The resident microbiota also contribute to the chemical defenses of the innate nonspecific host defenses.

The importance of the normal microbiota in host defenses is highlighted by the increased susceptibility to infectious diseases when the microbiota is disrupted or eliminated. Treatment with antibiotics can significantly deplete the normal microbiota of the gastrointestinal tract, providing an advantage for pathogenic bacteria to colonize and cause diarrheal infection. In the case of diarrhea caused by *Clostridium difficile*, the infection can be severe and potentially lethal. One strategy for treating *C. difficile* infections is fecal transplantation, which involves the transfer of fecal material from a donor (screened for potential pathogens) into the intestines of the recipient patient as a method of restoring the normal microbiota and combating *C. difficile* infections.

Table \(\PageIndex{3}\) provides a summary of the physical defenses discussed in this section.

**Table \(\PageIndex{3}\): Physical Defenses of Nonspecific Innate Immunity**
Defense | Examples | Function
---|---|---
Cellular barriers | Skin, mucous membranes, endothelial cells | Deny entry to pathogens
Mechanical defenses | Shedding of skin cells, mucociliary sweeping, peristalsis, flushing action of urine and tears | Remove pathogens from potential sites of infection
Microbiome | Resident bacteria of the skin, upper respiratory tract, gastrointestinal tract, and genitourinary tract | Compete with pathogens for cellular binding sites and nutrients

Exercise \(\PageIndex{5}\))

List two ways resident microbiota defend against pathogens.

**Key Concepts and Summary**

- **Nonspecific innate immunity** provides a first line of defense against infection by nonspecifically blocking entry of microbes and targeting them for destruction or removal from the body.
- The physical defenses of innate immunity include physical barriers, mechanical actions that remove microbes and debris, and the microbiome, which competes with and inhibits the growth of pathogens.
- The skin, mucous membranes, and endothelia throughout the body serve as physical barriers that prevent microbes from reaching potential sites of infection. Tight cell junctions in these tissues prevent microbes from passing through.
- Microbes trapped in dead skin cells or mucus are removed from the body by mechanical actions such as shedding of skin cells, mucociliary sweeping, coughing, peristalsis, and flushing of bodily fluids (e.g., urination, tears).
- Numerous chemical mediators produced endogenously and exogenously exhibit nonspecific antimicrobial functions.
- Many chemical mediators are found in body fluids such as sebum, saliva, mucus, gastric and intestinal fluids, urine, tears, cerumen, and vaginal secretions.
- Antimicrobial peptides (AMPs) found on the skin and in other areas of the body are largely produced in response to the presence of pathogens. These include dermcidin, cathelicidin, defensins, histatins, and bacteriocins.
- The resident microbiota provide a physical defense by occupying available cellular binding sites and competing with pathogens for available nutrients.

**Contributors and Attributions**

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