Section A: Nonspecific Defenses Against Infection

1. The skin and mucus membranes provide first-line barriers to infection
2. Phagocytic cells, inflammation, and antimicrobial proteins function early in infection
Introduction

• An animal must defend itself against unwelcome intruders - the many potentially dangerous viruses, bacteria, and other pathogens it encounters in the air, in food, and in water.

• It must also deal with abnormal body cells, which, in some cases, may develop into cancer.
• Three cooperative lines of defense have evolved to counter these threats.
  • Two of these are nonspecific - that is, they do not distinguish one infectious agent from another.

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• The first line of nonspecific defense is external, consisting of epithelial cells that cover and line our bodies and the secretions they produce.

• The second line of nonspecific defense is internal, involving phagocytic cells and antimicrobial proteins that indiscriminately attack invaders that penetrate the body’s outer barriers.

• The third line of defense, the immune system, responds in a specific way to particular toxins, microorganisms, aberrant body cells, and other substances marked by foreign molecules.

  • Specific defensive proteins called antibodies are produced by lymphocytes.
• An invading microbe must penetrate the external barrier formed by the skin and mucous membranes, which cover the surface and line the openings of an animal’s body.

• If it succeeds, the pathogen encounters the second line of nonspecific defense, interacting mechanisms that include phagocytosis, the inflammatory response, and antimicrobial proteins.
1. The skin and mucous membrane provide first-line barriers to infection

- Intact skin is a barrier that cannot normally be penetrated by bacteria or viruses, although even minute abrasions may allow their passage.

- Likewise, the mucous membranes that line the digestive, respiratory, and genitourinary tracts bar the entry of potentially harmful microbes.
• Beyond their role as a physical barrier, the skin and mucous membranes counter pathogens with chemical defenses.

• In humans, for example, secretions from sebaceous and sweat glands give the skin a pH ranging from 3 to 5, which is acidic enough to prevent colonization by many microbes.

• Microbial colonization is also inhibited by the washing action of saliva, tears, and mucous secretions that continually bathe the exposed epithelium.

• All these secretions contain antimicrobial proteins.

• One of these, the enzyme lysozyme, digests the cell walls of many bacteria, destroying them.
- *Mucus*, the viscous fluid secreted by cells of mucous membranes, also traps microbes and other particles that contact it.

- In the trachea, ciliated epithelial cells sweep out mucus with its trapped microbes, preventing them from entering the lungs.
• Microbes present in food or water, or those in swallowed mucus, must contend with the highly acidic environment of the stomach.
  • The acid destroys many microbes before they can enter the intestinal tract.
  • One exception, the virus hepatitis A, can survive gastric acidity and gains access to the body via the digestive tract.
2. Phagocytic cells, inflammation, and antimicrobial proteins function early in infection

- Microbes that penetrate the first line of defense face the second line of defense, which depends mainly on **phagocytosis**, the ingestion of invading organisms by certain types of white cells.

- Phagocyte function is intimately associated with an effective inflammatory response and also with certain antimicrobial proteins.
• The phagocytic cells called neutrophils constitute about 60%-70% of all white blood cells (leukocytes).

• Cells damaged by invading microbes release chemical signals that attract neutrophils from the blood.

• The neutrophils enter the infected tissue, engulfing and destroying microbes there.

• Neutrophils tend to self-destruct as they destroy foreign invaders, and their average life span is only a few days.
• **Monocytes**, about 5% of leukocytes, provide an even more effective phagocytic defense.

  • After a few hours in the blood, they migrate into tissues and develop into **macrophages**: large, long-lived phagocytes.

  • These cells extend long pseudopodia that can attach to polysaccharides on a microbe’s surface, engulfing the microbe by phagocytosis, and fusing the resulting vacuole with a lysosome.

Fig. 43.3
• The lysosome has two ways of killing trapped microbes.

  • First, it can generate toxic forms of oxygen, such as superoxide anion and nitric oxide.

  • Second, lysosomal enzymes, including lysozyme, digest microbial components.
• There are microbes that have evolved mechanisms for evading phagocytic destruction.
  • Some bacteria have outer capsules to which a macrophage cannot attach.
  • Others, like *Mycobacterium tuberculosis*, are readily engulfed but are resistant to lysosomal destruction and can even reproduce inside a macrophage.
  • These microorganisms are a particular problem for both nonspecific and specific defenses of the body.
• Some macrophages migrate throughout the body, while others reside permanently in certain tissues, including the lung, liver, kidney, connective tissue, brain, and especially in lymph nodes and the spleen.
• The fixed macrophages in the spleen, lymph nodes, and other lymphatic tissues are particularly well located to contact infectious agents.

• Interstitial fluid, perhaps containing pathogens, is taken up by lymphatic capillaries, and flows as lymph, eventually returning to the blood circulatory system.

• Along the way, lymph must pass through numerous lymph nodes, where any pathogens present encounter macrophages and lymphocytes.

• Microorganisms, microbial fragments, and foreign molecules that enter the blood encounter macrophages when they become trapped in the netlike architecture of the spleen.
• **Eosinophils**, about 1.5% of all leukocytes, contribute to defense against large parasitic invaders, such as the blood fluke, *Schistosoma mansoni*.

  • Eosinophils position themselves against the external wall of a parasite and discharge destructive enzymes from cytoplasmic granules.
• **Natural killer (NK) cells** do not attack microorganisms directly but destroy virus-infected body cells.
  • They also attack abnormal body cells that could become cancerous.
  • NK cells mount an attack on the cell’s membrane, causing the cell to lyse.
• Damage to tissue by a physical injury or by the entry of microorganisms triggers a localized inflammatory response.

• Damaged cells or bacteria release chemical signals that cause nearby capillaries to dilate and become more permeable, leading to clot formation at the injury.

• Increased local blood supply leads to the characteristic swelling, redness, and heat of inflammation.
Fig. 43.5
• One of the chemical signals of the inflammatory response is **histamine**.

  • Histamine is released by circulating leucocytes called **basophils** and by **mast cells** in connective tissue.

  • Histamine triggers both dilation and increased permeability of nearby capillaries.

  • Leukocytes and damaged tissue cells also discharge **prostaglandins** and other substances that promote blood flow to the site of injury.
Enhanced blood flow and vessel permeability have several effects.

- First, they aid in delivering clotting elements to the injured area.
  - Clotting marks the beginning of the repair process and helps block the spread of microbes elsewhere.
- Second, this also enhances the migration of phagocytic cells from the blood into the injured tissues.
  - Phagocyte migration usually begins within an hour after injury.
• Chemotactic factor released by invading bacteria and injured tissues, and **chemokines** secreted by blood vessel endothelial cells and monocytes, attract phagocytes to the area.

• Chemokines constitute a group of about 50 different proteins that bind to receptors on many types of leukocytes and induce numerous other changes central to inflammation.

• For example, they induce the production of toxic forms of oxygen in phagocyte lysosomes and the release of histamine from basophils.
• Neutrophils are the first phagocytes to arrive at the point of assault, followed by macrophages that have developed from migrating monocytes.

• Macrophages not only phagocytose pathogens and their products, but also clean up damaged tissue cells and the remains of neutrophils destroyed in the phagocytic process.

• The pus that accumulates at the site of some infections consists mostly of dead phagocytic cells and the fluid and proteins that leaked from capillaries during the inflammatory response.

• This pus is usually absorbed by the body within a few days.
• Severe tissue damage or infection may trigger a systemic (widespread) nonspecific response.

• In a severe infection, such as meningitis or appendicitis, the number of leukocytes in the blood may increase severalfold within a few hours after the initial inflammatory events.

• Fever, another systemic response to infection, can be triggered by toxins from pathogens or by pyrogens released by certain leukocytes.

• This resets the body’s thermostat and the higher temperature contributes to defense by inhibiting growth of some microbes, facilitating phagocytosis, and speeding up repair of tissues.
• Certain bacterial infections can induce an overwhelming systemic inflammatory response leading to a condition known as *septic shock*.

  • Characterized by high fever and low blood pressure, septic shock is the most common cause of death in U.S. critical care units.

  • Clearly, while local inflammation is an essential step toward healing, widespread inflammation can be devastating.
• A variety of proteins function in nonspecific defense either by attacking microbes directly or by impeding their reproduction.

• In addition to lysozyme, other antimicrobial agents include about 20 serum proteins, known collectively as the complement system.

• These carry out a cascade of steps that lead to lysis of microbes.

• Some complement components work with chemokins to attract phagocytic cells to sites of infection.
Another set of proteins that provide nonspecific defenses are the **interferons**, which are secreted by virus-infected cells.

- While they do not seem to benefit the infected cell, these proteins diffuse to neighboring cells and induce them to produce other chemicals that inhibit viral reproduction.

- Interferon limits cell-to-cell spread of viruses, helping to control viral infection.

- Because they are nonspecific, interferons produced in response to one virus may confer short-term resistance to unrelated viruses.

- One type of interferon activates phagocytes.
• To summarize the nonspecific defense systems, the first line of defense, the skin and mucous membranes, prevents most microbes from entering the body.

• The second line of defense uses phagocytes, natural killer cells, inflammation, and antimicrobial proteins to defend against microbes that have managed to enter the body.

• These two lines of defense are nonspecific in that they do not distinguish among pathogens.