The Immune System & Bacteria: Friends or Foes?

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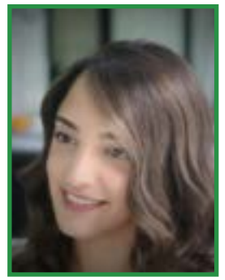

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Introduction

Traditionally, the immune system has been defined as a complex network of organs, vessels, cells and cellular products that plays a pivotal role in fighting pathogens and in the overall maintenance and regulation of bodily functions. Cells and antibodies of the immune system are constantly circulating in the human body and surveilling all tissues and organs: lymphocytes, macrophages, neutrophils, plasma cells, dendritic cells, as well as various immunoglobulins, all working together to ensure that invaders are detected, disposed of and remembered for future infections.

Transmission modes of bacteria

Bacteria can be transmitted to humans from various sources. Human-to-human transmission can be through direct contact via airborne droplets or aerosols, contaminated objects, or a vector such as a tick or a fly. Non-human-to-human transmission occurs from contaminated sources: for example, water like *Vibrio cholerae*, food like *Bacillus cereus*, or from animals like *Bartonella henselae*. The main points of entry of bacteria into the human body are the respiratory tract, genitourinary tract, gastrointestinal tract, or via the skin. After bacteria have invaded tissues and organs and multiplied, the infection can spread through the vasculature to other tissues and cause more systemic symptoms and complications.

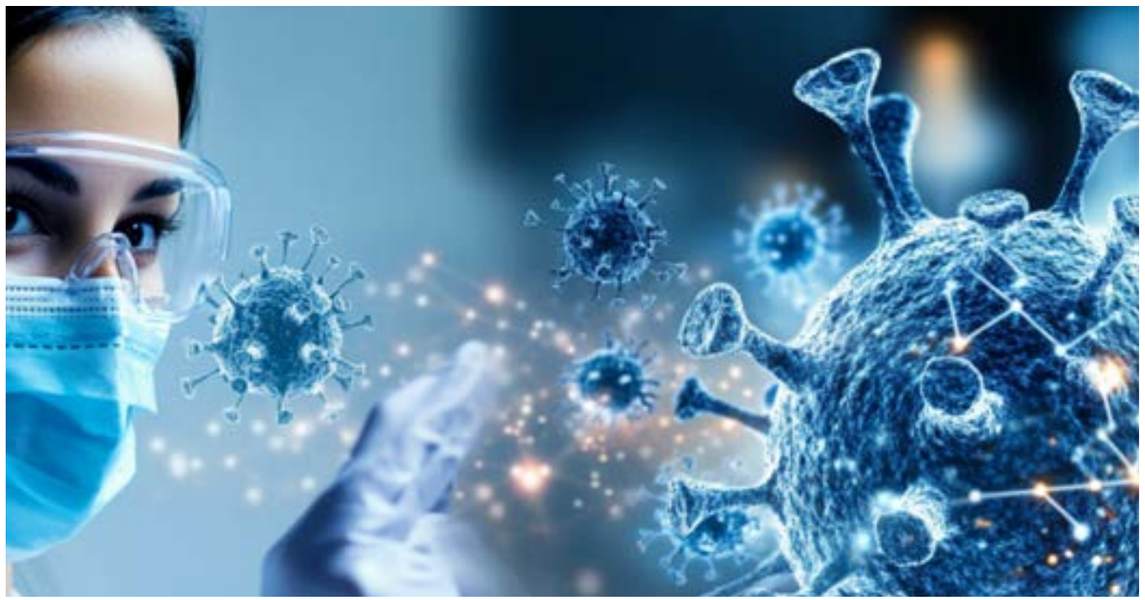
Types of immunity with bacteria

The immune system is characteristically divided into two major components: the innate immune system, which constitutes the first line of defense against pathogens, and the adaptive immune system, which provides a specifically targeted and effective response to pathogens including bacteria.

1. Role of the innate immune system:
The innate immune system is typically related to three components: first, the presence of physical barriers that provide a shield against bacterial entry such as the skin, mucus membranes, and bodily fluids (saliva, tears). Second, Immune cells such as neutrophils, macrophages, and natural killer (NK) cells, are among the first cells to respond to an injury or infection and play a critical role in this rapid and nonspecific response. Third, the body's inflammatory response acts as a stimulus and attractant for these cells to be recruited to the site of infection and inflammation, whereby immune cells can engulf and phagocytose the bacteria. An inflammatory reaction involves a variety of cytokines, produced by immune cells in response to a pathogen, each with a unique function. For example, IL-1, IL-6, and TNF-α promote inflammation and recruit immune cells to the infection site. Macrophages are responsible for phagocytosis of bacteria, and NK cells can directly kill bacteria. Dendritic cells (DCs) play a crucial role in the innate immune response as they can internalize pathogens through phagocytosis, pinocytosis, or endocytosis, process and load them on major histocompatibility complex (MHC) class I or II molecules to present them to cells of the adaptive immune response, especially T cells, inducing their proliferation and activation.

Another vital component of the immune system is the complement system, a group of proteins that work with antibodies to produce three major results. First, complement proteins C3b which can coat bacteria and facilitate phagocytosis. Second, C5a proteins that act as attractants to immune cells to direct them to the site of infection, a process called chemotaxis. Finally, C5b-C9 that can form a membrane attack complex (MAC) which forms pores in the cell membranes of bacteria, causing cell lysis and death.

2. Role of the adaptive immune system
Despite its crucial roles, the innate immune system does not act alone: the initial nonspecific response fills a gap between the start of an infection and the initiation, after a few days, of the targeted "attack" by the adaptive immune system's B cells and T cells. These cells are also responsible for a lasting memory of pathogens which helps sensitize the immune system, so it can recognize and react quicker to future infections. B cells have a dual role: they produce antibodies such as IgM, the first antibody produced in response to infection and is the first line of defense against bacterial pathogens; IgG is the most abundant antibody and is responsible for long-term protection; and IgA is found in mucosal areas and plays a role in local immunity. These antibodies play diverse roles, as they can activate complement, neutralize bacteria, and promote phagocytosis. Importantly, B cells act similarly to dendritic cells (DCs): they function as antigen-presenting cells (APCs) as they process and expose specific antigens from bacteria on their MHC molecules so they can be presented to naïve T cells, causing T cell maturation and activation. T cells have many subtypes and many functions, but they are traditionally thought of in terms of their ability to carry out immune-mediated cell death. The two major types of T cells are helper CD4+ T cells, which assist other immune cells in a variety of immune mechanisms: for instance, Th1 CD4+ T cells produce IL-2, TNF-alpha, and IFN-gamma and stimulate macrophages to destroy intracellular pathogens, whereas Th2 promote class switching and



stimulate B cells to produce IgE antibodies. Naïve T cells can also mature into cytotoxic CD8+ T cells, whose main function is to directly kill infected cells.

The absence, deficiency, or dysfunction of one or more of these cellular or humoral immune mechanisms, or their suppression by medications or corticosteroids, leaves the individual immunodeficient, not able to respond properly to bacterial attack.

Bacteria and immunodeficient individuals:

Immunodeficient people are vulnerable to invasion by viral, fungal, and bacterial pathogens. Immunocompromised patients are at a higher likelihood of infection by certain bacteria, most commonly *Staphylococcus aureus, streptococcus viridans, escherichia coli*, but also such as *Listeria monocytogenes, Nocardia spp,* and *Mycobacterium spp*. Individuals with complement deficiencies are also at a higher chance of infections: people with C5b-C9 deficiencies are at a higher risk of Neisseria spp infection, as they are unable to form a MAC complex to lyse and destroy the bacterial cell. Asplenic or sickle cell patients are also more susceptible to bacterial infections, especially encapsulated bacteria such as *Haemophilus influenzae* or *Streptococcus pneumoniae*, due to the loss of splenic macrophages that help clear bacterial cells and capsules protecting bacteria against phagocytosis.

Bacterial infection and the immune response:

Bacteria cause disease by two major processes that trigger, in a healthy individual, an immune response: (1) the production of toxins or (2) the invasion of a tissue causing inflammation. There are two categories of toxins produced by bacteria: exotoxins and endotoxins. Exotoxins are proteins produced and secreted by gram-positive or gram-negative bacteria, usually encoded in plasmid genes. Exotoxins have a variety of mechanisms of action: for example, *E. Coli* heat-labile toxin ADP-ribosylates and activates adenylate cyclase, increasing cAMP, whereas *Pseudomonas aeurginosa*'s exotoxin A ADP-ribosylates and inactivates elongation factor 2. Alternatively, *Clostridiodes* difficile produces two exotoxins: A which causes watery diarrhea and B that is cytotoxic, damaging the colonic mucosa and forming pseudomembranes which make bacteria more resistant to treatment and less accessible to the cells of the immune system.

On the other hand, endotoxins are present on the cell wall of gram-negative bacteria, in the lipopolysaccharide (LPS) molecule, and specifically the Lipid A component. Endotoxins, though generally less toxic than exotoxins, are the major cause of septic shock and can cause fever, hypotension, and disseminated intravascular coagulation (DIC). The mechanism of action of endotoxins relies on their binding to host cell LPS-binding proteins in the plasma, which subsequently bind to the surface of macrophages, eliciting a signaling cascade resulting in the production of cytokines, TNF-alpha, and nitric oxide. Additionally, endotoxins activate the complement, and the coagulation cascades, increasing vascular permeability and causing DIC.

Besides the secretion of toxins, another mechanism of pathogenicity of bacteria is direct invasion and inflammation, for instance via the secretion of enzymes. For example, *Streptococcus pyogenes* secretes collagenase and hyaluronidase which degrade collagen and hyaluronic acid in human tissues and facilitate the spread of bacteria in subcutaneous tissues, causing cellulitis. Immunoglobulins produced by the host immune cells, such as IgA and IgG may also become vulnerable to bacterial destruction, cleaving and inactivating immunoglobulin molecules and enhancing the bacteria's effect on host cells. Notably, some intracellular bacteria evade the immune system by taking up residence in neutrophils *(Neisseria gonorrhoeae*) or macrophages *(Legionella, Brucella*).

Conclusion:

The immune system's ability to recognize, respond to, and remember bacterial invaders is essential for protecting the body against bacterial diseases. It employs both innate and adaptive mechanisms to protect the body from bacterial pathogens. The interplay between the innate and adaptive immune systems, as well as the complement cascade and other immune cells, ensure a comprehensive and efficient defense system against bacterial infections. The immune system has a remarkable ability to recognize, control, and respond to bacterial infections, regardless of the many ways bacteria can enter the body, proliferate, and invade tissues and cells to cause disease. While vaccines and various antimicrobial agents are available to help the immune system fight infection, the need for a well-functioning immune system remains critical, and immunosuppressed individuals must take additional measures to remain healthy as they are more susceptible to infections.