

Episode #45 – The Immune System: Part 2 September 24, 2021

Types of immunity

The function of the immune system[1] is to distinguish self from nonself and eliminate potentially harmful molecules and cells from the body. The immune system also has the capacity to recognize and destroy abnormal cells that derive from host tissues (i.e., cancer cells). There are 3 types of immunity: innate, acquired, and passive.

Innate immunity[2]

Innate or natural immunity is the level of immunity an individual is born with. It does not require previous exposure to an antigen[3] to work effectively. It responds to invaders immediately, without needing to learn to recognize them. This response is more general and non-specific (i.e., the response is similar for all foreign invaders). Innate immunity recognizes only a limited number of antigens on foreign invaders. However, these antigens are present on many different pathogens. The consensus has been the innate immunity keeps no memory of the invaders and their specific antigens although very recent research suggests this may not be entirely true. [1] [2]

Innate immunity includes the external barriers against pathogens, such as skin, cornea of the eyes, and mucous membranes of the respiratory, digestive, urinary, and reproductive tracts. Other examples of innate immunity include cough reflex, enzymes in tears and sweat, and stomach acid. [1] [3] [4]

Several types of leukocytes (white blood cells) are also involved in innate immunity, such as neutrophils, macrophages, monocytes, dendritic cells, natural killer (NK) cells, eosinophils, basophils, and mast cells. [2] [5]

- Neutrophils circulate in the bloodstream and must be signaled to leave the bloodstream and enter the tissues. The signal can come from invading bacteria, complement proteins,[4] or damaged tissue, all of which produce substances that attract neutrophils to the infection (i.e., chemotaxis). Neutrophils will then ingest

[1] Refer to Episode #44 for more information on the immune system.
[2] Refer to Episode #6 for information on periodontal disease and the innate immune response.
[3] Antigens are any molecule capable of being recognized by the immune system and thus stimulate an immune response.
[4] Complement proteins have many functions, including killing bacteria and other foreign cells, making foreign cells easier for macrophages to identify and ingest, attracting macrophages and neutrophils to the site of infection, neutralizing viruses, promoting antibody formation, and helping the body eliminate dead cells.

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bacteria and other foreign cells. They also contain granules that release enzymes to help kill and digest these invaders. [5]

Neutrophils also release a meshwork of chromatin fibres called neutrophil extracellular traps (NETs) in the surrounding tissue. NETs immobilize and kill invading pathogens, helping to prevent them from spreading. [5] [6]

- Macrophages develop from monocytes. Monocytes become macrophages when they move from the bloodstream to the tissues. Macrophages stay in the tissues and ingest bacteria, foreign cells, and damaged and dead cells. [5]

- Dendritic cells are derived from leukocytes and reside in the skin, lymph nodes, and tissues throughout the body. Dendritic cells ingest bacteria, foreign cells, and damaged and dead cells. [1] [7]

- Natural killer (NK) cells are formed ready to recognize and kill virus-infected cells and cancer cells by inducing apoptosis.[5] NK cells recognize and attach to these cells, then release enzymes and other substances that damage the outer cellular membranes. NK cells are important in the initial defense against viral infections. They also produce cytokines that regulate some functions of T cells, B cells, and macrophages. [7]

- Eosinophils circulate in the bloodstream. They release substances from their granules (e.g., enzymes) when foreign cells (e.g., microorganisms, parasites) are encountered. These substances make pores in the foreign cell's membranes. Their main role is to attach to and kill parasites. However, they also produce substances involved in inflammation and allergic reactions. [5] [8]

- Basophils contain granules filled with histamine that they release when an allergen is encountered. Histamine increases blood flow to damaged tissues, resulting in swelling and inflammation. They also produce substances that attract neutrophils and eosinophils to an infection. [5]

- Mast cells are present in tissues. They release histamine and other substances involved in inflammatory and allergic reactions when they encounter an allergen. [1] [2] [5]

Other components involved in innate immunity are cytokines and the complement system. [5]

Cytokines are chemical messengers produced by leukocytes and other cells of the immune system when an antigen is detected. There are many different cytokines that

[5] Apoptosis, also called cellular suicide, is a programmed cell death where the cell actively destroys itself to maintain the balance of cell multiplication.

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perform a variety of roles, such as stimulating an immune response, inhibiting immune cell activity to help end an immune response, or interfering with viral replication. Cytokines also participate in acquired immunity. [5]

Key cytokines in the innate immune response include tumour necrosis factor alpha (TNF-α), interleukin-1 (IL-1), interleukin-10 (IL-10), interleukin-12 (IL-12), interferon-alpha (IFN-α), interferon-beta (IFN-β), interferon-gamma (IFN-γ), and chemokines.

- TNF-α is a key regulator of acute inflammation. It mediates the recruitment of macrophages and neutrophils to infection sites. It also acts on the hypothalamus to generate fever.
- IL-1 is an inflammatory cytokine involved in the activation of T cells. It also acts on the hypothalamus to generate fever.
- IL-10 is primarily an anti-inflammatory cytokine that helps to dampen the immune response.
- IL-12 causes other immune cells to make cytokines (e.g., IFN-γ) and increases the growth of T cells.
- IFN-α, IFN-β, and IFN-γ inhibit viral replication in cells.
- Chemokines are a large group of chemotactic cytokines produced by numerous leukocytes and other cells in the body. They recruit leukocytes to infection sites via chemotaxis.[6] [9]

The complement system consists of over thirty complement proteins that work in a sequence. This sequence is called a complement cascade because one protein activates another, which activates another, and so on to protect the body from pathogens. The complement system's main role is to help identify, destroy, and remove pathogens (e.g., bacteria, viruses) as well as the body's own damaged cells and proteins. Complement proteins also participate in acquired immunity. [5]

Acquired immunity

Acquired immunity, also referred to as adaptive, active, or specific immunity, develops throughout life with exposure to various antigens or through vaccination.[7] It is sometimes referred to as immunological memory because the immune system remembers previous pathogens and generates an antigen-specific immune response. [3]

Natural acquired immunity occurs when an individual is exposed to the pathogen through infection with the actual disease, triggering the body to produce antibodies (immunoglobulins) against that disease. [10]

Vaccine-induced immunity occurs when antigens (e.g., in the form of an inactivated or killed virus) are introduced into the body via vaccination to stimulate the immune system to produce antibodies without the individual having to contract the disease first. [3] [11]

[6] Chemotaxis is the process where a chemical substance attracts cells to a particular site.
[7] Refer to Episodes #15, 28, 39, and 40 for more information on vaccines and immunization.

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Acquired immunity takes time to develop after initial exposure to a new antigen. However subsequently, the antigen is remembered, and future responses to that antigen are quicker and more effective than responses that occurred after the first exposure (i.e., it learns, adapts, and remembers). Acquired immunity is long-lasting, and sometimes life-long. [12] [10]

Components of acquired immunity include B cells and T cells, dendritic cells, cytokines, and the complement system. [12]

B cells and T cells are involved in the two types of acquired immunity: humoral immunity and cell-mediated immunity that enable the body to defend itself in a targeted way against antigens (e.g., bacteria, viruses, and toxins). B cells and T cells work together in the immune response. [2] [13]

Humoral immunity is triggered by B cells. B cells secrete antigen-specific antibodies which circulate in the blood and act upon extracellular microbes and their toxins. [2]

B cells respond to antigens in two stages, specifically, a primary immune response and a secondary immune response.

- Primary immune response occurs when B cells first encounter an antigen. The antigen attaches to a receptor located on the B cell's surface, stimulating the B cells to change into memory cells or plasma cells. Helper T cells also assist B cells in this process. Memory B cells remember the specific antigen upon future reexposure and plasma cells produce antibodies specific to the antigen. The primary immune response is slow because it takes several days for the plasma cells to produce enough specific antibodies against the antigen. [12]

- Secondary immune response occurs whenever B cells reencounter the same antigen. Memory B cells will rapidly respond, multiply, change into plasma cells, and produce the antigen-specific antibodies. The secondary immune response is quick and very effective. [12]

Cell-mediated immunity is triggered by T cells. Antibodies are not produced in cell-mediated immunity, instead, T cells destroy the infected cells by inducing apoptosis. Cell-mediated immunity acts on intracellular microbes (e.g., viruses, bacteria, and parasites) and tumour cells. T cells typically require antigen-presenting cells to present antigen fragments to them in order for them to recognize an invader. Examples of antigen-presenting cells are B cells, dendritic cells, macrophages, and Langerhans cells.[8] [7]

Dendritic cells are antigen-presenting cells that play a role in cell-mediated immunity. Follicular dendritic cells are a type of dendritic cell located in lymph nodes. These cells present unprocessed (intact) antigen that are attached to an antibody (i.e., antibody-

[8] Langerhans cells are antigen-presenting cells located in the skin and mucosa. [46]

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antigen complex[9]) to B cells. Follicular dendritic cells help B cells respond to an antigen. [12]

Cytokines serve as chemical messengers to regulate the acquired immune response, for example, by stimulating the growth and differentiation of lymphocytes. Key cytokines in the acquired immune response include interleukin-2 (IL-2), interleukin-4 (IL-4), interleukin-5 (IL-5), transforming growth factor beta (TGF-β), IL-10, and IFN-γ. [9]

- IL-2 is the key growth factor for T cells and induces the growth of B cells. It can also activate monocytes and NK cells.
- IL-4 triggers naïve T cells[10] to develop into T helper type 2 (Th2) cells and stimulates the generation of differentiated Th2 cells.
- IL-5 promotes the proliferation and differentiation of B cells and eosinophils from hematopoietic stem cells[11] and activates eosinophils.
- TGF-β is primarily an anti-inflammatory cytokine produced by T cells and many other cell types. It inhibits T cell proliferation and macrophage activation. It also acts on polymorphonuclear leukocytes (PMNs) and endothelial cells to stop the effects of pro-inflammatory cytokines.
- IL-10 is primarily an anti-inflammatory cytokine that helps to dampen the immune response.
- IFN-γ inhibits viral replication in cells. [9]

The complement system's main role is to help identify, destroy, and remove pathogens, damaged cells, and proteins. [5]

Passive immunity

Passive immunity is provided when an individual is given antibodies against pathogens rather than producing them through their own immune system. For example, a newborn baby receives passive immunity from its mother when the mother's antibodies pass through the placenta or are received via breast milk. The mother's antibodies give the baby temporary immunity to diseases to which the mother has been exposed. For instance, maternal immunoglobulin G (IgG), the only immunoglobulin that can pass through the placenta, provides protection to the fetus during pregnancy and to the baby during its first few months of life. [3] [10] [14]

[9] Antigen-antibody complex, also called an immune complex, is formed when an antibody binds (attaches) to an antigen.

[10] A naïve T cell is a T cell that has matured and been released by the thymus but has not yet encountered its corresponding antigen (i.e., naïve T cells are in the stage between maturity and activation). [63]

[11] Hematopoietic stem cells, also called blood stem cells, are immature cells that can develop (differentiate) into all types of blood cells, including leukocytes, erythrocytes (red blood cells), and platelets. They are found in the peripheral blood and bone marrow. [64]

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Immunoglobulin A (IgA) and other antimicrobial factors in breast milk (e.g., IgG, leukocytes, complement proteins, lysozyme,[12] lactoferrin[13]) also help protect the baby by conferring immunity against many infections during the early months of life. [10] [15]

An individual can also receive passive immunity through antibody-containing plasma (i.e., immunoglobulin [Ig], also known as gamma globulin or immune globulin), which may be given when immediate protection from a specific pathogen is needed. It is also used to treat certain types of immune disorders in which there are low amounts of antibodies in the blood. Ig replacement therapy is generally administered intravenously (i.e., intravenous immunoglobulin [IVIg]) or subcutaneously (i.e., subcutaneous immunoglobulin therapy [SCIG]). There are advantages and disadvantages for each route of administration. IVIg allows for higher doses over a short time and historically has been the standard route of administration. SCIG may be used, for example, if a person experiences serious side effects from IVIg.

IVIg contains the pooled IgG immunoglobulins from the plasma of approximately over a thousand healthy blood donors. IVIg is used to treat many different autoimmune disorders, infections, and other conditions. For example, IVIg may be used to treat immune thrombocytopenia (ITP),[14] Kawasaki disease,[15] Guillain-Barré syndrome,[16] systemic lupus erythematosus (SLE)[17] multiple myeloma,[18] and myasthenia gravis.[19] Additionally, it may be used to help prevent infections in individuals who have had a stem cell or organ transplant. Currently, more than one hundred inflammatory and autoimmune disorders are treated with IVIg. [16] [17] [18] [19] [20]

Passive immunity provides immediate protection, whereas acquired immunity usually takes several weeks to develop. However, passive immunity only lasts a few weeks or months. [10]

[12] Lysozyme is an enzyme occurring naturally in human tears, saliva, and other body fluids capable of destroying certain bacteria by hydrolyzing (breaking down) polysaccharides in their cell walls.
[13] Lactoferrin is a protein found in milk (human and cow), tears, mucus, and bile, and is synthesized by neutrophils. It is involved in fighting infection and inflammation and it acts as an antioxidant. [65]
[14] Immune thrombocytopenia (ITP), also called idiopathic thrombocytopenic purpura or immune thrombocytopenic purpura, is an autoimmune bleeding disorder characterized by abnormally low levels of platelets. [69]
[15] Kawasaki disease, also called Kawasaki syndrome or mucocutaneous lymph node syndrome (MLNS), is an acute multisystem inflammatory disease of blood vessels (vasculitis) that primarily affects infants and young children. It may be an autoimmune disorder; however, the cause is yet unknown. [70]
[16] Guillain-Barré syndrome (GBS) is a type of autoimmune disorder that causes inflammation of the peripheral nerves. [71]
[17] Systemic lupus erythematosus (SLE), also referred to as lupus, is an autoimmune disorder that that can affect the joints and many organs (e.g., skin, heart, lungs, kidneys, nervous system). [72]
[18] Multiple myeloma, also called Kahler disease, myelomatosis, and plasma cell myeloma, is a rare form of cancer characterized by excessive production of plasma cells in the bone marrow. [73]
[19] Myasthenia gravis (MG) is a chronic autoimmune disorder in which antibodies destroy nerve-muscle communication, resulting in weakness of the skeletal (voluntary) muscles, especially muscles of the eyes, mouth, throat, and limbs. [74]

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Immune system disorders
Categories of immune system disorders include immunodeficiency, autoimmunity, and hypersensitivity.

Immunodeficiency disorders occur when one or more parts of the immune system malfunction, impairing its ability to defend against foreign invaders (e.g., bacteria, viruses, fungi) or abnormal cells (e.g., cancer cells). As a result, frequent, unusual, or unusually severe or prolonged infections occur. Cancer (e.g., lymphomas) may also develop. Additionally, up to 25% of individuals who have an immunodeficiency disorder also have an autoimmune disorder (e.g., immune thrombocytopenia). [21]

There are two types of immunodeficiency disorders: primary immunodeficiency disorders and secondary immunodeficiency disorders. [21] [22]

- Primary immunodeficiency disorders are genetically determined and can be hereditary. For instance, they may be caused by mutations in a specific gene. For example, if the mutated gene is on the X chromosome, the resulting disorder is called an X-linked disorder. X-linked disorders occur more frequently in boys. Approximately 60% of individuals with primary immunodeficiency disorders are male. [21] [22]

  These disorders typically become evident during infancy or childhood because the child typically experiences abnormally frequent and unusual infections. However, some are not recognized until adulthood. There are over one hundred primary immunodeficiency disorders and all are relatively rare. [21] [22]

  Primary immunodeficiency disorders are classified by the main component of the immune system that is deficient, absent, or defective. There are 5 categories:

  - Humoral immunity deficiencies involve B cell defects that cause antibody (immunoglobulin) deficiencies leading to serum antibody decrease predisposing the individual to bacterial infections. B cell defects account for 50-60% of primary immunodeficiencies. The most common B cell disorder is selective IgA deficiency.[20] [22]

  - Cellular immunity deficiencies involve T cell defects that predispose an individual to viral and fungal infections and other opportunistic infections. T cell disorders also cause Ig deficiencies because the B cell and T cell immune systems are interdependent. Primary NK cell defects are very rare, but predispose an individual to viral infections and tumours. T cell defects account for approximately 5-10% of primary immunodeficiencies. The most

[20] Selective IgA deficiency is characterized by an undetectable level of IgA in the blood and secretions but no other immunoglobulin deficiencies. [75]

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common T cell disorders are chronic mucocutaneous candidiasis,[21] DiGeorge syndrome,[22] X-linked lymphoproliferative syndrome,[23] and zeta-associated protein 70 (ZAP-70) deficiency.[24] [22]

- Combined humoral and cellular immunity deficiencies involve B cell and T cell defects. They account for approximately 20% of primary immunodeficiencies. An example of this disorder is severe combined immunodeficiency (SCID).[25] [22]

- Phagocytic cell defects impair the ability of phagocytes such as monocytes, macrophages, and granulocytes (e.g., neutrophils, eosinophils) to kill pathogens. Phagocytic cell defects account for 10-15% of primary immunodeficiencies. The most common phagocytic cell defects are Chédiak-Higashi syndrome,[26] chronic granulomatous disease,[27] cyclic neutropenia,[28] and leukocyte adhesion deficiency.[29] [22]

[21] Chronic mucocutaneous candidiasis (CMC) is characterized by persistent candida infections of the mucous membranes, scalp, skin, and nails. [76]
[22] DiGeorge syndrome (DGS), also called 22q11.2 deletion syndrome and several other names, is caused by the deletion of a small piece of chromosome 22. The disorder can cause a variety of signs and symptoms, such as heart abnormalities, frequent infections, cleft palate, and thymus gland abnormalities. [77]
[23] X-linked lymphoproliferative (XLP) syndrome, also called Duncan syndrome and several other names, is associated with a defect on the X chromosome termed SH2DIA so only males are affected. It is characterized by life-long vulnerability to Epstein-Barr virus (EBV) infection, which can lead to severe and fatal infectious mononucleosis, lymphomas, combined immunodeficiency and, less commonly, aplastic anemia (inability to produce red blood cells), or vasculitis. [76]
[24] Zeta-associated protein 70 (ZAP-70) deficiency is characterized by recurrent infections similar to those in severe combined immunodeficiency (SCID) in infants and young children. The deficiency may not be diagnosed until children are several years old. [79]
[25] Severe combined immunodeficiency (SCID) is a group of rare congenital syndromes with little or no immune responses resulting in frequent recurring life-threatening bacterial, fungal, and viral infections. [78]
[26] Chédiak-Higashi syndrome (CHS), also called Begnez-Cesar's Syndrome and several other names, is characterized by reduced pigment in the skin and eyes, immune deficiency with an increased susceptibility to infections, and a tendency to bruise and bleed easily. [80]
[27] Chronic granulomatous disease (CGD) affects neutrophils, monocytes, macrophages, and eosinophils and is characterized by recurrent bacterial and fungal infections. It can also be associated with the formation of granulomatous lesions of the skin, lungs, bones, and lymph nodes formed by collections of inflammatory leukocytes. [81] [84]
[28] Cyclic neutropenia, also called cyclic hematopoiesis, cyclic leucopenia, or periodic neutropenia, is characterized by recurrent episodes of abnormally low levels of neutrophils recurring approximately every 21 days and lasting about 3-5 days. This leads to frequent infections of the sinuses, respiratory tract, and skin. Individuals often develop ulcers in the mouth and colon, pharyngitis, gingivitis, recurrent fever, and abdominal pain. [83]
[29] Leukocyte adhesion deficiency (LAD) is characterized by recurrent, life-threatening infections and poor wound healing from surgery or trauma. Individuals with this condition are predisposed to periodontal disease. LAD is caused by a mutation in the gene *ITGB2*. [82]

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- Complement proteins deficiencies result in defective opsonization,[30] phagocytosis, and lysis of pathogens and in defective clearance of antigen-antibody complexes. This leads to recurrent infections (due to defective opsonization) and autoimmune disorders, such as lupus due to defective clearance of antigen-antibody complexes. Complement deficiencies account for ≤ 2% of primary immunodeficiency disorders. [22]

- Secondary immunodeficiency disorders are acquired disorders that generally develop later in life and are more common than primary immunodeficiency disorders. Some of these disorders shorten life span, some persist throughout life but do not affect life span, and a few will resolve with or without treatment. Causes may include the use of certain drugs or therapies (e.g., chemotherapeutic drugs, immunosuppressants, corticosteroids, radiation therapy), other disorders (e.g., diabetes, cancer such as leukemia and lymphoma), viral infections (e.g., human immunodeficiency virus (HIV), cytomegalovirus, Epstein-Barr virus, measles virus), and bacterial infections (e.g., mycobacterial infections). Severe burns or dermatitis can lead to immunodeficiency from loss of serum proteins, especially IgG and albumin. Other causes can include malnutrition (e.g., calcium and zinc deficiencies), alcoholism, and older age (e.g., due to reduced T cell production), which can lead to impaired immune responses. [3] [21] [22]

Autoimmune disorders occur when the immune system mistakenly targets healthy cells as foreign pathogens or faulty cells (i.e., the immune system cannot distinguish self from nonself). Symptoms of autoimmune disorders depend on the type of disorder and the part of the body affected. Examples, of autoimmune diseases include celiac disease, type 1 diabetes mellitus, rheumatoid arthritis, Graves' disease, Hashimoto's thyroiditis, lupus, pemphigus,[31] and Sjögren's syndrome. Many autoimmune disorders are more common among women. [23] [24]

Triggers of autoimmune disorders may include:

- Tissues altered, for example, by viruses, drugs, sunlight, or radiation, appear as foreign substances (i.e., autoantigens[32]) to the immune system which results in the immune system producing autoantibodies.[33] For example, a virus may infect and alter tissue cells. The altered cells are then attacked by the immune system.
- Antibodies to a foreign antigen attack tissues of the body that appear to be structurally or biologically similar (i.e., cross-react[34]). For example, antibodies to the

[30] Opsonization is an immune process which uses opsonins (e.g., antibodies and complement proteins) to tag foreign pathogens for elimination by phagocytes. [40] [56]
[31] Refer to Episode #30 for more information on pemphigus.
[32] Autoantigens are endogenous (self) antigens, that despite being a normal tissue constituent, are targeted by the immune system (e.g., in autoimmune disease). [34]
[33] Autoantibodies are antibodies made against the body's own tissues or organs (i.e., the immune system fails to distinguish self from nonself). Some autoimmune diseases are caused by autoantibodies. [32] [33]
[34] Cross-reactivity occurs when the immune system identifies proteins in one substance (e.g., latex) and the proteins in another (e.g., kiwi, banana, avocado) as being similar, which results in an immune response to the structurally similar or biologically related substances. [35]

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bacteria that cause strep throat or scarlet fever (i.e., group A *Streptococcus*) may cross-react with an antigen in human heart muscle leading to rheumatic fever.[35]

- A substance in the body that is normally isolated to a specific area of the body is released into the bloodstream causing an autoimmune reaction. For example, trauma to the eye can cause the fluid in the eyeball to be released into the bloodstream. The fluid stimulates the immune system to identify the eye as foreign and attack it leading to sympathetic ophthalmia.[36] [23] [24]

It is usually unknown why something triggers an autoimmune disorder in one individual and not another. However, genetic factors maybe involved. Specifically, some individuals have genes that slightly increase their susceptibility to developing an autoimmune disorder, rather than the disorder itself being inherited. [3] [23]

Hypersensitivity disorders occur when the immune system overreacts to normally harmless substances. Severe reactions can damage healthy tissue. For example, anaphylaxis is an acute, widespread, potentially life-threatening IgE-mediated allergic reaction. Anaphylaxis does not usually occur after the first exposure to an allergen but may occur after reexposure.

During an anaphylactic reaction, the antigen interacts with IgE on basophils and mast cells. This triggers release of histamine, leukotrienes,[37] and other mediators that cause diffuse smooth muscle contraction resulting in bronchoconstriction, vomiting, and diarrhea; and vasodilation with plasma leakage causing urticaria (hives) and angioedema.[38]

Triggers of anaphylaxis typically include drugs (e.g., penicillin), foods (e.g., nuts, seafood, eggs), latex, and animal venoms (e.g., from snakes, spiders, jellyfish, bees, wasps). [3] [25] [26]

Take home messages

It is important for oral healthcare professionals to have an overall understanding of the immune system. Treatment advances have extended life span and decreased mortality for many people with immune system disorders and compromised immune systems. Oral healthcare professionals will see clients with these conditions so it is essential to understand the etiology and pathophysiology of these conditions and their corresponding prescribed medications and therapies. It is also important for interprofessional collaboration when working with members of the healthcare team to optimize client health and care.

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[35] Rheumatic fever (RF) is an autoimmune disease that inflames the body's tissues (e.g., joints, heart). RF may develop after strep throat or scarlet fever infections that are not properly treated. [66]

[36] Sympathetic ophthalmia is inflammation of the uveal tract (uveitis) that occurs in one eye after injury or surgery to the other eye. The uveal tract consists of the iris, ciliary body, and the choroid of the eye. [67]

[37] Leukotrienes are pro-inflammatory mediators the body releases after contact with an allergen. They contribute to pathophysiologic features of allergic rhinitis (e.g., nasal passage swelling, increased mucus production, stuffy or runny nose, itchy skin) and allergy-induced asthma (e.g., tightening of airway muscles). [68]

[38] Angioedema is swelling (usually localized) of the subcutaneous tissues.

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Glossary of Terms

Acquired immunity, also called **adaptive**, **active**, or **specific immunity**, develops throughout life with exposure to various antigens or through vaccination. It is sometimes referred to as immunological memory because the immune system remembers previous pathogens and generates an antigen-specific immune response. [3]

Antibodies, also called **immunoglobulins (Ig)**, are proteins produced by B cells that tightly bind to the antigen of an invader, tagging the invader for attack or directly neutralizing it. The human body produces thousands of different antibodies, each specific to a given antigen. There are 5 classes of antibodies: IgM, IgG, IgA, IgE, and IgD. [1] [12]

Antibody-mediated immunity entails the activation of B cells and secretion of antibodies when in contact with an antigen. [27]

Antigen-antibody complex, also called an **immune complex**, is the binding (attaching) of an antibody to an antigen. Antigen-antibody complexes initiate immune responses. [28]

Antigens are any substance the immune system can recognize and can thus stimulate an immune response. Antigens include bacteria, viruses, parasites, toxins, chemicals, or other substances that come from outside the body. Body tissues and cells, including cancer cells, also have antigens on them that can illicit an immune response. [1] [29]

Antigen-presenting cells are a group of immune cells that mediate the cellular immune response by processing and presenting antigens for recognition by certain lymphocytes (e.g., T cells). Types of antigen-presenting cells include dendritic cells, macrophages, Langerhans cells, and B cells. [30]

Apoptosis, also called cellular suicide, is a programmed cell death where the cell actively destroys itself to maintain the balance of cell multiplication. It has an important role in maintaining the health of the body by eliminating old, unnecessary, and unhealthy cells. [31]

Autoantibodies are antibodies made against the body's own tissues or organs (i.e., the immune system fails to distinguish self from nonself). Some autoimmune diseases are caused by autoantibodies. [32] [33]

Autoantigens are endogenous (self) antigens that, despite being a normal tissue constituent, is targeted by the immune system (e.g., in autoimmune disease). [34]

B cells, also called **B lymphocytes**, are leukocytes that produce antibodies specific to the antigen that stimulated their production. [1]

Basophils are leukocytes that contain granules filled with histamine. When basophils encounter allergens (i.e., antigens that cause allergic reactions), they release histamine. Histamine increases blood flow to damaged tissues, resulting in swelling and

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inflammation. Basophils also release other mediators (e.g., heparin, an anticoagulant) that play a role in inflammation and produce substances that attract neutrophils and eosinophils to the site of infection. [1] [5]

Cell-mediated immunity is the acquired immune response involving T cells. Antibodies are not produced in cell-mediated immunity, instead, T cells destroy the infected cells by inducing apoptosis. Cell-mediated immunity acts on intracellular microbes (e.g., viruses, bacteria, and parasites) and tumour cells. [7]

Cells are the smallest unit of a living organism, composed of a nucleus and cytoplasm enclosed in a membrane. [1]

Chemokines are a large group of chemotactic cytokines produced by numerous leukocytes and other cells in the body. They recruit leukocytes to infection sites via chemotaxis. [9]

Chemotaxis is the process where a chemical substance attracts cells to a particular site. [1]

Complement system consists of more than thirty proteins that are involved in a series of reactions called the complement cascade. These series of reactions act in a sequence where one protein activates another, which activates another, and so on to defend the body against infection. Complement proteins have many functions, including killing bacteria and other foreign cells, making foreign cells easier for macrophages to identify and ingest, attracting macrophages and neutrophils to the site of infection, neutralizing viruses, promoting antibody formation, and helping the body eliminate dead cells. [1] [5]

Cross-reactivity occurs when the immune system identifies proteins in one substance (e.g., latex) and the proteins in another (e.g., kiwi, banana, avocado) as being similar, which results in an immune response to the structurally similar of biologically related substances. [35]

Cytokines are numerous different proteins secreted by immune and other body cells and act as the immune system's messengers to help regulate immune and inflammatory responses. There are proinflammatory and anti-inflammatory cytokines. [1]

Degranulation is the cellular process where cytoplasmic granules release their contents. [36]

Dendritic cells are derived from leukocytes and reside in the skin, lymph nodes, and tissues throughout the body. Most dendritic cells are antigen-presenting cells. Specifically, they ingest, process, and present antigens, enabling helper T cells to identify the antigen. Dendritic cells present antigen fragments to T cells in the lymph nodes. After T cells are presented with the antigen, they become activated. [1] [12]

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Eosinophils are leukocytes and a type of granulocyte that contain granules with enzymes that are released during infections, allergic reactions, and asthma. Their main function is to attach to and help immobilize and kill parasites. They can kill bacteria and other foreign cells too large to ingest. They also help destroy cancer cells. [1] [37]

Follicular dendritic cells (a type of dendritic cell) reside in lymph nodes and present unprocessed (intact) antigens that have been linked with antibody (antibody-antigen complex) to B cells. Follicular dendritic cells help B cells respond to an antigen. After B cells are presented with the antigen, they become activated. [12]

Granulocytes, also called **granular leukocytes** or **polymorphonuclear leukocytes (PMNs)**, are a type of leukocyte that contain granules with enzymes that are released during infections, allergic reactions, and asthma. Neutrophils, eosinophils, basophils, and mast cells are granular leukocytes. [38]

Helper T cells, also called **T helper cells (Th cells)**, **helper T lymphocytes**, **CD4-positive T lymphocyte**, **$CD4^+$ cells**, or **helper CD4 T cells**, are leukocytes that help B cells produce antibodies against foreign antigens, help killer T cells become active, and stimulate macrophages, enabling them to ingest infected or abnormal cells more efficiently. [1] [39]

Histocompatibility is literally the ability of tissues (Greek: *histos*) to get along with each other. Histocompatibility is determined by human leukocyte antigens (self-identification molecules). It is used to determine whether a transplanted tissue or organ will be accepted by the recipient. [1] [40]

Human leukocyte antigens (HLA), also called **human lymphocyte antigens** or **major histocompatibility complex (MHC)**, are a group of identification molecules located on the surface of all cells. They are in a combination that is almost unique for each person, thereby enabling the body to distinguish self from nonself. Human leukocyte antigen tests are done before a donor stem cell or organ transplant, to determine if tissues match between the donor and the transplant recipient. [1]

Humoral immunity is the acquired immune response involving the transformation of B cells into plasma cells that produce and secrete antibodies to a specific antigen. [2]

Immune complex, also called an **antigen-antibody complex**, is the binding (attaching) of an antibody to an antigen. Immune complexes initiate immune responses. [1]

Immune response is the reaction of the immune system to an antigen. [1]

Immunoglobulins (Ig), also called **antibodies**, are proteins produced by B cells that tightly bind to the antigen of an invader, tagging the invader for attack or directly neutralizing it. The human body produces thousands of different antibodies, each specific to a given antigen. There are 5 classes of antibodies: IgM, IgG, IgA, IgE, and IgD. [1] [12]

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Innate immunity, also called **natural immunity**, is the level of immunity an individual is born with. It does not require previous exposure to an antigen to work effectively. It responds to invaders immediately, without needing to learn to recognize them. This response is more general and non-specific (i.e., the response is similar for all foreign invaders). [1] [2]

Interferons (INFs) are cytokines that can induce cells to resist viral replication. Interferon-α (IFN-α) and interferon-β (IFN-β) are produced by leukocytes and fibroblasts, respectively, as well as by other cells. Interferon-γ (IFN-γ) is produced by CD4 Th1 cells, CD8 T cells, and natural killer (NK) cells. Primary action of IFN-γ is the activation of macrophages. [40]

Interleukin (IL) is a type of cytokine. Interleukins (IL-1 to IL-40) are produced by a wide variety of cells, including leukocytes, and have multiple effects on immune cell development and the regulation of immune responses. [1] [41] [42]

Interleukin-1 (IL-1) is a type of cytokine produced mainly by macrophages, but is also produced by B cells, dendritic cells, endothelium, monocytes, and NK cells. IL-1 helps lymphocytes fight infections. It also helps leukocytes pass through blood vessel walls to infection sites and causes fever by affecting the hypothalamus (area of the brain that controls body temperature). There are two forms of IL-1, alpha and beta, which act the same. Laboratory made IL-1 is used as a biological response modifier to boost the immune system in cancer therapy. [41] [42]

Interleukin-1-alpha (IL-1-alpha or IL-1α) is a type of cytokine and one form of interleukin-1 (IL-1). It is produced mainly by macrophages, but is also produced by B cells, dendritic cells, endothelium, monocytes, and NK cells. IL-1-alpha helps lymphocytes fight infections. It also helps leukocytes pass through blood vessel walls to infection sites and causes fever by affecting the hypothalamus (area of the brain that controls body temperature). The other form of IL-1, interleukin-1-beta, acts the same as IL-1-alfa. Laboratory made IL-1-alfa is used as a biological response modifier to boost the immune system in cancer therapy. [41]

Interleukin-1-beta (IL-1-beta or IL-1β) is a type of cytokine and is one form of interleukin-1 (IL-1). It is produced mainly by macrophages but is also produced by B cells, dendritic cells, endothelium, monocytes, and NK cells. IL-1-alpha helps lymphocytes fight infections. It also helps leukocytes pass through blood vessel walls to infection sites and causes fever by affecting the hypothalamus (area of the brain that controls body temperature). The other form of IL-1, IL-1-alpha, acts the same as IL-1-beta. Laboratory made IL-1-beta is used as a biological response modifier to boost the immune system in cancer therapy. [41]

Interleukin-2 (IL-2) is a type of cytokine made by T cells. It increases the growth and activity of other T cells and B cells, and causes antibody synthesis. Laboratory made IL-2 (Aldesleukin) is used as a biological response modifier to boost the immune system in cancer therapy. [41] [42]

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Interleukin-3 (IL-3) is a type of cytokine made mainly by T cells, but it is also produced by NK cells and mast cells. It increases the number of blood cells made by the bone marrow and stimulation of mast cell growth. Laboratory made IL-3 is used as a biological response modifier to boost the immune system in cancer therapy. [41] [42]

Interleukin-4 (IL-4) is a type of cytokine made by T helper cells, mast cells, NK cells, and natural killer T cells. It causes B cells to increase and to make antibodies. It also increases the production of T cells and stimulates mast cell proliferation. Laboratory made IL-4 is used as a biological response modifier to boost the immune system in cancer therapy. [42]

Interleukin-5 (IL-5) is a type of cytokine made by T helper cells and mast cells. It causes B cells to make more antibodies and increases the number of eosinophils. Laboratory made IL-5 is used as a biological response modifier to boost the immune system in cancer therapy. [41] [42]

Interleukin-6 (IL-6) is a type of cytokine made by T cells, B cells, dendritic cells, fibroblasts, macrophages, and monocytes. It causes B cells to make more antibodies. It also causes fever by affecting the hypothalamus (area of the brain that controls body temperature). Laboratory made IL-6 is used as a biological response modifier to boost the immune system in cancer therapy. [41] [42]

Interleukin-7 (IL-7) is a type of cytokine made by bone marrow cells and thymus stromal cells.[39] It causes the growth of T cells and B cells. Laboratory made IL-7 is used as a biological response modifier to boost the immune system in cancer therapy. IL-7 is also called lymphopoietin-1. [41] [42]

Interleukin-8 (IL-8) is a chemotactic cytokine (i.e., chemokine) made by endothelial cells, macrophages, and monocytes. Its main function is to mediate chemotaxis and activation of neutrophils. [41] [42]

Interleukin-9 (IL-9) is a type of cytokine produced by T helper cells, mast cells, natural killer T cells, and regulatory T cells. It causes thymocyte[40] proliferation and mast cell activation. [41] [42]

Interleukin-10 (IL-10) is a type of cytokine made by macrophages, B cells, monocytes, and T helper cells. It reduces inflammation by blocking production of cytokines by immune cells. It also increases antibody production by plasma cells and helps them live longer. Laboratory made IL-10 is used as a biological response modifier to boost the immune system. [41] [42]

Interleukin-11 (IL-11) is a type of cytokine made by support cells in the bone marrow. It causes the growth of several types of blood cells. Traditionally regarded as an anti-inflammatory cytokine, it can function as a proinflammatory cytokine, suggesting its

[39] Stromal cell is a type of cell that makes up certain types of connective tissue (supporting tissue that surrounds other tissues and organs).
[40] Thymocytes are immune cells that mature into T cells in the thymus.

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complex role in immune response. It also enhances antigen-specific antibody responses. [41] [42] [43]

Interleukin-12 (IL-12) is a type of cytokine made mainly by B cells and macrophages but is also made by dendritic cells and monocytes. It causes other immune cells to make cytokines and increases the growth of T cells. It may also block angiogenesis (growth of new blood vessels). Laboratory made IL-12 is used as a biological response modifier to boost the immune system in cancer therapy. [41] [42]

Interleukin-13 (IL-13) is a type of cytokine made by T helper cells, natural killer T cells, and mast cells. It reduces inflammation by blocking production of cytokines by macrophages. It also increases the number and activity of B cells. Laboratory made IL-13 is used as a biological response modifier to boost the immune system in cancer therapy. [41] [42] [44]

Interleukin-14 (IL-14) is a type of cytokine made by T cells. Its main effects are stimulating activated B cell proliferation and inhibiting immunoglobulin secretion. [42]

Interleukin-15 (IL-15) is a type of cytokine made by B cells, dendritic cells, macrophages, monocytes, NK cells, and T cells. It increases the number of T cells, NK cells, and activated B cells. It also induces cytokine production, cytotoxicity of NK cells, and chemotactic activity for T cells. [41] [42]

Interleukin-16 (IL-16) is a type of cytokine made by helper T cells and killer T cells. It induces chemotactic activity for CD4 T cells, monocytes, and eosinophils. [41] [42]

Interleukin-17 (IL-17) is a type of cytokine made by T helper cells as well as natural killer T cells, and macrophages. It has a proinflammatory function and simulates the production of cytokines (e.g., TNF, IL-1, IL-8). [41] [42]

Interleukin-18 (IL-18) is a type of cytokine made by monocytes, macrophages, and dendritic cells. It causes IFN-gamma (IFN-γ) production by T leukocytes and enhances NK cell activity. [41] [42]

Interleukin-19 (IL-19) is a type of cytokine made by T helper cells. It is an anti-inflammatory molecule and promotes immune responses mediated by regulatory T cells. [42]

Interleukin-20 (IL-20) is a type of cytokine made by immune cells and activated epithelial cells. It plays a role in the cellular communication between epithelial cells and the immune system under inflammatory conditions. [42]

Interleukin-21 (IL-21) is a type of cytokine made by natural killer T cells and T helper cells. It helps to stimulate B cell and T cell proliferation and differentiation. It also enhances NK cell activity. [41] [42]

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Interleukin-22 (IL-22) is a type of cytokine made by NK cells and T cells. It has a proinflammatory function and a role in mucosal surface protection and tissue repair. [41] [42]

Interleukin-23 (IL-23) is a type of cytokine made by dendritic cells and macrophages. It helps to increase T helper cells. [41] [42]

Interleukin-24 (IL-24) is a type of cytokine made by B cells, macrophages, monocytes, and T cells. It helps to suppress tumour cell growth and induces apoptosis of tumour cells. It also helps with wound healing and protects against bacterial infections. [41] [42]

Interleukin-25 (IL-25) is a type of cytokine made mainly by dendritic cells. It acts on various types of cells, including T helper cells stimulating synthesis of various cytokines (e.g., IL-4, IL-13). [42]

Interleukin-26 (IL-26) is a type of cytokine made by T helper cells. It acts on epithelial and intestinal epithelial cells. It induces IL-10 expression, stimulates the production of IL-1-beta, IL-6, and IL-8. It also causes T helper cell generation. [42]

Interleukin-27 (IL-27) is a type of cytokine made by dendritic cells, monocytes, and macrophages. It helps to induce T helper cell production. [41] [42]

Interleukin-28 (IL-28) is a type of cytokine made by regulatory T cells. It acts on keratinocytes to recognize pathogens in the skin. It also plays a role in immune defense against viruses. [42]

Interleukin-29 (IL-29) is a type of cytokine made by virus-infected cells, dendritic cells, and regulatory T cells. It helps to increase viral protective responses of the immune system. [42]

Interleukin-30 (IL-30) is a type of cytokine made mainly by monocytes. It acts on monocytes, macrophages, dendritic cells, T cells, B cells, NK cells, mast cells, and endothelial cells. [42]

Interleukin-31 (IL-31) is a type of cytokine made mainly by T helper cells and dendritic cells. It has a proinflammatory and a chemotactic effect that direct polymorphonuclear cells, monocytes, and T cells to inflammatory lesions. It also stimulates chemokines production and synthesis of IL-6, IL-16, and IL-32. [42]

Inteleukin-32 (IL-32) is a type of cytokine made by NK cells and T cells. It has a proinflammatory effect and induces the synthesis of various cytokines (e.g., IL-6, IL-1-beta). [41] [42]

Interleukin-33 (IL-33) is a type of cytokine made by endothelial cells, stromal cells, and dendritic cells. It mediates T helper cell responses to help protect against parasites. [41] [42]

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Interleukin-34 (IL-34) is a type of cytokine made by various phagocytes and epithelial cells. It enhances IL-6 production and participates in the differentiation and development of antigen-presenting cells. [42]

Interleukin-35 (IL-35) is a type of cytokine made by regulatory T cells, macrophages, and dendritic cells. It is involved in lymphocyte differentiation and it exhibits immune-suppressive and anti-inflammatory effects. [41] [42]

Interleukin-36 (IL-36) is a type of cytokine made mainly by phagocytes. It has a proinflammatory effect and acts on T cells and NK cells regulating IFN-gamma (IFN-γ) synthesis. [42]

Interleukin-37 (IL-37) is a type of cytokine made by macrophages and inflamed tissue. It has an anti-inflammatory effect. [41] [42]

Interleukin-38 (IL-38) is a cytokine expressed by the placenta, tonsil's B cells, spleen, skin, and thymus. It acts on T cells and inhibits the synthesis of IL-17 and IL-22. [42]

Interleukin 39 (IL-39) is a cytokine made mainly by B cells. It acts on neutrophils inducing their differentiation or expansion. [42]

Interleukin-40 (IL-40) is a cytokine made in the bone marrow, fetal liver, and by activated B cells. It plays a vital role in the development of humoral immune responses. [42]

Killer T cells, also called **cytotoxic T cell**, **cytotoxic T lymphocyte (CTL)**, or **$CD8^+$ T cells**, are T cells that attach to infected cells (e.g., with a virus), foreign cells, and cancer cells and kill them. They are a type of leukocyte and a type of lymphocyte. [1] [45]

Langerhans cells are antigen-presenting cells located in the skin and mucosa. [46]

Leukocytes, also called **white blood cells**, exist in several different types, such as monocytes, lymphocytes (e.g., B cells, T cells), neutrophils, eosinophils, basophils, and macrophages. Each type of leukocyte has a different role in the immune system. [1] [47]

Leukotrienes are inflammatory mediators that are produced by macrophages and other cells. They play a significant role in the pathophysiology of asthma (e.g., airway constriction, inflammation, and mucous secretion). [27] [28]

Lymphatic system, also called the **lymphoid system**, is a network of tissues and organs that produce, store, and carry leukocytes that fight infections and other diseases. It also helps rid the body of toxins, waste, and other unwanted materials. The system includes the bone marrow, spleen, thymus, lymph nodes, Peyer's patches, and lymphatic vessels. [1] [40] [48]

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Lymphocytes are a type of leukocyte. There are two main types of lymphocytes: B lymphocytes (B cells) and T lymphocytes (T cells), which mediate humoral and cell-mediated immunity, respectively. B lymphocytes make antibodies, and T lymphocytes help kill tumour cells and help control immune responses. [1] [40] [49]

Macrophages are a type of leukocyte. They are large phagocytic cells that develop from monocytes. They ingest bacteria and other foreign cells and help T cells identify microorganisms and other foreign substances. Macrophages are normally present in most tissues (e.g., lungs, skin, liver, and other tissues). [1] [40]

Major histocompatibility complex (MHC), also called **human leukocyte antigens (HLA)** or **human lymphocyte antigens**, are a group of identification molecules located on the surface of all cells. They are in a combination that is almost unique for each individual, thereby enabling the body to distinguish self from nonself. Human leukocyte antigen tests are done before a donor stem cell or organ transplant, to determine if tissues match between the donor and the transplant recipient. [1] [50]

Mast cells are leukocytes found in connective tissues throughout the body, especially under the skin, near blood and lymph vessels, and in nerves, lungs and intestines. They play an important role in how the immune system responds to certain bacteria and parasites and they help control other types of immune responses. They have granules that contain chemicals such as histamine, heparin, cytokines, and growth factors. These chemicals are released during allergic reactions and certain immune responses and cause effects such as the widening of blood vessels and angiogenesis. During an allergic response, these chemicals can cause flushing and itching. In large amounts, they can also cause abdominal cramps, muscle pain, nausea, vomiting, diarrhea, low blood pressure, and shock. [1] [51]

Molecules are groups of atoms chemically combined to form a unique substance. A molecule is the smallest particle of a substance that has all of the physical and chemical properties of that substance. [1] [52]

Natural immunity, also called **innate immunity**, is the level of immunity an individual is born with. It does not require previous exposure to an antigen to work effectively. It responds to invaders immediately, without needing to learn to recognize them. This response is more general and non-specific (i.e., the response is similar for all foreign invaders). [1] [2]

Natural killer cells (**NK cells**) are a type of leukocyte and a type of lymphocyte that contain granules that kill abnormal cells, such as viral infected cells and cancer cells. They are important in the initial defense against viral infections. Natural killer cells recognize and attach to infected cells or cancer cells, then release enzymes and other substances that damage the outer membranes of these cells. They also produce cytokines that regulate some functions of T cells, B cells, and macrophages. [1] [5] [53]

Natural killer T cells (**NKT cells**) are a type of T cell that also has certain features of natural killer (NK) cells. They can kill invading microorganisms (e.g., bacteria and

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viruses) by releasing cytokines. They can also kill certain cells (e.g., cancer cells) either directly or by causing other immune cells to kill them. If natural killer T cells become inactive, then this may contribute to the development and progression of certain diseases, such as cancer. [54]

Neutralizing antibodies (NAb) inhibit the infectivity of a virus or the toxicity of a toxin molecule by prohibiting entry into the host cell. This process of inactivation is called neutralization. [40] [55]

Neutrophil extracellular traps (NETs) are a meshwork of chromatin fibres released by neutrophils to immobilize and kill invading pathogens to help prevent the pathogens from spreading. [5] [6]

Neutrophils are leukocytes that ingest and kill bacteria and other foreign cells. They also release enzymes from their granules that kill microorganisms. They are one of the first cell types to travel to the site of an infection. Neutrophils are a type of granulocyte and a type of phagocyte. [1]

Non-neutralizing antibodies, also called **binding antibodies**, bind to a pathogen, but do not interfere with their infectivity. However, by binding to the pathogen, they alert the immune system to its presence so leukocytes can be sent to destroy it. [40] [55]

Opsonization is an immune process which uses opsonins (e.g., antibodies and complement proteins) to tag foreign pathogens for elimination by phagocytes. [56] [40]

Passive immunity is provided when an individual is given antibodies against pathogens rather than producing them through their own immune system. [10]

Phagocytes are a type of leukocyte that ingests and kills or destroys invading microorganisms, other cells, and cell fragments, and removes dead cells. They can also boost immune responses. Phagocytes include neutrophils, monocytes, and macrophages. [1] [57]

Phagocytosis is the process where a phagocyte (type of leukocyte) engulfs and ingests an invading microorganism, cell, or cell fragment, and removes dead cells. [1] [58]

Polymorphonuclear leukocytes (PMNs), also called **granular leukocytes** or **granulocytes**, are a type of leukocyte that contain granules with enzymes that are released during infections, allergic reactions, and asthma. Neutrophils, eosinophils, basophils, and mast cells are granular leukocytes. [38]

Receptor is a molecule on a cell's surface or inside a cell that can identify specific molecules that fit precisely into it (similar to a key fitting into a lock). [1]

Regulatory T cells, also called **suppressor T cells**, **T-regulatory cells**, **T regs**, **Tregs**, or **regulatory T lymphocyte**, are a type of leukocyte and a type of lymphocyte

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that help end an immune response by blocking the actions of some other types of lymphocytes, thus, preventing the immune system from becoming over-active. [1] [59]

Specific immunity, also called **acquired immunity**, **adaptive**, or **active immunity**, develops throughout life with exposure to various antigens or through vaccination. It is sometimes referred to as immunological memory because the immune system remembers previous pathogens and generates an antigen-specific immune response. [3]

T cells, also called **T lymphocytes** or **CD4 cells**, are leukocytes that are involved in acquired immunity. There are three types: helper, killer (cytotoxic), and regulatory. [1] [60]

T helper cells, also called **$CD4^+$ cells**, **CD4-positive cells**, **CD4-positive T lymphocytes**, **helper T cell**, or **helper T lymphocyte**, are a type of leukocyte and a type of lymphocyte that serves as a key mediator of immune function. For example, they stimulate killer T cells, macrophages, and B cells to make immune responses. [61] [62]

Transforming growth factor beta (TGF-β) is primarily an anti-inflammatory cytokine produced by T cells and many other cell types. TGF-β inhibits T cell proliferation and macrophage activation. It also acts on PMNs and endothelial cells to stop the effects of pro-inflammatory cytokines. [9]

Tumour necrosis factor (TNF) is a type of cytokine that activates cellular pathways to induce inflammation providing an important mechanism for controlling infection. There is a family of TNF proteins, each type playing a different role in the body. Examples of TNF include TNF-alpha (TNF-α) and TNF-beta (TNF-β). [11]

White blood cells, also called **leukocytes,** exist in several different types, such as monocytes, lymphocytes (e.g., B cells, T cells), neutrophils, eosinophils, basophils, and macrophages. Each type of white blood cell has a different role in the immune system. [1] [47]

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