

Episode #44 – Overview of the Immune System September 10, 2021

Immune system
The immune system is a complex network of cells, tissues, proteins, and organs. Its role is to protect the body from harmful materials by recognizing and responding to antigens (i.e., identifying foreign invaders as "nonself"). Antigens are materials (e.g., proteins, polysaccharides, lipids, or nucleic acids) on the surface of cells, viruses, fungi, or bacteria. Nonliving substances such as toxins, chemicals, drugs, and foreign particles (e.g., a splinter) can also be antigens. The immune system recognizes and destroys, or tries to destroy, substances that contain antigens. [1] [2]

The immune system's main tasks are to:
- Combat pathogens, such as bacteria, viruses, parasites, or fungi, and eliminate them from the body.
- Recognize and neutralize harmful substances from the environment.
- Fight disease-causing changes in the body, such as cancer cells.
- Recognize and clear away dead cells. [3] [4]

Components of the immune system
The immune system is comprised of several different components, including physical barriers, leukocytes, lymphoid organs, and molecules.

Physical barriers (e.g., skin; cornea of the eyes; membranes lining the respiratory, digestive, urinary, and reproductive tracts) play an important role in preventing microbes from reaching tissues that are susceptible to infection. These barriers also produce secretions (e.g., sweat, tears, mucus, stomach acid) that contain enzymes to help destroy pathogens. Mucus also helps to trap debris and particulate matter, including microbes which are then flushed out of the body.

Leukocytes (white blood cells) travel through blood vessels and into tissues to search for and attack antigens.

Lymphoid organs (i.e., organs and tissues of the lymph system) are organized tissues containing large numbers of lymphocytes in a structure of nonlymphoid cells. There are primary (central) and secondary (peripheral) lymphoid organs. [5]

> *Primary lymphoid organs* include the bone marrow and thymus. The bone marrow produces the different types of leukocytes (e.g., neutrophils, eosinophils, basophils,

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monocytes, B cells, and cells that develop into T cells [T cell precursors]). In the thymus, T cells mature and multiply and are trained to recognize foreign antigens and to ignore the body's own antigens. [6]

Secondary lymphoid organs include the spleen, lymph nodes, tonsils, appendix, and Peyer's patches.[1] These organs filter and trap antigens and provide an environment for immune cells to collect, mature, interact with each other and with the foreign substances, and generate a specific immune response. [6]

Molecules, such as cytokines, antibodies, and complement proteins, help to attract or activate other cells of the immune system. These molecules are dissolved in body fluid (e.g., plasma). [7] [8]

- Cytokines are the messengers of the immune system. Leukocytes and other cells of the immune system produce cytokines when an antigen is detected. There are many different types of cytokines that perform a variety of roles, including chemokines, interferons (IFNs), interleukins (ILs), lymphokines, and tumor necrosis factor (TNF). [9] [10]

  Chemokines induce chemotaxis[2] and migration of leukocytes to areas of inflammation to help the body combat infections, inflammatory conditions, and other diseases. [11] [12]

  Interferons (IFNs) inhibit viral replication in cells. They also activate natural killer T cells, which fight against the virus by destroying infected cells. Examples of interferons include IFN-alpha (IFN-α), IFN-beta **(**IFN-β), and IFN-gamma (IFN-γ). [11] [13] [14]

  Interleukins (ILs) are a type of messenger cytokine secreted by some leukocytes to affect other leukocytes. For example, they allow for communication between leukocytes and regulate immune cell growth, differentiation, maturation, and motility. They are also important in stimulating immune responses, such as inflammation. [10] [15] [16]

  Lymphokines are cytokines produced by lymphocytes. They attract additional immune cells to mount an immune response, for example by stimulating B cells to generate antibodies against an invading pathogen. [17]

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

[1] Peyer's patches are a group of lymphoid follicles located in the small intestine. They detect and respond to foreign antigens in the gastrointestinal tract. Antibodies secreted by B cells in Peyer's patches provide defense against ingested pathogens.
[2] Chemotaxis is the process where a chemical substance attracts cells to a particular site.

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- TNF-α (cachectin) is produced by B cells, dendritic cells,[3] macrophages, mast cells, monocytes, NK cells, and Th cells. Its main effects include cytotoxicity of tumour cells, activation of macrophages, and antiviral activity. It also induces certain cytokine secretion.
- TNF-β (lymphotoxin) is produced by killer T cells and T helper type 1 cells (Th1 cells). Its main effects include cytotoxicity of tumour cells, antiviral activity, and enhancing phagocytosis[4] by neutrophils and macrophages. [11]

- Antibodies, also called immunoglobulins, are proteins produced by B cells in response to infection or immunization.[5] Vaccines prompt the immune system to produce antibodies giving individuals the benefit of acquired immunity without having to contract the disease first. Vaccines work by introducing antigens (e.g., in the form of an inactivated or killed virus) into the body in order to stimulate the immune system. Antibodies produced by the body in response to the antigen will tightly bind[6] to the antigen of the invader and tag it for attack or directly neutralize[7] it. The human body produces thousands of different antibodies, each specific to a given antigen. [11] [18]

- Complement proteins form the complement system. The complement system consists of more than thirty complement proteins that act in a sequence. This sequence is called a complement cascade because one protein activates another, which activates another, and so on to defend the body against infection. [8] [14]

Leukocytes

Leukocytes (white blood cells) are produced in the bone marrow and circulate through the body via blood and lymphatic vessels on constant patrol for pathogens. They are stored in lymphoid organs (e.g., thymus, spleen, bone marrow, lymph nodes). When a target is located, leukocytes multiply and send out signals to other cell types to do the same.

Leukocytes produce interleukins (ILs). An interleukin is one of a group of related proteins produced by a wide variety of cells, including leukocytes. Interleukins regulate immune responses and are a type of cytokine. [4] [16] [19] [20]

[3] Dendritic cells are derived from leukocytes and reside in tissues. They are a type of antigen-presenting cell that help T cells recognize foreign antigens.
[4] Phagocytosis is the process where certain cells (phagocytes) ingest or engulf other cells or particles larger than 0.5 µm in diameter, including microorganisms, foreign substances, and apoptotic cells. Types of phagocytes include macrophages, neutrophils, and monocytes.
[5] Refer to Episodes #15, 28, 39, and 40 for more information on vaccines and immunization.
[6] 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. [55] [62]
[7] 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. [35] [55] [62]

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Many interleukins have been identified (i.e., IL-1 to IL-40),[8] each having multiple effects on immune cell development and the regulation of immune responses. Examples of interleukins include:

- **Interleukin-1** (IL-1) is produced mainly by macrophages, but is also produced by B cells, dendritic cells, endothelium, monocytes, and natural killer 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. [11] [16]

- **Interleukin-2** (IL-2) is made 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. [11] [16]

- **Interleukin-4** (IL-4) is made by T helper cells, mast cells, natural killer 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. [11] [16]

- **Interleukin-5** (IL-5) is 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. [11] [16]

- **Interleukin-6** (IL-6) is 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. Laboratory made IL-6 is used as a biological response modifier to boost the immune system in cancer therapy. [11] [16]

- **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. [11] [16]

- **Interleukin-10** (IL-10) is 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. [11] [16]

- **Interleukin-11** (IL-11) is made by support cells in the bone marrow. It causes the growth of several types of blood cells. Traditionally regarded as an anti-inflammatory

[8] Refer to the Glossary for more information on IL-1 to IL-40.

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cytokine, it can function as a proinflammatory cytokine, suggesting its complex role in immune response. It also enhances antigen-specific antibody responses. [11] [16] [21]

- **Interleukin-12** (IL-12) is made mainly by B cells and macrophages but also 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 interleukin-12 is used as a biological response modifier to boost the immune system in cancer therapy. [11] [16]

Leukocytes are grouped into 3 main classes: granulocytes, monocytes, and lymphocytes, based on their appearance under a light microscope. [22]

Granulocytes

Granulocytes, also called granular leukocytes or polymorphonuclear leukocytes (PMNs), are the most numerous of the leukocytes and help to rid the body of viruses, bacteria, and large parasites (e.g., protozoa,[9] helminths[10]) and are also key mediators of allergy and other forms of inflammation. They are characterized by the large number and chemical makeup of the granules occurring within the cytoplasm.[11] The granules are filled with enzymes and other substances that when released (i.e., degranulation) help kill and digest bacteria and other foreign cells. Granulocytes are approximately 12-15 micrometres in diameter, making them larger than erythrocytes (red blood cells). [14] [23] [24]

Granulocytes are continuously produced from stem cells in the bone marrow and only live for a few days. They enter the bloodstream and circulate for a few hours, then leave the circulation and die. Granulocytes are attracted to foreign materials by chemical signals produced by:

- Invading microorganisms,
- Damaged tissues, and
- Interaction between microbes and proteins in the blood plasma. [24]

Some microorganisms produce toxins that poison granulocytes, thereby escaping phagocytosis. Other microbes are indigestible and are not killed when ingested. As a result, granulocytes have limited effectiveness by themselves and require reinforcement

[9] Protozoa are single-celled organisms that are free-living or parasitic in nature. They can multiply in humans and cause serious infections from just a single organism. Human-to-human transmission of protozoa that live in a human's intestine typically occurs through the fecal-oral route (e.g., via contaminated food or water or person-to-person contact). Protozoa that live in human blood or tissue are transmitted to other humans by an arthropod vector (e.g., via a mosquito or sand fly bite).

[10] Helminths are large, multicellular organisms that are either free-living or parasitic in nature and generally visible to the naked eye in their adult stages. In their adult form, helminths cannot multiply in humans. Three main groups that are human parasites are flatworms, thorny-headed worms, and roundworms.

[11] Cytoplasm is the semifluid substance of a cell that is external to the nuclear membrane and internal to the cellular membrane

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by the mechanisms of specific immunity (e.g., antibody-mediated immune response). [24]

There are several types of granulocytes, each distinguished by the colour that their granules stain when treated with a compound dye, thus reflecting the differences in the chemical composition of the granules. [24]

Types of granulocytes include neutrophils, eosinophils, basophils, and mast cells.

Neutrophils tend to attack bacteria. Neutrophils make up 55-70% of all leukocytes and are one of the first cell types to travel to a site of infection. They help fight infection by ingesting microorganisms and/or releasing antimicrobial factors from specific granules. Neutrophils, along with macrophages, are the main phagocytic cells of the body. They also recruit, activate, and program other immune cells. [22] [25] [26]

Eosinophils help to destroy invading pathogens (e.g., viruses, bacteria, or parasites such as hookworms). They can ingest bacteria, but they also target foreign cells that are too large to ingest. Their granules release enzymes and other toxic substances when foreign cells are encountered. These substances make holes in the target cells' membranes.

Eosinophils circulate in the bloodstream. However, they are less active against bacteria than are neutrophils and macrophages. One of their main functions is to attach to and help immobilize and kill parasites. They also have a role in helping to destroy cancer cells and in inflammatory responses associated with allergies, eczema, and asthma. Individuals with allergies, asthma, or parasitic infections often have more eosinophils in the bloodstream than individuals without these disorders. [14] [27]

Basophils account for less than 3% of circulating leukocytes. They have a role in immune surveillance (e.g., detecting and destroying very early cancers, microbial pathogens, viruses, and parasites) and wound repair. They release granules that contain histamine that dilates blood vessels (e.g., during allergic reactions) and other mediators (e.g., heparin, an anticoagulant) that play a role in inflammation. [28] [29] [30]

Mast cells 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 are found in connective tissues throughout the body (e.g., under the skin, near blood vessels and lymph vessels, and in nerves, lungs and intestines). Their granules contain chemicals such as histamine, heparin, cytokines, and growth factors, which they release during allergic reactions and certain immune responses. These chemicals have several effects, including widening of blood vessels and angiogenesis. During an allergic response, they can cause flushing and itching. In large amounts, they can also cause abdominal cramps, nausea, vomiting, diarrhea, muscle pain, low blood pressure, and shock. [31]

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Monocytes
Monocytes constitute 4% to 8% of the total number of leukocytes in the blood. They move from the blood to the infection site, where they differentiate further into macrophages. [22]

Macrophages are scavengers that phagocytose whole or killed microorganisms. Thus, they are effective at direct destruction of pathogens and cleanup of cellular debris from infection sites. Macrophages and neutrophils are the main phagocytic cells of the body. However, macrophages are much larger and longer-lived than neutrophils. Some macrophages are important as antigen-presenting cells,[12] cells that phagocytose and degrade microbes and present portions of these microbes for recognition to T lymphocytes, thereby activating the specific acquired immune response. [22]

Lymphocytes
Lymphocytes are further divided into B lymphocytes, T lymphocytes, and natural killer cells and are responsible for the specific recognition of foreign agents and their subsequent removal from the host. [22]

B lymphocytes, also known as B cells, differentiate into plasma cells (also called plasmacytes) once they detect an antigen. The plasma cells produce antibodies, also called immunoglobulins, and help alert the T lymphocytes. There are 5 classes of immunoglobulins (antibodies) and several subclasses. [4] [32]

Classes of immunoglobulins include:

- Immunoglobulin M (IgM) – produced as a first response to a new infection or new antigen, delivering short-term protection. IgM production increases for several weeks and then declines as IgG production begins. [33]

- Immunoglobulin G (IgG) – comprises about 70-80% of the immunoglobulins in the blood. Specific IgG antibodies are produced during an initial infection or other antigen exposure, rising a few weeks after production begins, then decreasing and stabilizing. The body maintains a catalogue of IgG antibodies for quick reproduction when exposed to the same antigen. IgG antibodies form the basis of long-term protection against microorganisms. IgG has 4 subclasses: IgG_1, IgG_2, IgG_3, and IgG_4. [33]

- Immunoglobulin A (IgA) – comprises about 15% of the immunoglobulins in the blood. It is also found in saliva, tears, respiratory and gastric secretions, and breast milk. IgA provides protection against infection in mucosal areas of the body (e.g., respiratory tract [sinus and lungs], gastrointestinal tract [stomach and intestines]). IgA is passed from mother to baby during breastfeeding, helping to protect the

[12] 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). Examples of antigen-presenting cells include dendritic cells, macrophages, Langerhans cells, and B cells.

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baby's gastrointestinal tract. Substantial amounts of IgA are not produced by a baby until after 6 months of age. Thus, any IgA present in a baby's blood before this time is from the mother's breastmilk. IgA has 2 subclasses: IgA_1 and IgA_2. [33]

- Immunoglobulin D (IgD) – stays bound to B cells, helping them to initiate the immune response. However, their role is not completely understood. [33]

- Immunoglobulin E (IgE) – protects against parasite infections and is associated with allergies and allergic diseases. [33]

T lymphocytes, also known as T cells or CD4 cells, destroy compromised cells and help alert other leukocytes. T cells are produced in the bone marrow and are matured in the thymus. There are three main types of T cells: helper T cells, killer T cells, and regulatory T cells.

- Helper T cells, also called $CD4^+$ cells, T helper (Th) cells, or helper T lymphocytes, help to coordinate an immune response. Some helper T cells communicate with other cells, and some stimulate B cells to produce more antibodies, and others attract more T cells or phagocytes. These cells can be divided into 2 major types:
    - T helper type 1 cells (Th1) which secrete IL-2 and IFN-γ.
    - T helper type 2 cells (Th2) which secrete IL-4 and IL-5. [4] [6]

- Killer T cells, also called $CD8^+$ T cells, cytotoxic T lymphocytes (CTL), or cytotoxic T cells, attack other cells. They are important for immune defence against intracellular pathogens, including viruses and bacteria, and for tumour surveillance. They have 3 major mechanisms to kill infected or malignant cells. For example, they secrete cytokines, primarily tissue necrosis factor alpha (TNF-α) and IFN-γ, which have anti-tumour and anti-viral microbial effects. They also produce and release cytotoxic granules that create pores in the target cells' membranes to enter the cells ultimately resulting in apoptosis[13] of the infected cells. [4] [34]

- Regulatory T cells, also called suppressor T cells, T-regulatory cells, T regs or Tregs, do not activate the immune system like helper T cells. Instead, they have a protective function by shutting off the immune response when it is no longer required, thereby preventing excessive damage to normal cells and tissues. Regulatory T cells suppress the immune response through several mechanisms. For example, they produce anti-inflammatory cytokines that suppress the immune response, release molecules that kill activated immune cells, and change the way dendritic cells behave so they cannot activate T cells. [35] [36]

[13] Apoptosis, also called programmed cell death, is a form of cell death in which a series of molecular steps in a cell lead to its death. It is one method to rid the body of unneeded or abnormal cells. Apoptosis may be blocked in cancer cells.

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Natural killer (NK) cells contain granules with enzymes that can kill tumour cells or cells infected with a virus. [37]

Role of inflammation

Inflammation is the general term for the local accumulation of fluid, plasma proteins, and leukocytes that is initiated by physical injury, infection, or a local immune response made by the body to defend itself against a pathogen. It is also known as an inflammatory response. Its purpose is to localize and eliminate the injurious agent and to remove damaged tissue so the body can begin to heal. The cardinal signs are redness, heat, swelling, and pain, often accompanied by a loss of function. The process consists of changes in blood flow, an increase in permeability of blood vessels, and the migration of fluid, proteins, and leukocytes from the circulation to the site of tissue damage.

Acute inflammation is the term used to describe early and often transient episodes, whereas chronic inflammation occurs when the infection persists or during autoimmune diseases. Many different forms of inflammation are seen in different diseases. The cells that invade tissues undergoing inflammatory responses are often called inflammatory cells or an inflammatory infiltrate. [35] [38]

Take home messages:

It is important for oral healthcare providers to increase their knowledge on the immune system and its inflammatory response to develop a deeper understanding of:

- How the immune system works to defend the body against invading pathogens.
- Pathogenesis of diseases, such as COVID-19, gingivitis, and periodontitis, recognizing these conditions are primarily inflammatory diseases.
- How vaccines work to prevent infection.
- Periodontal disease prevention.
- How to interpret research articles on COVID-19 and other diseases.

Glossary of Terms

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. [7] [39]

Antibody-mediated immunity entails the activation of B cells and secretion of antibodies when in contact with an antigen. [40]

Antigen-antibody complex, also called an **immune complex**, is the binding (attaching) of an antibody to an antigen. Antigen-antibody complexes initiate immune responses. [41]

Antigens are any substance the immune system can recognize and can thus stimulate an immune response. Antigens include bacteria, viruses, parasites, toxins, chemicals,

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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. [7] [42]

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. [43]

B cells, also called **B lymphocytes**, are leukocytes that produce antibodies specific to the antigen that stimulated their production. [7]

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 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. [7] [14]

Cells are the smallest unit of a living organism, composed of a nucleus and cytoplasm enclosed in a membrane. [7]

Chemotaxis is the process where a chemical substance attracts cells to a particular site. [7]

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. [7] [14]

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. [7]

Degranulation is the cellular process where cytoplasmic granules release their contents. [44]

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. [7] [39]

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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. [7] [45]

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. [39]

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. [23]

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. [7] [46]

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. [7] [35]

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. [7]

Immune complex, also called an **antigen-antibody complex**, is the binding (attaching) of an antibody to an antigen. Immune complexes initiate immune responses. [7]

Immune response is the reaction of the immune system to an antigen. [7]

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. [7] [39]

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

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CD4 Th1 cells, CD8 T cells, and natural killer (NK) cells. Primary action of IFN-γ is the activation of macrophages. [35]

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. [7] [11] [16]

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. [11] [16]

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. [11]

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. [11]

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. [11] [16]

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. [11] [16]

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

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made IL-4 is used as a biological response modifier to boost the immune system in cancer therapy. [16]

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. [11] [16]

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. [11] [16]

Interleukin-7 (IL-7) is a type of cytokine made by bone marrow cells and thymus stromal cells.[14] 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. [11] [16]

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. [11] [16]

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[15] proliferation and mast cell activation. [11] [16]

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. [11] [16]

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 complex role in immune response. It also enhances antigen-specific antibody responses. [11] [16] [21]

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. [11] [16]

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[14] Stromal cell is a type of cell that makes up certain types of connective tissue (supporting tissue that surrounds other tissues and organs).

[15] Thymocytes are immune cells that mature into T cells in the thymus.

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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. [11] [16] [47]

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. [16]

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. [11] [16]

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. [11] [16]

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). [11] [16]

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. [11] [16]

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. [16]

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. [16]

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. [11] [16]

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. [11] [16]

Interleukin-23 (IL-23) is a type of cytokine made by dendritic cells and macrophages. It helps to increase T helper cells. [11] [16]

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. [11] [16]

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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). [16]

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. [16]

Interleukin-27 (IL-27) is a type of cytokine made by dendritic cells, monocytes, and macrophages. It helps to induce T helper cell production. [11] [16]

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. [16]

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. [16]

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. [16]

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. [16]

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). [11] [16]

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. [11] [16]

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. [16]

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. [11] [16]

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. [16]

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Interleukin-37 (IL-37) is a type of cytokine made by macrophages and inflamed tissue. It has an anti-inflammatory effect. [11] [16]

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. [16]

Interleukin 39 (IL-39) is a cytokine made mainly by B cells. It acts on neutrophils inducing their differentiation or expansion. [16]

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. [16]

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. [7] [48]

Langerhans cells are antigen-presenting cells located in the skin and mucosa. [49]

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. [7] [19]

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. [7] [35] [50]

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. [7] [35] [51]

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). [7] [35]

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. [7] [52]

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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. [7] [31]

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. [7] [53]

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. [7] [14] [37]

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 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. [35] [55]

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. [7]

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. [35] [55]

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. [7] [56]

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Phagocytosis is the process where a phagocyte (type of leukocyte) engulfs and ingests an invading microorganism, cell, or cell fragment, and removes dead cells. [7] [57]

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. [23]

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). [7]

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 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. [7] [58]

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. [7] [59]

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. [60] [61]

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. [7] [19]

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