Immune system

The immune system is a system of many biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue. In many species, the immune system can be classified into subsystems, such as the innate immune system versus the adaptive immune system, or humoral immunity versus cell-mediated immunity. In humans, the blood–brain barrier, blood–cerebrospinal fluid barrier, and similar fluid–brain barriers separate the peripheral immune system from the neuroimmune system which protects the brain.

Disorders of the immune system can result in autoimmune diseases, inflammatory diseases and cancer. Immunodeficiency occurs when the immune system is less active than normal, resulting in recurring and life-threatening infections. In humans, immunodeficiency can either be the result of a genetic disease such as severe combined immunodeficiency, acquired conditions such as HIV/AIDS, or the use of immunosuppressive medication. In contrast, autoimmunity results from a hyperactive immune system attacking normal tissues as if they were foreign organisms. Common autoimmune diseases include Hashimoto's thyroiditis, rheumatoid arthritis, diabetes mellitus type 1, and systemic lupus erythematosus. Immunology covers the study of all aspects of the immune system.

Immunology is a science that examines the structure and function of the immune system. It originates from medicine and early studies on the causes of immunity to disease. The earliest known reference to immunity was during the plague of Athens in 430 BC. Thucydides noted that people who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time. In the 18th century, Pierre-Louis Moreau de Maupertuis made experiments with scorpion venom and observed that certain dogs and mice were immune to this venom. This and other observations of acquired immunity were later exploited by Louis Pasteur in his development of vaccination and his proposed germ theory of disease. Pasteur's theory was in direct opposition to contemporary theories of disease, such as the miasma theory. It was not until Robert Koch's 1891 proofs, for which he was awarded a Nobel Prize in 1905, that microorganisms were confirmed as the cause of infectious disease. Viruses were confirmed as human pathogens in 1901, with the discovery of the yellow fever virus by Walter Reed.

The immune system protects organisms from infection with layered defenses of increasing specificity. In simple terms, physical barriers prevent pathogens such as bacteria and viruses from entering the organism. If a pathogen breaches these barriers, the innate immune system provides an immediate, but non-specific response. Innate immune systems are found in all plants and animals. If pathogens successfully evade the innate response, vertebrates possess a second layer of protection, the adaptive immune system, which is activated by the innate response. Here, the immune system adapts its response during an infection to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, in the form of an immunological memory, and allows the adaptive immune system to mount faster and stronger attacks each time this pathogen is encountered.

Both innate and adaptive immunity depend on the ability of the immune system to distinguish between self and non-self molecules. In immunology, self molecules are those components of an organism's body that can be distinguished from foreign substances by the immune system. Conversely, non-self molecules are those recognized as foreign molecules. One class of non-self molecules are called antigens (short for antibody generators) and are defined as substances that bind to specific immune receptors and elicit an immune response.

Microorganisms or toxins that successfully enter an organism encounter the cells and mechanisms of the innate immune system. The innate response is usually triggered when microbes are identified by pattern recognition receptors, which recognize components that are conserved among broad groups of microorganisms, or when damaged, injured or stressed cells send out alarm signals, many of which (but not all) are recognized by the same receptors as those that recognize pathogens. Innate immune defenses are non-specific, meaning these systems respond to pathogens in a generic way. This system does not

confer long-lasting immunity against a pathogen. The innate immune system is the dominant system of host defense in most organisms.

Several barriers protect organisms from infection, including mechanical, chemical, and biological barriers. The waxy cuticle of many leaves, the exoskeleton of insects, the shells and membranes of externally deposited eggs, and skin are examples of mechanical barriers that are the first line of defense against infection. However, as organisms cannot be completely sealed from their environments, other systems act to protect body openings such as the lungs, intestines, and the genitourinary tract. In the lungs, coughing and sneezing mechanically eject pathogens and other irritants from the respiratory tract. The flushing action of tears and urine also mechanically expels pathogens, while mucus secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms.

Chemical barriers also protect against infection. The skin and respiratory tract secrete antimicrobial peptides such as the β-defensins. Enzymes such as lysozyme and phospholipase A2 in saliva, tears, and breast milk are also antibacterials. Vaginal secretions serve as a chemical barrier following menarche, when they become slightly acidic, while semen contains defensins and zinc to kill pathogens. In the stomach, gastric acid and proteases serve as powerful chemical defenses against ingested pathogens.

Within the genitourinary and gastrointestinal tracts, commensal flora serve as biological barriers by competing with pathogenic bacteria for food and space and, in some cases, by changing the conditions in their environment, such as pH or available iron. This reduces the probability that pathogens will reach sufficient numbers to cause illness. However, since most antibiotics non-specifically target bacteria and do not affect fungi, oral antibiotics can lead to an "overgrowth" of fungi and cause conditions such as a vaginal candidiasis (a yeast infection). There is good evidence that re-introduction of probiotic flora, such as pure cultures of the lactobacilli normally found in unpasteurized yogurt, helps restore a healthy balance of microbial populations in intestinal infections in children and encouraging preliminary data in studies on bacterial gastroenteritis, inflammatory bowel diseases, urinary tract infection and post-surgical infections.

Inflammation is one of the first responses of the immune system to infection. The symptoms of inflammation are redness, swelling, heat, and pain, which are caused by increased blood flow into tissue. Inflammation is produced by eicosanoids and cytokines, which are released by injured or infected cells. Eicosanoids include prostaglandins that produce fever and the dilation of blood vessels associated with inflammation, and leukotrienes that attract certain white blood cells (leukocytes). Common cytokines include interleukins that are responsible for communication between white blood cells; chemokines that promote chemotaxis; and interferons that have anti-viral effects, such as shutting down protein synthesis in the host cell. Growth factors and cytotoxic factors may also be released. These cytokines and other chemicals recruit immune cells to the site of infection and promote healing of any damaged tissue following the removal of pathogens.

Phagocytosis is an important feature of cellular innate immunity performed by cells called 'phagocytes' that engulf, or eat, pathogens or particles. Phagocytes generally patrol the body searching for pathogens, but can be called to specific locations by cytokines. Once a pathogen has been engulfed by a phagocyte, it becomes trapped in an intracellular vesicle called a phagosome, which subsequently fuses with another vesicle called a lysosome to form a phagolysosome. The pathogen is killed by the activity of digestive enzymes or following a respiratory burst that releases free radicals into the phagolysosome. Phagocytosis evolved as a means of acquiring nutrients, but this role was extended in phagocytes to include engulfment of pathogens as a defense mechanism. Phagocytosis probably represents the oldest form of host defense, as phagocytes have been identified in both vertebrate and invertebrate animals.

Neutrophils and macrophages are phagocytes that travel throughout the body in pursuit of invading pathogens. Neutrophils are normally found in the bloodstream and are the most abundant type of phagocyte, normally representing 50% to 60% of the total circulating leukocytes. During the acute phase of inflammation, particularly as a result of bacterial infection, neutrophils migrate toward the site of inflammation in a process called chemotaxis, and are usually the first cells to arrive at the scene of infection. Macrophages are versatile cells that reside within tissues and produce a wide array of chemicals

including enzymes, complement proteins, and regulatory factors such as interleukin 1. Macrophages also act as scavengers, ridding the body of worn-out cells and other debris, and as antigen-presenting cells that activate the adaptive immune system.

Leukocytes (white blood cells) act like independent, single-celled organisms and are the second arm of the innate immune system. The innate leukocytes include the phagocytes (macrophages, neutrophils, and dendritic cells), mast cells, eosinophils, basophils, and natural killer cells. These cells identify and eliminate pathogens, either by attacking larger pathogens through contact or by engulfing and then killing microorganisms. Innate cells are also important mediators in the activation of the adaptive immune system.

Dendritic cells (DC) are phagocytes in tissues that are in contact with the external environment; therefore, they are located mainly in the skin, nose, lungs, stomach, and intestines. They are named for their resemblance to neuronal dendrites, as both have many spine-like projections, but dendritic cells are in no way connected to the nervous system. Dendritic cells serve as a link between the bodily tissues and the innate and adaptive immune systems, as they present antigens to T cells, one of the key cell types of the adaptive immune system.

Natural killer cells, or NK cells, are a component of the innate immune system which does not directly attack invading microbes. Rather, NK cells destroy compromised host cells, such as tumor cells or virus-infected cells, recognizing such cells by a condition known as "missing self." This term describes cells with low levels of a cell-surface marker called MHC I (major histocompatibility complex) – a situation that can arise in viral infections of host cells. They were named "natural killer" because of the initial notion that they do not require activation in order to kill cells that are "missing self." For many years it was unclear how NK cells recognize tumor cells and infected cells. It is now known that the MHC makeup on the surface of those cells is altered and the NK cells become activated through recognition of "missing self". Normal body cells are not recognized and attacked by NK cells because they express intact self MHC antigens. Those MHC antigens are recognized by killer cell immunoglobulin receptors (KIR) which essentially put the brakes on NK cells.

The adaptive immune system evolved in early vertebrates and allows for a stronger immune response as well as immunological memory, where each pathogen is "remembered" by a signature antigen. The adaptive immune response is antigen-specific and requires the recognition of specific "non-self" antigens during a process called antigen presentation. Antigen specificity allows for the generation of responses that are tailored to specific pathogens or pathogen-infected cells. The ability to mount these tailored responses is maintained in the body by "memory cells". Should a pathogen infect the body more than once, these specific memory cells are used to quickly eliminate it.

Both B cells and T cells carry receptor molecules that recognize specific targets. T cells recognize a "non-self" target, such as a pathogen, only after antigens (small fragments of the pathogen) have been processed and presented in combination with a "self" receptor called a major histocompatibility complex (MHC) molecule. There are two major subtypes of T cells: the killer T cell and the helper T cell. In addition there are regulatory T cells which have a role in modulating immune response. Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper T cells and regulatory T cells only recognize antigens coupled to Class II MHC molecules. These two mechanisms of antigen presentation reflect the different roles of the two types of T cell. A third, minor subtype are the γδ T cells that recognize intact antigens that are not bound to MHC receptors.

Killer T cells are a sub-group of T cells that kill cells that are infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional. As with B cells, each type of T cell recognizes a different antigen. Killer T cells are activated when their T cell receptor (TCR) binds to this specific antigen in a complex with the MHC Class I receptor of another cell. Recognition of this MHC:antigen complex is aided by a co-receptor on the T cell, called CD8. The T cell then travels throughout the body in search of cells where the MHC I receptors bear this antigen. When an activated T cell contacts such cells, it releases cytotoxins, such as perforin, which form pores in the target cell's plasma membrane, allowing ions, water

and toxins to enter. The entry of another toxin called granulysin (a protease) induces the target cell to undergo apoptosis. T cell killing of host cells is particularly important in preventing the replication of viruses. T cell activation is tightly controlled and generally requires a very strong MHC/antigen activation signal, or additional activation signals provided by "helper" T cells (see below).

Helper T cells express T cell receptors (TCR) that recognize antigen bound to Class II MHC molecules. The MHC:antigen complex is also recognized by the helper cell's CD4 co-receptor, which recruits molecules inside the T cell (e.g., Lck) that are responsible for the T cell's activation. Helper T cells have a weaker association with the MHC:antigen complex than observed for killer T cells, meaning many receptors (around 200–300) on the helper T cell must be bound by an MHC:antigen in order to activate the helper cell, while killer T cells can be activated by engagement of a single MHC:antigen molecule. Helper T cell activation also requires longer duration of engagement with an antigen-presenting cell. The activation of a resting helper T cell causes it to release cytokines that influence the activity of many cell types. Cytokine signals produced by helper T cells enhance the microbicidal function of macrophages and the activity of killer T cells. In addition, helper T cell activation causes an upregulation of molecules expressed on the T cell's surface, such as CD40 ligand (also called CD154), which provide extra stimulatory signals typically required to activate antibody-producing B cells.

Gamma delta T cells (γδ T cells) possess an alternative T cell receptor (TCR) as opposed to CD4+ and CD8+ (αβ) T cells and share the characteristics of helper T cells, cytotoxic T cells and NK cells. The conditions that produce responses from γδ T cells are not fully understood. Like other 'unconventional' T cell subsets bearing invariant TCRs, such as CD1d-restricted Natural Killer T cells, γδ T cells straddle the border between innate and adaptive immunity. On one hand, γδ T cells are a component of adaptive immunity as they rearrange TCR genes to produce receptor diversity and can also develop a memory phenotype. On the other hand, the various subsets are also part of the innate immune system, as restricted TCR or NK receptors may be used as pattern recognition receptors. For example, large numbers of human Vγ9/Vδ2 T cells respond within hours to common molecules produced by microbes, and highly restricted Vδ1+ T cells in epithelia respond to stressed epithelial cells.

A B cell identifies pathogens when antibodies on its surface bind to a specific foreign antigen. This antigen/antibody complex is taken up by the B cell and processed by proteolysis into peptides. The B cell then displays these antigenic peptides on its surface MHC class II molecules. This combination of MHC and antigen attracts a matching helper T cell, which releases lymphokines and activates the B cell. As the activated B cell then begins to divide, its offspring (plasma cells) secrete millions of copies of the antibody that recognizes this antigen. These antibodies circulate in blood plasma and lymph, bind to pathogens expressing the antigen and mark them for destruction by complement activation or for uptake and destruction by phagocytes. Antibodies can also neutralize challenges directly, by binding to bacterial toxins or by interfering with the receptors that viruses and bacteria use to infect cells.

When B cells and T cells are activated and begin to replicate, some of their offspring become long-lived memory cells. Throughout the lifetime of an animal, these memory cells remember each specific pathogen encountered and can mount a strong response if the pathogen is detected again. This is "adaptive" because it occurs during the lifetime of an individual as an adaptation to infection with that pathogen and prepares the immune system for future challenges. Immunological memory can be in the form of either passive short-term memory or active long-term memory.

Newborn infants have no prior exposure to microbes and are particularly vulnerable to infection. Several layers of passive protection are provided by the mother. During pregnancy, a particular type of antibody, called IgG, is transported from mother to baby directly across the placenta, so human babies have high levels of antibodies even at birth, with the same range of antigen specificities as their mother. Breast milk or colostrum also contains antibodies that are transferred to the gut of the infant and protect against bacterial infections until the newborn can synthesize its own antibodies. This is passive immunity because the fetus does not actually make any memory cells or antibodies—it only borrows them. This passive immunity is usually short-term, lasting from a few days up to several months. In medicine, protective passive immunity can also be transferred artificially from one individual to another via antibody-rich

serum.

Hormones can act as immunomodulators, altering the sensitivity of the immune system. For example, female sex hormones are known immunostimulators of both adaptive and innate immune responses. Some autoimmune diseases such as lupus erythematosus strike women preferentially, and their onset often coincides with puberty. By contrast, male sex hormones such as testosterone seem to be immunosuppressive. Other hormones appear to regulate the immune system as well, most notably prolactin, growth hormone and vitamin D.

When suffering from sleep deprivation, active immunizations may have a diminished effect and may result in lower antibody production, and a lower immune response, than would be noted in a well-rested individual. Additionally, proteins such as NFIL3, which have been shown to be closely intertwined with both T-cell differentiation and our circadian rhythms, can be affected through the disturbance of natural light and dark cycles through instances of sleep deprivation, shift work, etc. As a result, these disruptions can lead to an increase in chronic conditions such as heart disease, chronic pain, and asthma.

It is conjectured that a progressive decline in hormone levels with age is partially responsible for weakened immune responses in aging individuals. Conversely, some hormones are regulated by the immune system, notably thyroid hormone activity. The age-related decline in immune function is also related to decreasing vitamin D levels in the elderly. As people age, two things happen that negatively affect their vitamin D levels. First, they stay indoors more due to decreased activity levels. This means that they get less sun and therefore produce less cholecalciferol via UVB radiation. Second, as a person ages the skin becomes less adept at producing vitamin D.

The main response of the immune system to tumors is to destroy the abnormal cells using killer T cells, sometimes with the assistance of helper T cells. Tumor antigens are presented on MHC class I molecules in a similar way to viral antigens. This allows killer T cells to recognize the tumor cell as abnormal. NK cells also kill tumorous cells in a similar way, especially if the tumor cells have fewer MHC class I molecules on their surface than normal; this is a common phenomenon with tumors. Sometimes antibodies are generated against tumor cells allowing for their destruction by the complement system.

Unlike animals, plants lack phagocytic cells, but many plant immune responses involve systemic chemical signals that are sent through a plant. Individual plant cells respond to molecules associated with pathogens known as Pathogen-associated molecular patterns or PAMPs. When a part of a plant becomes infected, the plant produces a localized hypersensitive response, whereby cells at the site of infection undergo rapid apoptosis to prevent the spread of the disease to other parts of the plant. Systemic acquired resistance (SAR) is a type of defensive response used by plants that renders the entire plant resistant to a particular infectious agent. RNA silencing mechanisms are particularly important in this systemic response as they can block virus replication.

Overactive immune responses comprise the other end of immune dysfunction, particularly the autoimmune disorders. Here, the immune system fails to properly distinguish between self and non-self, and attacks part of the body. Under normal circumstances, many T cells and antibodies react with "self" peptides. One of the functions of specialized cells (located in the thymus and bone marrow) is to present young lymphocytes with self antigens produced throughout the body and to eliminate those cells that recognize self-antigens, preventing autoimmunity.

Immunodeficiencies occur when one or more of the components of the immune system are inactive. The ability of the immune system to respond to pathogens is diminished in both the young and the elderly, with immune responses beginning to decline at around 50 years of age due to immunosenescence. In developed countries, obesity, alcoholism, and drug use are common causes of poor immune function. However, malnutrition is the most common cause of immunodeficiency in developing countries. Diets lacking sufficient protein are associated with impaired cell-mediated immunity, complement activity, phagocyte function, IgA antibody concentrations, and cytokine production. Additionally, the loss of the thymus at an early age through genetic mutation or surgical removal results in severe immunodeficiency and a high susceptibility to infection.

Long-term active memory is acquired following infection by activation of B and T cells. Active immunity can also be generated artificially, through vaccination. The principle behind vaccination (also called immunization) is to introduce an antigen from a pathogen in order to stimulate the immune system and develop specific immunity against that particular pathogen without causing disease associated with that organism. This deliberate induction of an immune response is successful because it exploits the natural specificity of the immune system, as well as its inducibility. With infectious disease remaining one of the leading causes of death in the human population, vaccination represents the most effective manipulation of the immune system mankind has developed.

The success of any pathogen depends on its ability to elude host immune responses. Therefore, pathogens evolved several methods that allow them to successfully infect a host, while evading detection or destruction by the immune system. Bacteria often overcome physical barriers by secreting enzymes that digest the barrier, for example, by using a type II secretion system. Alternatively, using a type III secretion system, they may insert a hollow tube into the host cell, providing a direct route for proteins to move from the pathogen to the host. These proteins are often used to shut down host defenses.

In the mid-1950s, Frank Burnet, inspired by a suggestion made by Niels Jerne, formulated the clonal selection theory (CST) of immunity. On the basis of CST, Burnet developed a theory of how an immune response is triggered according to the self/nonself distinction: "self" constituents (constituents of the body) do not trigger destructive immune responses, while "nonself" entities (pathogens, an allograft) trigger a destructive immune response. The theory was later modified to reflect new discoveries regarding histocompatibility or the complex "two-signal" activation of T cells. The self/nonself theory of immunity and the self/nonself vocabulary have been criticized, but remain very influential.

Anti-inflammatory drugs are often used to control the effects of inflammation. Glucocorticoids are the most powerful of these drugs; however, these drugs can have many undesirable side effects, such as central obesity, hyperglycemia, osteoporosis, and their use must be tightly controlled. Lower doses of anti-inflammatory drugs are often used in conjunction with cytotoxic or immunosuppressive drugs such as methotrexate or azathioprine. Cytotoxic drugs inhibit the immune response by killing dividing cells such as activated T cells. However, the killing is indiscriminate and other constantly dividing cells and their organs are affected, which causes toxic side effects. Immunosuppressive drugs such as cyclosporin prevent T cells from responding to signals correctly by inhibiting signal transduction pathways.

In contrast, during wake periods differentiated effector cells, such as cytotoxic natural killer cells and CTLs (cytotoxic T lymphocytes), peak in order to elicit an effective response against any intruding pathogens. As well during awake active times, anti-inflammatory molecules, such as cortisol and catecholamines, peak. There are two theories as to why the pro-inflammatory state is reserved for sleep time. First, inflammation would cause serious cognitive and physical impairments if it were to occur during wake times. Second, inflammation may occur during sleep times due to the presence of melatonin. Inflammation causes a great deal of oxidative stress and the presence of melatonin during sleep times could actively counteract free radical production during this time.

When a T-cell encounters a foreign pathogen, it extends a vitamin D receptor. This is essentially a signaling device that allows the T-cell to bind to the active form of vitamin D, the steroid hormone calcitriol. T-cells have a symbiotic relationship with vitamin D. Not only does the T-cell extend a vitamin D receptor, in essence asking to bind to the steroid hormone version of vitamin D, calcitriol, but the T-cell expresses the gene CYP27B1, which is the gene responsible for converting the pre-hormone version of vitamin D, calcidiol into the steroid hormone version, calcitriol. Only after binding to calcitriol can T-cells perform their intended function. Other immune system cells that are known to express CYP27B1 and thus activate vitamin D calcidiol, are dendritic cells, keratinocytes and macrophages.

Pattern recognition receptors are proteins used by nearly all organisms to identify molecules associated with pathogens. Antimicrobial peptides called defensins are an evolutionarily conserved component of the innate immune response found in all animals and plants, and represent the main form of invertebrate systemic immunity. The complement system and phagocytic cells are also used by most forms of

invertebrate life. Ribonucleases and the RNA interference pathway are conserved across all eukaryotes, and are thought to play a role in the immune response to viruses.

Evolution of the adaptive immune system occurred in an ancestor of the jawed vertebrates. Many of the classical molecules of the adaptive immune system (e.g., immunoglobulins and T cell receptors) exist only in jawed vertebrates. However, a distinct lymphocyte-derived molecule has been discovered in primitive jawless vertebrates, such as the lamprey and hagfish. These animals possess a large array of molecules called Variable lymphocyte receptors (VLRs) that, like the antigen receptors of jawed vertebrates, are produced from only a small number (one or two) of genes. These molecules are believed to bind pathogenic antigens in a similar way to antibodies, and with the same degree of specificity.

It is likely that a multicomponent, adaptive immune system arose with the first vertebrates, as invertebrates do not generate lymphocytes or an antibody-based humoral response. Many species, however, utilize mechanisms that appear to be precursors of these aspects of vertebrate immunity. Immune systems appear even in the structurally most simple forms of life, with bacteria using a unique defense mechanism, called the restriction modification system to protect themselves from viral pathogens, called bacteriophages. Prokaryotes also possess acquired immunity, through a system that uses CRISPR sequences to retain fragments of the genomes of phage that they have come into contact with in the past, which allows them to block virus replication through a form of RNA interference. Offensive elements of the immune systems are also present in unicellular eukaryotes, but studies of their roles in defense are few.

Immunology is strongly experimental in everyday practice but is also characterized by an ongoing theoretical attitude. Many theories have been suggested in immunology from the end of the nineteenth century up to the present time. The end of the 19th century and the beginning of the 20th century saw a battle between "cellular" and "humoral" theories of immunity. According to the cellular theory of immunity, represented in particular by Elie Metchnikoff, it was cells – more precisely, phagocytes – that were responsible for immune responses. In contrast, the humoral theory of immunity, held, among others, by Robert Koch and Emil von Behring, stated that the active immune agents were soluble components (molecules) found in the organism’s “humors” rather than its cells.

Clearly, some tumors evade the immune system and go on to become cancers. Tumor cells often have a reduced number of MHC class I molecules on their surface, thus avoiding detection by killer T cells. Some tumor cells also release products that inhibit the immune response; for example by secreting the cytokine TGF-β, which suppresses the activity of macrophages and lymphocytes. In addition, immunological tolerance may develop against tumor antigens, so the immune system no longer attacks the tumor cells.

Hypersensitivity is an immune response that damages the body's own tissues. They are divided into four classes (Type I – IV) based on the mechanisms involved and the time course of the hypersensitive reaction. Type I hypersensitivity is an immediate or anaphylactic reaction, often associated with allergy. Symptoms can range from mild discomfort to death. Type I hypersensitivity is mediated by IgE, which triggers degranulation of mast cells and basophils when cross-linked by antigen. Type II hypersensitivity occurs when antibodies bind to antigens on the patient's own cells, marking them for destruction. This is also called antibody-dependent (or cytotoxic) hypersensitivity, and is mediated by IgG and IgM antibodies. Immune complexes (aggregations of antigens, complement proteins, and IgG and IgM antibodies) deposited in various tissues trigger Type III hypersensitivity reactions. Type IV hypersensitivity (also known as cell-mediated or delayed type hypersensitivity) usually takes between two and three days to develop. Type IV reactions are involved in many autoimmune and infectious diseases, but may also involve contact dermatitis (poison ivy). These reactions are mediated by T cells, monocytes, and macrophages.

An evasion strategy used by several pathogens to avoid the innate immune system is to hide within the cells of their host (also called intracellular pathogenesis). Here, a pathogen spends most of its life-cycle inside host cells, where it is shielded from direct contact with immune cells, antibodies and complement.

Some examples of intracellular pathogens include viruses, the food poisoning bacterium Salmonella and the eukaryotic parasites that cause malaria (Plasmodium falciparum) and leishmaniasis (Leishmania spp.). Other bacteria, such as Mycobacterium tuberculosis, live inside a protective capsule that prevents lysis by complement. Many pathogens secrete compounds that diminish or misdirect the host's immune response. Some bacteria form biofilms to protect themselves from the cells and proteins of the immune system. Such biofilms are present in many successful infections, e.g., the chronic Pseudomonas aeruginosa and Burkholderia cenocepacia infections characteristic of cystic fibrosis. Other bacteria generate surface proteins that bind to antibodies, rendering them ineffective; examples include Streptococcus (protein G), Staphylococcus aureus (protein A), and Peptostreptococcus magnus (protein L).

The mechanisms used to evade the adaptive immune system are more complicated. The simplest approach is to rapidly change non-essential epitopes (amino acids and/or sugars) on the surface of the pathogen, while keeping essential epitopes concealed. This is called antigenic variation. An example is HIV, which mutates rapidly, so the proteins on its viral envelope that are essential for entry into its host target cell are constantly changing. These frequent changes in antigens may explain the failures of vaccines directed at this virus. The parasite Trypanosoma brucei uses a similar strategy, constantly switching one type of surface protein for another, allowing it to stay one step ahead of the antibody response. Masking antigens with host molecules is another common strategy for avoiding detection by the immune system. In HIV, the envelope that covers the virion is formed from the outermost membrane of the host cell; such "self-cloaked" viruses make it difficult for the immune system to identify them as "non-self" structures.

Another important role of the immune system is to identify and eliminate tumors. This is called immune surveillance. The transformed cells of tumors express antigens that are not found on normal cells. To the immune system, these antigens appear foreign, and their presence causes immune cells to attack the transformed tumor cells. The antigens expressed by tumors have several sources; some are derived from oncogenic viruses like human papillomavirus, which causes cervical cancer, while others are the organism's own proteins that occur at low levels in normal cells but reach high levels in tumor cells. One example is an enzyme called tyrosinase that, when expressed at high levels, transforms certain skin cells (e.g. melanocytes) into tumors called melanomas. A third possible source of tumor antigens are proteins normally important for regulating cell growth and survival, that commonly mutate into cancer inducing molecules called oncogenes.

Larger drugs (>500 Da) can provoke a neutralizing immune response, particularly if the drugs are administered repeatedly, or in larger doses. This limits the effectiveness of drugs based on larger peptides and proteins (which are typically larger than 6000 Da). In some cases, the drug itself is not immunogenic, but may be co-administered with an immunogenic compound, as is sometimes the case for Taxol. Computational methods have been developed to predict the immunogenicity of peptides and proteins, which are particularly useful in designing therapeutic antibodies, assessing likely virulence of mutations in viral coat particles, and validation of proposed peptide-based drug treatments. Early techniques relied mainly on the observation that hydrophilic amino acids are overrepresented in epitope regions than hydrophobic amino acids; however, more recent developments rely on machine learning techniques using databases of existing known epitopes, usually on well-studied virus proteins, as a training set. A publicly accessible database has been established for the cataloguing of epitopes from pathogens known to be recognizable by B cells. The emerging field of bioinformatics-based studies of immunogenicity is referred to as immunoinformatics. Immunoproteomics is the study of large sets of proteins (proteomics) involved in the immune response.

In addition to the negative consequences of sleep deprivation, sleep and the intertwined circadian system have been shown to have strong regulatory effects on immunological functions affecting both the innate and the adaptive immunity. First, during the early slow-wave-sleep stage, a sudden drop in blood levels of cortisol, epinephrine, and norepinephrine induce increased blood levels of the hormones leptin, pituitary growth hormone, and prolactin. These signals induce a pro-inflammatory state through the production of the pro-inflammatory cytokines interleukin-1, interleukin-12, TNF-alpha and IFN-gamma. These cytokines then stimulate immune functions such as immune cells activation, proliferation, and differentiation. It is during this time that undifferentiated, or less differentiated, like naïve and central

memory T cells, peak (i.e. during a time of a slowly evolving adaptive immune response). In addition to these effects, the milieu of hormones produced at this time (leptin, pituitary growth hormone, and prolactin) support the interactions between APCs and T-cells, a shift of the Th1/Th2 cytokine balance towards one that supports Th1, an increase in overall Th cell proliferation, and naïve T cell migration to lymph nodes. This milieu is also thought to support the formation of long-lasting immune memory through the initiation of Th1 immune responses.

Pathogens can rapidly evolve and adapt, and thereby avoid detection and neutralization by the immune system; however, multiple defense mechanisms have also evolved to recognize and neutralize pathogens. Even simple unicellular organisms such as bacteria possess a rudimentary immune system, in the form of enzymes that protect against bacteriophage infections. Other basic immune mechanisms evolved in ancient eukaryotes and remain in their modern descendants, such as plants and invertebrates. These mechanisms include phagocytosis, antimicrobial peptides called defensins, and the complement system. Jawed vertebrates, including humans, have even more sophisticated defense mechanisms, including the ability to adapt over time to recognize specific pathogens more efficiently. Adaptive (or acquired) immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.

In humans, this response is activated by complement binding to antibodies that have attached to these microbes or the binding of complement proteins to carbohydrates on the surfaces of microbes. This recognition signal triggers a rapid killing response. The speed of the response is a result of signal amplification that occurs following sequential proteolytic activation of complement molecules, which are also proteases. After complement proteins initially bind to the microbe, they activate their protease activity, which in turn activates other complement proteases, and so on. This produces a catalytic cascade that amplifies the initial signal by controlled positive feedback. The cascade results in the production of peptides that attract immune cells, increase vascular permeability, and opsonize (coat) the surface of a pathogen, marking it for destruction. This deposition of complement can also kill cells directly by disrupting their plasma membrane.

The immune system protects organisms against what

disease

What are the agents the immune system detects known as

pathogens

Which part of the immune system protects the brain

neuroimmune system

What separates the neuroimmune system and peripheral immune system in humans

blood–brain barrier, blood–cerebrospinal fluid barrier

What are the agents detected by the immune system called

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What are the two different types of immunity

humoral immunity versus cell-mediated immunity

What are the two major subsystems of the immune system

innate immune system versus the adaptive immune system

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What happens when the immune system less active than normal

Immunodeficiency

What is the term for a hyperactive immune system that attacks normal tissues

autoimmunity

What field involves the study of the immune system

Immunology

What acquired condition results in immunodeficiency in humans

HIV/AIDS

Who won the Nobel Prize in 1905

Robert Koch

What did Robert Koch prove was the cause of infectious disease

microorganisms

What virus did Walter Reed discover

yellow fever virus

When was the first known historical reference to immunity

Athens in 430 BC

What type of immune systems are found in all plants and animals

Innate immune systems

What immune system is activated by the innate response

adaptive immune system

What allows the adaptive immune system to react faster and more strongly each subsequent time a pathogen is encountered

immunological memory

What is the first line of defense against pathogens that prevents them from entering an organism

physical barriers

The adaptive immune system must distinguish between what types of molecules

self and non-self

What molecules are parts of the body of an organism in immunology

self molecules

What molecules are recognized as foreign by the immune system

non-self molecules

What term is shorthand for antibody generators

antigens

Antigens bind to what in order to elicit a response of the immune system

specific immune receptors

What part of the innate immune system identifies microbes and triggers immune response

pattern recognition receptors

For most organisms, what is the dominant system of defense

innate immune system

Pattern recognition receptors recognize components present in broad groups of what

microorganisms

The innate immune system responds in a generic way, meaning it is what

non-specific

What is a mechanical barrier in insects that protects the insect

exoskeleton

What is an example of a mechanical barrier on leaves

The waxy cuticle

What responses protect the lungs by mechanically ejecting pathogens from the respiratory system

coughing and sneezing

What is secreted by the respiratory tract to trap microorganisms

mucus

The flushing action of what expels pathogens from the eyes

tears

What are the anitmicrobial peptides secreted by the skin called

β-defensins

What enzymes in saliva are antibacterial in nature

lysozyme and phospholipase A2

Semen contains what in order to kill pathogens

defensins and zinc

What compounds in the stomach protect against ingested pathogens

gastric acid and proteases

Vaginal secretions serve as a chemical protective barrier following what

menarche

What serves as a biological barrier by competing for space and food in the GI tract

commensal flora

Most antibiotics target bacteria and don't affect what class of organisms

fungi

What probiotic flora is found in unpasteurized yogurt

lactobacilli

Commensal flora can change what specific conditions of their environment in the gastrointestinal tract

pH or available iron

What is one of the first responses the immune system has to infection

Inflammation

What causes the symptoms of inflammation

increased blood flow into tissue

What compounds are released by injured or infected cells, triggering inflammation

eicosanoids and cytokines

Eicosanoids include what compounds that result in fever and blood vessel dilation

prostaglandins

What cytokines are responsible for communication between white blood cells

interleukins

What type of cells engulf or eat pathogens and foreign particles

phagocytes

Phagocytes can be called to a specific location by what

cytokines

When a pathogen has been eaten by a phagocyte it becomes trapped in what vesicle

phagosome

What is formed when a phagosome fuses with a lysosome

phagolysosome

Phagocytosis first evolved as means of doing what

acquiring nutrients

What are two types of phagocytes that travel through the body to find invading pathogens

Neutrophils and macrophages

What are the most abundant kind of phagocyte

Neutrophils

What percentage of leukocytes do neutrophils represent

50% to 60%

What is the process in which neutrophils move towards the site of inflammation called

chemotaxis

What is a regulatory factor produced by macrophages

interleukin 1

What are white blood cells known as

Leukocytes

What cells are the second arm of the innate immune system

Leukocytes (white blood cells)

Innate cells can act as mediators in the activation of what branch of the immune system

adaptive immune system

What are three kinds of phagocytes

macrophages, neutrophils, and dendritic cells

What are the phagocytes that are located in tissues in contact with the external environment called

Dendritic cells

Dendritic cells are named that because they resemble what

neuronal dendrites

What are one of the key cell types of the adaptive immune system

T cells

Dendritic cells present antigens to what cells of the adaptive nervous system

T cells

What is one part of the innate immune system

that doesn't attack microbes directly

Natural killer cells

Natural killer cells recognize cells that should be targeted by a condition known as what

missing self

Missing self desribes cells that only have small amounts of what cell-surface marker

MHC I (major histocompatibility complex)

MHC antigens on normal body cells are recognized by what receptor on NK cells

killer cell immunoglobulin receptors (KIR

In what types of organisms did the adaptive immune system first evolve

vertebrates

The adaptive immune system recognizes non-self antigens during a process called what

antigen presentation

Antigen specificity allows responses that are specific to certain types of what

pathogens or pathogen-infected cells

What are the two major subtypes of T cells

killer T cell and the helper T cell

What kind of T cells have the purpose of modulating the immune response

regulatory T cells

Killer T cells can only recognize antigens coupled to what kind of molecules

Class I MHC molecules

Helper and regulatory T cells can only recognize antigens coupled to what kind of molecules

Class II MHC molecules

What class of T cells recognizes intact antigens that are not associated with MHC receptors

γδ T cells

What kind of T cells kill cells that are infected with pathogens

Killer T cells

What is the receptor that killer T cells use to bind to specific antigens that are complexed with the MHC Class 1 receptor of another cell

T cell receptor (TCR)

What co-receptor on the T cell helps in recognizing the MHC-antigen complex

CD8

When an activated killer T cell finds cells where the MHC 1 receptor has specific antigens, it releases cytotoxins such as what

perforin

What toxin induces apoptosis in the target cell

granulysin

What co-receptor recruits molecules inside the T cell that are responsible for cell activation

CD4 co-receptor

How many receptors on a helper T cell must be bound to a MHC:antigen complex in order for the cell to be activated

around 200–300

The receptors on a killer T cell must bind to how many MHC: antigen complexes in order to activate the cell

a single MHC:antigen molecule

Activation of a helper T cell causes it to release what chemicals that influence cell activity

cytokines

What is a ligand on the cell surface that is upregulated after helper T cell activation

CD40 ligand

Gamma delta T cells share the characteristics of what other types of T cells

helper T cells, cytotoxic T cells and NK cells

Gamma delta T cells have a different version of what receptor

alternative T cell receptor (TCR)

What type of T cells help with both innnate and adaptive immunity

γδ T cells

Gamma delta T cells rearrange TCR genes to produce what

receptor diversity

What kind of human T cells respond to common molecules produced by microbes

Vγ9/Vδ2 T cells

What kind of cell identifies pathogens when the antibodies on its surface complex with a specific foreign antigen

B cell

What is the process by which the antigen/antibody complex is processed in to peptides

proteolysis

What does the matching helper T cell release when it binds with the MHC:antigen complex of the B cell

lymphokines

When B cells and T cells begin to replicate, what do some of their offspring cells become

long-lived memory cells

The function of long-lived memory cells is an example of what kind of immune response

adaptive

Immunological memory can take what two forms

passive short-term memory or active long-term memory

Long-lived memory cells can remember previous encounters with

what

specific pathogen

Newborns are vulnerable to infection because they have no previous exposure to what

microbes

What antibody is transported from the mother to baby across the placenta

IgG

Antibodies are transferred to the gut of the infant through what means

Breast milk or colostrum

Antibodies transported from the mother to an infant via the placenta is an example of what type of short-lived immunity

passive immunity

Hormones can alter the sensitivity of the immune system, so they can be referred to as what

immunomodulators

Female sex hormones are immunostimulators of which immune responses

adaptive and innate immune responses

What is an autoimmune disease that affects women preferentially

lupus erythematosus

What is the effect of testosterone on the male immune system

immunosuppressive

What is a protein that is closely intertwined with circadian rhythms

NFIL3

Disruptions in sleep can lead to increase in what chronic conditions

heart disease, chronic pain, and asthma

What kind of deprivation results in diminished immune response and lower antibody production

sleep deprivation

What is partially responsible for weakened immune response in older individuals

decline in hormone levels with age

As a person gets older, what does the skin produce less of

vitamin D

The production of what signalling molecules is regulated by the immune system

hormones

Older people get less sun and produce less of what chemical via UVB radiation

cholecalciferol

What type of immune cells help to destroy abnormal cells in tumors

killer T cells

Lots of tumor cells have fewer of what type of molecule on their surface

MHC class I molecules

Tumor antigens are complexed with MHC class I molecules in the same way as what antigens

viral antigens

The immune system also produces what molecules in order to allow for tumor destruction by the complement system

antibodies

Plants lack what kind of immune cells

phagocytic cells

Plant cells respond to the molecules associated with pathogens known as what

Pathogen-associated molecular patterns

Cells of the site of an infection in a plant undergo what process to prevent spread of the disease

apoptosis

What is a kind of defense response that makes the entire plant resistant to a particular agent

Systemic acquired resistance (SAR)

What is a mechanism that can help plants block virus replication

RNA silencing mechanisms

What kind of disorders are the result of an

overactive immune response

autoimmune disorders

In autoimmune disorders, the immune system doesn't distinguish between what types of cells

self and non-self

Where are the specialized cells that eliminate cells that recognize self-antigens located

thymus and bone marrow

Under normal conditions, T cells and antibodies produce what kind of peptides

"self" peptides

What kind of disorders occur when part of the immune system isn't active

Immunodeficiencies

In what two age groups is the strength of the immune system reduced

the young and the elderly

At what age do immune responses typically begin to decline

around 50 years of age

What are some causes of reduced immune function in developed countries

obesity, alcoholism, and drug use

What is the most common cause of

immunodeficiency in developing nations

malnutrition

By what process can active immunity be generated in an artificial manner

vaccination

What is the process of vaccination also known as

immunization

In the process of vaccination, what is introduced in order to develop a specific immunity

an antigen from a pathogen

Vaccination exploits what feature of the human immune system in order to be successful

natural specificity of the immune system

Bacteria often secrete what kind of proteins to ingest a physical barrier

enzymes

What kind of system of infection involves inserting a hollow tube into a host cell

type III secretion system

In a type III secretion system, proteins are transported to the host cell in order to do what

shut down host defenses

The success of pathogens is predicated on their ability to do what

elude host immune responses

Who formulated the idea of clonal selection theory of immunity

Frank Burnet

What are two examples of nonself entities in accordance with Frank Burnet's theory

pathogens, an allograft

What is the complex "two-signal" activation of T cells referred to

histocompatibility

What other scientist influence Frank Burnet when he was formulating his theory of immunity

Niels Jerne

What are the most powerful class of anti-inflammatory drugs

Glucocorticoids

Low doses of anti-inflammatories are sometimes used with what classes of drugs

cytotoxic or immunosuppressive drugs

What are two examples of cytotoxic or immunosuppressive drugs

methotrexate or azathioprine

What is an example of an immunosuppressive drug that prevents T cell activity by altering signal transduction pathways

cyclosporin

What are examples of differentiated effector cells that peak during wake periods

cytotoxic natural killer cells and CTLs (cytotoxic T lymphocytes)

What are two anti-inflammatory molecules that peak during awake hours

cortisol and catecholamines

Inflammation occurs during sleep times because of the presence of what molecule

melatonin

Melatonin during sleep can actively counteract the production of what

free radical production

What does a T cell extend when it encounters a foreign pathogen

a vitamin D receptor

What is the active form of vitamin D known as

calcitriol

What is the nature of the relationship between T-cells and vitamin D

symbiotic relationship

What gene is responsible for converting calcidiol into calcitriol

gene CYP27B1

Other than T cells, what other immune cells express CYP27B1

dendritic cells, keratinocytes and macrophages

What are the proteins that organisms use to identify molecules associated with pathogens

Pattern recognition receptors

What are the antimicrobial peptides that are the main form of invertebrate systemic immunity called

defensins

What cell type is also used for immune response in most types of invertebrate life

phagocytic cells

What pathway that plays a role in immune response to viruses is present in all eukaryotes

RNA interference pathway

What molecules of the adaptive immune system only exist in jawed vertebrates

immunoglobulins and T cell receptors

What are two examples of primitive jawless vertebrates

the lamprey and hagfish

Primitive jawless vertebrates possess an array of receptors referred to as what

Variable lymphocyte receptors (VLRs)

Evolution of what part of the immune system occurred in the evolutionary ancestor of jawed vertebrates

adaptive immune system

Invertebrates do not generate what type of cells that are a part of the vertebrate adaptive immune system

lymphocytes

What is the main defense mechanism of bacteria known as

the restriction modification system

The restriction modification system is used by bacteria for protection from what pathogens

bacteriophages

What is the system by which prokaryotes retain phage gene fragments that they have previously come in contact with

CRISPR

What were the two main theories of immunity at the end of the 19th century

"cellular" and "humoral" theories of immunity

Who was the main proponent of the cellular theory of immunity

Elie Metchnikoff

Under Elie Metchnikoff's cellular theory, what cells were responsible for immune response

phagocytes

What two scientists were proponents of the humoral theory of immunity

Robert Koch and Emil von Behring

According to the humoral theory of immunity, what were the bodies immune agents

soluble components (molecules)

Tumors that are able to evade the body's immune response can

become what

cancers

What receptors do tumor cells often have reduced concentrations of

MHC class I molecules

What is a chemical secreted by tumors that suppresses the immune response

cytokine TGF-β

Cytokine TBF-B suppresses the activity of what cell types

macrophages and lymphocytes

What is the name for a response of the immune system that damages the body's native tissues

Hypersensitivity

How many classes of immune hypersensitivity are there

four classes (Type I – IV)

What type of hypersensitivity is associated with allergies

Type I

What is the chemical that mediates Type 1 hypersensitivity

IgE

Antibody-dependent hypersensitivity belongs to what class of hypersensitivity

Type II hypersensitivity

What is the process by which pathogens evade the immune system by hiding inside the host cells called

intracellular pathogenesis

What food bacteria is an example of intracellular pathogenesis

Salmonella

What is the eukaryotic parasite responsible for malaria known as

Plasmodium falciparum

What bacteria lives inside a protective capsule that serves to prevent cell lysis

Mycobacterium tuberculosis

What protein does Staphylococcus aureus produce to make antibodies ineffective

protein A

What is the process by which the adaptive immune system is evaded by the chainging of non-essential epitopes called

antigenic variation

What is an example of a virus that uses antigenic variation

HIV

What is an example of a parasite that used the antigenic variation strategy to evade destruction

Trypanosoma brucei

What compounds can be masked with the molecules of the host cell in order for a virus to evade detection

antigens

What is the process by which the immune system identifies tumors called

immune surveillance

What is the virus in humans that causes cervical cancer

human papillomavirus

What is an example of an enzyme that can transform skin cells into tumors when expressed at high levels

tyrosinase

What are cancerous tumors of the skin known as

melanomas

What are the skin cells that can be transformed into tumors known as

melanocytes

At what size and larger can drugs elicit a neutralizing immune response

>500 Da

What kind of amino acids are overrepresented in epitope regions

hydrophilic amino acids

What is the study of proteins involved in immune response known as

Immunoproteomics

There is a public database of epitopes for pathogens known to be recognizable by what cells

B cells

What is the field of studying immunogenicity through bioinformatics known as

immunoinformatics

Drop in the blood levels of cortisol and epinephrine results in increase levels of what hormones

leptin, pituitary growth hormone, and prolactin

Hormones released during sleep support the interaction of T-cells and what species

APCs

Sleep hormones shift the cytokine balance to which cytokine

Th1

Sleep hormone release supports formation of immune memory by initiating what immune response

Th1 immune responses

The immune systems of bacteria have enzymes that protect against infection by what kind of cells

bacteriophage

What are antimicrobial peptides that evolved as immune defense in eukaryotes called

defensins

The idea of acquired immunity in jawed vertebrates is the basis of what medical treatment

vaccination

What is the ability to recognize and adapt to new specific pathogens called

Adaptive (or acquired) immunity

Complement proteins bind to what kind of molecules on the surface of microbes in order to elicit an immune response

carbohydrates

The speed of the killing response of the human immune system is a product of what process

signal amplification

What type of cascade results when complement proteins bind to microbes and activate their protease activity

catalytic cascade

How can the deposition of compliment kill invader cells directly

disrupting their plasma membrane