Immunology

Immunology is a broad branch of biomedical science that covers the study of all aspects of the immune system in all organisms. It deals with, among other things, the physiological functioning of the immune system in states of both health and disease; malfunctions of the immune system in immunological disorders (autoimmune diseases, hypersensitivities, immune deficiency, transplant rejection); the physical, chemical and physiological characteristics of the components of the immune system in vitro, in situ, and in vivo. Immunology has applications in several disciplines of science, and as such is further divided.

Histological examination of the immune system

Even before the concept of immunity (from *immunis*, Latin for "exempt") was developed, numerous early physicians characterized organs that would later prove to be part of the immune system. The key primary lymphoid organs of the immune system are thymus and bone marrow, and secondary lymphatic tissues such as spleen, tonsils, lymph vessels, lymph nodes, adenoids, and skin. When health conditions warrant, immune system organs including the thymus, spleen, portions of bone marrow, lymph nodes and secondary lymphatic tissues can be surgically excised for examination while patients are still alive.

Many components of the immune system are actually cellular in nature and not associated with any specific organ but rather are embedded or circulating in various tissues located throughout the body.

Classical immunology

Classical immunology ties in with the fields of epidemiology and medicine. It studies the relationship between the body systems, pathogens, and immunity. The earliest written mention of immunity can be traced back to the plague of Athens in 430 BCE. 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. Many other ancient societies have references to this phenomenon, but it was not until the 19th and 20th centuries before the concept developed into scientific theory.

The study of the molecular and cellular components that comprise the immune system, including their function and interaction, is the central science of immunology. The immune system has been divided into a more primitive innate immune system, and acquired or adaptive immune system of vertebrates, the latter of which is further divided into humoral and cellular components.

The humoral (antibody) response is defined as the interaction between antibodies and antigens. Antibodies are specific proteins released from a certain class of immune cells (B lymphocytes). Antigens are defined as anything that elicits generation of antibodies,

hence they are **Anti**body **Gen**erators. Immunology itself rests on an understanding of the properties of these two biological entities. However, equally important is the cellular response, which can not only kill infected cells in its own right, but is also crucial in controlling the antibody response. Put simply, both systems are highly interdependent.

In the 21st century, immunology has broadened its horizons with much research being performed in the more specialized niches of immunology. This includes the immunological function of cells, organs and systems not normally associated with the immune system, as well as the function of the immune system outside classical models of immunity.

Clinical immunology

Clinical immunology is the study of diseases caused by disorders of the immune system (failure, aberrant action, and malignant growth of the cellular elements of the system). It also involves diseases of other systems, where immune reactions play a part in the pathology and clinical features.

The diseases caused by disorders of the immune system fall into two broad categories: immunodeficiency, in which parts of the immune system fail to provide an adequate response (examples include chronic granulomatous disease), and autoimmunity, in which the immune system attacks its own host's body (examples include systemic lupus erythematosus, rheumatoid arthritis, Hashimoto's disease and myasthenia gravis). Other immune system disorders include different hypersensitivities, in which the system responds inappropriately to harmless compounds (asthma and other allergies) or responds too intensely.

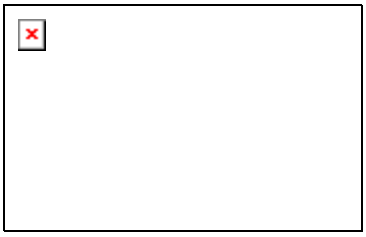
The most well-known disease that affects the immune system itself is AIDS, caused by HIV. AIDS is an immunodeficiency characterized by the lack of CD4+ ("helper") T cells and macrophages, which are destroyed by HIV.

Clinical immunologists also study ways to prevent transplant rejection, in which the immune system attempts to destroy allografts or xenografts.

Developmental Immunology

Adolescence is the age or biological time at which the human body starts to develop from an infantile form to a fully-grown adult. During this time several physical, physiological and immunological changes start to occur inside the developing human body. These changes are started and mediated by different hormones. Depending on the sex either testosterone or 17-β-oestradiol, act on male and female bodies accordingly, start acting at ages of 12 and 10 years (2). There is evidence that these steroids act directly not only on the primary and secondary sexual characteristics, but also have an effect on the development and regulation of the immune system (3). There is an increased risk in developing autoimmunity for pubescent and post pubescent females and males (4). There is also evidence of cell surface receptors on T cells and Macrophages that detect sex

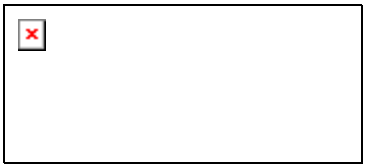
hormones in the system (5). The female sex hormone 17-β-oestradiol has been shown to regulate the level of immunological response (6). For example, compared to adult females, there is a greater drop in IgG levels than in those of IgA during the follicular phase of the menstrual cycle in adolescent females; also, other immune cells, like macrophages and Antigen Presenting Cells (APC), seem to respond to this fluctuation of 17-β-oestradiol, specifically in the mucosal layer on the womb of post pubescent females (7). It has been suggested that this level of control is achieved by the stimulation of peripheral blood monocytes cells (PBMC) by 17-β-oestradiol (7). Some male androgens, like testosterone, seem to suppress the stress response to infection; but other androgens like DeHydroepiandrosteron(DHEA) have the opposite effect, as it increases the immune response instead of down playing it (8). As in females, the male sex hormones seem to have more control of the immune system during puberty and the time right after than in fully developed adults. Other than hormonal changes physical changes like the involution of the Thymus during puberty will also affect the immunological response of the subject or patient (9). These differences occurring not only during development but also in sex hormones makes the development of vaccines or antitoxins extra challenging for the immunologist because it simply presents more variables to take into account at the time of designing and testing new treatment and vaccines (8)



The structure of DHEA

Neonates are said to be in a state of physiological immunodeficiency, because both their innate and adaptive immunological responses are greatly suppressed. In fact, many of the infections they acquire are caused by low virulence organisms like Staphylococcus and Pseudomonas. In neonates, opsonic activity and the ability to activate the complement cascade is very limited. For example, the mean level of C3 in a newborn is approximately 65% of that found in the adult. Phagocytic activity is also greatly impaired in newborns. This is not only due to lower opsonic activity, but mainly to a diminished up-regulation of integrin and selectin receptors, which limit the ability of neutrophils to interact with adhesion molecules in the endothelium. Their monocytes are slow and have a reduced ATP production, which also limits the newborns phagocitic activity. Although, the number of total lymphocytes is significantly higher than in adults, the cellular and humoral immunity is also impaired. Antigen presenting cells in newborns have a reduced capability to activate T cells. Also, T cells of a newborn proliferate poorly and produce very little amount, if any, of cytokines like IL-2, IL-4, IL-5, IL-12, and IFN-g which limits their capacity to activate the humoral response as well as the phagocitic activity of macrophage. B cells develop early in gestation but are not fully active. At birth most of the immunoglobulin present is maternal IgG. Because IgM, IgD, IgE and IgA don't cross the placenta, they are almost undetectable at birth. By breast feeding the mother provides

the newborn with some IgA. The passively acquired antibodies can protect the newborn up to 18 months, but their response is usually short-live and of low affinity (1).



Monocytes: An Artists Impression

The body's capability to react to antigen depends according to age (of the person), antigen type, maternal factors and the area where the antigen is presented. Once born, a child's immune system responds favorably to protein antigens while not as well to glycoproteins and polysaccharies. By 6-9 months after birth, a child's immune system begins to respond better (more strongly) to glycoproteins. Not until 12-24 months of age is there a marked improvement in the body's response to polysaccharides. This can be the reason for the specific time frames found in vaccination schedules [10]. Maternal factors also play a role in the body's immune response. As we know a child receives antibodies from the mother through breast milk and through the placenta. These antibodies have a beneficial and a negative response. If a child is exposed to the antibody for a particular antigen before being exposed to the antigen itself then the child will have a dampened response. According to Jaspen, the passively acquired maternal antibodies suppress the antibody response to active immunization [1] (We see it as not giving the child a chance to experience the antigen for itself; therefore the child is not exposed to as many antigen possibilities were it to experience the real thing). Similarly the response of T-cells to vaccination differs in children compared to adults. "Vaccines that induce Th1 responses in adults do not readily elicit neonatal TH1 responses" [1, 11]. Location where the antigen is found by the body is also an important factor. This is due to the ability (or lack thereof) of APC's to migrate to specific tissue. An example given is that when an antigen is presented in mucosa the local cells will have access to the antigen, and transfer that antigen to a central lymphatic node where it will be presented (simultaneously, APC's generally have a harder time reaching mucosa). Nevertheless, antigen found in the mucosa of the nasal cavity will induce a more wide spread response by activating both a mucosal and systemic response resulting in a response in the nasal lymphoid tissue, saliva and female genital tract [12]. In terms of general vaccination, the cellular response to live vaccines generally induces a stronger immune response unless the aforementioned circumstances are present.

Immunotherapy

Main article: Immunotherapy

The use of immune system components to treat a disease or disorder is known as immunotherapy. Immunotherapy is most commonly used in the context of the treatment of cancers together with chemotherapy (drugs) and radiotherapy (radiation). However, immunotherapy is also often used in the immunosuppressed (such as HIV patients) and people suffering from other immune deficiencies or autoimmune diseases.

Diagnostic immunology

Main article: Diagnostic immunology

The specificity of the bond between antibody and antigen has made it an excellent tool in the detection of substances in a variety of diagnostic techniques. Antibodies specific for a desired antigen can be conjugated with a radiolabel, fluorescent label, or color-forming enzyme and are used as a "probe" to detect it. However, the similarity between some antigens can lead to false positives and other errors in such tests by antibodies cross-reacting with antigens that aren't exact matches (13).

Evolutionary immunology

Study of the immune system in extant and extinct species is capable of giving us a key understanding of the evolution of species and the immune system.

A development of complexity of the immune system can be seen from simple phagocytotic protection of single celled organisms, to circulating antimicrobial peptides in insects to lymphoid organs in vertebrates. Of course, like much of evolutionary observation, these physical properties are often seen from the anthropocentric aspect. It should be recognized that every organism living today has an immune system absolutely capable of protecting it from most forms of harm; those organisms that did not adapt their immune systems to external threats are no longer around to be observed.

Insects and other arthropods, while not possessing true adaptive immunity, show highly evolved systems of innate immunity, and are additionally protected from external injury (and exposure to pathogens) by their chitinous shells.

Reproductive immunology

Reproductive immunology

This area of the immunology is devoted to the study of immunological aspects of the reproductive process including fetus acceptance. The term has also been used by fertility clinics to address fertility problems, recurrent miscarriages, premature deliveries, and dangerous complications such as pre-clampsia.

Thymus

In human anatomy, the **thymus** is an organ located in the upper anterior portion of the chest cavity just behind the sternum. The main function of the thymus is to provide an area for maturation, and is vital in protecting against autoimmunity.

The thymus was known to the Ancient Greeks. Galen was the first to note that the size of the organ changed over the duration of a person's life.[1]

Due to the large numbers of apoptotic lymphocytes, the thymus was originally dismissed as a "lymphocyte graveyard", without functional importance. The importance of the thymus in the immune system was discovered in 1961 by Jacques Miller, by surgically removing the thymus from three day old mice, and observing the subsequent deficiency in a lymphocyte population, subsequently named T cells after the organ of their origin.[2][3] Recently, advances in immunology have allowed the function of the thymus in T cell maturation to be more fully understood.

Function

In the two thymic lobes, lymphocyte precursors from the bone-marrow become thymocytes, and subsequently mature into T cells. Once mature, T cells emigrate from the thymus and constitute the peripheral T cell repertoire responsible for directing many facets of the adaptive immune system. Loss of the thymus at an early age through genetic mutation (as in DiGeorge Syndrome[4]) or surgical removal results in severe immunodeficiency and a high susceptibility to infection.[5]

The stock of T-lymphocytes is built up in early life, so the function of the thymus is diminished in adults. It is largely degenerated in elderly adults and is barely identifiable, consisting mostly of fatty tissue, but it continues to function as an endocrine gland important in stimulating the immune system.[6] Involution of the thymus has been linked to loss of immune function in the elderly, susceptibility to infection and to cancer.

The ability of T cells to recognize foreign antigens is mediated by the T cell receptor. The T cell receptor undergoes genetic rearrangement during thymocyte maturation, resulting in each T cell bearing a unique T cell receptor, specific to a limited set of peptide:MHC combinations. The random nature of the genetic rearrangement results in a requirement of central tolerance mechanisms to remove or inactivate those T cells which bear a T cell receptor with the ability to recognise self-peptides.

Phases of thymocyte maturation

The generation of T cells expressing distinct T cell receptors occurs within the thymus, and can be conceptually divided into three phases:

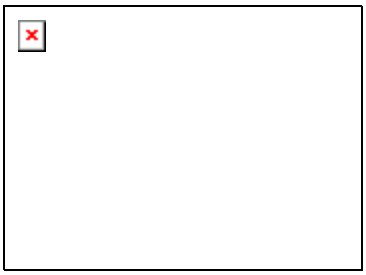
1. A rare population of hematopoietic progenitor cells enter the thymus from the blood, and expands by cell division to generate a large population of immature thymocytes.[7]
2. Immature thymocytes each make distinct T cell receptors by a process of gene rearrangement. This process is error-prone, and some thymocytes fail to make functional T cell receptors, whereas other thymocytes make T cell receptors that are autoreactive.[8] Growth factors include thymopoietin and thymosin.

3. Immature thymocytes undergo a process of selection, based on the specificity of their T cell receptors. This involves selection of T cells that are *functional (positive selection)*, and elimination of T cells that are *autoreactive (negative selection)*.

type:	**functional (positive selection)**	**autoreactive (negative selection)**
location:	cortex	medulla
Intrathymic T Cell Differentiation.JPG	In order to be *positively-selected*, thymocytes will have to interact with several cell surface molecules, MHC/HLA, to ensure reactivity and specificity[9]. Positive selection eliminates (apoptosis) weak binding cells and only takes high medium binding cells. (Binding refers to the ability of the T-cell receptors to bind to either MHC class I/II or peptide molecules.)	Negative selection is not 100% complete. Some autoreactive T cells escape thymic censorship, and are released into the circulation. Additional mechanisms of tolerance active in the periphery exist to silence these cells such as anergy, deletion, and regulatory T cells. If these peripheral tolerance mechanisms also fail, autoimmunity may arise.

Cells that pass both levels of selection are released into the bloodstream to perform vital immune functions.

Anatomy



anterior view of chest showing location and size of adult thymus

The thymus is of a pinkish-gray color, soft, and lobulated on its surfaces. At birth it is about 5 cm in length, 4 cm in breadth, and about 6 mm in thickness.[10] The organ enlarges during childhood, and atrophies at puberty. Unlike the liver, kidney and heart, for instance, the thymus is at its largest in children. The thymus reaches maximum weight (20 to 37 grams) by the time of puberty. It remains active only until puberty. Then with growing age, it starts to shrink. The thymus gland of older people is scarcely distinguishable from surrounding fatty tissue. As one ages the thymus slowly shrinks, eventually degenerating into tiny islands of fatty tissue. By the age of 75 years, the thymus gland weighs only 6 grams. In children the thymus is grayish-pink in colour and in adults it is yellow.

The thymus will, if examined when its growth is most active, be found to consist of two lateral lobes placed in close contact along the middle line, situated partly in the thorax, partly in the neck, and extending from the fourth costal cartilage upward, as high as the lower border of the thyroid gland. It is covered by the sternum, and by the origins of the sternohyoidei and sternothyreoidei.[10] Below, it rests upon the pericardium, being separated from the aortic arch and great vessels by a layer of fascia. In the neck, it lies on the front and sides of the trachea, behind the sternohyoidei and sternothyreoidei. The two lobes differ in size and may be united or separated.[10]

Development

Embryology

The two main components of the thymus, the lymphoid thymocytes and the thymic epithelial cells, have distinct developmental origins. The thymic epithelium is the first to develop, and appears in the form of two flask-shape endodermal diverticula, which arise, one on either side, from the third branchial pouch (pharyngeal pouch), and extend lateralward and backward into the surrounding mesoderm and neural crest-derived mesenchyme in front of the ventral aorta.

Here they meet and become joined to one another by connective tissue, but there is never any fusion of the thymus tissue proper. The pharyngeal opening of each diverticulum is soon obliterated, but the neck of the flask persists for some time as a cellular cord. By

further proliferation of the cells lining the flask, buds of cells are formed, which become surrounded and isolated by the invading mesoderm. Additional portions of thymus tissue are sometimes developed from the fourth branchial pouches. [11]

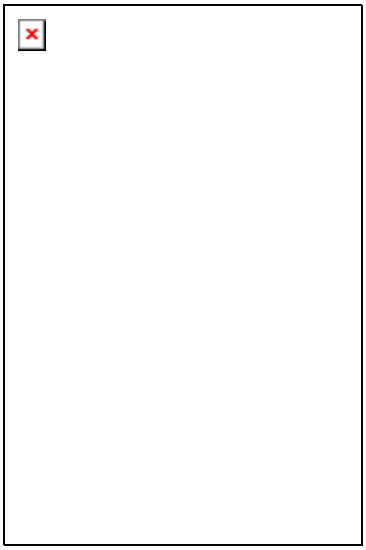
During the late stages of the development of the thymic epithelium, hematopoietic lymphoid cells from bone-marrow precursors migrate into the thymus and are aggregated to form lymphoid follicles.

The thymus continues to grow between birth and puberty and then begins to atrophy, a process directed by the high levels of circulating sex hormones. Proportional to thymic size, thymic activity (T cell output) is most active before puberty. Upon atrophy, the size and activity are dramatically reduced, and the organ is primarily replaced with fat (a phenomenon known as "organ involution"). The atrophy is due to the increased circulating level of sex hormones, and chemical or physical castration of an adult results in the thymus increasing in size and activity. [12] Patients with the autoimmune disease

Structure

Histology

Bone



Drawing of a human femur.

Bones are rigid organs that form part of the endoskeleton of vertebrates. They function to move, support, and protect the various organs of the body, produce red and white blood cells and store minerals. Bone tissue is a type of dense connective tissue. Because bones come in a variety of shapes and have a complex internal and external structure they are lightweight, yet strong and hard, in addition to fulfilling their many other functions. One of the types of tissue that makes up bone is the mineralized osseous tissue, also called bone tissue, that gives it rigidity and a honeycomb-like three-dimensional internal structure. Other types of tissue found in bones include marrow, endosteum and periosteum, nerves, blood vessels and cartilage. There are 206 bones in the adult human body[1] and 270 in an infant.[2]

Functions Bones have eleven main functions:

Mechanical

- Protection — Bones can serve to protect internal organs, such as the skull protecting the brain or the ribs protecting the heart and lungs.
- Shape — Bones provide a frame to keep the body supported.
- Movement — Bones, skeletal muscles, tendons, ligaments and joints function together to generate and transfer forces so that individual body parts or the whole body can be manipulated in three-dimensional space. The interaction between bone and muscle is studied in biomechanics.
- Sound transduction — Bones are important in the mechanical aspect of overshadowed hearing.

Synthetic

- Blood production — The marrow, located within the medullary cavity of long bones and interstices of cancellous bone, produces blood cells in a process called haematopoiesis.

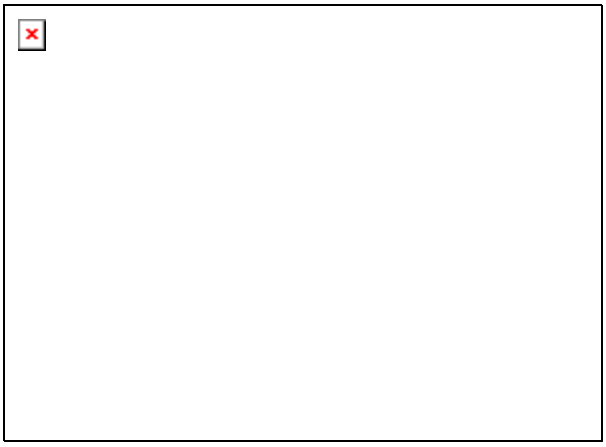
Metabolic

- Mineral storage — Bones act as reserves of minerals important for the body, most notably calcium and phosphorus.
- Growth factor storage — Mineralized bone matrix stores important growth factors such as insulin-like growth factors, transforming growth factor, bone morphogenetic proteins and others.
- Fat Storage — The yellow bone marrow acts as a storage reserve of fatty acids
- Acid-base balance — Bone buffers the blood against excessive pH changes by absorbing or releasing alkaline salts.
- Detoxification — Bone tissues can also store heavy metals and other foreign elements, removing them from the blood and reducing their effects on other tissues. These can later be gradually released for excretion.[*citation needed*]
- Endocrine organ - Bone controls phosphate metabolism by releasing fibroblast growth factor - 23 (FGF-23), which acts on kidney to reduce phosphate reabsorption.

Characteristics

The primary tissue of bone, osseous tissue, is a relatively hard and lightweight composite material, formed mostly of calcium phosphate in the chemical arrangement termed calcium hydroxylapatite (this is the osseous tissue that gives bones their rigidity). It has relatively high compressive strength but poor tensile strength of 104-121 MPa, meaning it resists pushing forces well, but not pulling forces. While bone is essentially brittle, it does have a significant degree of elasticity, contributed chiefly by collagen. All bones consist of living and dead cells embedded in the mineralized organic *matrix* that makes up the osseous tissue.

Bone marrow

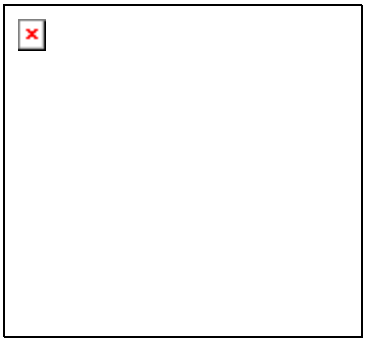


Gray's Anatomy illustration of cells in bone marrow

Bone marrow is the flexible tissue found in the hollow interior of bones. In adults, marrow in large bones produces new blood cells. It constitutes 4%[1] of total body weight, i.e. approximately 2.6 kg (5.7 lbs.) in adults.

Anatomy

Marrow types



A femur with a cortex of cortical bone and medulla of trabecular bone showing its red bone marrow and a focus of yellow bone marrow.

There are two types of bone marrow: **red marrow** (consisting mainly of myeloid tissue) and **yellow marrow** (consisting mainly of fat cells). Red blood cells, platelets and most white blood cells arise in red marrow. Both types of bone marrow contain numerous blood vessels and capillaries.

At birth, all bone marrow is red. With age, more and more of it is converted to the yellow type. About half of adult bone marrow is red.[1] Red marrow is found mainly in the flat bones, such as the hip bone, breast bone, skull, ribs, vertebrae and shoulder blades, and in the cancellous ("spongy") material at the epiphyseal ends of the long bones such as the

femur and humerus. Yellow marrow is found in the hollow interior of the middle portion of long bones.

In cases of severe blood periods, the body can convert yellow marrow back to red marrow to increase blood cell production.

Stroma

The *stroma of the bone marrow* is all tissue not directly involved in the primary function of hematopoiesis. The yellow bone marrow belongs here, and makes the majority of the bone marrow stroma, in addition to stromal cells located in the red bone marrow. Yellow bone marrow is found in the Medullary cavity.

Still, the stroma is indirectly involved in hematopoiesis, since it provides the *hematopoietic microenvironment* that facilitates hematopoiesis by the parenchymal cells. For instance, they generate colony stimulating factors, affecting hematopoiesis.

Cells that constitute the bone marrow stroma are:

- fibroblasts (reticular connective tissue)
- macrophages
- adipocytes
- osteoblasts
- osteoclasts
- endothelial cells forming the sinusoids

Macrophages contribute especially to red blood cell production. They deliver iron for hemoglobin-production.

Bone marrow barrier

The blood vessels constitute a barrier, inhibiting immature blood cells from leaving the bone marrow. Only mature blood cells contain the membrane proteins required to attach to and pass the blood vessel endothelium.

Hematopoietic stem cells may also cross the bone marrow barrier, and may thus be harvested from blood .

Stem cells

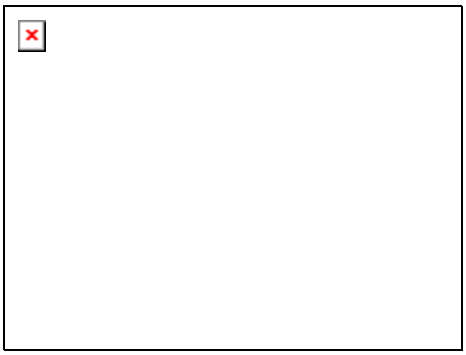
Mesenchymal stem cell

The bone marrow stroma contain *mesenchymal stem cells* (also called *marrow stromal cells*). These cells are multipotent stem cells that can differentiate into a variety of cell types. Cell types that MSCs have been shown to differentiate into in vitro or in vivo include osteoblasts, chondrocytes, myocytes, adipocytes, and, as described lately, beta-pancreatic islets cells. They can also transdifferentiate into neuronal cells.

Compartmentalization

There is biologic compartmentalization in the bone marrow, in that certain cell types tend to aggregate in specific areas. For instance, erythrocytes, macrophages and their precursors tend to gather around blood vessels, while granulocytes gather at the borders of the bone marrow.

Types of stem cells



Hematopoietic precursor cells: promyelocyte in the center, two metamyelocytes next to it and band cells from a bone marrow aspirate.

Bone marrow contains three types of stem cells:[2]

- Hematopoietic stem cells give rise to the three classes of blood cells that are found in the circulation: white blood cells (leukocytes), red blood cells (erythrocytes), and platelets (thrombocytes).
- Mesenchymal stem cells are found arrayed around the central sinus in the bone marrow. They have the capability to differentiate into osteoblasts, chondrocytes, myocytes, and many other types of cells. They also function as "gatekeeper" cells of the bone marrow.
- Endothelial stem cells

Diseases involving the bone marrow

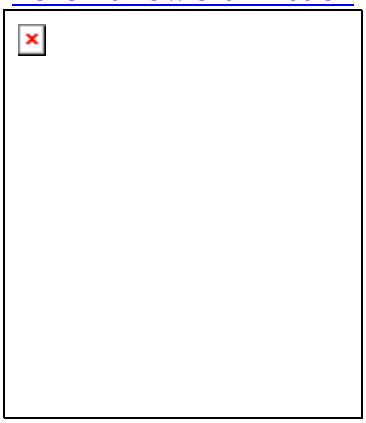
The normal bone marrow architecture can be displaced by malignancies or infections such as tuberculosis, leading to a decrease in the production of blood cells and blood platelets. In addition, cancers of the hematologic progenitor cells in the bone marrow can arise; these are the leukemias.

To diagnose diseases involving the bone marrow, a bone marrow aspiration is sometimes performed. This typically involves using a hollow needle to acquire a sample of red bone marrow from the crest of the ilium under general or local anesthesia. The average number of cells in a leg bone is about 440,000,000,000 (440×10^9).

Exposure to radiation or chemotherapy will kill many of the rapidly dividing cells of the bone marrow and will therefore result in a depressed immune system. Many of the symptoms of radiation sickness are due to damage to the bone marrow cells.

Examination

Bone marrow examination

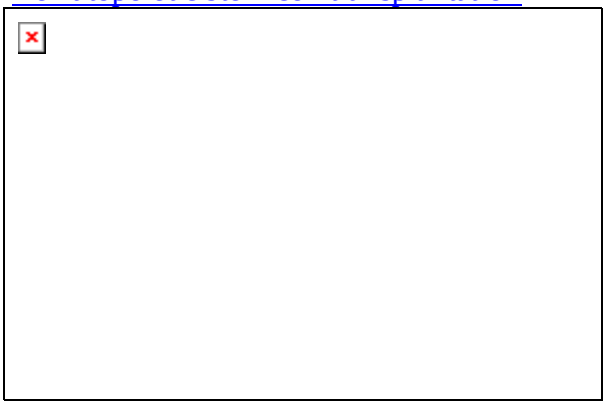


A Wright's stained bone marrow aspirate smear from a patient with leukemia.

Bone marrow examination is the pathologic analysis of samples of bone marrow obtained by *bone marrow biopsy* and *bone marrow aspiration*. Bone marrow examination is used in the diagnosis of a number of conditions, including leukemia, multiple myeloma, anemia, and pancytopenia. The bone marrow produces the cellular elements of the blood, including platelets, red blood cells and white blood cells. While much information can be gleaned by testing the blood itself (drawn from a vein by phlebotomy), it is sometimes necessary to examine the source of the blood cells in the bone marrow to obtain more information on hematopoiesis; this is the role of bone marrow aspiration and biopsy.

Donation and transplantation of bone marrow

Hematopoietic stem cell transplantation



Bone marrow harvest

It is possible to take hematopoietic stem cells from one person and then infuse them into another person (Allogenic) or into the same person at a later time (Autologous). If donor and recipient are compatible, these infused cells will then travel to the bone marrow and initiate blood cell production.

Transplantation from one person to another is performed in severe cases of disease of the bone marrow. The patient's marrow is first killed off with drugs or radiation, and then the new stem cells are introduced.

Before radiation therapy or chemotherapy in cases of cancer, some of the patient's hematopoietic stem cells are sometimes harvested and later infused back when the therapy is finished to restore the immune system.

Harvesting

The stem cells are harvested directly from the red marrow in the crest of the ilium, often under general anesthesia. The procedure is minimally invasive and does not require stitches afterwards. Depending on the donor health and reaction to the procedure, the actual harvesting can be an outpatient procedure or requiring 1–2 days of recovery in the hospital.[3] Another option is to administer certain drugs that stimulate the release of stem cells from the bone marrow into circulating blood.[4] An IV is inserted into the donor's arm, and the stem cells are filtered out of the blood. The procedure is similar to donating blood or platelets.

It may also be taken from the sternum. The tibia may seem a good source, since it is very superficial. However, except in children, this bone marrow does not contain any substantial amount of red bone marrow, only yellow bone marrow.[1]

In newborns, stem cells may be retrieved from the umbilical cord.[5]

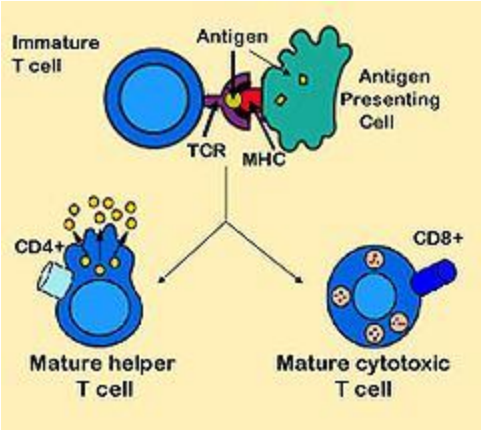
Bone marrow as a food

Many cultures utilize bone marrow as a food. The Vietnamese prize bone as the soup base for their national staple *phở*; Alaskan Natives eat the bone marrow of caribou and moose; Indians use slow-cooked marrow as the core ingredient of the Indian dish Nalli Nihari; Mexicans use beef bone marrow from leg bones, called tuetano, which is cooked and served as filling for tacos or tostadas; it is also considered to be the highlight of the Italian dish ossobuco (braised veal shanks). Though once used in various preparations, including pemmican, bone marrow has fallen out of favor as a food in the United States. In the Philippines, the soup "Bulalo" is made primarily of beef stock and marrow bones, seasoned with choice vegetables and boiled meat.

Diners in the 18th century used a marrow scoop (or marrow spoon), often of silver and with a long thin bowl, as a table implement for removing marrow from a bone.

Some anthropologists believe that early humans were scavengers rather than hunters. Marrow would then have been a major protein source for tool-using hominids, who were able to crack open the bones of carcasses left by top predators such as lions.[6]

Antigen-presenting cell



Antigen presentation stimulates T cells to become either "cytotoxic" CD8+ cells or "helper" CD4+ cells.
See also: Antigen presentation

An **antigen-presenting cell** (**APC**) or **accessory cell** is a cell that displays foreign antigen complex with major histocompatibility complex (MHC) on its surface. T-cells may recognize this complex using their T-cell receptor (TCR).

Types

APCs fall into two categories: professional or non-professional.

Most cells in the body can present antigen to $CD8^+$ T cells via MHC class I molecules and, thus, act as "APCs"; however, the term is often limited to those specialized cells that can prime T cells (i.e., activate a T cell that has not been exposed to antigen, termed a *naive T cell*). These cells, in general, express MHC class II as well as MHC class I molecules, and can stimulate $CD4^+$ ("helper") cells as well as $CD8^+$ ("cytotoxic") T cells, respectively.

To help distinguish between the two types of APCs, those that express MHC class II molecules are often called **professional antigen-presenting cells**.

Professional APCs

These professional APCs are very efficient at internalizing antigen, either by phagocytosis or by receptor-mediated endocytosis, and then displaying a fragment of the antigen, bound to a class II MHC molecule, on their membrane. The T cell recognizes and interacts with the antigen-class II MHC molecule complex on the membrane of the antigen-presenting cell. An additional co-stimulatory signal is then produced by the antigen-presenting cell, leading to activation of the T cell.

There are three main types of professional antigen-presenting cell:

- Dendritic cells, which have the broadest range of antigen presentation, and are probably the most important APC. Activated DCs are especially potent T_H cell activators because, as part of their composition, they express co-stimulatory molecules such as B7.
- Macrophages, which are also CD4+ and are therefore also susceptible to infection by HIV.
- B-cells, which expresses (as B cell receptor)and secretes a specific antibody, , can internalize the antigen which bind to its BCR and present it incorporated to MHC II molecule, but are inefficient APC for most other antigens.
- Certain activated epithelial cells

Non-professional

A non-professional APC does not constitutively express the Major histocompatibility complex proteins required for interaction with naive T cells; these are expressed only upon stimulation of the non-professional APC by certain cytokines such as IFN-γ. Non-professional APCs include:

- Fibroblasts (skin)
- Thymic epithelial cells
- Thyroid epithelial cells
- Glial cells (brain)
- Pancreatic beta cells
- Vascular endothelial cells

Interaction with T cells

After the APCs phagocytose pathogens, they usually migrate to the vast networks of lymph vessels and are carried via lymph flow to the draining lymph nodes (this network is collectively known as the Lymphatic system). The lymph nodes become a collection point to which APCs such as dendritic cells can interact with T cells. They do this by chemotaxis, which involves interacting with Chemokines that are expressed on the surface of cells (e.g., endothelial cells of the high endothelial venules) or have been released as chemical messengers to draw the APCs to the lymph nodes. During the migration, DCs undergo a process of maturation; in essence, they lose most of their ability to further engulf pathogens, and they develop an increased ability to communicate

with T cells. Enzymes within the cell digest the swallowed pathogen into smaller pieces containing epitopes, which are then presented to T cells using MHC.

Recent research indicates that only certain epitopes of a pathogen are presented because they are immunodominant, possibly as a function of their binding affinity to the MHC. The stronger binding affinity allows the complex to remain kinetically stable long enough to be recognized by T cells.

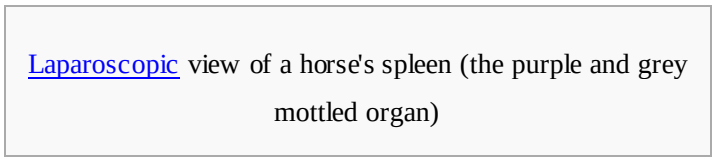
Spleen

Spleen

Illu spleen.jpg

Spleen

Horse spleen laparoscopic.jpg



Laparoscopic view of a horse's spleen (the purple and grey mottled organ)

The **spleen** is an organ found in all vertebrate animals with important roles in regard to red blood cells and the immune system.[1] In humans, it is located in the left upper quadrant of the abdomen. It removes old red blood cells, holds a reserve in case of hemorrhagic shock, especially in animals like horses (not in humans) and recycles iron.[2] It synthesizes antibodies in its white pulp, removes from the circulation antibody-coated bacteria and antibody-coated blood cells.[2][3] Recently it has been found to contain in reserve half the body's monocytes in its red pulp that upon moving to injured tissue such as the heart turn into dendritic cells and macrophages and aid wound healing.[4][5][6] It is one of the centers of activity of the reticuloendothelial system, and can be considered analogous to a large lymph node. Its absence leads to a predisposition to certain infections.[7]

Anatomy

The spleen is found in the upper left quadrant of the human abdomen. Spleens in healthy adult humans are approximately 11 centimeters in length. It usually weighs 150 grams and lies beneath the 9th to the 12th rib.[8]

Like the thymus, the spleen possesses only efferent lymphatic vessels.

The spleen is part of the lymphatic system.

The germinal centers are supplied by arterioles called *penicilliary radicles*.[9]

The spleen is unique with respect to its development within the gut. While most of the gut viscera are endodermally derived (with the exception of the neural-crest derived suprarenal gland), the spleen is derived from mesenchymal tissue [10]. Specifically, the spleen forms within and from the dorsal mesentery. However, it still shares the same blood supply—the celiac trunk--as the foregut organs.

Function

Area	Function	Composition
red pulp	Mechanical filtration of red blood cells. Reserve of monocytes[4]	• "sinuses" (or "sinusoids") which are filled with blood • "splenic cords" of reticular fibers • "marginal zone" bordering on white

		pulp
white pulp	Active immune response through humoral and cell-mediated pathways.	Composed of nodules, called Malpighian corpuscles. These are composed of: • "lymphoid follicles" (or "follicles"), rich in B-lymphocytes • "periarteriolar lymphoid sheaths" (PALS), rich in T-lymphocytes

Other functions of the spleen are less prominent, especially in the healthy adult:

- Production of opsonins, properdin, and tuftsin.
- Creation of red blood cells. While the bone marrow is the primary site of hematopoeisis in the adult, the spleen has important hematopoietic functions up until the fifth month of gestation. After birth, erythropoietic functions cease except in some hematologic disorders. As a major lymphoid organ and a central player in the reticuloendothelial system the spleen retains the ability to produce lymphocytes and, as such, remains an hematopoietic organ.
- Storage of red blood cells and other formed elements. In horses roughly 30% of the red blood cells are stored there. The red blood cells can be released when needed.[11] In humans, it does not act as a reservoir of blood cells.[12] It can also store platelets in case of an emergency.
- Storage of half the body's monocytes so that upon injury they can migrate to the injured tissue and transform into dendritic cells and macrophages and so assist wound healing.[4]

Effect of removal

Asplenia

Surgical removal causes:[5]

- modest increases in circulating white blood cells and platelets,
- diminished responsiveness to some vaccines,
- increased susceptibility to infection by bacteria and protozoa

A 28 year follow up of 740 veterans of World War II found that those who had been splenectomised showed a significant excess mortality from pneumonia (6 from expected 1.3) and ischaemic heart-disease (41 from expected 30) but not other conditions.[13]

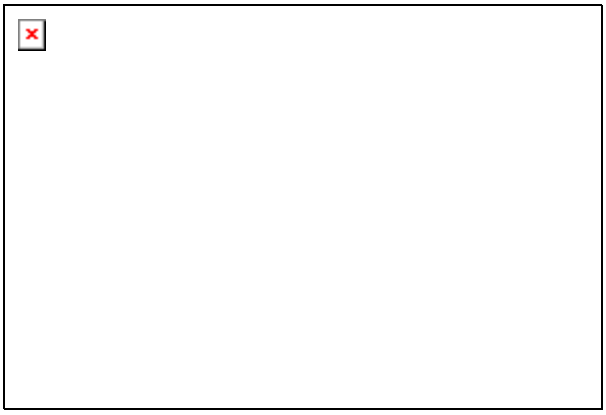
Disorders

Splenic disease

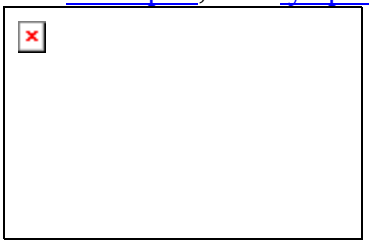
Disorders include splenomegaly, where the spleen is enlarged for various reasons, and asplenia, where the spleen is not present or functions abnormally.

Blood

Blood



Human blood smear:
a — erythrocytes; b — neutrophil;
c — eosinophil; d — lymphocyte.



A scanning electron microscope (SEM) image of a normal red blood cell, a platelet, and a white blood cell.

Blood is a specialized bodily fluid that delivers necessary substances to the body's cells — such as nutrients and oxygen — and transports waste products away from those same cells.

In vertebrates, it is composed of blood cells suspended in a liquid called blood plasma. Plasma, which comprises 55% of blood fluid, is mostly water (90% by volume),[1] and contains dissolved proteins, glucose, mineral ions, hormones, carbon dioxide (plasma being the main medium for excretory product transportation), platelets and blood cells themselves. The blood cells present in blood are mainly red blood cells (also called RBCs

or erythrocytes) and white blood cells, including leukocytes and platelets. The most abundant cells in vertebrate blood are red blood cells. These contain hemoglobin, an iron-containing protein, which facilitates transportation of oxygen by reversibly binding to this respiratory gas and greatly increasing its solubility in blood. In contrast, carbon dioxide is almost entirely transported extracellularly dissolved in plasma as bicarbonate ion.

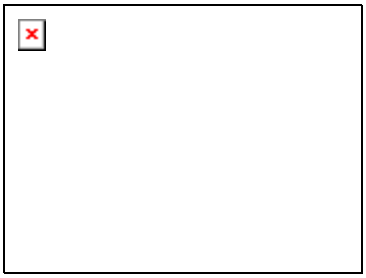
Vertebrate blood is bright red when its hemoglobin is oxygenated. Some animals, such as crustaceans and mollusks, use hemocyanin to carry oxygen, instead of hemoglobin. Insects and some molluscs use a fluid called hemolymph instead of blood, the difference being that hemolymph is not contained in a closed circulatory system. In most insects, this "blood" does not contain oxygen-carrying molecules such as hemoglobin because their bodies are small enough for their tracheal system to suffice for supplying oxygen.

Jawed vertebrates have an adaptive immune system, based largely on white blood cells. White blood cells help to resist infections and parasites. Platelets are important in the clotting of blood.[2] Arthropods, using hemolymph, have hemocytes as part of their immune system.

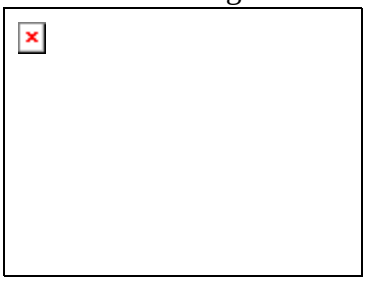
Blood is circulated around the body through blood vessels by the pumping action of the heart. In animals having lungs, arterial blood carries oxygen from inhaled air to the tissues of the body, and venous blood carries carbon dioxide, a waste product of metabolism produced by cells, from the tissues to the lungs to be exhaled.

Medical terms related to blood often begin with ***hemo-*** or ***hemato-*** (also spelled ***haemo-*** and ***haemato-***) from the Ancient Greek word αἷμα (*haima*) for "blood". In terms of anatomy and histology, blood is considered a specialized form of connective tissue, given its origin in the bones and the presence of potential molecular fibers in the form of fibrinogen.

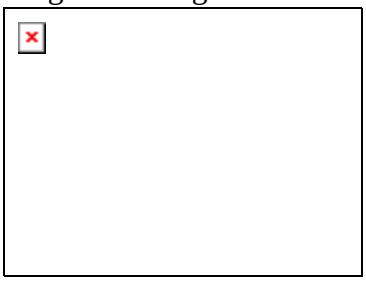
Blood circulation:
Red = oxygenated
Blue = deoxygenated



Human blood magnified 600 times

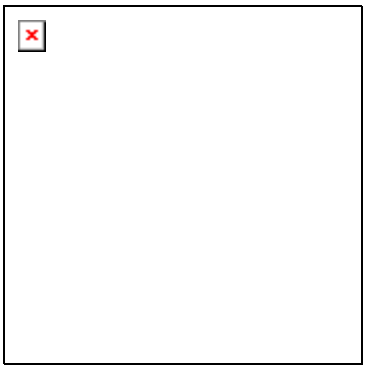


Frog blood magnified 600 times

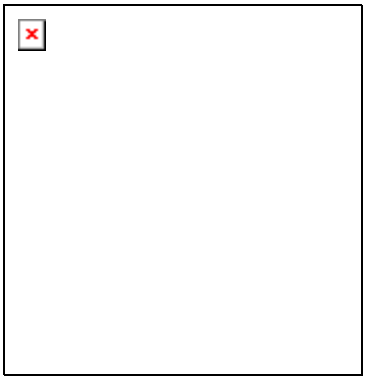


Fish blood magnified 600 times

Functions



Hemoglobin
green = heme groups
red & blue = protein subunits

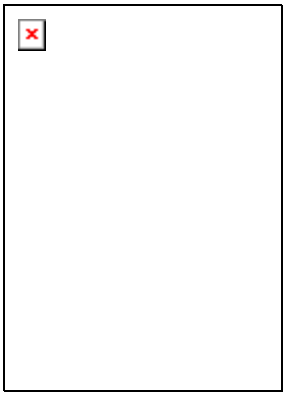


Heme

Blood performs many important functions within the body including:

- Supply of oxygen to tissues (bound to hemoglobin, which is carried in red cells)
- Supply of nutrients such as glucose, amino acids, and fatty acids (dissolved in the blood or bound to plasma proteins (e.g., blood lipids)
- Removal of waste such as carbon dioxide, urea, and lactic acid
- Immunological functions, including circulation of white blood cells, and detection of foreign material by antibodies
- Coagulation, which is one part of the body's self-repair mechanism
- Messenger functions, including the transport of hormones and the signaling of tissue damage
- Regulation of body pH (the normal pH of blood is in the range of 7.35–7.45)[3] (covering only 0.1 pH unit)
- Regulation of core body temperature
- Hydraulic functions

Constituents of human blood



Two tubes of EDTA-anticoagulated blood.
Left tube: after standing, the RBCs have settled at the bottom of the tube.
Right tube: contains freshly drawn blood.

Blood accounts for 7% of the human body weight,[4] with an average density of approximately 1060 kg/m^3, very close to pure water's density of 1000 kg/m^3.[5] The average adult has a blood volume of roughly 5 liters (1.3 gal), composed of plasma and several kinds of cells (occasionally called *corpuscles*); these formed elements of the blood are erythrocytes (red blood cells), leukocytes (white blood cells), and thrombocytes (platelets). By volume, the red blood cells constitute about 45% of whole blood, the plasma about 54.3%, and white cells about 0.7%.

Whole blood (plasma and cells) exhibits non-Newtonian fluid dynamics; its flow properties are adapted to flow effectively through tiny capillary blood vessels with less resistance than plasma by itself. In addition, if all human hemoglobin were free in the plasma rather than being contained in RBCs, the circulatory fluid would be too viscous for the cardiovascular system to function effectively.

Cells

One microliter of blood contains:

- **4.7 to 6.1 million (male), 4.2 to 5.4 million (female) erythrocytes:**[6] In mammals, mature red blood cells lack a nucleus and organelles. They contain the blood's hemoglobin and distribute oxygen. The red blood cells (together with endothelial vessel cells and other cells) are also marked by glycoproteins that define the different blood types. The proportion of blood occupied by red blood cells is referred to as the hematocrit, and is normally about 45%. The combined surface area of all red blood cells of the human body would be roughly 2,000 times as great as the body's exterior surface.[7]
- **4,000–11,000 leukocytes:**[8] White blood cells are part of the immune system; they destroy and remove old or aberrant cells and cellular debris, as well as attack infectious agents (pathogens) and foreign substances. The cancer of leukocytes is called leukemia.
- **200,000–500,000 thrombocytes:**[8] thrombocytes, also called platelets, are responsible for blood clotting (coagulation). They change fibrinogen into fibrin. This fibrin creates a mesh onto which red blood cells collect and clot, which then stops more blood from leaving the body and also helps to prevent bacteria from entering the body.

Constitution of normal blood

Parameter	Value
Hematocrit	45 ± 7 (38–52%) for males 42 ± 5 (37–47%) for females
pH	7.35–7.45
base excess	−3 to +3
PO_2	10–13 kPa (80–100 mm Hg)

Plasma

PCO_2	4.8–5.8 kPa (35–45 mm Hg)
HCO_3^-	21–27 mM
Oxygen saturation	Oxygenated: 98–99% Deoxygenated: 75%

About 55% of whole blood is blood plasma, a fluid that is the blood's liquid medium, which by itself is straw-yellow in color. The blood plasma volume totals of 2.7–3.0 litres (2.8–3.2 quarts) in an average human. It is essentially an aqueous solution containing 92% water, 8% blood plasma proteins, and trace amounts of other materials. Plasma circulates dissolved nutrients, such as glucose, amino acids, and fatty acids (dissolved in the blood or bound to plasma proteins), and removes waste products, such as carbon dioxide, urea, and lactic acid.

Other important components include:

- Serum albumin
- Blood-clotting factors (to facilitate coagulation)
- Immunoglobulins (antibodies)
- lipoprotein particles
- Various other proteins
- Various electrolytes (mainly sodium and chloride)

The term **serum** refers to plasma from which the clotting proteins have been removed. Most of the proteins remaining are albumin and immunoglobulins.

The normal pH of human arterial blood is approximately 7.40 (normal range is 7.35–7.45), a weakly alkaline solution. Blood that has a pH below 7.35 is too acidic, whereas blood pH above 7.45 is too alkaline. Blood pH, partial pressure of oxygen (pO_2), partial pressure of carbon dioxide (pCO_2), and HCO_3 are carefully regulated by a number of homeostatic mechanisms, which exert their influence principally through the respiratory system and the urinary system in order to control the acid-base balance and respiration. Plasma also circulates hormones transmitting their messages to various tissues. The list of normal reference ranges for various blood electrolytes is extensive.

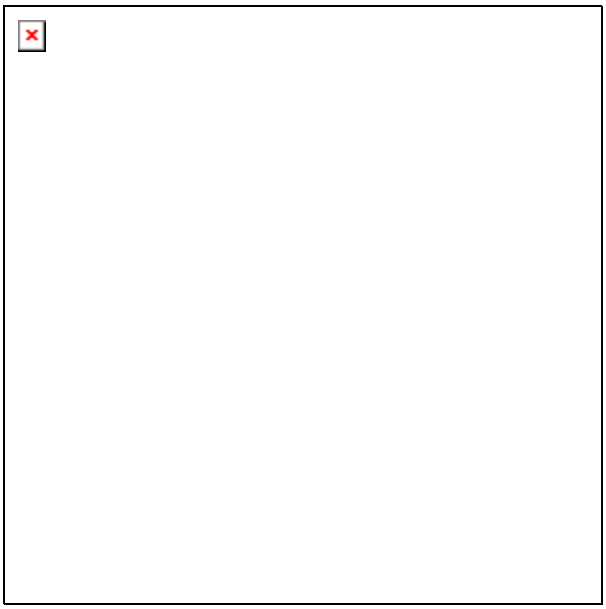
Blood in non-human vertebrates

Human blood is, in most respects, typical of that of mammals, although the precise details concerning cell numbers, size, protein structure, and so on, vary somewhat between species. In non-mammalian vertebrates, however, there are some key differences:[9]

- Red blood cells of non-mammalian vertebrates are flattened and ovoid in form, and retain their cell nuclei
- There is considerable variation in the types and proportions of white blood cells; for example, acidophils are generally more common than in humans
- Platelets are unique to mammals; in other vertebrates, small, nucleated, **spindle cells** are responsible for blood clotting instead

Physiology

Cardiovascular system



The circulation of blood through the human heart
Circulatory system

Blood is circulated around the body through blood vessels by the pumping action of the heart. In humans, blood is pumped from the strong left ventricle of the heart through arteries to peripheral tissues and returns to the right atrium of the heart through veins. It then enters the right ventricle and is pumped through the pulmonary artery to the lungs and returns to the left atrium through the pulmonary veins. Blood then enters the left ventricle to be circulated again. Arterial blood carries oxygen from inhaled air to all of the cells of the body, and venous blood carries carbon dioxide, a waste product of metabolism by cells, to the lungs to be exhaled. However, one exception includes pulmonary arteries, which contain the most deoxygenated blood in the body, while the pulmonary veins contain oxygenated blood.

Additional return flow may be generated by the movement of skeletal muscles, which can compress veins and push blood through the valves in veins toward the right atrium.

The blood circulation was famously described by William Harvey in 1628.[10]

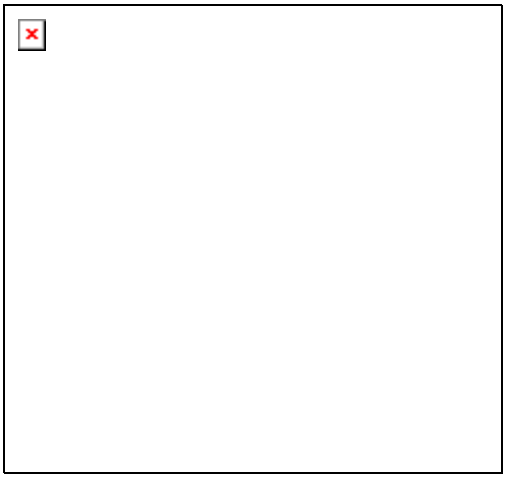
Production and degradation of blood cells

In vertebrates, the various cells of blood are made in the bone marrow in a process called hematopoiesis, which includes erythropoiesis, the production of red blood cells; and myelopoiesis, the production of white blood cells and platelets. During childhood, almost every human bone produces red blood cells; as adults, red blood cell production is limited

to the larger bones: the bodies of the vertebrae, the breastbone (sternum), the ribcage, the pelvic bones, and the bones of the upper arms and legs. In addition, during childhood, the thymus gland, found in the mediastinum, is an important source of lymphocytes.[11] The proteinaceous component of blood (including clotting proteins) is produced predominantly by the liver, while hormones are produced by the endocrine glands and the watery fraction is regulated by the hypothalamus and maintained by the kidney.

Healthy erythrocytes have a plasma life of about 120 days before they are degraded by the spleen, and the Kupffer cells in the liver. The liver also clears some proteins, lipids, and amino acids. The kidney actively secretes waste products into the urine.

Oxygen transport



Basic hemoglobin saturation curve. It is moved to the right in higher acidity (more dissolved carbon dioxide) and to the left in lower acidity (less dissolved carbon dioxide)

About 98.5% of the oxygen in a sample of arterial blood in a healthy human breathing air at sea-level pressure is chemically combined with the Hgb. About 1.5% is physically dissolved in the other blood liquids and not connected to Hgb. The hemoglobin molecule is the primary transporter of oxygen in mammals and many other species (for exceptions, see below). Hemoglobin has an oxygen binding capacity of between 1.36 and 1.37 ml O_2 per gram Hemoglobin,[12] which increases the total blood oxygen capacity seventyfold,[13] compared to if oxygen solely was carried by its solubility of 0.03 mL O_2 per litre blood per mmHg partial pressure of oxygen (approximately 100 mmHg in arteries).[13]

With the exception of pulmonary and umbilical arteries and their corresponding veins, arteries carry oxygenated blood away from the heart and deliver it to the body via arterioles and capillaries, where the oxygen is consumed; afterwards, venules, and veins carry deoxygenated blood back to the heart.

Under normal conditions in humans at rest, hemoglobin in blood leaving the lungs is about 98–99% saturated with oxygen. In a healthy adult at rest, *deoxygenated* blood

returning to the lungs is still approximately 75% saturated.[14][15] Increased oxygen consumption during sustained exercise reduces the oxygen saturation of venous blood, which can reach less than 15% in a trained athlete; although breathing rate and blood flow increase to compensate, oxygen saturation in arterial blood can drop to 95% or less under these conditions.[16] Oxygen saturation this low is considered dangerous in an individual at rest (for instance, during surgery under anesthesia. Sustained hypoxia (oxygenation of less than 90%), is dangerous to health, and severe hypoxia (saturations of less than 30%) may be rapidly fatal.[17]

A fetus, receiving oxygen via the placenta, is exposed to much lower oxygen pressures (about 21% of the level found in an adult's lungs), and, so, fetuses produce another form of hemoglobin with a much higher affinity for oxygen (hemoglobin F) in order to function under these conditions.[18]

Carbon dioxide transport

When blood flows through capillaries, carbon dioxide diffuses from the tissues into the blood. Some carbon dioxide is dissolved in the blood. Some carbon dioxide reacts with hemoglobin and other proteins to form carbamino compounds. The remaining carbon dioxide is converted to bicarbonate and hydrogen ions through the action of RBC carbonic anhydrase. Most carbon dioxide is transported through the blood in the form of bicarbonate ions.

Carbon dioxide (CO_2), the main cellular waste product is carried in blood mainly dissolved in plasma, in equilibrium with bicarbonate (HCO_3^-) and carbonic acid (H_2CO_3). 86–90% of CO_2 in the body is converted into carbonic acid, which can quickly turn into bicarbonate, the chemical equilibrium being important in the pH buffering of plasma.[19] Blood pH is kept in a narrow range (pH between 7.35 and 7.45).[20]

Transport of hydrogen ions

Some oxyhemoglobin loses oxygen and becomes deoxyhemoglobin. Deoxyhemoglobin binds most of the hydrogen ions as it has a much greater affinity for more hydrogen than does oxyhemoglobin.

Lymphatic system

Lymphatic system

In mammals, blood is in equilibrium with lymph, which is continuously formed in tissues from blood by capillary ultrafiltration. Lymph is collected by a system of small lymphatic vessels and directed to the thoracic duct, which drains into the left subclavian vein where lymph rejoins the systemic blood circulation.

Thermoregulation

Blood circulation transports heat throughout the body, and adjustments to this flow are an important part of thermoregulation. Increasing blood flow to the surface (e.g., during warm weather or strenuous exercise) causes warmer skin, resulting in faster heat loss. In contrast, when the external temperature is low, blood flow to the extremities and surface of the skin is reduced and to prevent heat loss and is circulated to the important organs of the body, preferentially.

Hydraulic functions

The restriction of blood flow can also be used in specialized tissues to cause engorgement, resulting in an erection of that tissue; examples are the erectile tissue in the penis, nipples, and clitoris.

Another example of a hydraulic function is the jumping spider, in which blood forced into the legs under pressure causes them to straighten for a powerful jump, without the need for bulky muscular legs.[21]

Invertebrates

In insects, the blood (more properly called hemolymph) is not involved in the transport of oxygen. (Openings called tracheae allow oxygen from the air to diffuse directly to the tissues). Insect blood moves nutrients to the tissues and removes waste products in an open system.

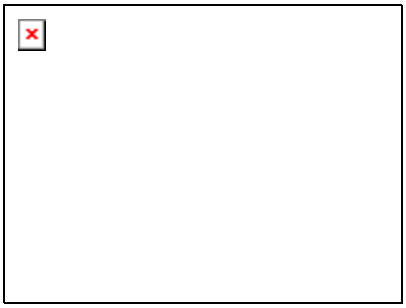
Other invertebrates use respiratory proteins to increase the oxygen-carrying capacity. Hemoglobin is the most common respiratory protein found in nature. Hemocyanin (blue) contains copper and is found in crustaceans and mollusks. It is thought that tunicates (sea squirts) might use vanabins (proteins containing vanadium) for respiratory pigment (bright-green, blue, or orange).

In many invertebrates, these oxygen-carrying proteins are freely soluble in the blood; in vertebrates they are contained in specialized red blood cells, allowing for a higher concentration of respiratory pigments without increasing viscosity or damaging blood filtering organs like the kidneys.

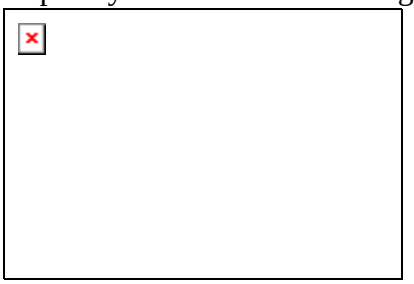
Giant tube worms have unusual hemoglobins that allow them to live in extraordinary environments. These hemoglobins also carry sulfides normally fatal in other animals.

Color

Hemoglobin



Capillary blood from a bleeding finger



Venous blood collected during blood donation

Hemoglobin is the principal determinant of the color of blood in vertebrates. Each molecule has four heme groups, and their interaction with various molecules alters the exact color. In vertebrates and other hemoglobin-using creatures, arterial blood and capillary blood are bright red, as oxygen imparts a strong red color to the heme group. Deoxygenated blood is a darker shade of red; this is present in veins, and can be seen during blood donation and when venous blood samples are taken. Blood in carbon monoxide poisoning is bright red, because carbon monoxide causes the formation of carboxyhemoglobin. In cyanide poisoning, the body cannot utilize oxygen, so the venous blood remains oxygenated, increasing the redness. While hemoglobin-containing blood is never blue, there are several conditions and diseases wherein the color of the heme groups make the skin appear blue. If the heme is oxidized, methaemoglobin, which is more brownish and cannot transport oxygen, is formed. In the rare condition sulfhemoglobinemia, arterial hemoglobin is partially oxygenated, and appears dark red with a bluish hue (cyanosis).

Veins in the skin appear blue for a variety of reasons only weakly dependent on the color of the blood. Light scattering in the skin, and the visual processing of color play roles as well.[22]

Skinks in the genus *Prasinohaema* have green blood due to a buildup of the waste product biliverdin.[23]

Hemocyanin

The blood of most molluscs — including cephalopods and gastropods — as well as some arthropods, such as horseshoe crabs, is blue, as it contains the copper-containing protein

hemocyanin at concentrations of about 50 grams per litre.[24] Hemocyanin is colorless when deoxygenated and dark blue when oxygenated. The blood in the circulation of these creatures, which generally live in cold environments with low oxygen tensions, is grey-white to pale yellow,[24] and it turns dark blue when exposed to the oxygen in the air, as seen when they bleed.[24] This is due to change in color of hemocyanin when it is oxidized.[24] Hemocyanin carries oxygen in extracellular fluid, which is in contrast to the intracellular oxygen transport in mammals by hemoglobin in RBCs.[24]

Pathology

General medical disorders

- Disorders of volume
  - Injury can cause blood loss through bleeding.[25] A healthy adult can lose almost 20% of blood volume (1L) before the first symptom, restlessness, begins, and 40% of volume (2L) before shock sets in. Thrombocytes are important for blood coagulation and the formation of blood clots, which can stop bleeding. Trauma to the internal organs or bones can cause internal bleeding, which can sometimes be severe.
  - Dehydration can reduce the blood volume by reducing the water content of the blood. This would rarely result in shock (apart from the very severe cases) but may result in orthostatic hypotension and fainting.
- Disorders of circulation
  - Shock is the ineffective perfusion of tissues, and can be caused by a variety of conditions including blood loss, infection, poor cardiac output.
  - Atherosclerosis reduces the flow of blood through arteries, because atheroma lines arteries and narrows them. Atheroma tends to increase with age, and its progression can be compounded by many causes including smoking, high blood pressure, excess circulating lipids (hyperlipidemia), and diabetes mellitus.
  - Coagulation can form a thrombosis, which can obstruct vessels.
  - Problems with blood composition, the pumping action of the heart, or narrowing of blood vessels can have many consequences including hypoxia (lack of oxygen) of the tissues supplied. The term *ischemia* refers to tissue that is inadequately perfused with blood, and *infarction* refers to tissue death (necrosis), which can occur when the blood supply has been blocked (or is very inadequate).

Hematological disorders

Hematology

- Anemia
  - Insufficient red cell mass (anemia) can be the result of bleeding, blood disorders like thalassemia, or nutritional deficiencies; and may require blood transfusion. Several countries have blood banks to fill the demand

for transfusable blood. A person receiving a blood transfusion must have a blood type compatible with that of the donor.
    - Sickle-cell anemia

- Disorders of cell proliferation
    - Leukemia is a group of cancers of the blood-forming tissues.
    - Non-cancerous overproduction of red cells (polycythemia vera) or platelets (essential thrombocytosis) may be premalignant.
    - Myelodysplastic syndromes involve ineffective production of one or more cell lines.

- Disorders of coagulation
    - Hemophilia is a genetic illness that causes dysfunction in one of the blood's clotting mechanisms. This can allow otherwise inconsequential wounds to be life-threatening, but more commonly results in hemarthrosis, or bleeding into joint spaces, which can be crippling.
    - Ineffective or insufficient platelets can also result in coagulopathy (bleeding disorders).
    - Hypercoagulable state (thrombophilia) results from defects in regulation of platelet or clotting factor function, and can cause thrombosis.

- Infectious disorders of blood
    - Blood is an important vector of infection. HIV, the virus, which causes AIDS, is transmitted through contact with blood, semen or other body secretions of an infected person. Hepatitis B and C are transmitted primarily through blood contact. Owing to blood-borne infections, bloodstained objects are treated as a biohazard.
    - Bacterial infection of the blood is bacteremia or sepsis. Viral Infection is viremia. Malaria and trypanosomiasis are blood-borne parasitic infections.

Carbon monoxide poisoning

Carbon monoxide poisoning

Substances other than oxygen can bind to hemoglobin; in some cases this can cause irreversible damage to the body. Carbon monoxide, for example, is extremely dangerous when carried to the blood via the lungs by inhalation, because carbon monoxide irreversibly binds to hemoglobin to form carboxyhemoglobin, so that less hemoglobin is free to bind oxygen, and less oxygen can be transported in the blood. This can cause suffocation insidiously. A fire burning in an enclosed room with poor ventilation presents a very dangerous hazard, since it can create a build-up of carbon monoxide in the air. Some carbon monoxide binds to hemoglobin when smoking tobacco.

Medical treatments

Blood products

Blood transfusion

Blood for transfusion is obtained from human donors by blood donation and stored in a blood bank. There are many different blood types in humans, the ABO blood group system, and the Rhesus blood group system being the most important. Transfusion of blood of an incompatible blood group may cause severe, often fatal, complications, so crossmatching is done to ensure that a compatible blood product is transfused.

Other blood products administered intravenously are platelets, blood plasma, cryoprecipitate, and specific coagulation factor concentrates.

Intravenous administration

Many forms of medication (from antibiotics to chemotherapy) are administered intravenously, as they are not readily or adequately absorbed by the digestive tract.

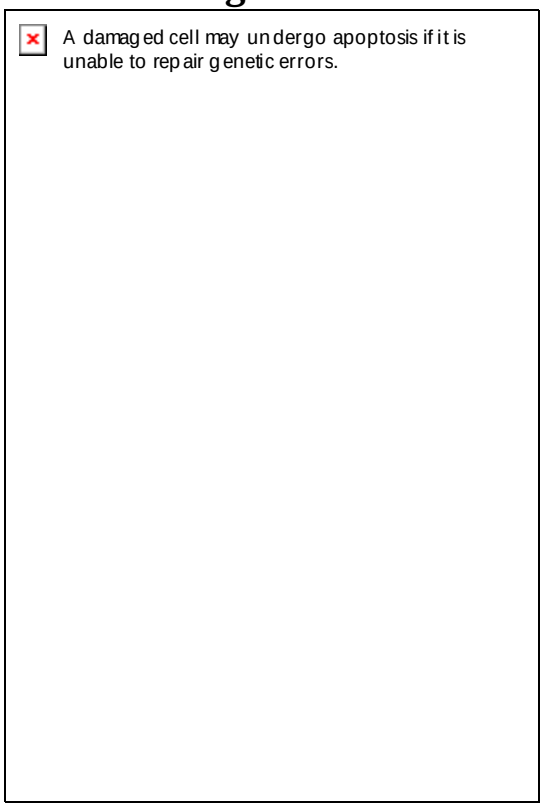
After severe acute blood loss, liquid preparations, generically known as plasma expanders, can be given intravenously, either solutions of salts (NaCl, KCl, $CaCl_2$ etc...) at physiological concentrations, or colloidal solutions, such as dextrans, human serum albumin, or fresh frozen plasma. In these emergency situations, a plasma expander is a more effective life-saving procedure than a blood transfusion, because the metabolism of transfused red blood cells does not restart immediately after a transfusion.

Bloodletting

bloodletting

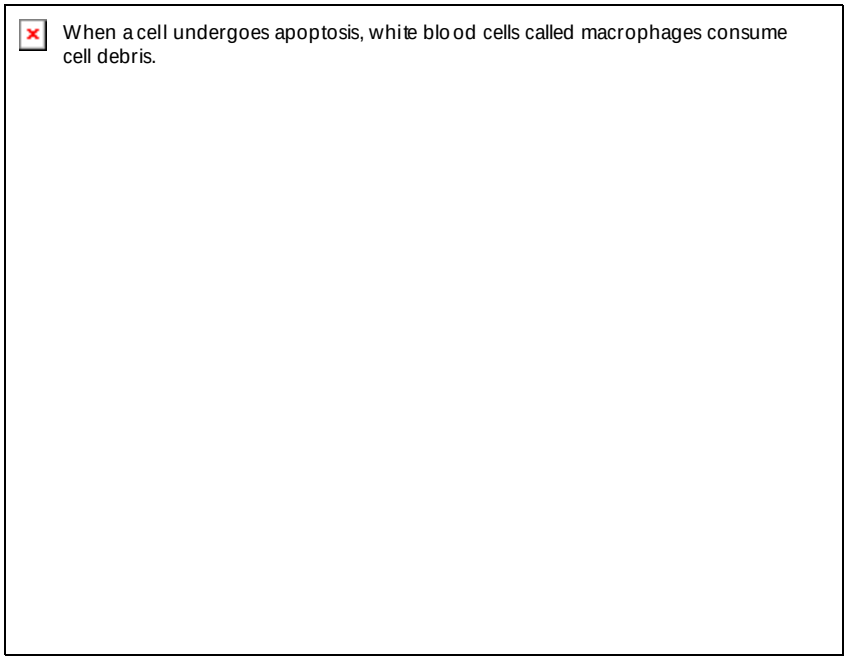
In modern evidence-based medicine, bloodletting is used in management of a few rare diseases, including hemochromatosis and polycythemia. However, bloodletting and leeching were common unvalidated interventions used until the 19th century, as many diseases were incorrectly thought to be due to an excess of blood, according to Hippocratic medicine.

Control of cell growth and division



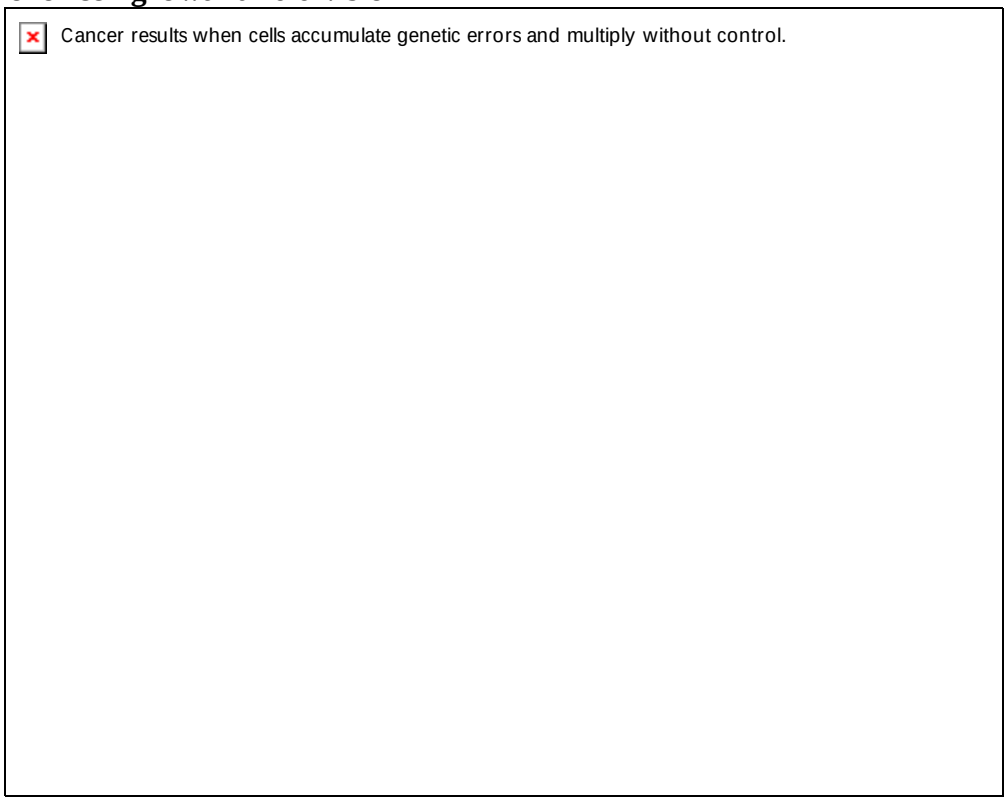
A damaged cell may undergo apoptosis if it is unable to repair genetic errors.

Control of cell growth and division



When a cell undergoes apoptosis, white blood cells called macrophages consume cell debris.

Control of cell growth and division



Cancer results when cells accumulate genetic errors and multiply without control.

Disease Inheritance

Most diseases do not follow simple patterns of inheritance.

Many factors influence a gene's ability to build proteins. For one thing, different mutations in the same gene can produce a wide range of effects. In cystic fibrosis, for example, the gene that controls mucus production can have more than 300 different mutations; some cause severe symptoms; some, mild symptoms; and some, no symptoms at all.

Disease Inheritance Is Complex

How can gene mutations affect health and development?

To function correctly, each cell depends on thousands of proteins to do their jobs in the right places at the right times. Sometimes, gene mutations prevent one or more of these proteins from working properly. By changing a gene's instructions for making a protein, a mutation can cause the protein to malfunction or to be missing entirely. When a mutation alters a protein that plays a critical role in the body, it can disrupt normal development or cause a medical condition. A condition caused by mutations in one or more genes is called a genetic disorder.

In some cases, gene mutations are so severe that they prevent an embryo from surviving until birth. These changes occur in genes that are essential for development, and often disrupt the development of an embryo in its earliest stages. Because these mutations have very serious effects, they are incompatible with life.

It is important to note that genes themselves do not cause disease—genetic disorders are caused by mutations that make a gene function improperly. For example, when people say that someone has "the cystic fibrosis gene," they are usually referring to a mutated version of the CFTR gene, which causes the disease. All people, including those without cystic fibrosis, have a version of the CFTR gene.

Looking at One of theChromosomes(chromosome 5)

Humans normally have 46 chromosomes in each cell, divided into 23 pairs. Two copies of chromosome 5, one copy inherited from each parent, form one of the pairs. Chromosome 5 spans about 181 million DNA building blocks (base pairs) and represents almost 6 percent of the total DNA in cells.

Identifying genes on each chromosome is an active area of genetic research. Because researchers use different approaches to predict the number of genes on each chromosome, the estimated number of genes varies. Chromosome 5 likely contains between 900 and 1,300 genes.

Genes on chromosome 5 are among the estimated 20,000 to 25,000 total genes in the human genome.

How are changes in chromosome 5 related to health conditions?

Many genetic conditions are related to changes in particular genes on chromosome 5. This list of disorders associated with genes on chromosome 5 provides links to additional information.

Changes in the structure or number of copies of a chromosome can also cause problems with health and development. The following chromosomal conditions are associated with such changes in chromosome 5.

cancers

Changes in the structure of chromosome 5 are associated with certain forms of cancer and conditions related to cancer. These changes are typically somatic, which means they are acquired during a person's lifetime and are present only in tumor cells. Deletions in the long (q) arm of the chromosome have been identified in a form of blood cancer known as acute myeloid leukemia (AML). These deletions also frequently occur in a disorder called myelodysplastic syndrome, which is a disease of the blood and bone marrow. People with this condition have a low number of red blood cells (anemia) and an increased risk of developing AML. When myelodysplastic syndrome is associated with a specific deletion in the long arm of chromosome 5, it is known as 5q- (5q minus) syndrome. Studies are under way to determine which genes in the deleted region of chromosome 5 are related to myelodysplastic syndrome and AML.

cri-du-chat syndrome

Cri-du-chat syndrome is caused by a deletion of the end of the short (p) arm of chromosome 5. This chromosomal change is written as 5p- (5p minus). The signs and symptoms of cri-du-chat syndrome are probably related to the loss of multiple genes in this region. Researchers are working to identify all of these genes and determine how their loss leads to the features of the disorder. They have discovered that in people with cri-du-chat syndrome, larger deletions tend to result in more severe intellectual disability and developmental delays than smaller deletions. They have also defined regions of the short arm of chromosome 5 that are associated with particular features of cri-du-chat syndrome. A specific region designated 5p15.3 is associated with a cat-like cry, and a nearby region called 5p15.2 is associated with intellectual disability, small head size (microcephaly), and distinctive facial features.

Crohn disease

Several regions of chromosome 5 have been associated with the risk of developing Crohn disease. For example, a combination of genetic variations in a region of DNA on the long (q) arm of the chromosome (5q31) has been shown to increase a person's chance of developing Crohn disease. Taken together, these variations are known as the inflammatory bowel disease 5 (IBD5) locus. This region of chromosome 5 contains several related genes that may be associated with Crohn disease risk, including SLC22A4 and SLC22A5.

Variations in a region of the short (p) arm of chromosome 5 designated 5p13.1 are also associated with Crohn disease risk. Researchers refer to this part of

chromosome 5 as a "gene desert" because it contains no known genes; however, it may contain stretches of DNA that help regulate nearby genes such as PTGER4. Research studies are under way to examine a possible connection between the PTGER4 gene and Crohn disease.

periventricular heterotopia

In a few cases, abnormalities in chromosome 5 have been associated with periventricular heterotopia, a disorder characterized by abnormal clumps of nerve cells (neurons) around fluid-filled cavities (ventricles) near the center of the brain. In each case, the affected individual had extra genetic material caused by an abnormal duplication of part of this chromosome. It is not known how this duplicated genetic material results in the signs and symptoms of periventricular heterotopia.

other chromosomal conditions

Other changes in the number or structure of chromosome 5 can have a variety of effects, including delayed growth and development, distinctive facial features, birth defects, and other medical problems. Changes to chromosome 5 include an extra segment of the short (p) or long (q) arm of the chromosome in each cell (partial trisomy 5p or 5q), a missing segment of the long arm of the chromosome in each cell (partial monosomy 5q), and a circular structure called ring chromosome 5. Ring chromosomes occur when a chromosome breaks in two places and the ends of the chromosome arms fuse together to form a circular structure.

Idiogram of chromosome 5

Geneticists use diagrams called ideograms as a standard representation for chromosomes. Ideograms show a chromosome's relative size and its banding pattern. A banding pattern is the characteristic pattern of dark and light bands that appears when a chromosome is stained with a chemical solution and then viewed under a microscope. These bands are used to describe the location of genes on each chromosome.

Ideogram of chromosome 5

Genes on chromosome 5

Back to chromosome 5 summary

Conditions related to genes on chromosome 5

Genetics Home Reference includes these genes on chromosome 5:

- ADAMTS2: ADAM metallopeptidase with thrombospondin type 1 motif, 2
- ALDH7A1: aldehyde dehydrogenase 7 family, member A1
- ANKH: ankylosis, progressive homolog (mouse)
- APC: adenomatous polyposis coli
- CTNND2: catenin (cadherin-associated protein), delta 2 (neural plakophilin-related arm-repeat protein)
- ERAP1: endoplasmic reticulum aminopeptidase 1
- ERCC8: excision repair cross-complementing rodent repair deficiency, complementation group 8
- F12: coagulation factor XII (Hageman factor)
- FBN2: fibrillin 2
- FGFR4: fibroblast growth factor receptor 4
- FLT4: fms-related tyrosine kinase 4
- GM2A: GM2 ganglioside activator
- GPR98: G protein-coupled receptor 98
- HEXB: hexosaminidase B (beta polypeptide)
- IRGM: immunity-related GTPase family, M
- MCCC2: methylcrotonoyl-Coenzyme A carboxylase 2 (beta)
- MSX2: msh homeobox 2
- MTRR: 5-methyltetrahydrofolate-homocysteine methyltransferase reductase
- NIPBL: Nipped-B homolog (Drosophila)
- NSD1: nuclear receptor binding SET domain protein 1
- RAD50: RAD50 homolog (S. cerevisiae)
- SAR1B: SAR1 homolog B (S. cerevisiae)
- SH3TC2: SH3 domain and tetratricopeptide repeats 2
- SIL1: SIL1 homolog, endoplasmic reticulum chaperone (S. cerevisiae)
- SLC1A3: solute carrier family 1 (glial high affinity glutamate transporter), member 3
- SLC22A5: solute carrier family 22 (organic cation/carnitine transporter), member 5
- SLC26A2: solute carrier family 26 (sulfate transporter), member 2
- SLC45A2: solute carrier family 45, member 2
- SMN1: survival of motor neuron 1, telomeric
- SMN2: survival of motor neuron 2, centromeric
- SNCAIP: synuclein, alpha interacting protein
- TCOF1: Treacher Collins-Franceschetti syndrome 1

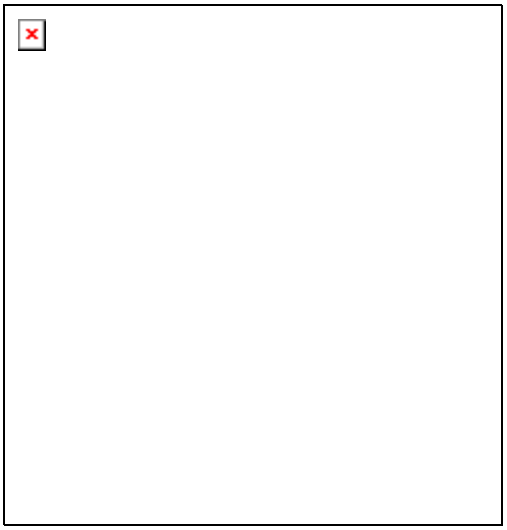
GeneCards provides a table of genes on chromosome 5 and disorders related to those genes.

Conditions related to genes on chromosome 5

Genetics Home Reference includes these conditions related to genes on chromosome 5:

- achondrogenesis
- amyotrophic lateral sclerosis
- ankylosing spondylitis
- atelosteogenesis type 2
- breast cancer
- Charcot-Marie-Tooth disease
- chylomicron retention disease
- Cockayne syndrome
- congenital contractural arachnodactyly
- Cornelia de Lange syndrome
- craniometaphyseal dysplasia
- cri-du-chat syndrome
- Crohn disease
- diastrophic dysplasia
- Ehlers-Danlos syndrome
- enlarged parietal foramina
- episodic ataxia
- familial adenomatous polyposis
- GM2-gangliosidosis, AB variant
- hereditary angioedema
- homocystinuria
- Marinesco-Sjögren syndrome
- 3-methylcrotonyl-coenzyme A carboxylase deficiency
- Milroy disease
- multiple epiphyseal dysplasia
- oculocutaneous albinism
- Parkinson disease
- primary carnitine deficiency
- pyridoxine-dependent epilepsy
- Sandhoff disease
- Sotos syndrome
- spinal muscular atrophy
- Treacher Collins syndrome
- Usher syndrome

The Immune system



A scanning electron microscope image of a single neutrophil (yellow), engulfing anthrax bacteria (orange).

An **immune system** is a system of biological structures and processes within an organism that protects against disease by identifying and killing pathogens and tumour cells. It detects a wide variety of agents, from viruses to parasitic worms, and needs to distinguish them from the organism's own healthy cells and tissues in order to function properly. Detection is complicated as pathogens can evolve rapidly, producing adaptations that avoid the immune system and allow the pathogens to successfully infect their hosts.

To survive this challenge, multiple mechanisms evolved that recognize and neutralize pathogens. Even simple unicellular organisms such as bacteria possess enzyme systems that protect against viral infections. Other basic immune mechanisms evolved in ancient eukaryotes and remain in their modern descendants, such as plants, fish, reptiles, and insects. These mechanisms include antimicrobial peptides called defensins, phagocytosis, and the complement system. Vertebrates such as humans have even more sophisticated defense mechanisms.[1] The immune systems of vertebrates consist of many types of proteins, cells, organs, and tissues, which interact in an elaborate and dynamic network. As part of this more complex immune response, the human immune system adapts over time to recognize specific pathogens more efficiently. This adaptation process is referred to as "adaptive immunity" or "acquired immunity" and creates immunological memory. Immunological memory created from a primary response to a specific pathogen, provides an enhanced response to secondary encounters with that same, specific pathogen. This process of acquired immunity is the basis of vaccination.

Disorders in the immune system can result in disease. Immunodeficiency occurs when the immune system is less active than normal, resulting in recurring and life-threatening infections. Immunodeficiency can either be the result of a genetic disease, such as severe combined immunodeficiency, or be produced by pharmaceuticals or an infection, such as the acquired immune deficiency syndrome (AIDS) that is caused by the retrovirus HIV. In contrast, autoimmune diseases result 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 lupus erythematosus. Immunology covers the study of all aspects of the immune system which has significant relevance to human health and diseases. Further investigation in this field is expected to play a serious role in promotion of health and treatment of diseases.

Layered defense

The immune system protects organisms from infection with layered defenses of increasing specificity. Most simply, 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.[2] However, if pathogens successfully evade the innate response, vertebrates possess a third 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.[3]

Components of the immune system	
Innate immune system	**Adaptive immune system**
Response is non-specific	Pathogen and antigen specific response
Exposure leads to immediate maximal response	Lag time between exposure and maximal response
Cell-mediated and humoral components	Cell-mediated and humoral components

No immunological memory	Exposure leads to immunological memory
Found in nearly all forms of life	Found only in jawed vertebrates

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.[4] Conversely, *non-self* molecules are those recognized as foreign molecules. One class of non-self molecules are called antigens (short for *anti*body *gen*erators) and are defined as substances that bind to specific immune receptors and elicit an immune response.[5]

Surface barriers

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 the mechanical barriers that are the first line of defense against infection.[5] However, as organisms cannot be completely sealed against 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.[6]

Chemical barriers also protect against infection. The skin and respiratory tract secrete antimicrobial peptides such as the β-defensins.[7] Enzymes such as lysozyme and phospholipase A2 in saliva, tears, and breast milk are also antibacterials.[8][9] Vaginal secretions serve as a chemical barrier following menarche, when they become slightly acidic, while semen contains defensins and zinc to kill pathogens.[10][11] 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.[12] This reduces the probability that pathogens will be able to 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).[13] There is good evidence that re-introduction of probiotic flora, such as pure cultures of the lactobacilli normally found in unpasteurized yoghurt, 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.[14][15][16]

Innate

Microorganisms or toxins that successfully enter an organism will 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,[17] 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.[18] Innate immune defenses are non-specific, meaning these systems respond to pathogens in a generic way.[5] 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.[2]

Humoral and chemical barriers

Inflammation

Inflammation is one of the first responses of the immune system to infection.[19] The symptoms of inflammation are redness and swelling, which are caused by increased blood flow into a 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).[20][21] 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.[22] 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.[23]

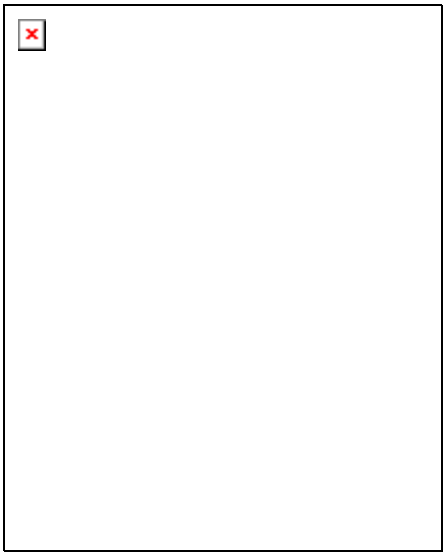
Complement system

The complement system is a biochemical cascade that attacks the surfaces of foreign cells. It contains over 20 different proteins and is named for its ability to "complement" the killing of pathogens by antibodies. Complement is the major humoral component of the innate immune response.[24][25] Many species have complement systems, including non-mammals like plants, fish, and some invertebrates.[26]

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.[27] 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.[28] 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.[24]

Cellular barriers



A scanning electron microscope image of normal circulating human blood. One can see red blood cells, several knobby white blood cells including lymphocytes, a monocyte, a neutrophil, and many small disc-shaped platelets.

Leukocytes (white blood cells) act like independent, single-celled organisms and are the second arm of the innate immune system.[5] 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.[26] Innate cells are also important mediators in the activation of the adaptive immune system.[3]

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.[5] 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.[29][30] Phagocytosis evolved as a means of acquiring nutrients, but this role was extended in phagocytes to include engulfment of pathogens as a defense mechanism.[31] Phagocytosis probably represents the oldest form of host defense, as phagocytes have been identified in both vertebrate and invertebrate animals.[32]

Neutrophils and macrophages are phagocytes that travel throughout the body in pursuit of invading pathogens.[33] 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.[34] 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.[35] 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.[3]

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.[36] 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 antigen to T cells, one of the key cell types of the adaptive immune system.[36]

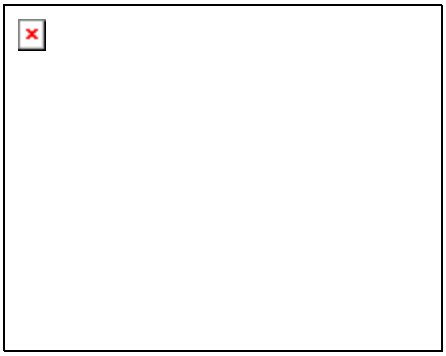
Mast cells reside in connective tissues and mucous membranes, and regulate the inflammatory response.[37] They are most often associated with allergy and anaphylaxis.[34] Basophils and eosinophils are related to neutrophils. They secrete chemical mediators that are involved in defending against parasites and play a role in allergic reactions, such as asthma.[38] Natural killer (NK cells) cells are leukocytes that attack and destroy tumor cells, or cells that have been infected by viruses.[39]

Adaptive

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.[40] 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.

Lymphocytes

The cells of the adaptive immune system are special types of leukocytes, called lymphocytes. B cells and T cells are the major types of lymphocytes and are derived from hematopoietic stem cells in the bone marrow.[26] B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response.

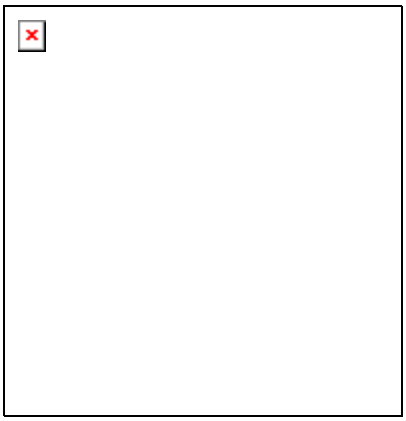


Association of a T cell with MHC class I or MHC class II, and antigen (in red)

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. Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper 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.[41]

In contrast, the B cell antigen-specific receptor is an antibody molecule on the B cell surface, and recognizes whole pathogens without any need for antigen processing. Each lineage of B cell expresses a different antibody, so the complete set of B cell antigen receptors represent all the antibodies that the body can manufacture.[26]

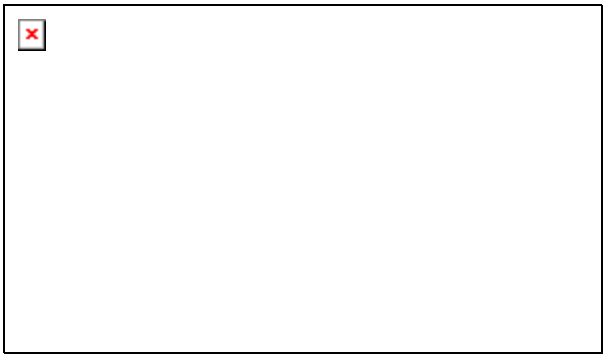
Killer T cells



Killer T cells directly attack other cells carrying foreign or abnormal antigens on their surfaces.[42]

Killer T cell are a sub-group of T cells that kill cells infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional.[43] As with B cells, each type of T cell recognises 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.[44] 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).[44]

Helper T cells



Function of T helper cells: Antigen presenting cells (APCs) present antigen on their Class II MHC molecules (MHC2). Helper T cells recognize these, with the help of their expression of CD4 co-receptor (CD4+). The activation of a resting helper T cell causes it

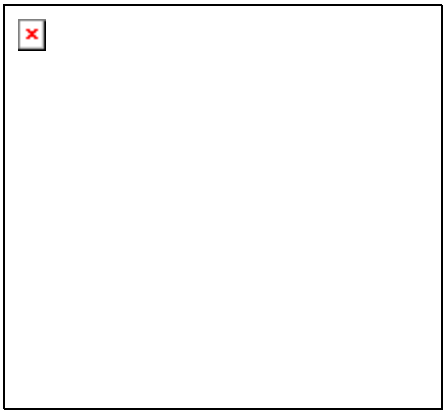
to release cytokines and other stimulatory signals (green arrows) that stimulate the activity of macrophages, killer T cells and B cells, the latter producing antibodies. The stimulation of B cells and macrophages succeeds a proliferation of T helper cells.

Helper T cells regulate both the innate and adaptive immune responses and help determine which types of immune responses the body will make to a particular pathogen.[45][46] These cells have no cytotoxic activity and do not kill infected cells or clear pathogens directly. They instead control the immune response by directing other cells to perform these tasks.

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.[47] 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.[5] 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.[48]

γδ 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.[49] 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 will respond to stressed epithelial cells.[50]



An antibody is made up of two heavy chains and two light chains. The unique variable region allows an antibody to recognize its matching antigen.[42]

B lymphocytes and antibodies

A B cell identifies pathogens when antibodies on its surface bind to a specific foreign antigen.[51] 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.[52] 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.[53]

Alternative adaptive immune system

Although the classical molecules of the adaptive immune system (e.g. antibodies and T cell receptors) exist only in jawed vertebrates, 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.[54]

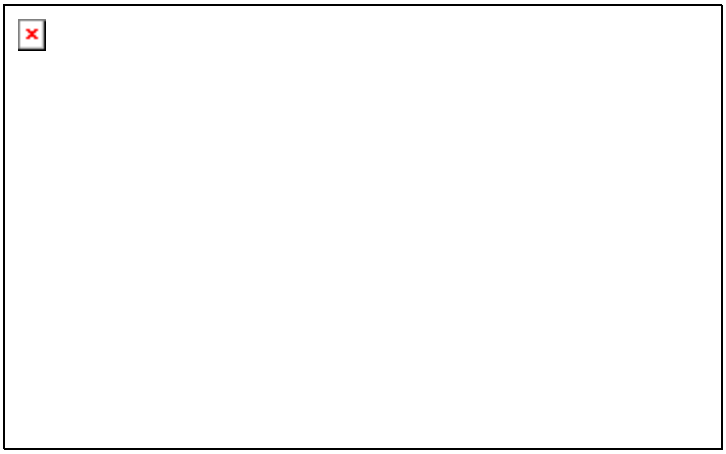
Immunological memory

When B cells and T cells are activated and begin to replicate, some of their offspring will become long-lived memory cells. Throughout the lifetime of an animal, these memory cells will 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 either be in the form of passive short-term memory or active long-term memory.

Passive 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.[55] 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.[56] 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.[57]



The time-course of an immune response begins with the initial pathogen encounter, (or initial vaccination) and leads to the formation and maintenance of active immunological memory.

Active memory and immunization

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.[5] 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.[26][58]

Most viral vaccines are based on live attenuated viruses, while many bacterial vaccines are based on acellular components of micro-organisms, including harmless toxin components.[5] Since many antigens derived from acellular vaccines do not strongly induce the adaptive response, most bacterial vaccines are provided with additional adjuvants that activate the antigen-presenting cells of the innate immune system and maximize immunogenicity.[59]

Disorders of human immunity

The immune system is a remarkably effective structure that incorporates specificity, inducibility and adaptation. Failures of host defense do occur, however, and fall into three broad categories: immunodeficiencies, autoimmunity, and hypersensitivities.

Immunodeficiencies

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.[60][61] In developed countries, obesity, alcoholism, and drug use are common causes of poor immune function.[61] However, malnutrition is the most common cause of immunodeficiency in developing countries.[61] Diets lacking sufficient protein are associated with impaired cell-mediated immunity, complement activity, phagocyte function, IgA antibody concentrations, and cytokine production. Deficiency of single nutrients such as iron; copper; zinc; selenium; vitamins A, C, E, and B_6; and folic acid (vitamin B_9) also reduces immune responses.[61] 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.[62]

Immunodeficiencies can also be inherited or 'acquired'.[5] Chronic granulomatous disease, where phagocytes have a reduced ability to destroy pathogens, is an example of an inherited, or congenital, immunodeficiency. AIDS and some types of cancer cause acquired immunodeficiency.[63][64]

Autoimmunity

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.[65] 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.[51]

Hypersensitivity

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 released from mast cells and basophils.[66] 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.[66] Immune complexes (aggregations of antigens, complement proteins, and IgG and IgM antibodies) deposited in various tissues trigger Type III hypersensitivity reactions.[66] 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.[66]

Other mechanisms

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.[1] 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.[67] 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.[68][69]

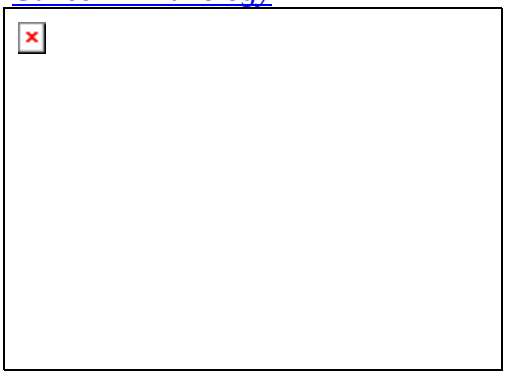
Pattern recognition receptors are proteins used by nearly all organisms to identify molecules associated with pathogens. Antimicrobial peptides called defensins are an evolutionarily conserved component of the innate immune response found in all animals and plants, and represent the main form of invertebrate systemic immunity.[1] 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.[70]

Unlike animals, plants lack phagocytic cells, and most plant immune responses involve systemic chemical signals that are sent through a plant.[71] 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.[71] RNA silencing mechanisms are particularly important in this systemic response as they can block virus replication.[72]

Tumor immunology

Cancer immunology



Macrophages have identified a cancer cell (the large, spiky mass). Upon fusing with the cancer cell, the macrophages (smaller white cells) will inject toxins that kill the tumor cell. Immunotherapy for the treatment of cancer is an active area of medical research.[73]

Another important role of the immune system is to identify and eliminate tumors. 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;[74] some are derived from oncogenic viruses like human papillomavirus, which causes cervical cancer,[75] 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.[76][77] 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.[74][78][79]

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.[77][80] 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.[81] 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.[82] Sometimes antibodies are generated against tumor cells allowing for their destruction by the complement system.[78]

Clearly, some tumors evade the immune system and go on to become cancers.[83] Tumor cells often have a reduced number of MHC class I molecules on their surface, thus avoiding detection by killer T cells.[81] 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.[84] In addition, immunological tolerance may develop against tumor antigens, so the immune system no longer attacks the tumor cells.[83]

Paradoxically, macrophages can promote tumor growth [85] when tumor cells send out cytokines that attract macrophages which then generate cytokines and growth factors that nurture tumor development. In addition, a combination of hypoxia in the tumor and a cytokine produced by macrophages induces tumor cells to decrease production of a protein that blocks metastasis and thereby assists spread of cancer cells.

Physiological regulation

Hormones can act as immunomodulators, altering the sensitivity of the immune system. For example, female sex hormones are known immunostimulators of both adaptive[86] and innate immune responses.[87] 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.[88] Other hormones appear to regulate the immune system as well, most notably prolactin, growth hormone and vitamin D.[89][90] It is conjectured that a progressive decline in hormone levels with age is partially responsible for weakened immune responses in aging individuals.[91] Conversely, some hormones are regulated by the immune system, notably thyroid hormone activity.[92]

Sleep

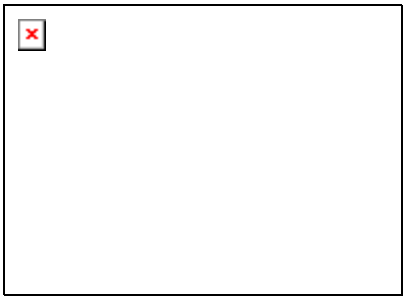
The immune system is enhanced by sleep and rest,[93] and is impaired by stress.[94] Sleep deprivation is detrimental to immune function, and sleep can be considered a vital part of the immune system. Viewed in this light, decreases in the length and quality of sleep in the population have far-reaching public health implications.[95] Complex feedback loops exist between the sleep cycle and immune response: acute infection causes changes in the sleep cycle, including an increase in slow-wave sleep relative to REM sleep.[96] Cytokines, a class of peptides, appear to be one of the main mechanisms through which the immune system and sleep cycle interact, as cytokines are produced by the immune system in response to infection, and also play a role in the normal sleep cycle.[97]

Nutrition and diet

The functioning of the immune system, like most systems in the body, is dependent on proper nutrition. It has been long known that severe malnutrition leads to immunodeficiency. Overnutrition is also associated with diseases such as diabetes and obesity which are known to affect immune function. More moderate malnutrition, as well as certain specific trace mineral and nutrient deficiencies, can also compromise the immune response.[98]

Specific foods may also affect the immune system; for example, fresh fruits, vegetables, and foods rich in certain fatty acids may foster a healthy immune system.[99] Likewise, fetal undernourishment can cause a lifelong impairment of the immune system.[100] In traditional medicine, some herbs are believed to stimulate the immune system, such as echinacea, licorice, ginseng, astragalus, sage, garlic, elderberry, shiitake and lingzhi mushrooms, and hyssop, as well as honey. Studies have suggested that such herbs can indeed stimulate the immune system,[101] although their mode of action is complex and difficult to characterize.

Manipulation in medicine



The immunosuppressive drug dexamethasone

The immune response can be manipulated to suppress unwanted responses resulting from autoimmunity, allergy, and transplant rejection, and to stimulate protective responses against pathogens that largely elude the immune system (see immunization). Immunosuppressive drugs are used to control autoimmune disorders or inflammation when excessive tissue damage occurs, and to prevent transplant rejection after an organ transplant.[26][102]

Anti-inflammatory drugs are often used to control the effects of inflammation. The glucocorticoids are the most powerful of these drugs; however, these drugs can have many undesirable side effects (*e.g.*, central obesity, hyperglycemia, osteoporosis) and their use must be tightly controlled.[103] Therefore, 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.[102] Immunosuppressive drugs such as ciclosporin prevent T cells from responding to signals correctly by inhibiting signal transduction pathways.[104]

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;[105] 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.[106] A publicly accessible database has been established for the cataloguing of epitopes from pathogens known to be recognizable by B cells.[107] The emerging field of bioinformatics-based studies of immunogenicity is referred to as *immunoinformatics*.[108]

Manipulation by pathogens

The success of any pathogen is dependent on its ability to elude host immune responses. Therefore, pathogens have developed several methods that allow them to successfully infect a host, while evading detection or destruction by the immune system.[109] Bacteria often overcome physical barriers by secreting enzymes that digest the barrier — for example, by using a type II secretion system.[110] 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.[111]

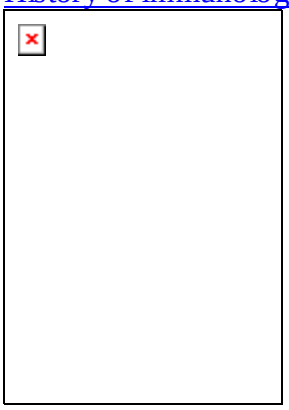
An evasion strategy used by several pathogens to avoid the innate immune system is to hide within the cells of their host (also called intracellular pathogenesis). Here, a pathogen spends most of its life-cycle inside host cells, where it is shielded from direct contact with immune cells, antibodies 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.[112] Many pathogens secrete compounds that diminish or misdirect the host's immune response.[109] 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.[113] 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).[114]

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.[115] 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.[116] Masking antigens with host molecules is another common strategy for avoiding detection by the immune system. In HIV, the envelope that covers the viron 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.[117]

History of immunology

History of immunology

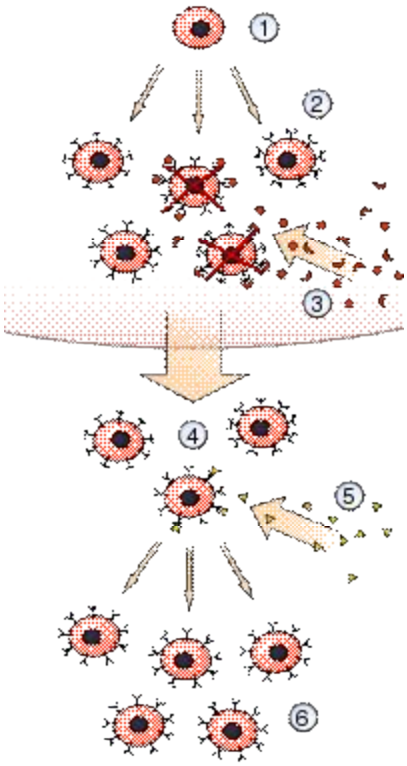


Paul Ehrlich

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 mention of 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.[118] This observation of acquired immunity was later exploited by Louis Pasteur in his development of vaccination and his proposed germ theory of disease.[119] 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.[120] Viruses were confirmed as human pathogens in 1901, with the discovery of the yellow fever virus by Walter Reed.[121]

Immunology made a great advance towards the end of the 19th century, through rapid developments, in the study of humoral immunity and cellular immunity.[122] Particularly important was the work of Paul Ehrlich, who proposed the side-chain theory to explain the specificity of the antigen-antibody reaction; his contributions to the understanding of humoral immunity were recognized by the award of a Nobel Prize in 1908, which was jointly awarded to the founder of cellular immunology, Elie Metchnikoff.[123]

Clonal selection



Clonal selection of lymphocytes: 1) A hematopoietic stem cell undergoes differentiation and genetic rearrangement to produce 2) immature lymphocytes with many different antigen receptors. Those that bind to 3) antigens from the body's own tissues are destroyed, while the rest mature into 4) inactive lymphocytes. Most of these will never encounter a matching 5) foreign antigen, but those that do are activated and produce 6) many clones of themselves.

The **clonal selection theory** has become a widely accepted model for how the immune system responds to infection and how certain types of B and T lymphocytes are selected for destruction of specific antigens invading the body.

Four Postulates of Clonal Selection Hypothesis

- Each lymphocyte bears a single type of receptor with a unique specificity.
- Receptor occupation is required for cell activation.
- The differentiated effector cells derived from an activated lymphocyte will bear receptors of identical specificity as the parental cell.
- Those lymphocytes bearing receptors for self molecules will be deleted at an early stage.

Early Work

In 1954, immunologist Niels Jerne put forward a theory which stated that there is already a vast array of lymphocytes in the body prior to any infection. The entrance of an antigen into the body results in the selection of only one type of lymphocyte to match it and produce a corresponding antibody to destroy the antigen.

This selection of only one type of lymphocyte results in it being cloned or reproduced by the body extensively to ensure there are enough antibodies produced to inhibit and prevent infection.

Further Work

Australian immunologist Frank Macfarlane Burnet with input from David W. Talmage worked on this model, and was the first to name it "clonal selection theory." Burnet explained immunological memory as the cloning of two types of lymphocyte. One clone acts immediately to combat infection whilst the other is longer lasting, remaining in the immune system for a long time, which results in immunity to that antigen. In 1958, Sir Gustav Nossal and Joshua Lederberg showed that one B cell always produces only one antibody, which was the first evidence for clonal selection theory. [1]

Theories Supported by Clonal Selection

Burnet and Peter Medawar worked together on understanding immunological tolerance, a phenomenon also explained by clonal selection. This is the organism's ability to tolerate the introduction of cells without an immune response as long as this occurs early in the organism's development. There are a vast number of lymphocytes occurring in the immune system ranging from cells which are tolerant of self tissue to cells which are not tolerant of self tissue. However, only cells that are tolerant to self tissue will survive the embryonic stage. If non-self tissue is introduced, the lymphocytes which develop will be the ones which included the non-self tissues as self tissue.

In 1949 Burnet proposed that under certain circumstances, tissues could be successfully transplanted into foreign recipients. This work has led to a much greater understanding of the immune system and also great advances in tissues transplantation. Burnet and Medawar shared the Nobel Prize for physiology and medicine in 1960.

A **hapten** is a small molecule that can elicit an immune response only when attached to a large carrier such as a protein; the carrier may be one that also does not elicit an immune response by itself. (In general, only large molecules, infectious agents, or insoluble foreign matter can elicit an immune response in the body.) Once the body has generated antibodies to a hapten-carrier adduct, the small-molecule hapten may also be able to bind to the antibody, but it will usually not initiate an immune response; usually only the hapten-carrier adduct can do this. Sometimes the small-molecule hapten can even block

immune response to the hapten-carrier adduct by preventing the adduct from binding to the antibody.

The concept of haptens emerged from the work of Karl Landsteiner[1] [2] who also pioneered the use of synthetic haptens to study immunochemical phenomena.[3]

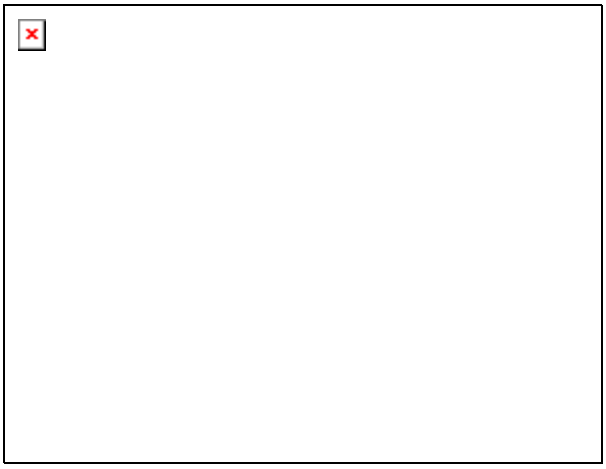
Examples of haptens

A well-known example of a hapten is urushiol, which is the toxin found in poison ivy. When absorbed through the skin from a poison ivy plant, urushiol undergoes oxidation in the skin cells to generate the actual hapten, a reactive molecule called a quinone, which then reacts with skin proteins to form hapten adducts. Usually, the first exposure only causes sensitization, in which there is a proliferation of effector T-cells. After a second exposure later, the proliferated T cells can become activated, generating an immune reaction, producing the typical blisters of poison ivy exposure.

Some haptens can induce autoimmune disease. An example is hydralazine, a blood pressure-lowering drug that occasionally can produce drug-induced lupus erythematosus in certain individuals. This also appears to be the mechanism by which the anaesthetic gas halothane can cause a life-threatening hepatitis, as well as the mechanism by which penicillin-class drugs causes autoimmune hemolytic anemia.

Other haptens that are commonly used in molecular biology applications include fluorescein, biotin, digoxigenin, and dinitrophenol.

Major histocompatibility complex




Protein images comparing the MHC I (1hsa) and MHC II (1dlh) molecules. (more details...)

The **major histocompatibility complex** (**MHC**) is a large genomic region or gene family found in most vertebrates. It is the most gene-dense region of the mammalian genome and plays an important role in the immune system and autoimmunity. The diversity of MHC is important in the immune diversity in the population. The proteins encoded by the MHC are expressed on the surface of cells in all jawed vertebrates, and display both *self* antigens (peptide fragments from the cell itself) and *nonself* antigens (e.g., fragments of invading microorganisms) to a type of white blood cell called a T cell that has the capacity to kill or co-ordinate the killing of pathogens and infected or malfunctioning cells.

Classification

In humans, the 3.6-Mb (3 600 000 base pairs) MHC region on chromosome 6 contains 140 genes between flanking genetic markers MOG and COL11A2.[1] About half have known immune functions (see human leukocyte antigen). The same markers in the marsupial *Monodelphis domestica* (gray short-tailed opossum) span 3.95 Mb and contain 114 genes, 87 shared with humans.[2]

Subgroups

The MHC region is divided into three subgroups, class I, class II, and class III.

Name	Function	Expression
MHC class I	Encodes heterodimeric peptide-binding proteins, as well as antigen-processing molecules such as TAP and Tapasin.	All nucleated cells. MHC class I proteins contain an α chain & β2-micro-globulin(not part of the MHC). They present antigen fragments to cytotoxic T-cells via the CD8 receptor on the cytotoxic T-cells and also bind inhibitory receptors on NK cells.
MHC class II	Encodes heterodimeric peptide-binding proteins and proteins that modulate antigen loading onto MHC class II proteins in the lysosomal compartment such as MHC II DM, MHC II DQ, MHC II DR, and MHC	On most immune system cells, specifically on antigen-presenting cells. MHC class II proteins contain α & β chains and they present antigen fragments to T-helper cells by binding to the CD4 receptor on the T-helper cells.

	II DP.	
MHC class III region	Encodes for other immune components, such as complement components (e.g., C2, C4, factor B) and some that encode cytokines (e.g., TNF-α) and also hsp.	Variable (see below).

Class III has a function very different from that of class I and class II, but, since it has a locus between the other two (on chromosome 6 in humans), they are frequently discussed together.

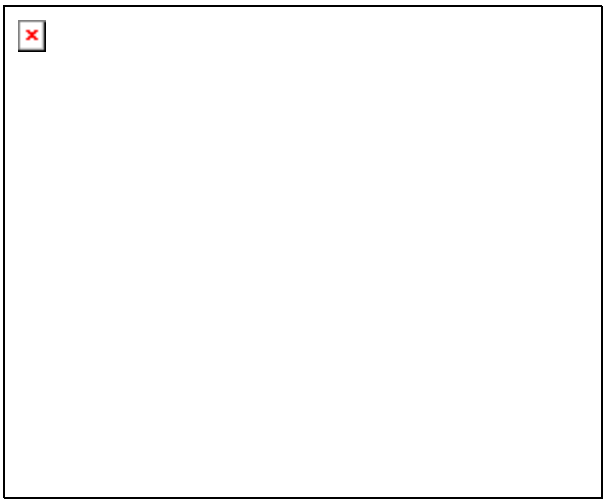
Responses

The MHC proteins act as "signposts" that display fragmented pieces of an *antigen* on the host cell's surface. These antigens may be *self* or *nonself*. If they are *nonself*, there are two ways by which the foreign protein can be processed and recognized as being "nonself".

- Phagocytic cells such as macrophages, neutrophils, and monocytes degrade foreign particles that are engulfed during a process known as phagocytosis. Degraded particles are then presented on MHC Class II molecules.[3]
- On the other hand, if a host cell was infected by a bacterium or virus, or was cancerous, it may have displayed the antigens on its surface with a *Class I MHC molecule*. In particular, cancerous cells and cells infected by a virus have a tendency to display unusual, *nonself* antigens on their surface. These nonself antigens, regardless of which type of MHC molecule they are displayed on, will initiate the specific immunity of the host's body.

Cells constantly process endogenous proteins and present them within the context of MHC I. Immune effector cells are trained not to react to self peptides within MHC, and as such are able to recognize when foreign peptides are being presented during an infection/cancer.

HLA genes



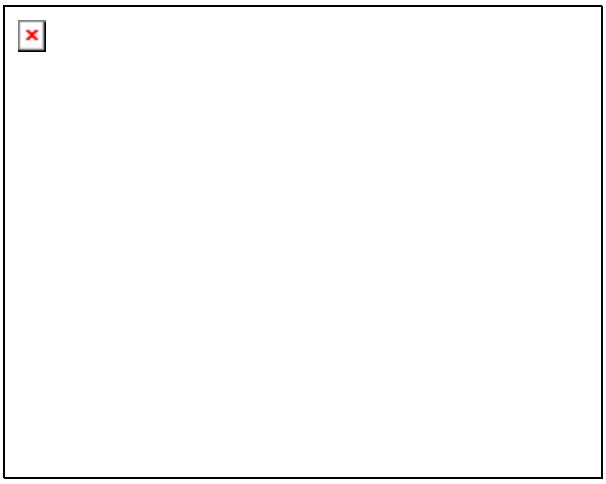
Codominant expression of HLA genes.
Human leukocyte antigen

The best-known genes in the MHC region are the subset that encodes antigen-presenting proteins on the cell surface. In humans, these genes are referred to as *human leukocyte antigen* (HLA) genes; however people often use the abbreviation MHC to refer to HLA gene products. To clarify the usage, some of the biomedical literature uses HLA to refer specifically to the HLA protein molecules and reserves MHC for the region of the genome that encodes for this molecule. This convention is not consistently adhered to, however.

The most intensely studied HLA genes are the nine so-called classical MHC genes: HLA-A, HLA-B, HLA-C, HLA-DPA1, HLA-DPB1, HLA-DQA1, HLA-DQB1, HLA-DRA, and HLA-DRB1. In humans, the MHC is divided into three regions: Class I, II, and III. The A, B, and C genes belong to MHC class I, whereas the six D genes belong to class II.

MHC has also attracted the attention of many evolutionary biologists, because of the high levels of allelic diversity found within its genes.[*citation needed*]

Molecular biology of MHC proteins



TCR-MHC bindings.

The classical MHC molecules (also referred to as HLA molecules in humans) have a vital role in the complex immunological dialogue that must occur between T cells and other cells of the body. At maturity, MHC molecules are anchored in the cell membrane, where they display short polypeptides to T cells, via the T cell receptors (TCR). The polypeptides may be "self," that is, originating from a protein created by the organism itself, or they may be foreign ("nonself"), originating from bacteria, viruses, pollen, and so on. The overarching design of the MHC-TCR interaction is that T cells should ignore self-peptides while reacting appropriately to the foreign peptides.

The immune system has *another* and equally important method for identifying an antigen: B cells with their membrane-bound antibodies, also known as B cell receptors (BCR). However, whereas the BCRs of B cells can bind to antigens without much outside help, the TCRs require "presentation" of the antigen through the help of MHC. For most of the time, however, MHC are kept busy presenting **self**-peptides, which T cells should appropriately ignore. A full-force immune response usually requires the activation of B cells via BCRs *and* T cells via the MHC-TCR interaction. This duplicity creates a system of "checks and balances" and underscores the immune system's potential for running amok and causing harm to the body (see autoimmune disorders).

MHC molecules retrieve polypeptides from the interior of the cell they are part of and display them on the cell's surface for recognition by T cells. However, MHC class I and MHC class II differ significantly in the method of peptide presentation.

MHC evolution and allelic diversity

MHC gene families are found in all vertebrates, though the gene composition and genomic arrangement vary widely. Chickens, for instance, have one of the smallest known MHC regions (19 genes), though most mammals have an MHC structure and composition fairly similar to that of humans. Research has determined that gene

duplication is responsible for much of the genetic diversity. In humans, the MHC is littered with many pseudogenes.

One of the most striking features of the MHC, in particular in humans, is the astounding allelic diversity found therein, and especially among the nine classical genes. In humans, the most conspicuously-diverse loci, HLA-A, HLA-B, and HLA-DRB1, have roughly 250, 500, and 300 known alleles respectively — diversity truly exceptional in the human genome. The MHC gene is the most polymorphic in the genome. Population surveys of the other classical loci routinely find tens to a hundred alleles — still highly diverse. Many of these alleles are quite ancient: It is often the case that an allele from a particular HLA gene is more closely related to an allele found in chimpanzees than it is to another human allele from the same gene.

In terms of phylogenetics, the marsupial MHC lies between eutherian mammals and the minimal essential MHC of birds, although it is closer in organization to non-mammals. Its Class I genes have amplified within the Class II region, resulting in a unique Class I/II region.[2]

The allelic diversity of MHC genes has created fertile grounds for evolutionary biologists. The most important task for theoreticians is to explain the evolutionary forces that have created and maintained such diversity. Most explanations invoke balancing selection (see polymorphism (biology)), a broad term that identifies any kind of natural selection in which no single allele is absolutely most fit. Frequency-dependent selection and heterozygote advantage are two types of balancing selection that have been suggested to explain MHC allelic diversity. However, recent models suggest that a high number of alleles is not plausibly achievable through heterozygote advantage alone. Pathogenic co-evolution, a counter-hypothesis has recently emerged; it theorizes that the most common alleles will be placed under the greatest pathogenic pressure, thus there will always be a tendency for the least common alleles to be positively selected for. This creates a "moving target" for pathogen evolution. As the pathogenic pressure decreases on the previously common alleles, their concentrations in the population will stabilize, and they will usually not go extinct if the population is large enough, and a large number of alleles will remain in the population as a whole. This explains the high degree of MHC polymorphism found in the population, although an individual can have a maximum of 18 MHC I or II alleles.

MHC and sexual selection

Interpersonal compatibility

It has been suggested that MHC plays a role in the selection of potential mates, via olfaction. MHC genes make molecules that enable the immune system to recognise invaders; in general, the more diverse the MHC genes of the parents the stronger the immune system of the offspring. It would be beneficial, therefore, to have evolved systems of recognizing individuals with different MHC genes and preferentially selecting them to breed with.

Yamazaki et al. (1976) showed this to be the case for male mice, which show a preference for females of different MHC. Similar results have been obtained with fish.[4]

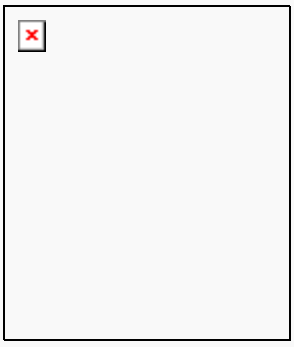
In 1995, Swiss biologist Claus Wedekind determined MHC-dissimilar mate selection tendencies in humans. In the experiment, a group of female college students smelled t-shirts that had been worn by male students for two nights, without deodorant, cologne, or scented soaps. An overwhelming number of women preferred the odors of men with dissimilar MHCs to their own. However, their preference was reversed if they were taking oral contraceptives.[5] The hypothesis is that MHCs affect mate choice and that oral contraceptives can interfere with this. A study in 2005 on 58 test subjects confirmed the second part - taking oral contraceptives made women prefer men with MHCs similar to their own.[6] However, without oral contraceptives, women had no particular preference, contradicting the earlier finding.[7] However, another study in 2002 showed results consistent with Wedekind's—paternally inherited HLA-associated odors influence odor preference and may serve as social cues.[8]

In 2008, Peter Donnelly and colleagues proposed that MHC is related to mating choice in some human populations.

Sickle-Cell Disease

Sickle-cell disease

Classification and external resources



Normal and sickle-shaped red blood cells

Sickle-cell disease, or **sickle-cell anaemia** (or **drepanocytosis**), is a life-long blood disorder characterized by red blood cells that assume an abnormal, rigid, sickle shape. Sickling decreases the cells' flexibility and results in a risk of various complications. The sickling occurs because of a mutation in the hemoglobin gene. Life expectancy is shortened, with studies reporting an average life expectancy of 42 and 48 years for males and females, respectively.[1]

Sickle-cell disease, usually presenting in childhood, occurs more commonly in people (or their descendants) from parts of tropical and sub-tropical regions where malaria is or was common. One-third of all indigenous inhabitants of Sub-Saharan Africa carry the gene[2], because in areas where malaria is common, there is a survival value in carrying only a single sickle-cell gene (sickle cell trait).[3] Those with only one of the two alleles of the sickle-cell disease are more resistant to malaria, since the infestation of the malaria plasmodium is halted by the sickling of the cells which it infests.

The prevalence of the disease in the United States is approximately 1 in 5,000, mostly affecting African Americans, according to the National Institutes of Health.[4]

Classification

Sickle-cell anaemia is the name of a specific form of sickle-cell disease in which there is homozygosity for the mutation that causes HbS. Sickle-cell anaemia is also referred to as "HbSS", "SS disease", "haemoglobin S" or permutations thereof. In heterozygous people, who have only one sickle gene and one normal adult hemoglobin gene, it is referred to as "HbAS" or "sickle cell trait". Other, rarer forms of sickle-cell disease include sickle-haemoglobin C disease (HbSC), sickle beta-plus-thalassaemia (HbS/β^{+}) and sickle beta-zero-thalassaemia (HbS/β^{0}). These other forms of sickle-cell disease are compound heterozygous states in which the person has only one copy of the mutation that causes HbS and one copy of another abnormal haemoglobin allele.

The term *disease* is applied, because the inherited abnormality causes a pathological condition that can lead to death and severe complications. Not all inherited variants of haemoglobin are detrimental, a concept known as genetic polymorphism.

In the US sickle-cell anemia usually occurs in black people, but sometimes occurs in Hispanic people. In the United States, about one in five hundred black births, and about one in 36,000 Hispanic births, have sickle-cell anemia.[5]

Signs and symptoms

Sickle-cell disease may lead to various acute and chronic complications, several of which are potentially lethal.

Vaso-occlusive crisis

The vaso-occlusive crisis is caused by sickle-shaped red blood cells that obstruct capillaries and restrict blood flow to an organ, resulting in ischemia, pain, and often organ damage. The frequency, severity, and duration of these crises vary considerably. Painful crises are treated with hydration and analgesics; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting.

Diphenhydramine is sometimes effective for the itching associated with the opioid use. Incentive spirometry, a technique to encourage deep breathing to minimise the development of atelectasis, is recommended.

Because of its narrow vessels and function in clearing defective red blood cells, the spleen is frequently affected. It is usually infarcted before the end of childhood in individuals suffering from sickle-cell anaemia. This autosplenectomy increases the risk of infection from encapsulated organisms;[6][7] preventive antibiotics and vaccinations are recommended for those with such asplenia.

One of the earliest clinical manifestations is dactylitis, presenting as early as six months of age, and may occur in children with sickle trait.[8] The crisis can last up to a month.[9] Another recognised type of sickle crisis is the acute chest syndrome, a condition characterised by fever, chest pain, difficulty breathing, and pulmonary infiltrate on a chest X-ray. Given that pneumonia and sickling in the lung can both produce these symptoms, the patient is treated for both conditions.[*citation needed*] It can be triggered by painful crisis, respiratory infection, bone-marrow embolisation, or possibly by atelectasis, opiate administration, or surgery.

Most episodes of sickle cell crises last between five and seven days.[10]

Other sickle-cell crises

- *Aplastic crises* are acute worsenings of the patient's baseline anaemia, producing pallor, tachycardia, and fatigue. This crisis is triggered by parvovirus B19, which directly affects erythropoiesis (production of red blood cells). Parvovirus infection nearly completely prevents red blood cell production for two to three days. In normal individuals, this is of little consequence, but the shortened red cell life of sickle-cell patients results in an abrupt, life-threatening situation. Reticulocyte counts drop dramatically during the disease, and the rapid turnover of red cells leads to the drop in hemoglobin. Most patients can be managed supportively; some need blood transfusion.
- *Splenic sequestration crises* are acute, painful enlargements of the spleen. The abdomen becomes bloated and very hard. Management is supportive, sometimes with blood transfusion.
- *Hemolytic crises* are acute accelerated drops in hemoglobin level. The red blood cells break down at a faster rate. This is particularly common in patients with co-existent G6PD deficiency. Management is supportive, sometimes with blood transfusions.

Complications

Sickle-cell anaemia can lead to various complications, including:

- Overwhelming post-(auto)splenectomy infection (OPSI), which is due to functional asplenia, caused by encapsulated organisms such as *Streptococcus*

pneumoniae and *Haemophilus influenzae*. Daily penicillin prophylaxis is the most commonly used treatment during childhood, with some haematologists continuing treatment indefinitely. Patients benefit today from routine vaccination for *H. influenzae*, *S. pneumoniae*, and *Neisseria meningitidis*.

- Stroke, which can result from a progressive vascular narrowing of blood vessels, preventing oxygen from reaching the brain. Cerebral infarction occurs in children, and cerebral hemorrhage in adults.
- Cholelithiasis (gallstones) and cholecystitis, which may result from excessive bilirubin production and precipitation due to prolonged haemolysis.
- Jaundice, yellowing of the skin, may occur due to the inability of the liver to effectively remove bilirubin from the filtering of damaged red blood cells out of the blood supply as well as blocks in the organ's blood supply.[11][12]
- Avascular necrosis (aseptic bone necrosis) of the hip and other major joints, which may occur as a result of ischemia.
- Decreased immune reactions due to hyposplenism (malfunctioning of the spleen).
- Priapism and infarction of the penis.
- Osteomyelitis (bacterial bone infection), which is most frequently caused by *Salmonella* in individuals with sickle-cell disease, whereas *Staphylococcus* is the most common causative organism in the general population.
- Opioid tolerance, which can occur as a normal, physiologic response to the therapeutic use of opiates. Addiction to opiates occurs no more commonly among individuals with sickle-cell disease than among other individuals treated with opiates for other reasons.
- Acute papillary necrosis in the kidneys.
- Leg ulcers.
- In eyes, background retinopathy, proliferative retinopathy, vitreous haemorrhages and retinal detachments, resulting in blindness. Regular annual eye checks are recommended.
- During pregnancy, intrauterine growth retardation, spontaneous abortion, and pre-eclampsia.
- Chronic pain: Even in the absence of acute vaso-occlusive pain, many patients have chronic pain that is not reported[13].
- Pulmonary hypertension (increased pressure on the pulmonary artery), leading to strain on the right ventricle and a risk of heart failure; typical symptoms are shortness of breath, decreased exercise tolerance and episodes of syncope[14].
- Chronic renal failure—manifests itself with hypertension (high blood pressure), proteinuria (protein loss in the urine), hematuria (loss of red blood cells in urine) and worsened anaemia. If it progresses to end-stage renal failure, it carries a poor prognosis.[15]

Heterozygotes

The heterozygous form (sickle cell trait) is almost always asymptomatic, and the only usual significant manifestation is the renal concentrating defect presenting with isosthenuria.

Diagnosis

In HbSS, the full blood count reveals haemoglobin levels in the range of 6–8 g/dL with a high reticulocyte count (as the bone marrow compensates for the destruction of sickle cells by producing more red blood cells). In other forms of sickle-cell disease, Hb levels tend to be higher. A blood film may show features of hyposplenism (target cells and Howell-Jolly bodies).

Sickling of the red blood cells, on a blood film, can be induced by the addition of sodium metabisulfite. The presence of sickle haemoglobin can also be demonstrated with the "sickle solubility test". A mixture of haemoglobin S (Hb S) in a reducing solution (such as sodium dithionite) gives a turbid appearance, whereas normal Hb gives a clear solution.

Abnormal haemoglobin forms can be detected on haemoglobin electrophoresis, a form of gel electrophoresis on which the various types of haemoglobin move at varying speeds. Sickle-cell haemoglobin (HgbS) and haemoglobin C with sickling (HgbSC)—the two most common forms—can be identified from there. The diagnosis can be confirmed with high-performance liquid chromatography (HPLC). Genetic testing is rarely performed, as other investigations are highly specific for HbS and HbC.[16]

An acute sickle-cell crisis is often precipitated by infection. Therefore, a urinalysis to detect an occult urinary tract infection, and chest X-ray to look for occult pneumonia should be routinely performed.[17]

Pathophysiology

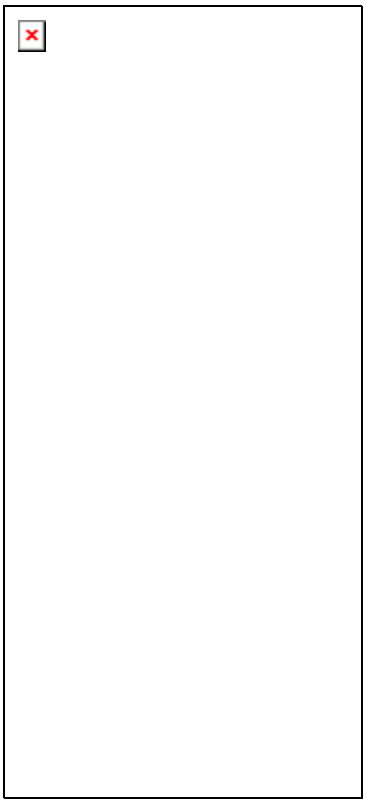
Sickle-cell anaemia is caused by a point mutation in the β-globin chain of haemoglobin, causing the amino acid glutamic acid to be replaced with the hydrophobic amino acid valine at the sixth position. The β-globin gene is found on the short arm of chromosome 11. The association of two wild-type α-globin subunits with two mutant β-globin subunits forms haemoglobin S (HbS). Under low-oxygen conditions (being at high altitude, for example), the absence of a polar amino acid at position six of the β-globin chain promotes the non-covalent polymerisation (aggregation) of haemoglobin, which distorts red blood cells into a sickle shape and decreases their elasticity.

The loss of red blood cell elasticity is central to the pathophysiology of sickle-cell disease. Normal red blood cells are quite elastic, which allows the cells to deform to pass through capillaries. In sickle-cell disease, low-oxygen tension promotes red blood cell sickling and repeated episodes of sickling damage the cell membrane and decrease the cell's elasticity. These cells fail to return to normal shape when normal oxygen tension is restored. As a consequence, these rigid blood cells are unable to deform as they pass through narrow capillaries, leading to vessel occlusion and ischaemia.

The actual anemia of the illness is caused by hemolysis, the destruction of the red cells inside the spleen, because of their misshape. Although the bone marrow attempts to

compensate by creating new red cells, it does not match the rate of destruction.[18] Healthy red blood cells typically live 90-120 days, but sickle cells only survive 10–20 days.[19]

Genetics

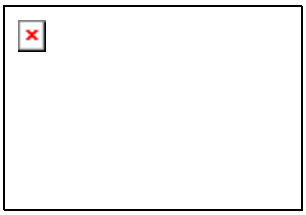


A single amino acid change causes haemoglobin proteins to form fibers.

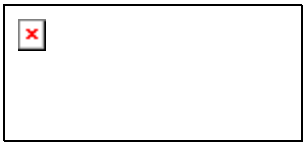
Sickle-cell gene mutation probably arose spontaneously in different geographic areas, as suggested by restriction endonuclease analysis. These variants are known as Cameroon, Senegal, Benin, Bantu and Saudi-Asian. Their clinical importance springs from the fact that some of them are associated with higher HbF levels, e.g., Senegal and Saudi-Asian variants, and tend to have milder disease.[20]

In people heterozygous for HgbS (carriers of sickling haemoglobin), the polymerisation problems are minor, because the normal allele is able to produce over 50% of the haemoglobin. In people homozygous for HgbS, the presence of long-chain polymers of HbS distort the shape of the red blood cell from a smooth donut-like shape to ragged and full of spikes, making it fragile and susceptible to breaking within capillaries. Carriers have symptoms only if they are deprived of oxygen (for example, while climbing a mountain) or while severely dehydrated. Under normal circumstances, these painful crises occur 0.8 times per year per patient.[*citation needed*] The sickle-cell disease occurs when the seventh amino acid (if we count the initial methionine), glutamic acid, is replaced by valine to change its structure and function.

Distribution of the sickle-cell trait shown in pink and purple



Historical distribution of malaria (no longer endemic in Europe) shown in green



Modern distribution of malaria

The gene defect is a known mutation of a single nucleotide (see single nucleotide polymorphism - SNP) (A to T) of the β-globin gene, which results in glutamate being substituted by valine at position 6. Haemoglobin S with this mutation are referred to as HbS, as opposed to the normal adult HbA. The genetic disorder is due to the mutation of a single nucleotide, from a GAG to GTG codon mutation. This is normally a benign mutation, causing *no* apparent effects on the secondary, tertiary, or quaternary structure of haemoglobin. What it does allow for, under conditions of low oxygen concentration, is the polymerization of the HbS itself. The deoxy form of haemoglobin exposes a hydrophobic patch on the protein between the E and F helices. The hydrophobic residues of the valine at position 6 of the beta chain in haemoglobin are able to associate with the hydrophobic patch, causing haemoglobin S molecules to aggregate and form fibrous precipitates.

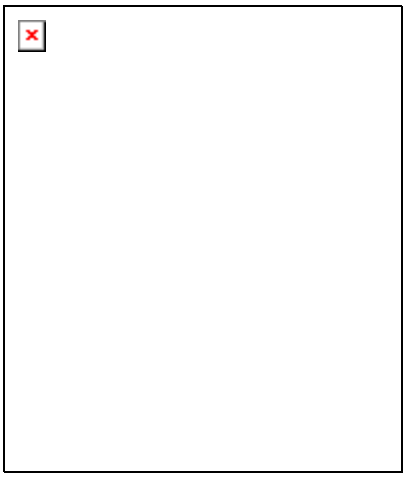
The allele responsible for sickle-cell anaemia is autosomal incomplete dominant and can be found on the short arm of chromosome 11. A person that receives the defective gene from both father and mother develops the disease; a person that receives one defective and one healthy allele remains healthy, but can pass on the disease and is known as a carrier. If two parents who are carriers have a child, there is a 1-in-4 chance of their child's developing the disease and a 1-in-2 chance of their child's being just a carrier. Since the gene is incompletely recessive, carriers can produce a few sickled red blood cells, not enough to cause symptoms, but enough to give resistance to malaria. Because of this, heterozygotes have a higher fitness than either of the homozygotes. This is known as heterozygote advantage.

Due to the adaptive advantage of the heterozygote, the disease is still prevalent, especially among people with recent ancestry in malaria-stricken areas, such as Africa, the Mediterranean, India and the Middle East.[21] Malaria was historically endemic to southern Europe, but it was declared eradicated in the mid-20th century, with the exception of rare sporadic cases.[22][23]

The Price equation is a simplified mathematical model of the genetic evolution of sickle-cell anaemia.

The malaria parasite has a complex life cycle and spends part of it in red blood cells. In a carrier, the presence of the malaria parasite causes the red blood cells with defective haemoglobin to rupture prematurely, making the plasmodium unable to reproduce. Further, the polymerization of Hb affects the ability of the parasite to digest Hb in the first place. Therefore, in areas where malaria is a problem, people's chances of survival actually increase if they carry sickle-cell trait (selection for the heterozygote).

In the USA, where there is no endemic malaria, the prevalence of sickle-cell anaemia among blacks is lower (about 0.25%) than in West Africa (about 4.0%) and is falling. Without endemic malaria from Africa, the sickle cell mutation is purely disadvantageous and will tend to be selected out of the affected population. Another factor limiting the spread of sickle-cell genes in North America is the absence of cultural proclivities to polygamy. [24]



Sickle-cell disease is inherited in the autosomal recessive pattern.

Inheritance

- Sickle-cell conditions are inherited from parents in much the same way as blood type, hair color and texture, eye color, and other physical traits.
- The types of hemoglobin a person makes in the red blood cells depend on what hemoglobin genes are inherited from his parents.

1. If one parent has sickle-cell anaemia (SS) and the other has sickle-cell trait (AS), there is a 50% chance of a child's having sickle-cell disease (SS) and a 50% chance of a child's having sickle-cell trait (AS).
2. When both parents have sickle-cell trait (AS), a child has a 25% chance (1 of 4) of sickle-cell disease (SS), as shown in the diagram.

Treatment

Cyanate

Dietary cyanate, from foods containing cyanide derivatives, has been used as a treatment for sickle- cell anemia.[25] In the laboratory, cyanate and thiocyanate irreversibly inhibit sickling of red blood cells drawn from sickle cell anemia patients.[26] However, the cyanate would have to be administered to the patient for a lifetime, as each new red blood cell created must be prevented from sickling at the time of creation. Cyanate also would be expelled via the urea of a patient every cycle of treatment. Also see nicosan.

Painful (vaso-occlusive) crisis

Most people with sickle-cell disease have intensely painful episodes called vaso-occlusive crises. The frequency, severity, and duration of these crises, however, vary tremendously. Painful crises are treated symptomatically with analgesics; pain management requires opioid administration at regular intervals until the crisis has settled. For milder crises, a subgroup of patients manage on NSAIDs (such as diclofenac or naproxen). For more severe crises, most patients require inpatient management for intravenous opioids; patient-controlled analgesia (PCA) devices are commonly used in this setting. Diphenhydramine is also an effective agent that is frequently prescribed by doctors in order to help control any itching associated with the use of opioids.

Folic acid and penicillin

Children born with sickle-cell disease will undergo close observation by the pediatrician and will require management by a hematologist to assure they remain healthy. These patients will take a 1 mg dose of folic acid daily for life. From birth to five years of age, they will also have to take penicillin daily due to the immature immune system that makes them more prone to early childhood illnesses.

Acute chest crisis

Management is similar to vaso-occlusive crisis, with the addition of antibiotics (usually a quinolone or macrolide, since wall-deficient ["atypical"] bacteria are thought to contribute to the syndrome),[27] oxygen supplementation for hypoxia, and close observation. Should the pulmonary infiltrate worsen or the oxygen requirements increase, simple blood transfusion or exchange transfusion is indicated. The latter involves the exchange of a significant portion of the patients red cell mass for normal red cells, which decreases the percent of haemoglobin S in the patient's blood.

Hydroxyurea

The first approved drug for the causative treatment of sickle-cell anaemia, hydroxyurea, was shown to decrease the number and severity of attacks in a study in 1995 (Charache *et al.*)[28] and shown to possibly increase survival time in a study in 2003 (Steinberg *et al.*).[29] This is achieved, in part, by reactivating fetal haemoglobin production in place of the haemoglobin S that causes sickle-cell anaemia. Hydroxyurea had previously been used as a chemotherapy agent, and there is some concern that long-term use may be harmful, but this risk has been shown to be either absent or very small and it is likely that the benefits outweigh the risks.[30]

Bone marrow transplants

Bone marrow transplants have proven to be effective in children.[31]

Future treatments

Various approaches are being sought for preventing sickling episodes as well as for the complications of sickle-cell disease. Other ways to modify hemoglobin switching are being investigated, including the use of phytochemicals such as nicosan. Gene therapy is under investigation.

Another treatment being investigated is Senicapoc.[32]

Situation of carriers

People who are known carriers of the disease often undergo genetic counseling before they have a child. A test to see if an unborn child has the disease takes either a blood sample from the fetus or a sample of amniotic fluid. Since taking a blood sample from a fetus has greater risks, the latter test is usually used.

After the mutation responsible for this disease was discovered in 1979, the U.S. Air Force required black applicants to test for the mutation. It dismissed 143 applicants because they were carriers, even though none of them had the condition. It eventually withdrew the requirement, but only after a trainee filed a lawsuit.[33]

History

This collection of clinical findings was unknown until the explanation of the sickle cells in 1904 by the Chicago cardiologist and professor of medicine James B. Herrick (1861-1954), whose intern Ernest Edward Irons (1877-1959) found "peculiar elongated and sickle-shaped" cells in the blood of Walter Clement Noel, a 20-year-old first-year dental student from Grenada, after Noel was admitted to the Chicago Presbyterian Hospital in December 1904 suffering from anaemia. [34]

Noel was readmitted several times over the next three years for "muscular rheumatism" and "bilious attacks". Noel completed his studies and returned to the capital of Grenada (St. George's) to practice dentistry. He died of pneumonia in 1916 and is buried in the Catholic cemetery at Sauteurs in the north of Grenada.[35]

The disease was named "sickle-cell anaemia" by Vernon Mason in 1922. However, some elements of the disease had been recognized earlier: A paper in the *Southern Journal of Medical Pharmacology* in 1846 described the absence of a spleen in the autopsy of a runaway slave. The African medical literature reported this condition in the 1870s, when it was known locally as *ogbanjes* ("children who come and go") because of the very high infant mortality rate caused by this condition. A history of the condition tracked reports back to 1670 in one Ghanaian family.[36] Also, the practice of using tar soap to cover blemishes caused by sickle-cell sores was prevalent in the black community.[*citation needed*]

Linus Pauling and colleagues were the first, in 1949, to demonstrate that sickle-cell disease occurs as a result of an abnormality in the haemoglobin molecule. This was the first time a genetic disease was linked to a mutation of a specific protein, a milestone in the history of molecular biology, and it was published in their paper "Sickle Cell Anemia, a Molecular Disease".

The origin of the mutation that led to the sickle-cell gene was initially thought to be in the Arabian peninsula, spreading to Asia and Africa. It is now known, from evaluation of chromosome structures, that there have been at least four independent mutational events, three in Africa and a fourth in either Saudi Arabia or central India. These independent events occurred between 3,000 and 6,000 generations ago, approximately 70-150,000 years.[37]

Thalassemia

Thalassemia (from θάλασσα, thalassa, sea + αἷμα, haima, blood; British spelling, "thalassaemia") is an inherited autosomal co-dominant blood disease. In thalassemia, the genetic defect results in reduced rate of synthesis of one of the globin chains that make up hemoglobin. Reduced synthesis of one of the globin chains can cause the formation of abnormal hemoglobin molecules, thus causing anemia, the characteristic presenting symptom of the thalassemias.

Thalassemia is a quantitative problem of too few globins synthesized, whereas sickle-cell anemia (a hemoglobinopathy) is a qualitative problem of synthesis of an incorrectly functioning globin. Thalassemias usually result in underproduction of normal globin proteins, often through mutations in regulatory genes. Hemoglobinopathies imply structural abnormalities in the globin proteins themselves.[1] The two conditions may overlap, however, since some conditions which cause abnormalities in globin proteins (hemoglobinopathy) also affect their production (thalassemia). Thus, some thalassemias are hemoglobinopathies, but most are not. Either or both of these conditions may cause anemia.

The disease is particularly prevalent among Mediterranean people, and this geographical association was responsible for its naming: *Thalassa (θάλασσα)* is Greek for the sea, *Haema (αἷμα)* is Greek for blood. In Europe, the highest concentrations of the disease are found in Greece and in parts of Italy, in particular, Southern Italy and the lower Po valley. The major Mediterranean islands (except the Balearics) such as Sicily, Sardinia, Malta, Corsica, Cyprus and Crete are heavily affected in particular. Other Mediterranean people, as well as those in the vicinity of the Mediterranean, also have high rates of thalassemia, including Middle Easterners and North Africans. Far from the Mediterranean, South Asians are also affected, with the world's highest concentration of carriers (18% of the population) being in the Maldives.

Prevalence

Generally, thalassemias are prevalent in populations that evolved in humid climates where malaria was endemic. It affects all races, as thalassemias protected these people from malaria due to the blood cells' easy degradation. Thalassemias are particularly associated with people of Mediterranean origin, Arabs, and Asians.[2] The Maldives has the highest incidence of Thalassemia in the world with a carrier rate of 18% of the population. The estimated prevalence is 16% in people from Cyprus, 1%[3] in Thailand, and 3-8% in populations from Bangladesh, China, India, Malaysia and Pakistan. There are also prevalences in descendants of people from Latin America and Mediterranean countries (e.g. Greece, Italy, Portugal, Spain, and others). A very low prevalence has been reported from people in Northern Europe (0.1%) and Africa (0.9%), with those in North Africa having the highest prevalence. Ancient Egyptians suffered from Thalassemia with as many as 40%[*citation needed*] of studied predynastic and dynastic mummies with the genetic defect. Today, it is particularly common in populations of indigenous ethnic minorities of Upper Egypt such as the Beja, Hadendoa, Saiddi and also peoples of the Delta, Red Sea Hill Region and especially amongst the Siwans.

[edit] Pathophysiology

The **thalassemias** are classified according to which chain of the hemoglobin molecule is affected. In α thalassemias, production of the α globin chain is affected, while in β thalassemia production of the β globin chain is affected.

Thalassemia produces a *deficiency* of α or β globin, unlike sickle-cell disease which produces a specific mutant form of β globin.

β globin chains are encoded by a single gene on chromosome 11; α globin chains are encoded by two closely linked genes on chromosome 16. Thus in a normal person with two copies of each chromosome, there are two loci encoding the β chain, and four loci encoding the α chain. Deletion of one of the α loci has a high prevalence in people of African or Asian descent, making them more likely to develop α thalassemias. β thalassemias are common in Africans, but also in Greeks and Italians.

[edit] Alpha (α) thalassemias

Alpha-thalassemia

The α thalassemias involve the genes HBA1[4] and HBA2,[5] inherited in a Mendelian recessive fashion. It is also connected to the deletion of the 16p chromosome. α thalassemias result in decreased alpha-globin production, therefore fewer alpha-globin chains are produced, resulting in an excess of β chains in adults and excess γ chains in newborns. The excess β chains form unstable tetramers (called Hemoglobin H or HbH of 4 beta chains) which have abnormal oxygen dissociation curves.

Beta (β) thalassemias

Beta-thalassemia

Beta thalassemias are due to mutations in the HBB gene on chromosome 11,[6] also inherited in an autosomal-recessive fashion. The severity of the disease depends on the nature of the mutation. Mutations are characterized as (β^o) if they prevent any formation of β chains (which is the most severe form of beta Thalassemia); they are characterized as (β^+) if they allow some β chain formation to occur. In either case there is a relative excess of α chains, but these do not form tetramers: rather, they bind to the red blood cell membranes, producing membrane damage, and at high concentrations they form toxic aggregates.

Delta (δ) thalassemia

Delta-thalassemia

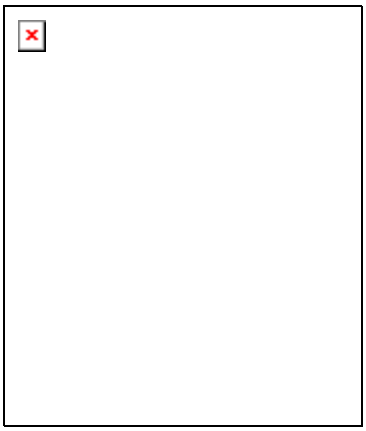
As well as alpha and beta chains being present in hemoglobin about 3% of adult hemoglobin is made of alpha and delta chains. Just as with beta thalassemia, mutations can occur which affect the ability of this gene to produce delta chains.

In combination with other hemoglobinopathies

Thalassemia can co-exist with other hemoglobinopathies. The most common of these are:

- hemoglobin E/thalassemia: common in Cambodia, Thailand, and parts of India; clinically similar to β thalassemia major or thalassemia intermedia.
- hemoglobin S/thalassemia, common in African and Mediterranean populations; clinically similar to sickle cell anemia, with the additional feature of splenomegaly
- hemoglobin C/thalassemia: common in Mediterranean and African populations, hemoglobin C/β^o thalassemia causes a moderately severe hemolytic anemia with splenomegaly; hemoglobin C/β^+ thalassemia produces a milder disease.

Genetic prevalence



Thalassemia has an autosomal recessive pattern of inheritance

α and β thalassemia are often inherited in an autosomal recessive fashion although this is not always the case. Cases of dominantly inherited α and β thalassemias have been reported, the first of which was in an Irish family who had a two deletions of 4 and 11 bp in exon 3 interrupted by an insertion of 5 bp in the β-globin gene. For the autosomal recessive forms of the disease both parents must be carriers in order for a child to be affected. If both parents carry a hemoglobinopathy trait, there is a 25% chance with each pregnancy for an affected child. Genetic counseling and genetic testing is recommended for families that carry a thalassemia trait.

There are an estimated 60-80 million people in the world who carry the beta thalassemia trait alone. This is a very rough estimate and the actual number of thalassemia Major patients is unknown due to the prevalence of thalassemia in less developed countries in the Middle East and Asia where genetic screening resources are limited. Countries such as India, Pakistan and Iran are seeing a large increase of thalassemia patients due to lack of genetic counseling and screening. There is growing concern that thalassemia may become a very serious problem in the next 50 years, one that will burden the world's blood bank supplies and the health system in general. There are an estimated 1,000 people living with Thalassemia Major in the United States and an unknown number of carriers. Because of the prevalence of the disease in countries with little knowledge of thalassemia, access to proper treatment and diagnosis can be difficult.

As with other genetically acquired disorders, genetic counseling is recommended.

Treatment

Patients with thalassemia minor usually do not require any specific treatment. Treatment for patients with thalassemia major includes chronic blood transfusion therapy, iron chelation, splenectomy, and allogeneic hematopoietic transplantation.

Medication

Medical therapy for beta thalassemia primarily involves iron chelation. Deferoxamine is the intravenously administered chelation agent currently approved for use in the United States. Deferasirox (Exjade) is an oral iron chelation drug also approved in the US in 2005.

The antioxidant indicaxanthin, found in beets, in a spectrophotometric study showed that indicaxanthin can reduce perferryl-Hb generated in solution from met-Hb and hydrogen peroxide, more effectively than either Trolox or Vitamin C. Collectively, results demonstrate that indicaxanthin can be incorporated into the redox machinery of β-thalassemic RBC and defend the cell from oxidation, possibly interfering with perferryl-Hb, a reactive intermediate in the hydroperoxide-dependent Hb degradation.[7]

Carrier detection

- A screening policy exists in Cyprus to reduce the incidence of thalassemia, which since the program's implementation in the 1970s (which also includes pre-natal screening and abortion) has reduced the number of children born with the hereditary blood disease from 1 out of every 158 births to almost zero.[8]
- In Iran as a premarital screening, the man's red cell indices are checked first, if he has microcytosis (mean cell haemoglobin < 27 pg or mean red cell volume < 80 fl), the woman is tested. When both are microcytic their haemoglobin A2 concentrations are measured. If both have a concentration above 3.5% (diagnostic of thalassaemia trait) they are referred to the local designated health post for genetic counseling.[9]

In 2008, in Chennai, a baby was selectively implanted in order to be a cure for his sister's thalassemia. The child was born from an embryo screened to be free of the disease before implantation with In vitro fertilization. The baby's supply of immunocompatible cord blood was saved for transplantation to his sister. The transplantation was considered successful.[10]

Benefits

Being a carrier of the disease may confer a degree of protection against malaria, and is quite common among people from Italian or Greek origin, and also in some African and Indian regions. This is probably by making the red blood cells *more* susceptible to the less lethal species *Plasmodium vivax*, simultaneously making the host RBC environment unsuitable for the merozoites of the lethal strain *Plasmodium falciparum*. This is believed to be a selective survival advantage for patients with the various thalassemia traits. In that respect it resembles another genetic disorder, sickle-cell disease.

Epidemiological evidence from Kenya suggests another reason: protection against severe anemia may be the advantage.[11]

People diagnosed with heterozygous (carrier) Beta-Thalassemia have some protection against coronary heart disease.[12]

Additional facts

Recently, increasing reports suggest that up to 5% of patients with beta-thalassemias produce fetal hemoglobin (HbF), and use of hydroxyurea also has a tendency to increase the production of HbF, by as yet unexplained mechanisms.[*citation needed*]

Giving a happy ending to a poignant family tale and raising fresh hope of leveraging stem cell therapy, a group of doctors and specialists in Chennai and Coimbatore have registered the first successful treatment of thalassaemia in a child using a sibling's umbilical cord blood.[13]