

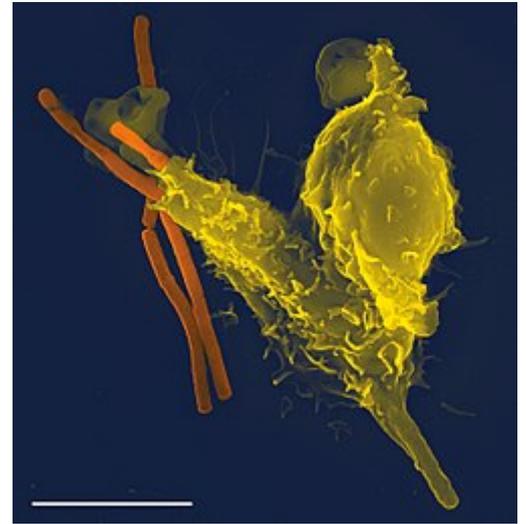
# Immune system

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The **immune system** is a host defense system comprising many biological structures and processes within an organism that protects against disease. To function properly, an immune system must detect a wide variety of agents, known as pathogens, from viruses to parasitic worms, and distinguish them from the organism's own healthy tissue. In many species, there are two major subsystems of the immune system: the innate immune system and the adaptive immune system. Both subsystems use humoral immunity and cell-mediated immunity to perform their functions. In humans, the blood–brain barrier, blood–cerebrospinal fluid barrier, and similar fluid–brain barriers separate the peripheral immune system from the neuroimmune system, which protects the brain.

Pathogens can rapidly evolve and adapt, and thereby avoid detection and neutralization by the immune system; however, multiple defense mechanisms have also evolved to recognize and neutralize pathogens. Even simple unicellular organisms such as bacteria possess a rudimentary immune system in the form of enzymes that protect against bacteriophage infections. Other basic immune mechanisms evolved in ancient eukaryotes and remain in their modern descendants, such as plants and invertebrates. These mechanisms include phagocytosis, antimicrobial peptides called defensins, and the complement system. Jawed vertebrates, including humans, have even more sophisticated defense mechanisms,<sup>[1]</sup> including the ability to adapt over time to recognize specific pathogens more efficiently. Adaptive (or acquired) immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.

Disorders of the immune system can result in autoimmune diseases, inflammatory diseases and cancer.<sup>[2]</sup> Immunodeficiency occurs when the immune system is less active than normal, resulting in recurring and life-threatening infections. In humans, immunodeficiency can either be the result of a genetic disease such as severe combined immunodeficiency, acquired conditions such as HIV/AIDS, or the use of immunosuppressive medication. In contrast, autoimmunity results from a hyperactive immune system attacking normal tissues as if they were foreign organisms. Common autoimmune diseases include Hashimoto's thyroiditis, rheumatoid arthritis, diabetes mellitus type 1, and systemic lupus erythematosus. Immunology covers the study of all aspects of the immune system.



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

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# Layered defense

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The immune system protects its host from infection with layered defenses of increasing specificity. In simple terms, physical barriers prevent pathogens such as bacteria and viruses from entering the organism. If a pathogen breaches these barriers, the innate immune system provides an immediate, but non-specific response. Innate immune systems are found in all plants and animals.<sup>[3]</sup> If pathogens successfully evade the innate response, vertebrates possess a second layer of protection, the adaptive immune system, which is activated by the innate response. Here, the immune system adapts its response during an infection to improve its recognition of the pathogen. This improved response is then retained after the pathogen has been eliminated, in the form of an immunological memory, and allows the adaptive immune system to mount faster and stronger attacks each time this pathogen is encountered.<sup>[4][5]</sup>

Components of the immune system

<u>Innate immune system</u>	<u>Adaptive immune system</u>
Response is non-specific	Pathogen and <u>antigen</u> specific response
Composed of leukocytes	Composed of antigens, B cells, T cells
Exposure leads to immediate maximal response	Lag time between exposure and maximal response
<u>Cell-mediated</u> and <u>humoral</u> components	<u>Cell-mediated</u> and <u>humoral</u> components
No immunological memory	Exposure leads to immunological memory
Found in nearly all forms of life	Found only in <u>jawed vertebrates</u>

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.<sup>[6]</sup> Conversely, *non-self* molecules are those recognized as foreign molecules. One class of non-self molecules are called antigens (short for *antibody generators*) and are defined as substances that bind to specific immune receptors and elicit an immune response.<sup>[7]</sup>

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 through the placenta, so human babies have high levels of antibodies even at birth, with the same range of antigen specificities as their mother.<sup>[8]</sup> 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.<sup>[9]</sup> 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.<sup>[10]</sup>

## Innate immune system

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Microorganisms or toxins that successfully enter an organism encounter the cells and mechanisms of the innate immune system. The innate response is usually triggered when microbes are identified by pattern recognition receptors, which recognize components that are conserved among broad groups of microorganisms,<sup>[11]</sup> 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.<sup>[12]</sup> Innate immune defenses are non-specific, meaning these systems respond to pathogens in a generic way.<sup>[7]</sup> 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.<sup>[3]</sup>

## Pattern recognition by cells

Cells in the innate immune system use pattern recognition receptors (PRRs) to recognize molecular structures that are produced by microbial pathogens. PRRs are germline-encoded host sensors, which detect molecules typical for the pathogens.<sup>[13]</sup> They are proteins expressed, mainly, by cells of the innate immune system, such as dendritic cells, macrophages, monocytes, neutrophils and epithelial cells,<sup>[14][15]</sup> to identify two classes of molecules: pathogen-associated molecular patterns (PAMPs), which are associated with microbial pathogens, and damage-associated molecular patterns (DAMPs), which are associated with components of host's cells that are released during cell damage or death.

### Toll-like receptors

Recognition of extracellular or endosomal pathogen-associated molecular patterns (PAMPs) is mediated by transmembrane proteins known as toll-like receptors (TLRs).<sup>[16]</sup> TLRs share a typical structural motif, the Leucine rich repeats (LRR), which give them their specific appearance and are also responsible for TLR functionality.<sup>[17]</sup> Toll-like receptors were first discovered in *Drosophila* and trigger the synthesis and secretion of cytokines and activation of other host defense programs that are necessary for both innate or adaptive immune responses. To date, ten functional members of the TLR family have been described in humans.<sup>[18]</sup>

### Cytosolic receptors

Cells in the innate immune system have pattern recognition receptors that detect infection or cell damage in the cytosol. Three major classes of these cytosolic receptors are NOD-like receptors, RIG (retinoic acid-inducible gene)-like receptors, and cytosolic DNA sensors.<sup>[19]</sup>

### Inflammasomes

Inflammasomes are multiprotein complexes (consist of an NLR, the adaptor protein ASC, and the effector molecule pro-caspase-1) that form in response to cytosolic PAMPs and DAMPs, whose function is to generate active forms of the inflammatory cytokines IL-1 $\beta$  and IL-18.<sup>[20]</sup>

## Surface barriers

Several barriers protect organisms from infection, including mechanical, chemical, and biological barriers. The waxy cuticle of most leaves, the exoskeleton of insects, the shells and membranes of externally deposited eggs, and skin are examples of mechanical barriers that are the first line of defense against infection.<sup>[7]</sup> However, as organisms cannot be completely sealed from their environments, other systems act to protect body openings such as the lungs, intestines, and the genitourinary tract. In the lungs, coughing and sneezing mechanically eject pathogens and other irritants from the respiratory tract. The flushing action of tears and urine also mechanically expels pathogens, while mucus secreted by the respiratory and gastrointestinal tract serves to trap and entangle microorganisms.<sup>[21]</sup>

Chemical barriers also protect against infection. The skin and respiratory tract secrete antimicrobial peptides such as the  $\beta$ -defensins.<sup>[22]</sup> Enzymes such as lysozyme and phospholipase A2 in saliva, tears, and breast milk are also antibacterials.<sup>[23][24]</sup> Vaginal secretions serve as a chemical barrier following menarche, when they

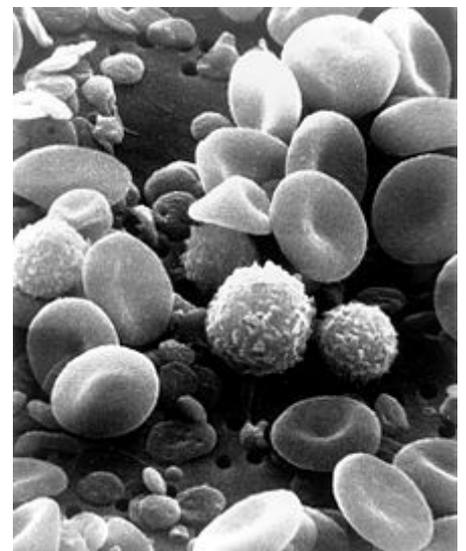
become slightly acidic, while semen contains defensins and zinc to kill pathogens.<sup>[25][26]</sup> In the stomach, gastric acid serves as a powerful chemical defense against ingested pathogens.<sup>[27]</sup>

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.<sup>[28]</sup> As a result of the symbiotic relationship between commensals and the immune system, the probability that pathogens will reach sufficient numbers to cause illness is reduced. 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).<sup>[29]</sup> There is good evidence that re-introduction of probiotic flora, such as pure cultures of the lactobacilli normally found in unpasteurized yogurt, helps restore a healthy balance of microbial populations in intestinal infections in children and encouraging preliminary data in studies on bacterial gastroenteritis, inflammatory bowel diseases, urinary tract infection and post-surgical infections.<sup>[30][31][32]</sup>

## Cellular components

Leukocytes (white blood cells) act like independent, single-celled organisms and are the second arm of the innate immune system.<sup>[7]</sup> The innate leukocytes include the phagocytes (macrophages, neutrophils, and dendritic cells), innate lymphoid 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.<sup>[33]</sup> Innate cells are also important mediators in lymphoid organ development and the activation of the adaptive immune system.<sup>[34]</sup>

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.<sup>[7]</sup> 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.<sup>[35][36]</sup> Phagocytosis evolved as a means of acquiring nutrients, but this role was extended in phagocytes to include engulfment of pathogens as a defense mechanism.<sup>[37]</sup> Phagocytosis probably represents the oldest form of host defense, as phagocytes have been identified in both vertebrate and invertebrate animals.<sup>[38]</sup>



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.

## Phagocytes

Neutrophils and macrophages are phagocytes that travel throughout the body in pursuit of invading pathogens.<sup>[39]</sup> 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,<sup>[40]</sup> and consisting of neutrophil-killer and neutrophil-cager subpopulations. 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 cytokines, while they can also act as scavengers that rid the body of worn-out cells and other debris, and as antigen-presenting cells that activate the adaptive immune system.<sup>[41]</sup>

## Dendritic cells

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.<sup>[42]</sup> They are named for their resemblance to neuronal dendrites, as both have many spine-like projections, but dendritic cells are in no way connected to the nervous system. Dendritic cells serve as a link between the bodily tissues and the innate and adaptive immune systems, as they present antigens to T cells, one of the key cell types of the adaptive immune system.<sup>[42]</sup>

## Granulocytes

Granulocytes are leukocytes that have granules in their cytoplasm. In this category are neutrophils, mast cells, basophils, and eosinophils. Mast cells reside in connective tissues and mucous membranes, and regulate the inflammatory response.<sup>[43]</sup> They are most often associated with allergy and anaphylaxis.<sup>[40]</sup> 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.<sup>[44]</sup>

## Innate lymphoid cells

Innate lymphoid cells (ILCs) are a group of innate immune cells that are derived from common lymphoid progenitor (CLP) and belong to the lymphoid lineage. These cells are defined by absence of antigen specific B or T cell receptor because of the lack of recombination activating gene (RAG). ILCs do not express myeloid or dendritic cell markers.<sup>[45]</sup>

Natural killer cells, one of member ILCs, are lymphocytes and a component of the innate immune system which does not directly attack invading microbes.<sup>[46]</sup> Rather, NK cells destroy compromised host cells, such as tumor cells or virus-infected cells, recognizing such cells by a condition known as "missing self." This term describes cells with low levels of a cell-surface marker called MHC I (major histocompatibility complex)—a situation that can arise in viral infections of host cells.<sup>[33]</sup> They were named "natural killer" because of the initial notion that they do not require activation in order to kill cells that are "missing self." For many years it was unclear how NK cells recognize tumor cells and infected cells. It is now known that the MHC makeup on the surface of those cells is altered and the NK cells become activated through recognition of "missing self". Normal body cells are not recognized and attacked by NK cells because they express intact self MHC antigens. Those MHC antigens are recognized by killer cell immunoglobulin receptors (KIR) which essentially put the brakes on NK cells.<sup>[47]</sup>

## Inflammation

Inflammation is one of the first responses of the immune system to infection.<sup>[48]</sup> The symptoms of inflammation are redness, swelling, heat, and pain, which are caused by increased blood flow into tissue. Inflammation is produced by eicosanoids and cytokines, which are released by injured or infected cells. Eicosanoids include prostaglandins that produce fever and the dilation of blood vessels associated with inflammation, and leukotrienes that attract certain white blood cells (leukocytes).<sup>[49][50]</sup> 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.<sup>[51]</sup> 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.<sup>[52]</sup>

## Complement system

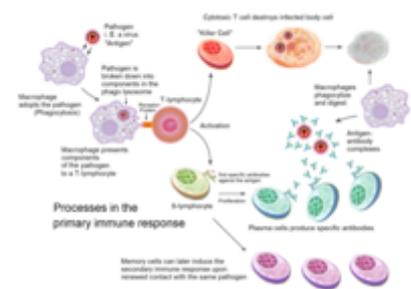
The complement system is a biochemical cascade that attacks the surfaces of foreign cells. It contains over 20 different proteins and is named for its ability to "complement" the killing of pathogens by antibodies. Complement is the major humoral component of the innate immune response.<sup>[53][54]</sup> Many species have complement systems, including non-mammals like plants, fish, and some invertebrates.<sup>[33]</sup>

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.<sup>[55]</sup> The speed of the response is a result of signal amplification that occurs after 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.<sup>[56]</sup> 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.<sup>[53]</sup>

## Adaptive immune system

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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.<sup>[57]</sup> 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.



Overview of the processes involved in the primary immune response

## The recognition of antigen

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.<sup>[33]</sup> B cells are involved in the humoral immune response, whereas T cells are involved in cell-mediated immune response.

Killer T cells only recognize antigens coupled to Class I MHC molecules, while helper T cells and regulatory T cells only recognize antigens coupled to Class II MHC molecules. These two mechanisms of antigen presentation reflect the different roles of the two types of T cell. A third, minor subtype are the  $\gamma\delta$  T cells that recognize intact antigens that are not bound to MHC receptors.<sup>[58]</sup> The double-positive T cells are exposed to a wide variety of self-antigens in the thymus, in which iodine is necessary for its thymus development and activity.<sup>[59]</sup>

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.<sup>[33]</sup>

## Antigen presentation to T lymphocytes

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.

## Cell mediated immunity

There are two major subtypes of T cells: the killer T cell and the helper T cell. In addition there are regulatory T cells which have a role in modulating immune response.

### Killer T cells

Killer T cells are a sub-group of T cells that kill cells that are infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional.<sup>[60]</sup> As with B cells, each type of T cell recognizes a different antigen. Killer T cells are activated when their T-cell receptor (TCR) binds to this specific antigen in a complex with the MHC Class I receptor of another cell. Recognition of this MHC:antigen complex is aided by a co-receptor on the T cell, called CD8. The T cell then travels throughout the body in search of cells where the MHC I receptors bear this antigen. When an activated T cell contacts such cells, it releases cytotoxins, such as perforin, which form pores in the target cell's plasma membrane, allowing ions, water and toxins to enter. The entry of another toxin called granulysin (a protease) induces the target cell to undergo apoptosis.<sup>[61]</sup> 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).<sup>[61]</sup>

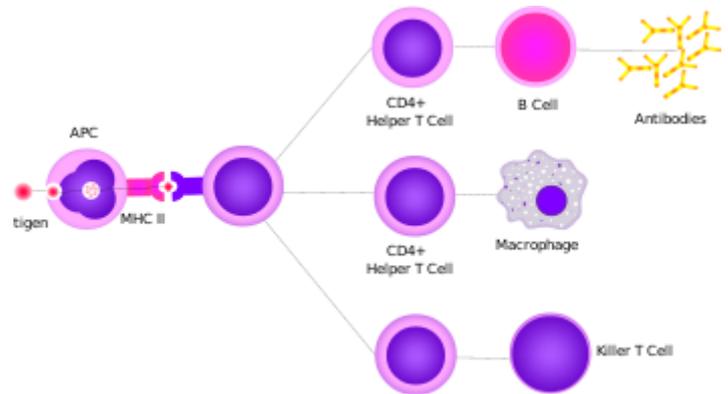
### Helper T cells

Helper T cells regulate both the innate and adaptive immune responses and help determine which immune responses the body makes to a particular pathogen.<sup>[62][63]</sup> 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.<sup>[64]</sup> 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.<sup>[7]</sup> 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.<sup>[65]</sup>

## Gamma delta T cells

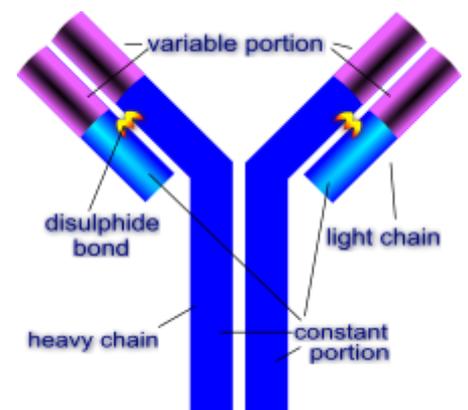
Gamma delta T cells ( $\gamma\delta$  T cells) possess an alternative T-cell receptor (TCR) as opposed to CD4+ and CD8+ ( $\alpha\beta$ ) T cells and share the characteristics of helper T cells, cytotoxic T cells and NK cells. The conditions that produce responses from  $\gamma\delta$  T cells are not fully understood. Like other 'unconventional' T cell subsets bearing invariant TCRs, such as CD1d-restricted natural killer T cells,  $\gamma\delta$  T cells straddle the border between innate and adaptive immunity.<sup>[66]</sup> On one hand,  $\gamma\delta$  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 V $\gamma$ 9/V $\delta$ 2 T cells respond within hours to common molecules produced by microbes, and highly restricted V $\delta$ 1+ T cells in epithelia respond to stressed epithelial cells.<sup>[58]</sup>



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.

## The humoral immune response

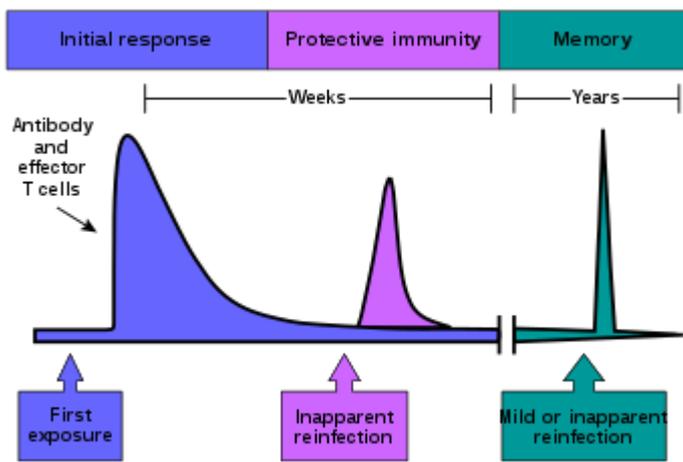
A B cell identifies pathogens when antibodies on its surface bind to a specific foreign antigen.<sup>[68]</sup> This antigen/antibody complex is taken up by the B cell and processed by proteolysis into peptides. The B cell then displays these antigenic peptides on its surface MHC class II molecules. This combination of MHC and antigen attracts a matching helper T cell, which releases lymphokines and activates the B cell.<sup>[69]</sup> 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.<sup>[70]</sup>



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.<sup>[67]</sup>

## Immunological memory

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



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.

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.<sup>[78]</sup> Other hormones appear to regulate the immune system as well, most notably prolactin, growth hormone and vitamin D.<sup>[79][80]</sup>

## Vitamin D

When a T-cell encounters a foreign pathogen, it extends a vitamin D receptor. This is essentially a signaling device that allows the T-cell to bind to the active form of vitamin D, the steroid hormone calcitriol. T-cells have a symbiotic relationship with vitamin D. Not only does the T-cell extend a vitamin D receptor, in essence asking to bind to the steroid hormone version of vitamin D, calcitriol, but the T-cell expresses the gene CYP27B1, which is the gene responsible for converting the pre-hormone version of vitamin D, calcidiol into the steroid hormone version, calcitriol. Only after binding to calcitriol can T-cells perform their intended function. Other immune system cells that are known to express CYP27B1 and thus activate vitamin D calcidiol, are dendritic cells, keratinocytes and macrophages.<sup>[81][82]</sup>

It is conjectured that a progressive decline in hormone levels with age is partially responsible for weakened immune responses in aging individuals.<sup>[83]</sup> Conversely, some hormones are regulated by the immune system, notably thyroid hormone activity.<sup>[84]</sup> The age-related decline in immune function is also related to decreasing vitamin D levels in the elderly. As people age, two things happen that negatively affect their vitamin D levels. First, they stay indoors more due to decreased activity levels. This means that they get less sun and therefore produce less cholecalciferol via UVB radiation. Second, as a person ages the skin becomes less adept at producing vitamin D.<sup>[85]</sup>

## Sleep and rest

The immune system is affected by sleep and rest,<sup>[86]</sup> and sleep deprivation is detrimental to immune function.<sup>[87]</sup> Complex feedback loops involving cytokines, such as interleukin-1 and tumor necrosis factor- $\alpha$  produced in response to infection, appear to also play a role in the regulation of non-rapid eye movement (REM) sleep.<sup>[88]</sup> Thus the immune response to infection may result in changes to the sleep cycle, including an increase in slow-wave sleep relative to REM sleep.<sup>[89]</sup>

## Physiological regulation

The immune system is involved in many aspects of physiological regulation in the body. The immune system interacts intimately with other systems, such as the endocrine <sup>[71][72]</sup> and the nervous <sup>[73][74][75]</sup> systems. The immune system also plays a crucial role in embryogenesis (development of the embryo), as well as in tissue repair and regeneration.

## Hormones

Hormones can act as immunomodulators, altering the sensitivity of the immune system. For example, female sex hormones are known immunostimulators of both adaptive<sup>[76]</sup> and innate immune responses.<sup>[77]</sup> Some

When suffering from sleep deprivation, active immunizations may have a diminished effect and may result in lower antibody production, and a lower immune response, than would be noted in a well-rested individual. Additionally, proteins such as NFIL3, which have been shown to be closely intertwined with both T-cell differentiation and our circadian rhythms, can be affected through the disturbance of natural light and dark cycles through instances of sleep deprivation, shift work, etc. As a result, these disruptions can lead to an increase in chronic conditions such as heart disease, chronic pain, and asthma.<sup>[90]</sup>

In addition to the negative consequences of sleep deprivation, sleep and the intertwined circadian system have been shown to have strong regulatory effects on immunological functions affecting both the innate and the adaptive immunity. First, during the early slow-wave-sleep stage, a sudden drop in blood levels of cortisol, epinephrine, and norepinephrine induce increased blood levels of the hormones leptin, pituitary growth hormone, and prolactin. These signals induce a pro-inflammatory state through the production of the pro-inflammatory cytokines interleukin-1, interleukin-12, TNF-alpha and IFN-gamma. These cytokines then stimulate immune functions such as immune cells activation, proliferation, and differentiation. It is during this time that undifferentiated, or less differentiated, like naïve and central memory T cells, peak (i.e. during a time of a slowly evolving adaptive immune response). In addition to these effects, the milieu of hormones produced at this time (leptin, pituitary growth hormone, and prolactin) support the interactions between APCs and T-cells, a shift of the T<sub>h</sub>1/T<sub>h</sub>2 cytokine balance towards one that supports T<sub>h</sub>1, an increase in overall T<sub>h</sub> cell proliferation, and naïve T cell migration to lymph nodes. This milieu is also thought to support the formation of long-lasting immune memory through the initiation of Th1 immune responses.<sup>[91]</sup>

In contrast, during wake periods differentiated effector cells, such as cytotoxic natural killer cells and CTLs (cytotoxic T lymphocytes), peak in order to elicit an effective response against any intruding pathogens. As well during awake active times, anti-inflammatory molecules, such as cortisol and catecholamines, peak. There are two theories as to why the pro-inflammatory state is reserved for sleep time. First, inflammation would cause serious cognitive and physical impairments if it were to occur during wake times. Second, inflammation may occur during sleep times due to the presence of melatonin. Inflammation causes a great deal of oxidative stress and the presence of melatonin during sleep times could actively counteract free radical production during this time.<sup>[91][92]</sup>

## Nutrition and diet

Overnutrition is 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.<sup>[93]</sup>

Foods rich in certain fatty acids may foster a healthy immune system.<sup>[94]</sup> Likewise, fetal undernourishment can cause a lifelong impairment of the immune system.<sup>[95]</sup>

## Repair and regeneration

The immune system, particularly the innate component, plays a decisive role in tissue repair after an insult.<sup>[96][97][98][99][100]</sup> Key actors include macrophages and neutrophils, but other cellular actors, including  $\gamma\delta$  T cells, innate lymphoid cells (ILCs), and regulatory T cells (Tregs), are also important. The plasticity of immune cells and the balance between pro-inflammatory and anti-inflammatory signals are crucial aspects of efficient tissue repair.<sup>[100]</sup> Immune components and pathways are involved in regeneration as well, for example in amphibians. According to one hypothesis, organisms that can regenerate could be less immunocompetent than organisms that cannot regenerate.<sup>[101][102]</sup>

## Disorders of human immunity

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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.<sup>[103][104]</sup> In developed countries, obesity, alcoholism, and drug use are common causes of poor immune function, while malnutrition is the most common cause of immunodeficiency in developing countries.<sup>[104]</sup> Diets lacking sufficient protein are associated with impaired cell-mediated immunity, complement activity, phagocyte function, IgA antibody concentrations, and cytokine production. Additionally, the loss of the thymus at an early age through genetic mutation or surgical removal results in severe immunodeficiency and a high susceptibility to infection.<sup>[105]</sup>

Immunodeficiencies can also be inherited or 'acquired'.<sup>[7]</sup> 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.<sup>[106][107]</sup>

## Autoimmunity

Overactive immune responses form 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.<sup>[108]</sup> 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.<sup>[68]</sup>

## 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, which triggers degranulation of mast cells and basophils when cross-linked by antigen.<sup>[109]</sup> 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.<sup>[109]</sup> Immune complexes (aggregations of antigens, complement proteins, and IgG and IgM antibodies) deposited in various tissues trigger Type III hypersensitivity reactions.<sup>[109]</sup> 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.<sup>[109]</sup>

## Idiopathic inflammation

Inflammation is one of the first responses of the immune system to infection,<sup>[48]</sup> but it can appear without known cause.

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).<sup>[49][50]</sup> 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.<sup>[51]</sup> 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.<sup>[52]</sup>

## Manipulation in medicine

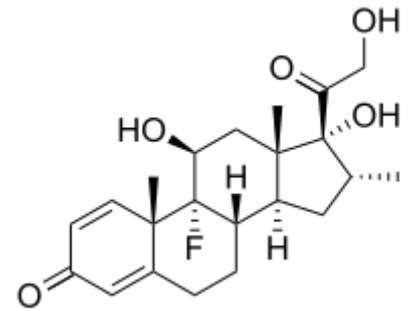
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The immune response can be manipulated to suppress unwanted responses resulting from autoimmunity, allergy, and transplant rejection, and to stimulate protective responses against pathogens that largely elude the immune system (see immunization) or cancer.

### Immunosuppression

Immunosuppressive drugs are used to control autoimmune disorders or inflammation when excessive tissue damage occurs, and to prevent transplant rejection after an organ transplant.<sup>[33][110]</sup>

Anti-inflammatory drugs are often used to control the effects of inflammation. Glucocorticoids are the most powerful of these drugs; however, these drugs can have many undesirable side effects, such as central obesity, hyperglycemia, osteoporosis, and their use must be tightly controlled.<sup>[111]</sup> 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.<sup>[110]</sup> Immunosuppressive drugs such as cyclosporin prevent T cells from responding to signals correctly by inhibiting signal transduction pathways.<sup>[112]</sup>



The immunosuppressive drug dexamethasone

### Immunostimulation

Cancer immunotherapy covers the medical ways to stimulate the immune system to attack cancer tumours.

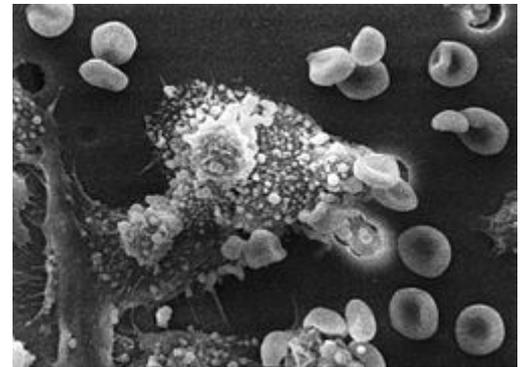
### Vaccination

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.<sup>[7]</sup> 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.<sup>[33][113]</sup>

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.<sup>[7]</sup> 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.<sup>[114]</sup>

## Tumor immunology

Another important role of the immune system is to identify and eliminate tumors. This is called **immune surveillance**. The *transformed cells* of tumors express antigens that are not found on normal cells. To the immune system, these antigens appear foreign, and their presence causes immune cells to attack the transformed tumor cells. The antigens expressed by tumors have several sources;<sup>[116]</sup> some are derived from oncogenic viruses like human papillomavirus, which causes cancer of the cervix,<sup>[117]</sup> vulva, vagina, penis, anus, mouth, and throat,<sup>[118]</sup> 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.<sup>[119][120]</sup> 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.<sup>[116][121][122]</sup>



Macrophages have identified a cancer cell (the large, spiky mass). Upon fusing with the cancer cell, the macrophages (smaller white cells) inject toxins that kill the tumor cell. Immunotherapy for the treatment of cancer is an active area of medical research.<sup>[115]</sup>

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.<sup>[120][123]</sup> 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.<sup>[124]</sup> 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.<sup>[125]</sup> Sometimes antibodies are generated against tumor cells allowing for their destruction by the complement system.<sup>[121]</sup>

Clearly, some tumors evade the immune system and go on to become cancers.<sup>[126][127]</sup> Tumor cells often have a reduced number of MHC class I molecules on their surface, thus avoiding detection by killer T cells.<sup>[124][126]</sup> Some tumor cells also release products that inhibit the immune response; for example by secreting the cytokine TGF- $\beta$ , which suppresses the activity of macrophages and lymphocytes.<sup>[126][128]</sup> In addition, immunological tolerance may develop against tumor antigens, so the immune system no longer attacks the tumor cells.<sup>[126][127]</sup>

Paradoxically, macrophages can promote tumor growth<sup>[129]</sup> when tumor cells send out cytokines that attract macrophages, which then generate cytokines and growth factors such as tumor-necrosis factor alpha that nurture tumor development or promote stem-cell-like plasticity.<sup>[126]</sup> 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.<sup>[126]</sup> Anti-tumor M1 macrophages are recruited in early phases to tumor development but are progressively differentiated to M2 with pro-tumor effect, an immunosuppressor switch. The hypoxia reduces the cytokine production for the anti-tumor response and progressively macrophages acquire pro-tumor M2 functions driven by the tumor microenvironment, including IL-4 and IL-10.<sup>[130]</sup>

## Predicting immunogenicity

Larger drugs (>500 Da) can provoke a neutralizing immune response, meaning that the immune system produces neutralizing antibodies that counteract the action of the drugs, 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).<sup>[131]</sup> 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,<sup>[132]</sup> 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.<sup>[133]</sup> A publicly accessible database has been established for the cataloguing of epitopes from pathogens known to be recognizable by B cells.<sup>[134]</sup> The emerging field of bioinformatics-based studies of immunogenicity is referred to as immunoinformatics.<sup>[135]</sup> Immunoproteomics is the study of large sets of proteins (proteomics) involved in the immune response.

## Evolution and other mechanisms

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### Evolution of the immune system

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.<sup>[1]</sup> 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.<sup>[136]</sup> 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.<sup>[137][138]</sup> Prokaryotes also possess other defense mechanisms.<sup>[139][140]</sup> Offensive elements of the immune systems are also present in unicellular eukaryotes, but studies of their roles in defense are few.<sup>[141]</sup>

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.<sup>[1]</sup> 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.<sup>[142]</sup>

Unlike animals, plants lack phagocytic cells, but many plant immune responses involve systemic chemical signals that are sent through a plant.<sup>[143]</sup> Individual plant cells respond to molecules associated with pathogens known as Pathogen-associated molecular patterns or PAMPs.<sup>[144]</sup> 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.<sup>[143]</sup> RNA silencing mechanisms are particularly important in this systemic response as they can block virus replication.<sup>[145]</sup>

### Alternative adaptive immune system

Evolution of the adaptive immune system occurred in an ancestor of the jawed vertebrates. Many of the classical molecules of the adaptive immune system (e.g., immunoglobulins and T-cell receptors) exist only in jawed vertebrates. However, a distinct lymphocyte-derived molecule has been discovered in primitive jawless vertebrates, such as the lamprey and hagfish. These animals possess a large array of molecules called Variable lymphocyte receptors (VLRs) that, like the antigen receptors of jawed vertebrates, are produced from only a small number (one or two) of genes. These molecules are believed to bind pathogenic antigens in a similar way to antibodies, and with the same degree of specificity.<sup>[146]</sup>

## Manipulation by pathogens

The success of any pathogen depends on its ability to elude host immune responses. Therefore, pathogens evolved several methods that allow them to successfully infect a host, while evading detection or destruction by the immune system.<sup>[147]</sup> Bacteria often overcome physical barriers by secreting enzymes that digest the barrier, for example, by using a type II secretion system.<sup>[148]</sup> 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.<sup>[149]</sup>

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.<sup>[150]</sup> Many pathogens secrete compounds that diminish or misdirect the host's immune response.<sup>[147]</sup> 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.<sup>[151]</sup> 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).<sup>[152]</sup>

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.<sup>[153]</sup> 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.<sup>[154]</sup> Masking antigens with host molecules is another common strategy for avoiding detection by the immune system. In HIV, the envelope that covers the virion is formed from the outermost membrane of the host cell; such "self-cloaked" viruses make it difficult for the immune system to identify them as "non-self" structures.<sup>[155]</sup>

## History of immunology

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Immunology is a science that examines the structure and function of the immune system. It originates from medicine and early studies on the causes of immunity to disease. The earliest known reference to immunity was during the plague of Athens in 430 BC. Thucydides noted that people who had recovered from a previous bout of the disease could nurse the sick without contracting the illness a second time.<sup>[156]</sup> In the 18th century, Pierre-Louis Moreau de Maupertuis made experiments with scorpion venom and observed that certain dogs and mice were immune to this venom.<sup>[157]</sup> In the 10th century, Persian physician al-Razi (also known as Rhazes) wrote the first recorded theory of acquired immunity,<sup>[158][159]:6</sup> noting that a smallpox bout protected

its survivors from future infections. Although he explained the immunity in terms of "excess moisture" getting expelled from the blood—therefore preventing the disease to occur for a second time—this theory explained many observations about smallpox known during this time.<sup>[159]:7</sup>

These and other observations of acquired immunity were later exploited by Louis Pasteur in his development of vaccination and his proposed germ theory of disease.<sup>[160]</sup> 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.<sup>[161]</sup> Viruses were confirmed as human pathogens in 1901, with the discovery of the yellow fever virus by Walter Reed.<sup>[162]</sup>

Immunology made a great advance towards the end of the 19th century, through rapid developments, in the study of humoral immunity and cellular immunity.<sup>[163]</sup> 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.<sup>[164]</sup>

## Theoretical approaches to the immune system

Immunology is strongly experimental in everyday practice but is also characterized by an ongoing theoretical attitude. Many theories have been suggested in immunology from the end of the nineteenth century up to the present time. The end of the 19th century and the beginning of the 20th century saw a battle between "cellular" and "humoral" theories of immunity. According to the cellular theory of immunity, represented in particular by Elie Metchnikoff, it was cells—more precisely, phagocytes—that were responsible for immune responses. In contrast, the humoral theory of immunity, held, among others, by Robert Koch and Emil von Behring, stated that the active immune agents were soluble components (molecules) found in the organism's "humors" rather than its cells.<sup>[159][165][166]</sup>

In the mid-1950s, Frank Burnet, inspired by a suggestion made by Niels Jerne,<sup>[167]</sup> formulated the clonal selection theory (CST) of immunity.<sup>[168]</sup> On the basis of CST, Burnet developed a theory of how an immune response is triggered according to the self/nonself distinction: "self" constituents (constituents of the body) do not trigger destructive immune responses, while "nonself" entities (pathogens, an allograft) trigger a destructive immune response.<sup>[169]</sup> The theory was later modified to reflect new discoveries regarding histocompatibility or the complex "two-signal" activation of T cells.<sup>[170]</sup> The self/nonself theory of immunity and the self/nonself vocabulary have been criticized,<sup>[166][171][172]</sup> but remain very influential.<sup>[173][174]</sup>

More recently, several theoretical frameworks have been suggested in immunology, including "autopoietic" views,<sup>[175]</sup> "cognitive immune" views,<sup>[176]</sup> the "danger model" (or "danger theory"),<sup>[171]</sup> and the "discontinuity" theory.<sup>[177][178][179]</sup> The danger model, suggested by Polly Matzinger and colleagues, has been very influential, arousing many comments and discussions.<sup>[180][181][182][183]</sup>

## Organs

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The following organs and body parts play a role in the immune system.

- Lymphatic vessels
- Lymph nodes
- Thymus
- Spleen
- Bone marrow

- [Appendix](#)
- [Tonsils](#)
- [Adenoid](#)
- [Peyer's patches](#)

## See also

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- [Cataphylaxis](#)
- [Clonal selection](#)
- [Fc receptor](#)
- [Hapten](#)
- [Human physiology](#)
- [Immune network theory](#)
- [Immune system receptors](#)
- [ImmunoGrid, a project to model the mammalian, and specifically human, immune system using Grid technologies](#)
- [Immunoproteomics](#)
- [Immunostimulator](#)
- [Original antigenic sin](#)
- [Plant disease resistance](#)
- [Polyclonal response](#)
- [Tumor antigens](#)
- [Vaccine-naive](#)
- [Mucosal immunology](#)

## References

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1. Beck G, Habitat GS (November 1996). "Immunity and the Invertebrates" (<http://www.scs.carleton.ca/~soma/biosec/readings/sharkimmu-sciam-Nov1996.pdf>) (PDF). *Scientific American*. **275** (5): 60–66. Bibcode:1996SciAm.275e..60B (<https://ui.adsabs.harvard.edu/abs/1996SciAm.275e..60B>). doi:10.1038/scientificamerican1196-60 (<https://doi.org/10.1038%2Fscientificamerican1196-60>). PMID 8875808 (<https://pubmed.ncbi.nlm.nih.gov/8875808>). Retrieved 1 January 2007.
2. O'Byrne KJ, Dalglish AG (August 2001). "Chronic immune activation and inflammation as the cause of malignancy" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2364095>). *British Journal of Cancer*. **85** (4): 473–83. doi:10.1054/bjoc.2001.1943 (<https://doi.org/10.1054%2Fbjoc.2001.1943>). PMC 2364095 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2364095>). PMID 11506482 (<https://pubmed.ncbi.nlm.nih.gov/11506482>).
3. Litman GW, Cannon JP, Dishaw LJ (November 2005). "Reconstructing immune phylogeny: new perspectives" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683834>). *Nature Reviews. Immunology*. **5** (11): 866–79. doi:10.1038/nri1712 (<https://doi.org/10.1038%2Fnri1712>). PMC 3683834 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3683834>). PMID 16261174 (<https://pubmed.ncbi.nlm.nih.gov/16261174>).
4. Restifo NP, Gattinoni L (October 2013). "Lineage relationship of effector and memory T cells" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858177>). *Current Opinion in Immunology*. **25** (5): 556–63. doi:10.1016/j.coi.2013.09.003 (<https://doi.org/10.1016%2Fj.coi.2013.09.003>). PMC 3858177 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3858177>). PMID 24148236 (<https://pubmed.ncbi.nlm.nih.gov/24148236>).

5. Kurosaki T, Kometani K, Ise W (March 2015). "Memory B cells". *Nature Reviews. Immunology*. **15** (3): 149–59. doi:10.1038/nri3802 (<https://doi.org/10.1038/nri3802>). PMID 25677494 (<https://pubmed.ncbi.nlm.nih.gov/25677494>).
6. Smith A.D. (Ed) *Oxford dictionary of biochemistry and molecular biology*. (2000) [1997] Oxford University Press. ISBN 0-19-854768-4, p. 592
7. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walters P (2002). *Molecular Biology of the Cell* (<https://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=mboc4.TOC&depth=2>) (Fourth ed.). New York and London: Garland Science. ISBN 978-0-8153-3218-3.
8. Saji F, Samejima Y, Kamiura S, Koyama M (May 1999). "Dynamics of immunoglobulins at the fetomaternal interface". *Reviews of Reproduction*. **4** (2): 81–89. doi:10.1530/ror.0.0040081 (<https://doi.org/10.1530/ror.0.0040081>). PMID 10357095 (<https://pubmed.ncbi.nlm.nih.gov/10357095>).
9. Van de Perre P (July 2003). "Transfer of antibody via mother's milk". *Vaccine*. **21** (24): 3374–76. doi:10.1016/S0264-410X(03)00336-0 ([https://doi.org/10.1016/S0264-410X\(03\)00336-0](https://doi.org/10.1016/S0264-410X(03)00336-0)). PMID 12850343 (<https://pubmed.ncbi.nlm.nih.gov/12850343>).
10. Keller MA, Stiehm ER (October 2000). "Passive immunity in prevention and treatment of infectious diseases" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC88952>). *Clinical Microbiology Reviews*. **13** (4): 602–14. doi:10.1128/CMR.13.4.602-614.2000 (<https://doi.org/10.1128/CMR.13.4.602-614.2000>). PMC 88952 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC88952>). PMID 11023960 (<https://pubmed.ncbi.nlm.nih.gov/11023960>).
11. Medzhitov R (October 2007). "Recognition of microorganisms and activation of the immune response". *Nature*. **449** (7164): 819–26. Bibcode:2007Natur.449..819M (<https://ui.adsabs.harvard.edu/abs/2007Natur.449..819M>). doi:10.1038/nature06246 (<https://doi.org/10.1038/nature06246>). PMID 17943118 (<https://pubmed.ncbi.nlm.nih.gov/17943118>).
12. Matzinger P (April 2002). "The danger model: a renewed sense of self" (<http://www.scs.carleton.ca/~soma/biosec/readings/matzinger-science.pdf>) (PDF). *Science*. **296** (5566): 301–05. Bibcode:2002Sci...296..301M (<https://ui.adsabs.harvard.edu/abs/2002Sci...296..301M>). doi:10.1126/science.1071059 (<https://doi.org/10.1126/science.1071059>). PMID 11951032 (<https://pubmed.ncbi.nlm.nih.gov/11951032>). S2CID 13615808 (<https://api.semanticscholar.org/CorpusID:13615808>).
13. Kumar H, Kawai T, Akira S (February 2011). "Pathogen recognition by the innate immune system". *International Reviews of Immunology*. **30** (1): 16–34. doi:10.3109/08830185.2010.529976 (<https://doi.org/10.3109/08830185.2010.529976>). PMID 21235323 (<https://pubmed.ncbi.nlm.nih.gov/21235323>).
14. Alberts B, Johnson A, Lewis J, Raff M, Roberts K, Walter P (2002). "Innate Immunity" (<https://www.ncbi.nlm.nih.gov/books/NBK26846/>). *Molecular Biology of the Cell* (4th ed.). New York: Garland Science – via NCBI Bookshelf.
15. Schroder K, Tschopp J (March 2010). "The inflammasomes". *Cell*. **140** (6): 821–32. doi:10.1016/j.cell.2010.01.040 (<https://doi.org/10.1016/j.cell.2010.01.040>). PMID 20303873 (<https://pubmed.ncbi.nlm.nih.gov/20303873>). S2CID 16916572 (<https://api.semanticscholar.org/CorpusID:16916572>).
16. Beutler B, Jiang Z, Georgel P, Crozat K, Croker B, Rutschmann S, Du X, Hoebe K (2006). "Genetic analysis of host resistance: Toll-like receptor signaling and immunity at large" (<https://api.semanticscholar.org/paper/c8b16a237b5f46b8ad6de013d140ddba41fff614>). *Annual Review of Immunology*. **24**: 353–89. doi:10.1146/annurev.immunol.24.021605.090552 (<https://doi.org/10.1146/annurev.immunol.24.021605.090552>). PMID 16551253 (<https://pubmed.ncbi.nlm.nih.gov/16551253>). S2CID 20991617 (<https://api.semanticscholar.org/CorpusID:20991617>).
17. Botos I, Segal DM, Davies DR (April 2011). "The structural biology of Toll-like receptors" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3075535>). *Structure*. **19** (4): 447–59. doi:10.1016/j.str.2011.02.004 (<https://doi.org/10.1016/j.str.2011.02.004>). PMC 3075535 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3075535>). PMID 21481769 (<https://pubmed.ncbi.nlm.nih.gov/21481769>).

18. Takeda K, Kaisho T, Akira S (2003). "Toll-like receptors". *Annual Review of Immunology*. **21**: 335–76. doi:10.1146/annurev.immunol.21.120601.141126 (<https://doi.org/10.1146%2Fannurev.immunol.21.120601.141126>). PMID 12524386 (<https://pubmed.ncbi.nlm.nih.gov/12524386>).
19. Thompson MR, Kaminski JJ, Kurt-Jones EA, Fitzgerald KA (June 2011). "Pattern recognition receptors and the innate immune response to viral infection" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186011>). *Viruses*. **3** (6): 920–40. doi:10.3390/v3060920 (<https://doi.org/10.3390%2Fv3060920>). PMC 3186011 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3186011>). PMID 21994762 (<https://pubmed.ncbi.nlm.nih.gov/21994762>).
20. Platnich JM, Muruve DA (February 2019). "NOD-like receptors and inflammasomes: A review of their canonical and non-canonical signaling pathways". *Archives of Biochemistry and Biophysics*. **670**: 4–14. doi:10.1016/j.abb.2019.02.008 (<https://doi.org/10.1016%2Fj.abb.2019.02.008>). PMID 30772258 (<https://pubmed.ncbi.nlm.nih.gov/30772258>).
21. Boyton RJ, Openshaw PJ (2002). "Pulmonary defences to acute respiratory infection" (<https://doi.org/10.1093/bmb/61.1.1>). *British Medical Bulletin*. **61** (1): 1–12. doi:10.1093/bmb/61.1.1 (<https://doi.org/10.1093%2Fbmb%2F61.1.1>). PMID 11997295 (<https://pubmed.ncbi.nlm.nih.gov/11997295>).
22. Agerberth B, Gudmundsson GH (2006). "Host antimicrobial defence peptides in human disease". *Current Topics in Microbiology and Immunology*. **306**: 67–90. doi:10.1007/3-540-29916-5\_3 ([https://doi.org/10.1007%2F3-540-29916-5\\_3](https://doi.org/10.1007%2F3-540-29916-5_3)). ISBN 978-3-540-29915-8. PMID 16909918 (<https://pubmed.ncbi.nlm.nih.gov/16909918>).
23. Moreau JM, Girgis DO, Hume EB, Dajcs JJ, Austin MS, O'Callaghan RJ (September 2001). "Phospholipase A(2) in rabbit tears: a host defense against *Staphylococcus aureus*" (<http://iovs.arvojournals.org/article.aspx?articleid=2200058>). *Investigative Ophthalmology & Visual Science*. **42** (10): 2347–54. PMID 11527949 (<https://pubmed.ncbi.nlm.nih.gov/11527949>).
24. Hankiewicz J, Swierczek E (December 1974). "Lysozyme in human body fluids". *Clinica Chimica Acta; International Journal of Clinical Chemistry*. **57** (3): 205–09. doi:10.1016/0009-8981(74)90398-2 (<https://doi.org/10.1016%2F0009-8981%2874%2990398-2>). PMID 4434640 (<https://pubmed.ncbi.nlm.nih.gov/4434640>).
25. Fair WR, Couch J, Wehner N (February 1976). "Prostatic antibacterial factor. Identity and significance". *Urology*. **7** (2): 169–77. doi:10.1016/0090-4295(76)90305-8 (<https://doi.org/10.1016%2F0090-4295%2876%2990305-8>). PMID 54972 (<https://pubmed.ncbi.nlm.nih.gov/54972>).
26. Yenugu S, Hamil KG, Birse CE, Ruben SM, French FS, Hall SH (June 2003). "Antibacterial properties of the sperm-binding proteins and peptides of human epididymis 2 (HE2) family; salt sensitivity, structural dependence and their interaction with outer and cytoplasmic membranes of *Escherichia coli*" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1223422>). *The Biochemical Journal*. **372** (Pt 2): 473–83. doi:10.1042/BJ20030225 (<https://doi.org/10.1042%2FBJ20030225>). PMC 1223422 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1223422>). PMID 12628001 (<https://pubmed.ncbi.nlm.nih.gov/12628001>).
27. Smith JL (2003). "The role of gastric acid in preventing foodborne disease and how bacteria overcome acid conditions". *J Food Prot*. **66** (7): 1292–1303. doi:10.4315/0362-028X-66.7.1292 (<https://doi.org/10.4315%2F0362-028X-66.7.1292>). PMID 12870767 (<https://pubmed.ncbi.nlm.nih.gov/12870767>).
28. Gorbach SL (February 1990). "Lactic acid bacteria and human health". *Annals of Medicine*. **22** (1): 37–41. doi:10.3109/07853899009147239 (<https://doi.org/10.3109%2F07853899009147239>). PMID 2109988 (<https://pubmed.ncbi.nlm.nih.gov/2109988>).
29. Hill LV, Embil JA (February 1986). "Vaginitis: current microbiologic and clinical concepts" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1490817>). *CMAJ*. **134** (4): 321–31. PMC 1490817 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1490817>). PMID 3510698 (<https://pubmed.ncbi.nlm.nih.gov/3510698>).

30. Reid G, Bruce AW (August 2003). "Urogenital infections in women: can probiotics help?" (<http://www.ncbi.nlm.nih.gov/pmc/articles/PMC1742800>). *Postgraduate Medical Journal*. **79** (934): 428–32. doi:10.1136/pmj.79.934.428 (<https://doi.org/10.1136%2Fpmj.79.934.428>). PMC 1742800 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1742800>). PMID 12954951 (<https://pubmed.ncbi.nlm.nih.gov/12954951>).
31. Salminen SJ, Gueimonde M, Isolauri E (May 2005). "Probiotics that modify disease risk" (<https://doi.org/10.1093/jn/135.5.1294>). *The Journal of Nutrition*. **135** (5): 1294–98. doi:10.1093/jn/135.5.1294 (<https://doi.org/10.1093%2Fjn%2F135.5.1294>). PMID 15867327 (<https://pubmed.ncbi.nlm.nih.gov/15867327>).
32. Reid G, Jass J, Sebulsy MT, McCormick JK (October 2003). "Potential uses of probiotics in clinical practice" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC207122>). *Clinical Microbiology Reviews*. **16** (4): 658–72. doi:10.1128/CMR.16.4.658-672.2003 (<https://doi.org/10.1128%2FCMR.16.4.658-672.2003>). PMC 207122 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC207122>). PMID 14557292 (<https://pubmed.ncbi.nlm.nih.gov/14557292>).
33. Janeway CA, Jr. (2005). *Immunobiology* (6th ed.). Garland Science. ISBN 0-443-07310-4.
34. Withers DR (June 2016). "Innate lymphoid cell regulation of adaptive immunity" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5011676>). *Immunology*. **149** (2): 123–30. doi:10.1111/imm.12639 (<https://doi.org/10.1111%2Fimm.12639>). PMC 5011676 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5011676>). PMID 27341319 (<https://pubmed.ncbi.nlm.nih.gov/27341319>).
35. Ryter A (1985). "Relationship between ultrastructure and specific functions of macrophages". *Comparative Immunology, Microbiology and Infectious Diseases*. **8** (2): 119–33. doi:10.1016/0147-9571(85)90039-6 (<https://doi.org/10.1016%2F0147-9571%2885%2990039-6>). PMID 3910340 (<https://pubmed.ncbi.nlm.nih.gov/3910340>).
36. Langermans JA, Hazenbos WL, van Furth R (September 1994). "Antimicrobial functions of mononuclear phagocytes". *Journal of Immunological Methods*. **174** (1–2): 185–94. doi:10.1016/0022-1759(94)90021-3 (<https://doi.org/10.1016%2F0022-1759%2894%2990021-3>). PMID 8083520 (<https://pubmed.ncbi.nlm.nih.gov/8083520>).
37. May RC, Machesky LM (March 2001). "Phagocytosis and the actin cytoskeleton" (<http://jcs.biologists.org/cgi/pmidlookup?view=long&pmid=11228151>). *Journal of Cell Science*. **114** (Pt 6): 1061–77. PMID 11228151 (<https://pubmed.ncbi.nlm.nih.gov/11228151>).
38. Salzet M, Tasiemski A, Cooper E (2006). "Innate immunity in lophotrochozoans: the annelids". *Current Pharmaceutical Design*. **12** (24): 3043–50. doi:10.2174/138161206777947551 (<https://doi.org/10.2174%2F138161206777947551>). PMID 16918433 (<https://pubmed.ncbi.nlm.nih.gov/16918433>). S2CID 28520695 (<https://api.semanticscholar.org/CorpusID:28520695>).
39. Zen K, Parkos CA (October 2003). "Leukocyte-epithelial interactions". *Current Opinion in Cell Biology*. **15** (5): 557–64. doi:10.1016/S0955-0674(03)00103-0 (<https://doi.org/10.1016%2FS0955-0674%2803%2900103-0>). PMID 14519390 (<https://pubmed.ncbi.nlm.nih.gov/14519390>).
40. Stvrtinová V, Jakubovský J, Hulín I (1995). *Inflammation and Fever from Pathophysiology: Principles of Disease* (<https://web.archive.org/web/20010711220523/http://nic.savba.sk/logos/books/scientific/lnffever.html>). Computing Centre, Slovak Academy of Sciences: Academic Electronic Press. ISBN 80-967366-1-2. Archived from the original (<http://nic.savba.sk/logos/books/scientific/lnffever.html>) on 11 July 2001. Retrieved 1 January 2007.
41. Rua R, McGavern DB (September 2015). "Elucidation of monocyte/macrophage dynamics and function by intravital imaging" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4763596>). *Journal of Leukocyte Biology*. **98** (3): 319–32. doi:10.1189/jlb.4RI0115-006RR (<https://doi.org/10.1189%2Fjlb.4RI0115-006RR>). PMC 4763596 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4763596>). PMID 26162402 (<https://pubmed.ncbi.nlm.nih.gov/26162402>).
42. Guermonprez P, Valladeau J, Zitvogel L, Théry C, Amigorena S (2002). "Antigen presentation and T cell stimulation by dendritic cells". *Annual Review of Immunology*. **20** (1): 621–67. doi:10.1146/annurev.immunol.20.100301.064828 (<https://doi.org/10.1146%2Fannurev.immunol.20.100301.064828>). PMID 11861614 (<https://pubmed.ncbi.nlm.nih.gov/11861614>).

43. Krishnaswamy G, Ajitawi O, Chi DS (2006). "The human mast cell: an overview". *Mast Cells. Methods in Molecular Biology*. **315**. pp. 13–34. doi:10.1385/1-59259-967-2:013 (<https://doi.org/10.1385%2F1-59259-967-2%3A013>). ISBN 1-59259-967-2. PMID 16110146 (<https://pubmed.ncbi.nlm.nih.gov/16110146>).
44. Kariyawasam HH, Robinson DS (April 2006). "The eosinophil: the cell and its weapons, the cytokines, its locations". *Seminars in Respiratory and Critical Care Medicine*. **27** (2): 117–27. doi:10.1055/s-2006-939514 (<https://doi.org/10.1055%2Fs-2006-939514>). PMID 16612762 (<https://pubmed.ncbi.nlm.nih.gov/16612762>).
45. Spits H, Cupedo T (2012). "Innate lymphoid cells: emerging insights in development, lineage relationships, and function". *Annual Review of Immunology*. **30**: 647–75. doi:10.1146/annurev-immunol-020711-075053 (<https://doi.org/10.1146%2Fannurev-immunol-020711-075053>). PMID 22224763 (<https://pubmed.ncbi.nlm.nih.gov/22224763>).
46. Gabrielli S, Ortolani C, Del Zotto G, Luchetti F, Canonico B, Buccella F, Artico M, Papa S, Zamai L (2016). "The Memories of NK Cells: Innate-Adaptive Immune Intrinsic Crosstalk" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5204097>). *Journal of Immunology Research*. **2016**: 1376595. doi:10.1155/2016/1376595 (<https://doi.org/10.1155%2F2016%2F1376595>). PMC 5204097 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5204097>). PMID 28078307 (<https://pubmed.ncbi.nlm.nih.gov/28078307>).
47. Rajalingam R (2012). *Overview of the killer cell immunoglobulin-like receptor system. Methods in Molecular Biology. Methods in Molecular Biology™*. **882**. pp. 391–414. doi:10.1007/978-1-61779-842-9\_23 ([https://doi.org/10.1007%2F978-1-61779-842-9\\_23](https://doi.org/10.1007%2F978-1-61779-842-9_23)). ISBN 978-1-61779-841-2. PMID 22665247 (<https://pubmed.ncbi.nlm.nih.gov/22665247>).
48. Kawai T, Akira S (February 2006). "Innate immune recognition of viral infection". *Nature Immunology*. **7** (2): 131–37. doi:10.1038/ni1303 (<https://doi.org/10.1038%2Fni1303>). PMID 16424890 (<https://pubmed.ncbi.nlm.nih.gov/16424890>).
49. Miller SB (August 2006). "Prostaglandins in health and disease: an overview". *Seminars in Arthritis and Rheumatism*. **36** (1): 37–49. doi:10.1016/j.semarthrit.2006.03.005 (<https://doi.org/10.1016%2Fj.semarthrit.2006.03.005>). PMID 16887467 (<https://pubmed.ncbi.nlm.nih.gov/16887467>).
50. Ogawa Y, Calhoun WJ (October 2006). "The role of leukotrienes in airway inflammation". *The Journal of Allergy and Clinical Immunology*. **118** (4): 789–98, quiz 799–800. doi:10.1016/j.jaci.2006.08.009 (<https://doi.org/10.1016%2Fj.jaci.2006.08.009>). PMID 17030228 (<https://pubmed.ncbi.nlm.nih.gov/17030228>).
51. Le Y, Zhou Y, Iribarren P, Wang J (April 2004). "Chemokines and chemokine receptors: their manifold roles in homeostasis and disease" (<http://www.cmi.ustc.edu.cn/1/2/95.pdf>) (PDF). *Cellular & Molecular Immunology*. **1** (2): 95–104. PMID 16212895 (<https://pubmed.ncbi.nlm.nih.gov/16212895>).
52. Martin P, Leibovich SJ (November 2005). "Inflammatory cells during wound repair: the good, the bad and the ugly". *Trends in Cell Biology*. **15** (11): 599–607. doi:10.1016/j.tcb.2005.09.002 (<https://doi.org/10.1016%2Fj.tcb.2005.09.002>). PMID 16202600 (<https://pubmed.ncbi.nlm.nih.gov/16202600>).
53. Rus H, Cudrici C, Niculescu F (2005). "The role of the complement system in innate immunity". *Immunologic Research*. **33** (2): 103–12. doi:10.1385/IR:33:2:103 (<https://doi.org/10.1385%2FIR:33:2:103>). PMID 16234578 (<https://pubmed.ncbi.nlm.nih.gov/16234578>).
54. Degn SE, Thiel S (August 2013). "Humoral pattern recognition and the complement system". *Scandinavian Journal of Immunology*. **78** (2): 181–93. doi:10.1111/sji.12070 (<https://doi.org/10.1111%2Fsji.12070>). PMID 23672641 (<https://pubmed.ncbi.nlm.nih.gov/23672641>).
55. Liszewski MK, Farries TC, Lublin DM, Rooney IA, Atkinson JP (1996). "Control of the complement system" (<https://archive.org/details/advancesinimmuno61dixo/page/201>). *Advances in Immunology*. **61**: 201–283. doi:10.1016/S0065-2776(08)60868-8 ([https://doi.org/10.1016%2FS0065-2776\(08\)60868-8](https://doi.org/10.1016%2FS0065-2776(08)60868-8)). ISBN 978-0-12-022461-6. PMID 8834497 (<https://pubmed.ncbi.nlm.nih.gov/8834497>).

56. Sim RB, Tsiftoglou SA (February 2004). "Proteases of the complement system". *Biochemical Society Transactions*. **32** (Pt 1): 21–27. doi:10.1042/BST0320021 (<https://doi.org/10.1042%2FBST0320021>). PMID 14748705 (<https://pubmed.ncbi.nlm.nih.gov/14748705>). S2CID 24505041 (<https://api.semanticscholar.org/CorpusID:24505041>).
57. Pancer Z, Cooper MD (2006). "The evolution of adaptive immunity". *Annual Review of Immunology*. **24** (1): 497–518. doi:10.1146/annurev.immunol.24.021605.090542 (<https://doi.org/10.1146%2Fannurev.immunol.24.021605.090542>). PMID 16551257 (<https://pubmed.ncbi.nlm.nih.gov/16551257>).
58. Holtmeier W, Kabelitz D (2005). "gammadelta T cells link innate and adaptive immune responses". *Chemical Immunology and Allergy*. **86**: 151–83. doi:10.1159/000086659 (<https://doi.org/10.1159%2F000086659>). ISBN 3-8055-7862-8. PMID 15976493 (<https://pubmed.ncbi.nlm.nih.gov/15976493>).
59. Venturi S, Venturi M (September 2009). "Iodine, thymus, and immunity". *Nutrition*. **25** (9): 977–79. doi:10.1016/j.nut.2009.06.002 (<https://doi.org/10.1016%2Fj.nut.2009.06.002>). PMID 19647627 (<https://pubmed.ncbi.nlm.nih.gov/19647627>).
60. Harty JT, Tvinnereim AR, White DW (2000). "CD8+ T cell effector mechanisms in resistance to infection". *Annual Review of Immunology*. **18** (1): 275–308. doi:10.1146/annurev.immunol.18.1.275 (<https://doi.org/10.1146%2Fannurev.immunol.18.1.275>). PMID 10837060 (<https://pubmed.ncbi.nlm.nih.gov/10837060>).
61. Radoja S, Frey AB, Vukmanovic S (2006). "T-cell receptor signaling events triggering granule exocytosis". *Critical Reviews in Immunology*. **26** (3): 265–90. doi:10.1615/CritRevImmUnol.v26.i3.40 (<https://doi.org/10.1615%2FCritRevImmUnol.v26.i3.40>). PMID 16928189 (<https://pubmed.ncbi.nlm.nih.gov/16928189>).
62. Abbas AK, Murphy KM, Sher A (October 1996). "Functional diversity of helper T lymphocytes". *Nature*. **383** (6603): 787–93. Bibcode:1996Natur.383..787A (<https://ui.adsabs.harvard.edu/abs/1996Natur.383..787A>). doi:10.1038/383787a0 (<https://doi.org/10.1038%2F383787a0>). PMID 8893001 (<https://pubmed.ncbi.nlm.nih.gov/8893001>).
63. McHeyzer-Williams LJ, Malherbe LP, McHeyzer-Williams MG (2006). "Helper T cell-regulated B cell immunity". *Current Topics in Microbiology and Immunology*. **311**: 59–83. doi:10.1007/3-540-32636-7\_3 ([https://doi.org/10.1007%2F3-540-32636-7\\_3](https://doi.org/10.1007%2F3-540-32636-7_3)). ISBN 978-3-540-32635-9. PMID 17048705 (<https://pubmed.ncbi.nlm.nih.gov/17048705>).
64. Kovacs B, Maus MV, Riley JL, Derimanov GS, Koretzky GA, June CH, Finkel TH (November 2002). "Human CD8+ T cells do not require the polarization of lipid rafts for activation and proliferation" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC137535>). *Proceedings of the National Academy of Sciences of the United States of America*. **99** (23): 15006–11. Bibcode:2002PNAS...9915006K (<https://ui.adsabs.harvard.edu/abs/2002PNAS...9915006K>). doi:10.1073/pnas.232058599 (<https://doi.org/10.1073%2Fpnas.232058599>). PMC 137535 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC137535>). PMID 12419850 (<https://pubmed.ncbi.nlm.nih.gov/12419850>).
65. Grewal IS, Flavell RA (1998). "CD40 and CD154 in cell-mediated immunity". *Annual Review of Immunology*. **16** (1): 111–35. doi:10.1146/annurev.immunol.16.1.111 (<https://doi.org/10.1146%2Fannurev.immunol.16.1.111>). PMID 9597126 (<https://pubmed.ncbi.nlm.nih.gov/9597126>).
66. Girardi M (January 2006). "Immunosurveillance and immunoregulation by gammadelta T cells". *The Journal of Investigative Dermatology*. **126** (1): 25–31. doi:10.1038/sj.jid.5700003 (<https://doi.org/10.1038%2Fsj.jid.5700003>). PMID 16417214 (<https://pubmed.ncbi.nlm.nih.gov/16417214>).
67. "Understanding the Immune System: How it Works" ([https://web.archive.org/web/20070103005411/http://www.niaid.nih.gov/Publications/immune/the\\_immune\\_system.pdf](https://web.archive.org/web/20070103005411/http://www.niaid.nih.gov/Publications/immune/the_immune_system.pdf)) (PDF). National Institute of Allergy and Infectious Diseases (NIAID). Archived from the original ([https://www.niaid.nih.gov/publications/immune/the\\_immune\\_system.pdf](https://www.niaid.nih.gov/publications/immune/the_immune_system.pdf)) (PDF) on 3 January 2007. Retrieved 1 January 2007.

68. Sproul TW, Cheng PC, Dykstra ML, Pierce SK (2000). "A role for MHC class II antigen processing in B cell development". *International Reviews of Immunology*. **19** (2–3): 139–55. doi:10.3109/08830180009088502 (<https://doi.org/10.3109%2F08830180009088502>). PMID 10763706 (<https://pubmed.ncbi.nlm.nih.gov/10763706>). S2CID 6550357 (<https://api.semanticscholar.org/CorpusID:6550357>).
69. Parker DC (1993). "T cell-dependent B cell activation". *Annual Review of Immunology*. **11**: 331–60. doi:10.1146/annurev.iy.11.040193.001555 (<https://doi.org/10.1146%2Fannurev.iy.11.040193.001555>). PMID 8476565 (<https://pubmed.ncbi.nlm.nih.gov/8476565>).
70. Murphy K, Weaver C (2016). "10: The Humoral Immune Response". *Immunobiology* (9 ed.). Garland Science. ISBN 978-0-8153-4505-3.
71. Wick G, Hu Y, Schwarz S, Kroemer G (October 1993). "Immunoendocrine communication via the hypothalamo-pituitary-adrenal axis in autoimmune diseases". *Endocrine Reviews*. **14** (5): 539–63. doi:10.1210/edrv-14-5-539 (<https://doi.org/10.1210%2Fedrv-14-5-539>). PMID 8262005 (<https://pubmed.ncbi.nlm.nih.gov/8262005>).
72. Kroemer G, Brezinschek HP, Faessler R, Schauenstein K, Wick G (June 1988). "Physiology and pathology of an immunoendocrine feedback loop". *Immunology Today*. **9** (6): 163–5. doi:10.1016/0167-5699(88)91289-3 (<https://doi.org/10.1016%2F0167-5699%2888%2991289-3>). PMID 3256322 (<https://pubmed.ncbi.nlm.nih.gov/3256322>).
73. Trakhtenberg EF, Goldberg JL (October 2011). "Immunology. Neuroimmune communication". *Science*. **334** (6052): 47–8. Bibcode:2011Sci...334...47T (<https://ui.adsabs.harvard.edu/abs/2011Sci...334...47T>). doi:10.1126/science.1213099 (<https://doi.org/10.1126%2Fscience.1213099>). PMID 21980100 (<https://pubmed.ncbi.nlm.nih.gov/21980100>).
74. Veiga-Fernandes H, Mucida D (May 2016). "Neuro-Immune Interactions at Barrier Surfaces" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871617>). *Cell*. **165** (4): 801–11. doi:10.1016/j.cell.2016.04.041 (<https://doi.org/10.1016%2Fj.cell.2016.04.041>). PMC 4871617 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4871617>). PMID 27153494 (<https://pubmed.ncbi.nlm.nih.gov/27153494>).
75. "Neuroimmune communication" (<https://doi.org/10.1038/nn.4496>). *Nature Neuroscience*. **20** (2): 127. February 2017. doi:10.1038/nn.4496 (<https://doi.org/10.1038%2Fnn.4496>). PMID 28092662 (<https://pubmed.ncbi.nlm.nih.gov/28092662>).
76. Wira CR, Crane-Godreau M, Grant K (2004). "Endocrine regulation of the mucosal immune system in the female reproductive tract". In Ogra PL, Mestecky J, Lamm ME, Strober W, McGhee JR, Bienenstock J (eds.). *Mucosal Immunology*. San Francisco: Elsevier. ISBN 0-12-491543-4.
77. Lang TJ (December 2004). "Estrogen as an immunomodulator". *Clinical Immunology*. **113** (3): 224–30. doi:10.1016/j.clim.2004.05.011 (<https://doi.org/10.1016%2Fj.clim.2004.05.011>). PMID 15507385 (<https://pubmed.ncbi.nlm.nih.gov/15507385>).
- Moriyama A, Shimoya K, Ogata I, Kimura T, Nakamura T, Wada H, Ohashi K, Azuma C, Saji F, Murata Y (July 1999). "Secretory leukocyte protease inhibitor (SLPI) concentrations in cervical mucus of women with normal menstrual cycle" (<https://doi.org/10.1093/molehr/5.7.656>). *Molecular Human Reproduction*. **5** (7): 656–61. doi:10.1093/molehr/5.7.656 (<https://doi.org/10.1093%2Fmolehr%2F5.7.656>). PMID 10381821 (<https://pubmed.ncbi.nlm.nih.gov/10381821>).
- Cutolo M, Sulli A, Capellino S, Villaggio B, Montagna P, Seriolo B, Straub RH (2004). "Sex hormones influence on the immune system: basic and clinical aspects in autoimmunity". *Lupus*. **13** (9): 635–38. doi:10.1191/0961203304lu1094oa (<https://doi.org/10.1191%2F0961203304lu1094oa>). PMID 15485092 (<https://pubmed.ncbi.nlm.nih.gov/15485092>).
- King AE, Critchley HO, Kelly RW (February 2000). "Presence of secretory leukocyte protease inhibitor in human endometrium and first trimester decidua suggests an antibacterial protective role" (<https://doi.org/10.1093/molehr/6.2.191>). *Molecular Human Reproduction*. **6** (2): 191–96. doi:10.1093/molehr/6.2.191 (<https://doi.org/10.1093%2Fmolehr%2F6.2.191>). PMID 10655462 (<https://pubmed.ncbi.nlm.nih.gov/10655462>).

78. Fimmel S, Zouboulis CC (2005). "Influence of physiological androgen levels on wound healing and immune status in men". *The Aging Male*. **8** (3–4): 166–74. doi:10.1080/13685530500233847 (<https://doi.org/10.1080%2F13685530500233847>). PMID 16390741 (<https://pubmed.ncbi.nlm.nih.gov/16390741>).
79. Dorshkind K, Horseman ND (June 2000). "The roles of prolactin, growth hormone, insulin-like growth factor-I, and thyroid hormones in lymphocyte development and function: insights from genetic models of hormone and hormone receptor deficiency". *Endocrine Reviews*. **21** (3): 292–312. doi:10.1210/er.21.3.292 (<https://doi.org/10.1210%2Fer.21.3.292>). PMID 10857555 (<https://pubmed.ncbi.nlm.nih.gov/10857555>).
80. Nagpal S, Na S, Rathnachalam R (August 2005). "Noncalcemic actions of vitamin D receptor ligands" (<https://doi.org/10.1210/er.2004-0002>). *Endocrine Reviews*. **26** (5): 662–87. doi:10.1210/er.2004-0002 (<https://doi.org/10.1210%2Fer.2004-0002>). PMID 15798098 (<https://pubmed.ncbi.nlm.nih.gov/15798098>).
81. von Essen MR, Kongsbak M, Schjerling P, Olgaard K, Odum N, Geisler C (April 2010). "Vitamin D controls T cell antigen receptor signaling and activation of human T cells". *Nature Immunology*. **11** (4): 344–49. doi:10.1038/ni.1851 (<https://doi.org/10.1038%2Fni.1851>). PMID 20208539 (<https://pubmed.ncbi.nlm.nih.gov/20208539>).
82. Sigmundsdottir H, Pan J, Debes GF, Alt C, Habtezion A, Soler D, Butcher EC (March 2007). "DCs metabolize sunlight-induced vitamin D3 to 'program' T cell attraction to the epidermal chemokine CCL27". *Nature Immunology*. **8** (3): 285–93. doi:10.1038/ni1433 (<https://doi.org/10.1038%2Fni1433>). PMID 17259988 (<https://pubmed.ncbi.nlm.nih.gov/17259988>).
83. Hertoghe T (December 2005). "The "multiple hormone deficiency" theory of aging: is human senescence caused mainly by multiple hormone deficiencies?" (<https://semanticscholar.org/paper/09ca0e60ff5b4733b4066454440ef8611495cb4c>). *Annals of the New York Academy of Sciences*. **1057** (1): 448–65. Bibcode:2005NYASA1057..448H (<https://ui.adsabs.harvard.edu/abs/2005NYASA1057..448H>). doi:10.1196/annals.1322.035 (<https://doi.org/10.1196%2Fannals.1322.035>). PMID 16399912 (<https://pubmed.ncbi.nlm.nih.gov/16399912>).
84. Klein JR (March 2006). "The immune system as a regulator of thyroid hormone activity" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2768616>). *Experimental Biology and Medicine*. **231** (3): 229–36. doi:10.1177/153537020623100301 (<https://doi.org/10.1177%2F153537020623100301>). PMC 2768616 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2768616>). PMID 16514168 (<https://pubmed.ncbi.nlm.nih.gov/16514168>).
85. Mosekilde L (March 2005). "Vitamin D and the elderly". *Clinical Endocrinology*. **62** (3): 265–81. doi:10.1111/j.1365-2265.2005.02226.x (<https://doi.org/10.1111%2Fj.1365-2265.2005.02226.x>). PMID 15730407 (<https://pubmed.ncbi.nlm.nih.gov/15730407>).
86. Lange T, Perras B, Fehm HL, Born J (2003). "Sleep enhances the human antibody response to hepatitis A vaccination" (<http://www.psychosomaticmedicine.org/content/65/5/831.full.pdf>) (PDF). *Psychosomatic Medicine*. **65** (5): 831–35. doi:10.1097/01.PSY.0000091382.61178.F1 (<https://doi.org/10.1097%2F01.PSY.0000091382.61178.F1>). PMID 14508028 (<https://pubmed.ncbi.nlm.nih.gov/14508028>). S2CID 43856632 (<https://api.semanticscholar.org/CorpusID:43856632>).
87. Bryant PA, Trinder J, Curtis N (June 2004). "Sick and tired: Does sleep have a vital role in the immune system?". *Nature Reviews Immunology*. **4** (6): 457–67. doi:10.1038/nri1369 (<https://doi.org/10.1038%2Fnri1369>). PMID 15173834 (<https://pubmed.ncbi.nlm.nih.gov/15173834>).
88. Krueger JM, Majde JA (May 2003). "Humoral links between sleep and the immune system: research issues". *Annals of the New York Academy of Sciences*. **992** (1): 9–20. Bibcode:2003NYASA.992....9K (<https://ui.adsabs.harvard.edu/abs/2003NYASA.992....9K>). doi:10.1111/j.1749-6632.2003.tb03133.x (<https://doi.org/10.1111%2Fj.1749-6632.2003.tb03133.x>). PMID 12794042 (<https://pubmed.ncbi.nlm.nih.gov/12794042>).
89. Majde JA, Krueger JM (December 2005). "Links between the innate immune system and sleep". *The Journal of Allergy and Clinical Immunology*. **116** (6): 1188–98. doi:10.1016/j.jaci.2005.08.005 (<https://doi.org/10.1016%2Fj.jaci.2005.08.005>). PMID 16337444 (<https://pubmed.ncbi.nlm.nih.gov/16337444>).

90. "Sleep's Effects On Your Immune System Revealed In New Body Clock Study" ([http://www.huffingtonpost.com/2013/11/08/sleep-immune-system-body-clock\\_n\\_4235943.html](http://www.huffingtonpost.com/2013/11/08/sleep-immune-system-body-clock_n_4235943.html)). 8 November 2013.
91. Besedovsky L, Lange T, Born J (January 2012). "Sleep and immune function" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256323>). *Pflügers Archiv*. **463** (1): 121–37. doi:10.1007/s00424-011-1044-0 (<https://doi.org/10.1007%2Fs00424-011-1044-0>). PMC 3256323 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3256323>). PMID 22071480 (<https://pubmed.ncbi.nlm.nih.gov/22071480>).
92. "Can Better Sleep Mean Catching fewer Colds?" (<https://web.archive.org/web/20140509003219/http://www.webmd.com/sleep-disorders/excessive-sleepiness-10/immune-system-lack-of-sleep>). Archived from the original (<http://www.webmd.com/sleep-disorders/excessive-sleepiness-10/immune-system-lack-of-sleep/>) on 9 May 2014. Retrieved 28 April 2014.
93. R.M. Suskind, C.L. Lachney, J.N. Udall, Jr., "Malnutrition and the Immune Response (<https://books.google.com/books?hl=en&lr=&id=K5MekeZP1CMC&oi=fnd&pg=PA285&dq=malnutrition+immune+system&ots=rTBYIJJoPJ8&sig=bMwK6YPhiwjs2qcWI5p-V4Mupok#v=onepage&q=malnutrition%20immune%20system&f=false>)", in: *Dairy products in human health and nutrition*, M. Serrano-Ríos, ed., CRC Press, 1994, pp. 285–300
94. Pond CM (July 2005). "Adipose tissue and the immune system". *Prostaglandins, Leukotrienes, and Essential Fatty Acids*. **73** (1): 17–30. doi:10.1016/j.plefa.2005.04.005 (<https://doi.org/10.1016%2Fj.plefa.2005.04.005>). PMID 15946832 (<https://pubmed.ncbi.nlm.nih.gov/15946832>).
95. Langley-Evans SC, Carrington LJ (2006). "Diet and the developing immune system". *Lupus*. **15** (11): 746–52. doi:10.1177/0961203306070001 (<https://doi.org/10.1177%2F0961203306070001>). PMID 17153845 (<https://pubmed.ncbi.nlm.nih.gov/17153845>). S2CID 30576003 (<https://api.semanticscholar.org/CorpusID:30576003>).
96. Park JE, Barbul A (May 2004). "Understanding the role of immune regulation in wound healing" ([http://www.americanjournalofsurgery.com/article/S0002-9610\(03\)00296-4/fulltext](http://www.americanjournalofsurgery.com/article/S0002-9610(03)00296-4/fulltext)). *American Journal of Surgery*. **187** (5A): 11S–16S. doi:10.1016/s0002-9610(03)00296-4 (<https://doi.org/10.1016%2Fs0002-9610%2803%2900296-4>). PMID 15147986 (<https://pubmed.ncbi.nlm.nih.gov/15147986>).
97. Burzyn D, Kuswanto W, Kolodin D, Shadrach JL, Cerletti M, Jang Y, Sefik E, Tan TG, Wagers AJ, Benoist C, Mathis D (December 2013). "A special population of regulatory T cells potentiates muscle repair" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3894749>). *Cell*. **155** (6): 1282–95. doi:10.1016/j.cell.2013.10.054 (<https://doi.org/10.1016%2Fj.cell.2013.10.054>). PMC 3894749 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3894749>). PMID 24315098 (<https://pubmed.ncbi.nlm.nih.gov/24315098>).
98. Leoni G, Neumann PA, Sumagin R, Denning TL, Nusrat A (September 2015). "Wound repair: role of immune-epithelial interactions" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916915>). *Mucosal Immunology*. **8** (5): 959–68. doi:10.1038/mi.2015.63 (<https://doi.org/10.1038%2Fmi.2015.63>). PMC 4916915 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4916915>). PMID 26174765 (<https://pubmed.ncbi.nlm.nih.gov/26174765>).
99. Wynn TA, Vannella KM (March 2016). "Macrophages in Tissue Repair, Regeneration, and Fibrosis" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4794754>). *Immunity*. **44** (3): 450–462. doi:10.1016/j.immuni.2016.02.015 (<https://doi.org/10.1016%2Fj.immuni.2016.02.015>). PMC 4794754 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4794754>). PMID 26982353 (<https://pubmed.ncbi.nlm.nih.gov/26982353>).
00. Laurent P, Jolivel V, Manicki P, Chiu L, Contin-Bordes C, Truchetet ME, Pradeu T (2017). "Immune-Mediated Repair: A Matter of Plasticity" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5403426>). *Frontiers in Immunology*. **8**: 454. doi:10.3389/fimmu.2017.00454 (<https://doi.org/10.3389%2Ffimmu.2017.00454>). PMC 5403426 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5403426>). PMID 28484454 (<https://pubmed.ncbi.nlm.nih.gov/28484454>).

01. Eming SA, Hammerschmidt M, Krieg T, Roers A (July 2009). "Interrelation of immunity and tissue repair or regeneration". *Seminars in Cell & Developmental Biology*. Regenerative Biology and Medicine: INuclear Transport in Development and Disease. **20** (5): 517–27. doi:10.1016/j.semcdb.2009.04.009 (<https://doi.org/10.1016%2Fj.semcdb.2009.04.009>). PMID 19393325 (<https://pubmed.ncbi.nlm.nih.gov/19393325>).
02. Godwin JW, Pinto AR, Rosenthal NA (January 2017). "Chasing the recipe for a pro-regenerative immune system" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338634>). *Seminars in Cell & Developmental Biology*. Innate immune pathways in wound healing/Peromyscus as a model system. **61**: 71–79. doi:10.1016/j.semcdb.2016.08.008 (<https://doi.org/10.1016%2Fj.semcdb.2016.08.008>). PMC 5338634 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5338634>). PMID 27521522 (<https://pubmed.ncbi.nlm.nih.gov/27521522>).
03. Aw D, Silva AB, Palmer DB (April 2007). "Immunosenescence: emerging challenges for an ageing population" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2265901>). *Immunology*. **120** (4): 435–46. doi:10.1111/j.1365-2567.2007.02555.x (<https://doi.org/10.1111%2Fj.1365-2567.2007.02555.x>). PMC 2265901 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2265901>). PMID 17313487 (<https://pubmed.ncbi.nlm.nih.gov/17313487>).
04. Chandra RK (August 1997). "Nutrition and the immune system: an introduction" (<https://doi.org/10.1093/ajcn/66.2.460S>). *The American Journal of Clinical Nutrition*. **66** (2): 460S–63S. doi:10.1093/ajcn/66.2.460S (<https://doi.org/10.1093%2Fajcn%2F66.2.460S>). PMID 9250133 (<https://pubmed.ncbi.nlm.nih.gov/9250133>).
05. Miller JF (July 2002). "The discovery of thymus function and of thymus-derived lymphocytes". *Immunological Reviews*. **185** (1): 7–14. doi:10.1034/j.1600-065X.2002.18502.x (<https://doi.org/10.1034%2Fj.1600-065X.2002.18502.x>). PMID 12190917 (<https://pubmed.ncbi.nlm.nih.gov/12190917>).
06. Joos L, Tamm M (2005). "Breakdown of pulmonary host defense in the immunocompromised host: cancer chemotherapy". *Proceedings of the American Thoracic Society*. **2** (5): 445–48. doi:10.1513/pats.200508-097JS (<https://doi.org/10.1513%2Fpats.200508-097JS>). PMID 16322598 (<https://pubmed.ncbi.nlm.nih.gov/16322598>).
07. Copeland KF, Heeney JL (December 1996). "T helper cell activation and human retroviral pathogenesis" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC239461>). *Microbiological Reviews*. **60** (4): 722–42. doi:10.1128/MMBR.60.4.722-742.1996 (<https://doi.org/10.1128%2FMMBR.60.4.722-742.1996>). PMC 239461 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC239461>). PMID 8987361 (<https://pubmed.ncbi.nlm.nih.gov/8987361>).
08. Miller JF (1993). "Self-nonsel discrimination and tolerance in T and B lymphocytes". *Immunologic Research*. **12** (2): 115–30. doi:10.1007/BF02918299 (<https://doi.org/10.1007%2FBF02918299>). PMID 8254222 (<https://pubmed.ncbi.nlm.nih.gov/8254222>). S2CID 32476323 (<https://api.semanticscholar.org/CorpusID:32476323>).
09. Ghaffar A (2006). "Immunology – Chapter Seventeen: Hypersensitivity States" (<http://www.microbiologybook.org/book/immunol-sta.htm>). *Microbiology and Immunology On-line*. University of South Carolina School of Medicine. Retrieved 29 May 2016.
10. Taylor AL, Watson CJ, Bradley JA (October 2005). "Immunosuppressive agents in solid organ transplantation: Mechanisms of action and therapeutic efficacy". *Critical Reviews in Oncology/Hematology*. **56** (1): 23–46. doi:10.1016/j.critrevonc.2005.03.012 (<https://doi.org/10.1016%2Fj.critrevonc.2005.03.012>). PMID 16039869 (<https://pubmed.ncbi.nlm.nih.gov/16039869>).
11. Barnes PJ (March 2006). "Corticosteroids: the drugs to beat". *European Journal of Pharmacology*. **533** (1–3): 2–14. doi:10.1016/j.ejphar.2005.12.052 (<https://doi.org/10.1016%2Fj.ejphar.2005.12.052>). PMID 16436275 (<https://pubmed.ncbi.nlm.nih.gov/16436275>).
12. Masri MA (July 2003). "The mosaic of immunosuppressive drugs". *Molecular Immunology*. **39** (17–18): 1073–77. doi:10.1016/S0161-5890(03)00075-0 (<https://doi.org/10.1016%2FS0161-5890%2803%2900075-0>). PMID 12835079 (<https://pubmed.ncbi.nlm.nih.gov/12835079>).

13. Death and DALY estimates for 2002 by cause for WHO Member States. (<http://www.who.int/healthinfo/bod/en/index.html>) World Health Organization. Retrieved on 1 January 2007.
14. Singh M, O'Hagan D (November 1999). "Advances in vaccine adjuvants". *Nature Biotechnology*. **17** (11): 1075–81. doi:10.1038/15058 (<https://doi.org/10.1038%2F15058>). PMID 10545912 (<https://pubmed.ncbi.nlm.nih.gov/10545912>).
15. Morgan RA, Dudley ME, Wunderlich JR, et al. (October 2006). "Cancer Regression in Patients After Transfer of Genetically Engineered Lymphocytes" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267026>). *Science*. **314** (5796): 126–29. Bibcode:2006Sci...314..126M (<https://ui.adsabs.harvard.edu/abs/2006Sci...314..126M>). doi:10.1126/science.1129003 (<https://doi.org/10.1126%2Fscience.1129003>). PMC 2267026 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2267026>). PMID 16946036 (<https://pubmed.ncbi.nlm.nih.gov/16946036>).
16. Andersen MH, Schrama D, Thor Straten P, Becker JC (January 2006). "Cytotoxic T cells". *The Journal of Investigative Dermatology*. **126** (1): 32–41. doi:10.1038/sj.jid.5700001 (<https://doi.org/10.1038%2Fsj.jid.5700001>). PMID 16417215 (<https://pubmed.ncbi.nlm.nih.gov/16417215>).
17. Boon T, van der Bruggen P (March 1996). "Human tumor antigens recognized by T lymphocytes" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2192342>). *The Journal of Experimental Medicine*. **183** (3): 725–29. doi:10.1084/jem.183.3.725 (<https://doi.org/10.1084%2Fjem.183.3.725>). PMC 2192342 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC2192342>). PMID 8642276 (<https://pubmed.ncbi.nlm.nih.gov/8642276>).
18. Ljubojevic S, Skerlev M (2014). "HPV-associated diseases". *Clinics in Dermatology*. **32** (2): 227–34. doi:10.1016/j.clindermatol.2013.08.007 (<https://doi.org/10.1016%2Fj.clindermatol.2013.08.007>). PMID 24559558 (<https://pubmed.ncbi.nlm.nih.gov/24559558>).
19. Castelli C, Rivoltini L, Andreola G, Carrabba M, Renkvist N, Parmiani G (March 2000). "T-cell recognition of melanoma-associated antigens". *Journal of Cellular Physiology*. **182** (3): 323–31. doi:10.1002/(SICI)1097-4652(200003)182:3<323::AID-JCP2>3.0.CO;2-# (<https://doi.org/10.1002%2F%28SICI%291097-4652%28200003%29182%3A3%3C323%3A%3AAID-JCP2%3E3.0.CO%3B2-%23>). PMID 10653598 (<https://pubmed.ncbi.nlm.nih.gov/10653598>).
20. Romero P, Cerottini JC, Speiser DE (2006). "The human T cell response to melanoma antigens". *Advances in Immunology*. **92**: 187–224. doi:10.1016/S0065-2776(06)92005-7 (<https://doi.org/10.1016%2FS0065-2776%2806%2992005-7>). ISBN 978-0-12-373636-9. PMID 17145305 (<https://pubmed.ncbi.nlm.nih.gov/17145305>).
21. Guevara-Patiño JA, Turk MJ, Wolchok JD, Houghton AN (2003). "Immunity to cancer through immune recognition of altered self: studies with melanoma". *Advances in Cancer Research*. **90**: 157–77. doi:10.1016/S0065-230X(03)90005-4 (<https://doi.org/10.1016%2FS0065-230X%2803%2990005-4>). ISBN 978-0-12-006690-2. PMID 14710950 (<https://pubmed.ncbi.nlm.nih.gov/14710950>).
22. Renkvist N, Castelli C, Robbins PF, Parmiani G (March 2001). "A listing of human tumor antigens recognized by T cells". *Cancer Immunology, Immunotherapy*. **50** (1): 3–15. doi:10.1007/s002620000169 (<https://doi.org/10.1007%2Fs002620000169>). PMID 11315507 (<https://pubmed.ncbi.nlm.nih.gov/11315507>).
23. Gerloni M, Zanetti M (June 2005). "CD4 T cells in tumor immunity" (<https://zenodo.org/record/1066157>). *Springer Seminars in Immunopathology*. **27** (1): 37–48. doi:10.1007/s00281-004-0193-z (<https://doi.org/10.1007%2Fs00281-004-0193-z>). PMID 15965712 (<https://pubmed.ncbi.nlm.nih.gov/15965712>). S2CID 25182066 (<https://api.semanticscholar.org/CorpusID:25182066>).
24. Seliger B, Ritz U, Ferrone S (January 2006). "Molecular mechanisms of HLA class I antigen abnormalities following viral infection and transformation". *International Journal of Cancer*. **118** (1): 129–38. doi:10.1002/ijc.21312 (<https://doi.org/10.1002%2Fijc.21312>). PMID 16003759 (<https://pubmed.ncbi.nlm.nih.gov/16003759>).
25. Hayakawa Y, Smyth MJ (2006). "Innate immune recognition and suppression of tumors". *Advances in Cancer Research*. **95**: 293–322. doi:10.1016/S0065-230X(06)95008-8 (<https://doi.org/10.1016%2FS0065-230X%2806%2995008-8>). ISBN 978-0-12-006695-7. PMID 16860661 (<https://pubmed.ncbi.nlm.nih.gov/16860661>).

26. Syn NL, Teng MW, Mok TS, Soo RA (December 2017). "De-novo and acquired resistance to immune checkpoint targeting". *The Lancet. Oncology*. **18** (12): e731–e741. doi:10.1016/s1470-2045(17)30607-1 (<https://doi.org/10.1016%2Fs1470-2045%2817%2930607-1>). PMID 29208439 (<https://pubmed.ncbi.nlm.nih.gov/29208439>).
27. Seliger B (2005). "Strategies of tumor immune evasion". *BioDrugs*. **19** (6): 347–54. doi:10.2165/00063030-200519060-00002 (<https://doi.org/10.2165%2F00063030-200519060-00002>). PMID 16392887 (<https://pubmed.ncbi.nlm.nih.gov/16392887>).
28. Frumento G, Piazza T, Di Carlo E, Ferrini S (September 2006). "Targeting tumor-related immunosuppression for cancer immunotherapy". *Endocrine, Metabolic & Immune Disorders Drug Targets*. **6** (3): 233–7. doi:10.2174/187153006778250019 (<https://doi.org/10.2174%2F187153006778250019>). PMID 17017974 (<https://pubmed.ncbi.nlm.nih.gov/17017974>).
29. Stix G (July 2007). "A malignant flame. Understanding chronic inflammation, which contributes to heart disease, Alzheimer's and a variety of other ailments, may be a key to unlocking the mysteries of cancer" ([https://web.archive.org/web/20110716015048/http://podcast.sciam.com/daily/pdf/sa\\_d\\_podcast\\_070619.pdf](https://web.archive.org/web/20110716015048/http://podcast.sciam.com/daily/pdf/sa_d_podcast_070619.pdf)) (PDF). *Scientific American*. **297** (1): 60–67. Bibcode:2007SciAm.297a..60S (<https://ui.adsabs.harvard.edu/abs/2007SciAm.297a..60S>). doi:10.1038/scientificamerican0707-60 (<https://doi.org/10.1038%2Fscientificamerican0707-60>). PMID 17695843 (<https://pubmed.ncbi.nlm.nih.gov/17695843>). Archived from the original ([http://podcast.sciam.com/daily/pdf/sa\\_d\\_podcast\\_070619.pdf](http://podcast.sciam.com/daily/pdf/sa_d_podcast_070619.pdf)) (PDF) on 16 July 2011.
30. Cervantes-Villagrana RD, Albores-García D, Cervantes-Villagrana AR, García-Acevez SJ (18 June 2020). "Tumor-induced Neurogenesis and Immune Evasion as Targets of Innovative Anti-Cancer Therapies" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7303203>). *Signal Transduct Target Ther*. **5** (1): 99. doi:10.1038/s41392-020-0205-z (<https://doi.org/10.1038%2Fs41392-020-0205-z>). PMC 7303203 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7303203>). PMID 32555170 (<https://pubmed.ncbi.nlm.nih.gov/32555170>).
31. Baker MP, Reynolds HM, Lumericisi B, Bryson CJ (October 2010). "Immunogenicity of protein therapeutics: The key causes, consequences and challenges" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3062386>). *Self/Nonself*. **1** (4): 314–322. doi:10.4161/self.1.4.13904 (<https://doi.org/10.4161%2Fself.1.4.13904>). PMC 3062386 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3062386>). PMID 21487506 (<https://pubmed.ncbi.nlm.nih.gov/21487506>).
32. Welling GW, Weijer WJ, van der Zee R, Welling-Wester S (September 1985). "Prediction of sequential antigenic regions in proteins". *FEBS Letters*. **188** (2): 215–18. doi:10.1016/0014-5793(85)80374-4 (<https://doi.org/10.1016%2F0014-5793%2885%2980374-4>). PMID 2411595 (<https://pubmed.ncbi.nlm.nih.gov/2411595>).
33. Söllner J, Mayer B (2006). "Machine learning approaches for prediction of linear B-cell epitopes on proteins". *Journal of Molecular Recognition*. **19** (3): 200–08. doi:10.1002/jmr.771 (<https://doi.org/10.1002%2Fjmr.771>). PMID 16598694 (<https://pubmed.ncbi.nlm.nih.gov/16598694>).
34. Saha S, Bhasin M, Raghava GP (2005). "Bcipep: a database of B-cell epitopes" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1173103>). *BMC Genomics*. **6**: 79. doi:10.1186/1471-2164-6-79 (<https://doi.org/10.1186%2F1471-2164-6-79>). PMC 1173103 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1173103>). PMID 15921533 (<https://pubmed.ncbi.nlm.nih.gov/15921533>).
35. Flower DR, Doytchinova IA (2002). "Immunoinformatics and the prediction of immunogenicity". *Applied Bioinformatics*. **1** (4): 167–76. PMID 15130835 (<https://pubmed.ncbi.nlm.nih.gov/15130835>).
36. Bickle TA, Krüger DH (June 1993). "Biology of DNA restriction" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC372918>). *Microbiological Reviews*. **57** (2): 434–50. doi:10.1128/MMBR.57.2.434-450.1993 (<https://doi.org/10.1128%2FMMBR.57.2.434-450.1993>). PMC 372918 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC372918>). PMID 8336674 (<https://pubmed.ncbi.nlm.nih.gov/8336674>).

37. Barrangou R, Fremaux C, Deveau H, Richards M, Boyaval P, Moineau S, Romero DA, Horvath P (March 2007). "CRISPR provides acquired resistance against viruses in prokaryotes". *Science*. **315** (5819): 1709–12. Bibcode:2007Sci...315.1709B (<https://ui.adsabs.harvard.edu/abs/2007Sci...315.1709B>). doi:10.1126/science.1138140 (<https://doi.org/10.1126%2Fscience.1138140>). hdl:20.500.11794/38902 (<https://hdl.handle.net/20.500.11794%2F38902>). PMID 17379808 (<https://pubmed.ncbi.nlm.nih.gov/17379808>).
38. Brouns SJ, Jore MM, Lundgren M, Westra ER, Slijkhuis RJ, Snijders AP, Dickman MJ, Makarova KS, Koonin EV, van der Oost J (August 2008). "Small CRISPR RNAs guide antiviral defense in prokaryotes" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5898235>). *Science*. **321** (5891): 960–64. Bibcode:2008Sci...321..960B (<https://ui.adsabs.harvard.edu/abs/2008Sci...321..960B>). doi:10.1126/science.1159689 (<https://doi.org/10.1126%2Fscience.1159689>). PMC 5898235 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5898235>). PMID 18703739 (<https://pubmed.ncbi.nlm.nih.gov/18703739>).
39. Hille F, Charpentier E (November 2016). "CRISPR-Cas: biology, mechanisms and relevance" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5052741>). *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*. **371** (1707): 20150496. doi:10.1098/rstb.2015.0496 (<https://doi.org/10.1098%2Frstb.2015.0496>). PMC 5052741 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5052741>). PMID 27672148 (<https://pubmed.ncbi.nlm.nih.gov/27672148>).
40. Koonin EV (February 2017). "Evolution of RNA- and DNA-guided antiviral defense systems in prokaryotes and eukaryotes: common ancestry vs convergence" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5303251>). *Biology Direct*. **12** (1): 5. doi:10.1186/s13062-017-0177-2 (<https://doi.org/10.1186%2Fs13062-017-0177-2>). PMC 5303251 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5303251>). PMID 28187792 (<https://pubmed.ncbi.nlm.nih.gov/28187792>).
41. Bayne CJ (2003). "Origins and evolutionary relationships between the innate and adaptive arms of immune systems" (<https://doi.org/10.1093/icb/43.2.293>). *Integr. Comp. Biol.* **43** (2): 293–99. doi:10.1093/icb/43.2.293 (<https://doi.org/10.1093%2Ficb%2F43.2.293>). PMID 21680436 (<https://pubmed.ncbi.nlm.nih.gov/21680436>).
42. Stram Y, Kuzntzova L (June 2006). "Inhibition of viruses by RNA interference" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7088519>). *Virus Genes*. **32** (3): 299–306. doi:10.1007/s11262-005-6914-0 (<https://doi.org/10.1007%2Fs11262-005-6914-0>). PMC 7088519 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7088519>). PMID 16732482 (<https://pubmed.ncbi.nlm.nih.gov/16732482>).
43. Schneider, David. "Innate Immunity – Lecture 4: Plant immune responses" (<http://web.stanford.edu/class/mi104/Plant%20immunity.pdf>) (PDF). Stanford University Department of Microbiology and Immunology. Retrieved 1 January 2007.
44. Jones JD, Dangl JL (November 2006). "The plant immune system" (<https://doi.org/10.1038/nature05286>). *Nature*. **444** (7117): 323–29. Bibcode:2006Natur.444..323J (<https://ui.adsabs.harvard.edu/abs/2006Natur.444..323J>). doi:10.1038/nature05286 (<https://doi.org/10.1038%2Fnature05286>). PMID 17108957 (<https://pubmed.ncbi.nlm.nih.gov/17108957>).
45. Baulcombe D (September 2004). "RNA silencing in plants". *Nature*. **431** (7006): 356–63. Bibcode:2004Natur.431..356B (<https://ui.adsabs.harvard.edu/abs/2004Natur.431..356B>). doi:10.1038/nature02874 (<https://doi.org/10.1038%2Fnature02874>). PMID 15372043 (<https://pubmed.ncbi.nlm.nih.gov/15372043>).
46. Alder MN, Rogozin IB, Iyer LM, Glazko GV, Cooper MD, Pancer Z (December 2005). "Diversity and function of adaptive immune receptors in a jawless vertebrate" (<https://doi.org/10.1126/science.1119420>). *Science*. **310** (5756): 1970–73. Bibcode:2005Sci...310.1970A (<https://ui.adsabs.harvard.edu/abs/2005Sci...310.1970A>). doi:10.1126/science.1119420 (<https://doi.org/10.1126%2Fscience.1119420>). PMID 16373579 (<https://pubmed.ncbi.nlm.nih.gov/16373579>).
47. Finlay BB, McFadden G (February 2006). "Anti-immunology: evasion of the host immune system by bacterial and viral pathogens". *Cell*. **124** (4): 767–82. doi:10.1016/j.cell.2006.01.034 (<https://doi.org/10.1016%2Fj.cell.2006.01.034>). PMID 16497587 (<https://pubmed.ncbi.nlm.nih.gov/16497587>). S2CID 15418509 (<https://api.semanticscholar.org/CorpusID:15418509>).

48. Cianciotto NP (December 2005). "Type II secretion: a protein secretion system for all seasons". *Trends in Microbiology*. **13** (12): 581–88. doi:10.1016/j.tim.2005.09.005 (<https://doi.org/10.1016%2Fj.tim.2005.09.005>). PMID 16216510 (<https://pubmed.ncbi.nlm.nih.gov/16216510>).
49. Winstanley C, Hart CA (February 2001). "Type III secretion systems and pathogenicity islands". *Journal of Medical Microbiology*. **50** (2): 116–26. doi:10.1099/0022-1317-50-2-116 (<https://doi.org/10.1099%2F0022-1317-50-2-116>). PMID 11211218 (<https://pubmed.ncbi.nlm.nih.gov/11211218>).
50. Finlay BB, Falkow S (June 1997). "Common themes in microbial pathogenicity revisited" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC232605>). *Microbiology and Molecular Biology Reviews*. **61** (2): 136–69. doi:10.1128/61.2.136-169.1997 (<https://doi.org/10.1128%2F61.2.136-169.1997>). PMC 232605 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC232605>). PMID 9184008 (<https://pubmed.ncbi.nlm.nih.gov/9184008>).
51. Kobayashi H (2005). "Airway biofilms: implications for pathogenesis and therapy of respiratory tract infections". *Treatments in Respiratory Medicine*. **4** (4): 241–53. doi:10.2165/00151829-200504040-00003 (<https://doi.org/10.2165%2F00151829-200504040-00003>). PMID 16086598 (<https://pubmed.ncbi.nlm.nih.gov/16086598>). S2CID 31788349 (<https://api.semanticscholar.org/CorpusID:31788349>).
52. Housden NG, Harrison S, Roberts SE, Beckingham JA, Graille M, Stura E, Gore MG (June 2003). "Immunoglobulin-binding domains: Protein L from *Peptostreptococcus magnus*". *Biochemical Society Transactions*. **31** (Pt 3): 716–18. doi:10.1042/BST0310716 (<https://doi.org/10.1042%2FBST0310716>). PMID 12773190 (<https://pubmed.ncbi.nlm.nih.gov/12773190>). S2CID 10322322 (<https://api.semanticscholar.org/CorpusID:10322322>).
53. Burton DR, Stanfield RL, Wilson IA (October 2005). "Antibody vs. HIV in a clash of evolutionary titans" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1257708>). *Proceedings of the National Academy of Sciences of the United States of America*. **102** (42): 14943–48. Bibcode:2005PNAS..10214943B (<https://ui.adsabs.harvard.edu/abs/2005PNAS..10214943B>). doi:10.1073/pnas.0505126102 (<https://doi.org/10.1073%2Fpnas.0505126102>). PMC 1257708 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1257708>). PMID 16219699 (<https://pubmed.ncbi.nlm.nih.gov/16219699>).
54. Taylor JE, Rudenko G (November 2006). "Switching trypanosome coats: what's in the wardrobe?". *Trends in Genetics*. **22** (11): 614–20. doi:10.1016/j.tig.2006.08.003 (<https://doi.org/10.1016%2Fj.tig.2006.08.003>). PMID 16908087 (<https://pubmed.ncbi.nlm.nih.gov/16908087>).
55. Cantin R, Méthot S, Tremblay MJ (June 2005). "Plunder and stowaways: incorporation of cellular proteins by enveloped viruses" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1112128>). *Journal of Virology*. **79** (11): 6577–87. doi:10.1128/JVI.79.11.6577-6587.2005 (<https://doi.org/10.1128%2FJVI.79.11.6577-6587.2005>). PMC 1112128 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1112128>). PMID 15890896 (<https://pubmed.ncbi.nlm.nih.gov/15890896>).
56. Retief FP, Cilliers L (January 1998). "The epidemic of Athens, 430–426 BC". *South African Medical Journal = Suid-Afrikaanse Tydskrif vir Geneeskunde*. **88** (1): 50–53. PMID 9539938 (<https://pubmed.ncbi.nlm.nih.gov/9539938>).
57. Ostoya P (1954). "Maupertuis et la biologie". *Revue d'histoire des sciences et de leurs applications*. **7** (1): 60–78. doi:10.3406/rhs.1954.3379 (<https://doi.org/10.3406%2Frhs.1954.3379>).
58. Doherty M, Robertson MJ (December 2004). "Some early Trends in Immunology". *Trends in Immunology*. **25** (12): 623–31. doi:10.1016/j.it.2004.10.008 (<https://doi.org/10.1016%2Fj.it.2004.10.008>). PMID 15530829 (<https://pubmed.ncbi.nlm.nih.gov/15530829>).
59. Silverstein AM (1989). *A History of Immunology* (<https://books.google.com/books?id=J3Hg4I6GrYoC>). Academic Press. ISBN 978-0-08-092583-7.
60. Plotkin SA (April 2005). "Vaccines: past, present and future" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095920>). *Nature Medicine*. **11** (4 Suppl): S5–11. doi:10.1038/nm1209 (<https://doi.org/10.1038%2Fnm1209>). PMC 7095920 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7095920>). PMID 15812490 (<https://pubmed.ncbi.nlm.nih.gov/15812490>).

61. The Nobel Prize in Physiology or Medicine 1905 ([http://nobelprize.org/nobel\\_prizes/medicine/aureates/1905/](http://nobelprize.org/nobel_prizes/medicine/aureates/1905/)) Nobelprize.org Accessed 8 January 2009.
62. Major Walter Reed, Medical Corps, U.S. Army (<https://web.archive.org/web/20071023070838/http://www.wramc.amedd.army.mil/welcome/history/>) Walter Reed Army Medical Center. Accessed 8 January 2007.
63. Metchnikoff E (1905). *Immunity in Infective Diseases* (<https://archive.org/details/immunityininfec01metcgoog>) (Full Text Version: Internet Archive). Translated by Binnie FG. Cambridge University Press. LCCN 68025143 (<https://lccn.loc.gov/68025143>). "history of humoral immunity."
64. The Nobel Prize in Physiology or Medicine 1908 ([http://nobelprize.org/nobel\\_prizes/medicine/aureates/1908/](http://nobelprize.org/nobel_prizes/medicine/aureates/1908/)) Nobelprize.org Accessed 8 January 2007
65. Tauber AI, Chernyak L (1991). *Metchnikoff and the Origins of Immunology*. New York: Oxford University Press.
66. Tauber AI (1994). *The Immune Self: Theory or Metaphor?*. Cambridge: Cambridge University Press. PMID 8172646 (<https://pubmed.ncbi.nlm.nih.gov/8172646>).
67. Jerne NK (November 1955). "The Natural-selection Theory of Anti-body Formation" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC534292>). *Proceedings of the National Academy of Sciences of the United States of America*. **41** (11): 849–57. Bibcode:1955PNAS...41..849J (<http://ui.adsabs.harvard.edu/abs/1955PNAS...41..849J>). doi:10.1073/pnas.41.11.849 (<https://doi.org/10.1073/pnas.41.11.849>). PMC 534292 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC534292>). PMID 16589759 (<https://pubmed.ncbi.nlm.nih.gov/16589759>).
68. Burnet FM (1959). *The Clonal Selection Theory of Acquired Immunity*. Cambridge: Cambridge University Press.
69. Burnet FM (1969). *Cellular Immunology: Self and Notself*. Cambridge: Cambridge University Press.
70. Bretscher P, Cohn M (1970). "A theory of self-nonsel self discrimination". *Science*. **169** (3950): 1042–49. Bibcode:1970Sci...169.1042B (<https://ui.adsabs.harvard.edu/abs/1970Sci...169.1042B>). doi:10.1126/science.169.3950.1042 (<https://doi.org/10.1126/science.169.3950.1042>). PMID 4194660 (<https://pubmed.ncbi.nlm.nih.gov/4194660>). S2CID 26916828 (<https://api.semanticscholar.org/CorpusID:26916828>).
71. Matzinger P (April 2002). "The danger model: a renewed sense of self" (<http://www.scs.carleton.ca/~soma/biosec/readings/matzinger-science.pdf>) (PDF). *Science*. **296** (5566): 301–05. Bibcode:2002Sci...296..301M (<https://ui.adsabs.harvard.edu/abs/2002Sci...296..301M>). doi:10.1126/science.1071059 (<https://doi.org/10.1126/science.1071059>). PMID 11951032 (<https://pubmed.ncbi.nlm.nih.gov/11951032>). S2CID 13615808 (<https://api.semanticscholar.org/CorpusID:13615808>).
72. Pradeu (2012). *The Limits of the Self: Immunology and Biological Identity*. New York: Oxford University Press.
73. Langman RE, Cohn M (June 2000). "A minimal model for the self-nonsel self discrimination: a return to the basics". *Seminars in Immunology*. **12** (3): 189–95, discussion 257–344. doi:10.1006/smim.2000.0231 (<https://doi.org/10.1006/smim.2000.0231>). PMID 10910739 (<https://pubmed.ncbi.nlm.nih.gov/10910739>).
74. Clark WR (2008). *In Defense of Self: How the Immune System Really Works*. New York: Oxford University Press.
75. Coutinho A, Forni L, Holmberg D, Ivars F, Vaz N (June 1984). "From an antigen-centered, clonal perspective of immune responses to an organism-centered, network perspective of autonomous activity in a self-referential immune system". *Immunol. Rev.* **79**: 151–68. doi:10.1111/j.1600-065x.1984.tb00492.x (<https://doi.org/10.1111/j.1600-065x.1984.tb00492.x>). PMID 6235170 (<https://pubmed.ncbi.nlm.nih.gov/6235170>).
76. Irun C (2000). *Tending Adam's garden: Evolving the cognitive immune self*. San Diego: Academic Press.

77. Pradeu T, Carosella ED (November 2006). "On the definition of a criterion of immunogenicity" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1693837>). *Proceedings of the National Academy of Sciences of the United States of America*. **103** (47): 17858–61. Bibcode:2006PNAS..10317858P (<https://ui.adsabs.harvard.edu/abs/2006PNAS..10317858P>). doi:10.1073/pnas.0608683103 (<https://doi.org/10.1073%2Fpnas.0608683103>). PMC 1693837 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC1693837>). PMID 17101995 (<https://pubmed.ncbi.nlm.nih.gov/17101995>).
78. Pradeu T, Jaeger S, Vivier E (October 2013). "The speed of change: towards a discontinuity theory of immunity?" ([http://philsci-archive.pitt.edu/10046/1/Pradeu-Jaeger-Vivier\\_Discontinuity\\_theory\\_Final\\_draft.pdf](http://philsci-archive.pitt.edu/10046/1/Pradeu-Jaeger-Vivier_Discontinuity_theory_Final_draft.pdf)) (PDF). *Nature Reviews. Immunology*. **13** (10): 764–69. doi:10.1038/nri3521 (<https://doi.org/10.1038%2Fnri3521>). PMID 23995627 (<https://pubmed.ncbi.nlm.nih.gov/23995627>). S2CID 11366176 (<https://api.semanticscholar.org/CorpusID:11366176>).
79. Pradeu T, Vivier E (July 2016). "The discontinuity theory of immunity" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5321532>). *Science Immunology*. **1** (1): aag0479. doi:10.1126/sciimmunol.aag0479 (<https://doi.org/10.1126%2Fsciimmunol.aag0479>). PMC 5321532 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5321532>). PMID 28239677 (<https://pubmed.ncbi.nlm.nih.gov/28239677>).
80. Janeway CA, Goodnow CC, Medzhitov R (May 1996). "Danger – pathogen on the premises! Immunological tolerance". *Current Biology*. **6** (5): 519–22. doi:10.1016/S0960-9822(02)00531-6 (<https://doi.org/10.1016%2FS0960-9822%2802%2900531-6>). PMID 8805259 (<https://pubmed.ncbi.nlm.nih.gov/8805259>).
81. Vance RE (2000). "Cutting edge commentary: a Copernican revolution? Doubts about the danger theory" (<http://www.jimmunol.org/content/jimmunol/165/4/1725.full.pdf>) (PDF). *Journal of Immunology*. **165** (4): 1725–28. doi:10.4049/jimmunol.165.4.1725 (<https://doi.org/10.4049%2Fjimmunol.165.4.1725>). PMID 10925247 (<https://pubmed.ncbi.nlm.nih.gov/10925247>).
82. Matzinger P (May 2012). "The evolution of the danger theory. Interview by Lauren Constable, Commissioning Editor" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4803042>). *Expert Review of Clinical Immunology*. **8** (4): 311–17. doi:10.1586/eci.12.21 (<https://doi.org/10.1586%2Feci.12.21>). PMC 4803042 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4803042>). PMID 22607177 (<https://pubmed.ncbi.nlm.nih.gov/22607177>).
83. Pradeu T, Cooper EL (2012). "The danger theory: 20 years later" (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3443751>). *Frontiers in Immunology*. **3**: 287. doi:10.3389/fimmu.2012.00287 (<https://doi.org/10.3389%2Ffimmu.2012.00287>). PMC 3443751 (<https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3443751>). PMID 23060876 (<https://pubmed.ncbi.nlm.nih.gov/23060876>).

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## External links

- Immune System (<http://uhaweb.hartford.edu/BUGL/immune.htm>) – from the University of Hartford (high school/undergraduate level)
- Microbiology and Immunology On-Line Textbook (<https://web.archive.org/web/20070102153438/http://pathmicro.med.sc.edu/book/immunol-sta.htm>) – from the University of South Carolina School of Medicine (undergraduate level)
- Immunobiology; Fifth Edition (<https://www.ncbi.nlm.nih.gov/books/bv.fcgi?call=bv.View..ShowTOC&rid=imm.TOC&depth=10>) – Online version of the textbook by Charles Janeway (Advanced undergraduate/graduate level)
- Stanley Falkow's talk: "Host-Pathogen Interaction and Human Disease" (<https://www.ibiology.org/microbiology/host-pathogen-interactions-human-disease/>)

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