

# Adaptive immune system

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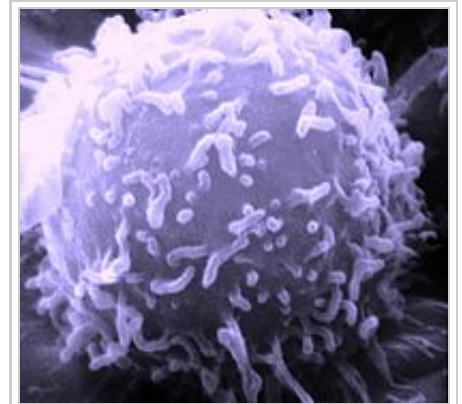
*See also: Immune system, Passive immunity, and Innate immune system*

The **adaptive immune system**, also known as the **acquired immune system** or, more rarely, as the **specific immune system**, is composed of highly specialized, systemic cells and processes that eliminate or prevent pathogen growth. One of the two main immunity strategies found in vertebrates (the other being innate immunity), acquired immunity creates immunological memory after an initial response to a specific pathogen, leading to an enhanced response to subsequent encounters with that same pathogen. This process of acquired immunity is the basis of vaccination.

In acquired immunity, pathogen-specific receptors are "acquired" during the lifetime of the organism (whereas in innate immunity pathogen-specific receptors are already encoded in the germline)... The acquired response is said to be "adaptive" because it prepares the body's immune system for future challenges (though it can actually also be maladaptive when it results in autoimmunity).<sup>[n 1]</sup>

The system is highly adaptable because of somatic hypermutation (a process of accelerated somatic mutations), and V(D)J recombination (an irreversible genetic recombination of antigen receptor gene segments). This mechanism allows a small number of genes to generate a vast number of different antigen receptors, which are then uniquely expressed on each individual lymphocyte. Because the gene rearrangement leads to an irreversible change in the DNA of each cell, all of the progeny (offspring) of that cell will then inherit genes encoding the same receptor specificity, including the Memory B cells and Memory T cells that are the keys to long-lived specific immunity.

A theoretical framework explaining the workings of the acquired immune system is provided by immune network theory. This theory, which builds on established concepts of clonal selection, is being applied in the search for an HIV vaccine.



A scanning electron microscope (SEM) image of a single human lymphocyte

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## Functions

Acquired immunity is triggered in vertebrates when a pathogen evades the innate immune system and (1) generates a threshold level of antigen and (2) generates "stranger" or "danger" signals activating dendritic cells.<sup>[1]</sup>

The major functions of the acquired immune system include:

- the recognition of specific "non-self" antigens in the presence of "self", during the process of antigen presentation.
- the generation of responses that are tailored to maximally eliminate specific pathogens or pathogen-infected cells.
- the development of immunological memory, in which each pathogen is "remembered" by a signature antibodies or T cell receptors, this is also known as the "anamnestic response". These memory cells can be called upon to quickly eliminate a pathogen should subsequent infections occur.

## Lymphocytes

*Main article: Lymphocyte*

The cells of the acquired immune system are T and B lymphocytes; lymphocytes are a subset of leukocyte. B cells and T cells are the major types of lymphocytes. The human body has about 2 trillion lymphocytes, constituting 20–40% of white blood cells (WBCs); their total mass is about the same as the brain or liver.<sup>[2]</sup> The peripheral blood contains 2% of circulating lymphocytes; the rest move within the tissues and lymphatic system.<sup>[2]</sup>

B cells and T cells are derived from the same multipotent hematopoietic stem cells, and are morphologically indistinguishable from one another until after they are activated.<sup>[3]</sup> B cells play a large role in the humoral immune response, whereas T cells are intimately involved in cell-mediated immune responses. In all vertebrates except Agnatha, B cells and T cells are produced by stem cells in the bone marrow.<sup>[3]</sup> T progenitors migrate from the bone marrow to the thymus where they are called thymocytes and where they develop into T cells. In humans, approximately 1–2% of the lymphocyte pool recirculates each hour to optimize the opportunities for antigen-specific lymphocytes to find their specific antigen within the secondary lymphoid tissues.<sup>[4]</sup>

In an adult animal, the peripheral lymphoid organs contain a mixture of B and T cells in at least three stages of differentiation:

- naive cells that have matured, left the bone marrow or thymus, have entered the lymphatic system, but that have yet to encounter their cognate antigen,
- effector cells that have been activated by their cognate antigen, and are actively involved in eliminating a pathogen.
- memory cells – the long-lived survivors of past infections.

## Antigen presentation

*Main article: Antigen presentation*

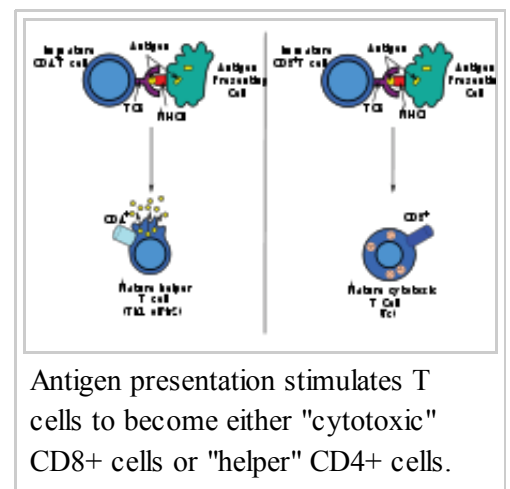
Acquired immunity relies on the capacity of immune cells to distinguish between the body's own cells and unwanted invaders. The host's cells express "self" antigens. These antigens are different from those on the surface of bacteria or on the surface of virus-infected host cells ("non-self" or "foreign" antigens). The acquired immune response is triggered by recognizing foreign antigen in the cellular context of a danger-activated dendritic cell.

With the exception of non-nucleated cells (including erythrocytes), all cells are capable of presenting antigen through the function of major histocompatibility complex (MHC) molecules.<sup>[3]</sup> Some cells are specially equipped to present antigen, and to prime naive T cells. Dendritic cells and B-cells (and to a lesser extent macrophages) are equipped with special "co-stimulatory" ligands recognized by co-stimulatory receptors on T cells, and are termed professional antigen presenting cells (APC).

Several T cells subgroups can be activated by professional APCs, and each type of T cell is specially equipped to deal with each unique toxin or bacterial and viral pathogen. The type of T cell activated, and the type of response generated depends, in part, on the context in which the APC first encountered the antigen.<sup>[1]</sup>

### Exogenous antigens

Dendritic cells engulf exogenous pathogens, such as bacteria, parasites or toxins in the tissues and then migrate, via chemotactic signals, to the T cell enriched lymph nodes. During migration, dendritic cells undergo a process of maturation in which they lose most of their ability to engulf other pathogens and develop an ability to communicate with T-cells. The dendritic cell uses enzymes to chop the pathogen into smaller pieces, called antigens. In the lymph node, the dendritic cell will display these "non-self" antigens on its surface by coupling them to a "self"-receptor called the Major histocompatibility complex, or MHC (also known in humans as Human leukocyte antigen (HLA)).<sup>[1]</sup> This MHC:antigen complex is recognized by T-cells passing through the lymph node. Exogenous antigens are usually displayed on MHC class II molecules, which activate CD4+ helper T-cells.<sup>[1]</sup>



### Endogenous antigens

Endogenous antigens are produced by viruses replicating within a host cell.<sup>[1]</sup> The host cell uses enzymes to digest virally associated proteins, and displays these pieces on its surface to T-cells by coupling them to MHC. Endogenous antigens are typically displayed on MHC class I molecules, and activate CD8+ cytotoxic T-cells. With the exception of non-nucleated cells (including erythrocytes), MHC class I is expressed by all host cells.<sup>[1]</sup>

# T lymphocytes

*Main article: T cell*

## CD8+ T lymphocytes and cytotoxicity

*Main article: Cytotoxic T cell*

Cytotoxic T cells (also known as TC, killer T cell, or cytotoxic T-lymphocyte (CTL)) are a sub-group of T cells which induce the death of cells that are infected with viruses (and other pathogens), or are otherwise damaged or dysfunctional.<sup>[1]</sup>

Naive cytotoxic T cells are activated when their T-cell receptor (TCR) strongly interacts with a peptide-bound MHC class I molecule. This affinity depends on the type and orientation of the antigen/MHC complex, and is what keeps the CTL and infected cell bound together.<sup>[1]</sup> Once activated, the CTL undergoes a process called clonal expansion in which it gains functionality, and divides rapidly, to produce an army of "armed"-effector cells. Activated CTL will then travel throughout the body in search of cells bearing that unique MHC Class I + peptide.

When exposed to these infected or dysfunctional somatic cells, effector CTL release perforin and granzyme: cytotoxins which form pores in the target cell's plasma membrane, allowing ions and water to flow into the infected cell, and causing it to burst or lyse.<sup>[1]</sup> CTL release granzyme, a serine protease that enters cells via pores to induce apoptosis (cell death). To limit extensive tissue damage during an infection, CTL 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>[1]</sup>

Upon resolution of the infection, most of the effector cells will die and be cleared away by phagocytes, but a few of these cells will be retained as memory cells.<sup>[3]</sup> Upon a later encounter with the same antigen, these memory cells quickly differentiate into effector cells, dramatically shortening the time required to mount an effective response.

## Helper T-cells

*Main article: T helper cell*

CD4+ lymphocytes, or helper T cells, are immune response mediators, and play an important role in establishing and maximizing the capabilities of the acquired immune response.<sup>[1]</sup> These cells have no cytotoxic or phagocytic activity; and cannot kill infected cells or clear pathogens, but, in essence "manage" 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 activation of a naive helper T-cell causes it to release cytokines, which influences the activity of many cell types, including the APC (Antigen Presenting Cell) that activated it. Helper T-cells require a much milder activation stimulus than cytotoxic T cells. Helper T cells can provide extra signals that "help" activate cytotoxic cells.<sup>[3]</sup>

## Th1 and Th2: helper T cell responses

Two types of effector CD4+ T helper cell responses can be induced by a professional APC, designated Th1 and Th2, each designed to eliminate different types of pathogens. The factors that dictate whether an infection will trigger a Th1 or Th2 type response are not fully understood, but the response generated does play an

important role in the clearance of different pathogens.<sup>[1]</sup>

The Th1 response is characterized by the production of Interferon-gamma, which activates the bactericidal activities of macrophages, and induces B cells to make opsonizing (coating) and complement-fixing antibodies, and leads to "cell-mediated immunity".<sup>[1]</sup> The Th2 response is characterized by the release of Interleukin 4, which results in the activation of B cells to make neutralizing non-cytolytic antibodies, leading to "humoral immunity".<sup>[1]</sup> Generally, Th1 responses are more effective against intracellular pathogens (viruses and bacteria that are inside host cells), while Th2 responses are more effective against extracellular bacteria, parasites including helminths and toxins.<sup>[1]</sup> Like cytotoxic T cells, most of the CD4+ helper cells will die upon resolution of infection, with a few remaining as CD4+ memory cells.

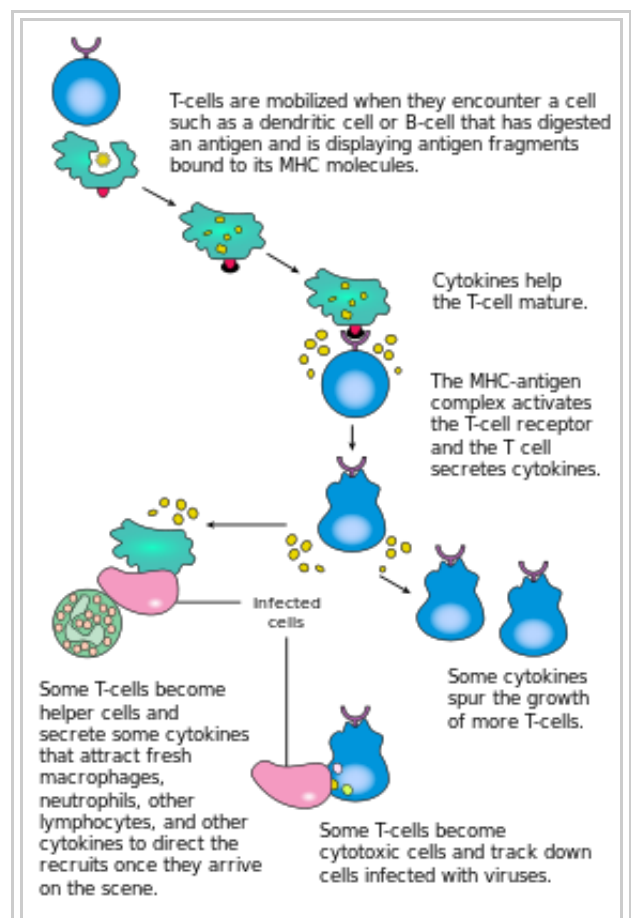
HIV is able to subvert the immune system by attacking the CD4+ T cells, precisely the cells that could drive the destruction of the virus, but also the cells that drive immunity against all other pathogens encountered during an organism's lifetime.<sup>[3]</sup>

A third type of T lymphocyte, the regulatory T cells (Treg), limits and suppresses the immune system, and may control aberrant immune responses to self-antigens; an important mechanism in controlling the development of autoimmune diseases.<sup>[3]</sup>

## $\gamma\delta$ T cells

*Main article: gamma/delta T cells*

$\gamma\delta$  T cells (gamma delta cells) possess an alternative T cell receptor (TCR) as opposed to CD4+ and CD8+  $\alpha\beta$  T cells and share characteristics of helper T cells, cytotoxic T cells and natural killer cells. Like other 'unconventional' T cell subsets bearing invariant TCRs, such as CD1d-restricted Natural Killer T cells,  $\gamma\delta$  T cells exhibit characteristics that place them at the border between innate and acquired immunity. On one hand,  $\gamma\delta$  T cells may be considered a component of acquired immunity in that they rearrange TCR genes via V(D)J recombination, which also produces junctional diversity, and develop a memory phenotype. On the other hand however, the various subsets may also be considered part of the innate immune system where a restricted TCR and/or NK receptors may be used as a pattern recognition receptor. For example, according to this paradigm, large numbers of V $\gamma$ 9/V $\delta$ 2 T cells respond within hours to common molecules produced by microbes, and highly restricted intraepithelial V $\delta$ 1 T cells will respond to stressed epithelial cells.



The T lymphocyte activation pathway. T cells contribute to immune defenses in two major ways: some direct and regulate immune responses; others directly attack infected or cancerous cells.<sup>[5]</sup>

## B lymphocytes and antibody production

*Main article: B cell*



B Cells are the major cells involved in the creation of antibodies that circulate in blood plasma and lymph, known as humoral immunity. Antibodies (also known as immunoglobulin, Ig), are large Y-shaped proteins used by the immune system to identify and neutralize foreign objects. In mammals there are five types of antibody: IgA, IgD, IgE, IgG, and IgM, differing in biological properties, each has evolved to handle different kinds of antigens. Upon activation, B cells produce antibodies, each of which recognizes a unique antigen, and neutralize specific pathogens.<sup>[1]</sup>

Like the T cell receptor, B cells express a unique B cell receptor (BCR), in this case, an immobilized antibody molecule. All the BCR of any one clone of B cells recognizes and binds to only one particular antigen. A critical difference between B cells and T cells is how each cell "sees" an antigen. T cells recognize their cognate antigen in a processed form – as a peptide in the context of an MHC molecule,<sup>[1]</sup> while B cells recognize antigens in their native form.<sup>[1]</sup> Once a B cell encounters its cognate (or specific) antigen (and receives additional signals from a helper T cell (predominately Th2 type)), it further differentiates into an effector cell, known as a plasma cell.<sup>[1]</sup>

Plasma cells are short lived cells (2–3 days) which secrete antibodies. These antibodies bind to antigens, making them easier targets for phagocytes, and trigger the complement cascade.<sup>[1]</sup> About 10% of plasma cells will survive to become long-lived antigen specific memory B cells.<sup>[1]</sup> Already primed to produce specific antibodies, these cells can be called upon to respond quickly if the same pathogen re-infects the host; while the host experiences few, if any, symptoms.

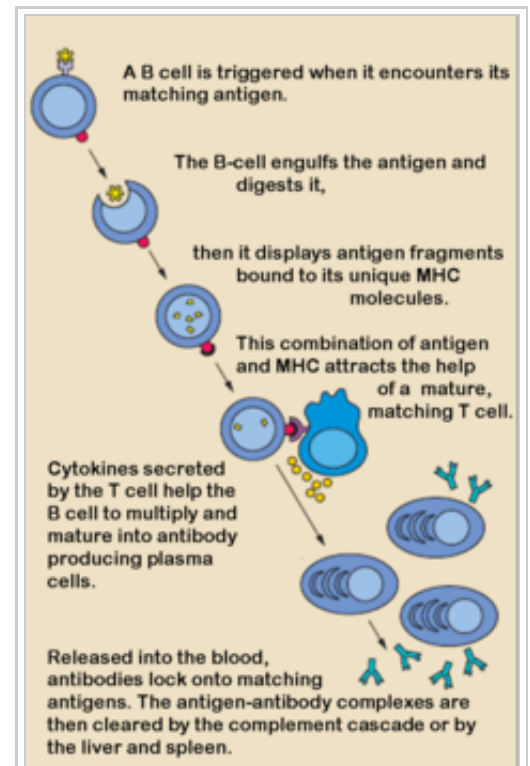
## Alternative acquired immune system

Although the classical molecules of the acquired immune system (e.g. antibodies and T cell receptors) exist only in jawed vertebrates, a distinct lymphocyte-derived molecule has been discovered in primitive jawless vertebrates, such as the lamprey and hagfish. These animals possess a large array of molecules called variable lymphocyte receptors (VLRs for short) 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>[6]</sup>

## Immunological memory

*For more details on this topic, see Immunity (medical).*

When B cells and T cells are activated some will become *memory cells*. Throughout the lifetime of an animal these memory cells form a database of effective B and T lymphocytes. Upon interaction with a previously encountered antigen, the appropriate memory cells are selected and activated. In this manner, the second and subsequent exposures to an antigen produce a stronger and faster immune response. This is "adaptive" because the body's immune system prepares itself for future challenges, but is "maladaptive" of course if the receptors are autoimmune. Immunological memory can either be in the form of *passive* short-term memory or *active* long-term memory.



The B lymphocyte activation pathway. B cells function to protect the host by producing antibodies that identify and neutralize foreign objects like bacteria and viruses.<sup>[5]</sup>

## Passive memory

Passive memory is usually short-term, lasting between a few days and several months. Newborn infants have had no prior exposure to microbes and are particularly vulnerable to infection. Several layers of passive protection are provided by the mother. *In utero*, maternal IgG is transported directly across the placenta, so that at birth, human babies have high levels of antibodies, with the same range of antigen specificities as their mother.<sup>[1]</sup> Breast milk contains antibodies that are transferred to the gut of the infant, protecting against bacterial infections, until the newborn can synthesize its own antibodies.<sup>[1]</sup>

This is passive immunity because the fetus does not actually make any memory cells or antibodies: It only borrows them. Short-term passive immunity can also be transferred artificially from one individual to another via antibody-rich serum.

## Active Memory

Active immunity is generally long-term and can be acquired by infection followed by B cells and T cells activation, or artificially acquired by vaccines, in a process called immunization.

### Immunization

Historically, infectious disease has been the leading cause of death in the human population. Over the last century, two important factors have been developed to combat their spread; sanitation and immunization.<sup>[3]</sup> Immunization (commonly referred to as vaccination) is the deliberate induction of an immune response, and represents the single most effective manipulation of the immune system that scientists have developed.<sup>[3]</sup> Immunizations are successful because they utilize the immune system's natural specificity as well as its inducibility.

The principle behind immunization is to introduce an antigen, derived from a disease-causing organism, that stimulates the immune system to develop protective immunity against that organism, but which does not **itself** cause the pathogenic effects of that organism. An antigen (short for *antibody generator*), is defined as any substance that binds to a specific antibody and elicits an adaptive immune response.<sup>[2]</sup>

Most viral vaccines are based on live attenuated viruses, while many bacterial vaccines are based on acellular components of microorganisms, including harmless toxin components.<sup>[2]</sup> Many antigens derived from acellular vaccines do not strongly induce an acquired response, and most bacterial vaccines require the addition of *adjuvants* that activate the antigen presenting cells of the innate immune system to enhance immunogenicity.<sup>[3]</sup>

## Immunological diversity

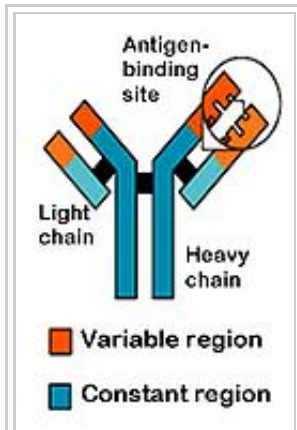
Most large molecules, including virtually all proteins and many polysaccharides, can serve as antigens.<sup>[1]</sup> The parts of an antigen that interact with an antibody molecule or a lymphocyte receptor, are called epitopes. Most antigens contain a variety of epitopes and can stimulate the production of antibodies, specific T cell responses, or both.<sup>[1]</sup>

A very small proportion (less than 0.01%) of the total lymphocytes are able to bind to a particular antigen, which suggests that only a few cells will respond to each antigen.<sup>[3]</sup>

For the acquired response to "remember" and eliminate a large number of pathogens the immune system must be able to distinguish between many different antigens,<sup>[2]</sup> and the receptors that recognize antigens must be produced in a huge variety of configurations, essentially one receptor (at least) for each different pathogen that

might ever be encountered. Even in the absence of antigen stimulation, a human is capable of producing more than 1 trillion different antibody molecules.<sup>[3]</sup> Millions of genes would be required to store the genetic information used to produce these receptors, but, the entire human genome contains fewer than 25,000 genes.<sup>[7]</sup>

This myriad of receptors are produced through a process known as clonal selection.<sup>[1][2]</sup> According to the clonal selection theory, at birth, an animal will randomly generate a vast diversity of lymphocytes (each bearing a unique antigen receptor) from information encoded in a small family of genes. In order to generate each unique antigen receptor, these genes will have undergone a process called V(D)J recombination, or *combinatorial diversification*, in which one gene segment recombines with other gene segments to form a single unique gene. It is this assembly process that generates the enormous diversity of receptors and antibodies, before the body ever encounters antigens, and enables the immune system to respond to an almost unlimited diversity of antigens.<sup>[1]</sup> Throughout the lifetime of an animal, those lymphocytes that can react against the antigens an animal actually encounters, will be selected for action, directed against anything that expresses that antigen.



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>[5]</sup>

It is important to note that the innate and acquired portions of the immune system work together and not in spite of each other. The acquired arm, B and T cells, would be unable to function without the input of the innate system. T cells are useless without antigen-presenting cells to activate them, and B cells are crippled without T cell help. On the other hand, the innate system would likely be overrun with pathogens without the specialized action of the acquired immune response.

## Acquired immunity during pregnancy

The cornerstone of the immune system is the recognition of "self" versus "non-self". Therefore, the mechanisms which protect the human fetus (which is considered "non-self") from attack by the immune system, are particularly interesting. Although no comprehensive explanation has emerged to explain this mysterious, and often repeated, lack of rejection, two classical reasons may explain how the fetus is tolerated. The first is that the fetus occupies a portion of the body protected by a non-immunological barrier, the uterus, which the immune system does not routinely patrol.<sup>[1]</sup> The second is that the fetus itself may promote local immunosuppression in the mother, perhaps by a process of active nutrient depletion.<sup>[1]</sup> A more modern explanation for this induction of tolerance is that specific glycoproteins expressed in the uterus during pregnancy suppress the uterine immune response (see eu-FEDS).

During pregnancy in viviparous mammals (all mammals except Monotremes), endogenous retroviruses (ERVs) are activated and produced in high quantities during the implantation of the embryo. They are currently known to possess immunosuppressive properties, suggesting a role in protecting the embryo from its mother's immune system. Also viral fusion proteins apparently cause the formation of the placental syncytium<sup>[8]</sup> in order to limit the exchange of migratory cells between the developing embryo and the body of the mother (something an epithelium will not do sufficiently, as certain blood cells are specialized to be able to insert themselves between adjacent epithelial cells). The immunodepressive action was the initial normal behavior of the virus, similar to HIV. The fusion proteins were a way to spread the infection to other cells by simply merging them with the infected one (HIV does this too). It is believed that the ancestors of modern viviparous mammals evolved after an infection by this virus, enabling the fetus to survive the immune system of the mother.<sup>[9]</sup>

The human genome project found several thousand ERVs classified into 24 families.<sup>[10]</sup>

## Immune network theory



*Main article: Immune network theory*

A theoretical framework explaining the workings of the acquired immune system is provided by immune network theory, based on interactions between idiotypes (unique molecular features of one clonotype, i.e. the unique set of antigenic determinants of the variable portion of an antibody) and 'anti-idiotypes' (antigen receptors that react with the idotype as if it were a foreign antigen). This theory, which builds on the existing clonal selection hypothesis and since 1974 has been developed mainly by Niels Jerne and Geoffrey W. Hoffmann, is seen as being relevant to the understanding of the HIV pathogenesis and the search for an HIV vaccine.

## Evolution

The adaptive immune system, which has been best studied in mammals, originated in a jawed fish approximately 500 million years ago. Most of the molecules, cells, tissues, and associated mechanisms of this system of defense are found cartilaginous fishes.<sup>[11]</sup> Lymphocyte receptors, Ig and TCR, are found in all jawed vertebrates. The most ancient Ig class, IgM, is membrane-bound and then secreted upon stimulation of cartilaginous fish B cells. Another isotype, shark IgW, is related to mammalian IgD. TCRs, both  $\alpha/\beta$  and  $\gamma/\delta$ , are found in all animals from gnathostomes to mammals. The organization of gene segments that undergo gene rearrangement differs in cartilaginous fishes, which have a cluster form as compared to the translocon form in bony fish to mammals. Like TCR and Ig, the MHC is found only in jawed vertebrates. Genes involved in antigen processing and presentation, as well as the class I and class II genes, are closely linked within the MHC of almost all studied species.

Lymphoid cells can be identified in some pre-vertebrate deuterostomes (i.e. sea urchins).<sup>[12]</sup> These bind antigen with pattern recognition receptors (PRRs) of the innate immune system. In jawless fishes, two subsets of lymphocytes use variable lymphocyte receptors (VLRs) for antigen binding.<sup>[13]</sup> Diversity is generated by a cytosine deaminase mediated rearrangement of LRR-based DNA segments.<sup>[14]</sup> There is no evidence for the recombination activating genes (RAGs) that rearrange Ig and TCR gene segments in jawed vertebrates.

The evolution of the AIS, based on Ig, TCR, and MHC molecules, is thought to have arisen from two major evolutionary events: the transfer of the RAG transposon (possibly of viral origin) and two whole genome duplications.<sup>[11]</sup> Though the molecules of the AIS are well-conserved, they are also rapidly evolving. Yet, a comparative approach finds that many features are quite uniform across taxa. All the major features of the AIS arose early and quickly. Jawless fishes have a different AIS that relies on gene rearrangement to generate diversity but has little else in common with the jawed vertebrate AIS. The innate immune system, which has an important role in AIS activation, is the most important defense system of invertebrates and plants.

## See also

- Affinity maturation
- Allelic exclusion
- Anergy
- Immune tolerance
- Immunosuppression
- Original antigenic sin
- Somatic hypermutation
- Polyclonal response

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## External links

- The Center for Modeling Immunity to Enteric Pathogens (MIEP) (<http://www.modelingimmunity.org>)

## Notes and references

### Notes

- <sup>^</sup> Technically, both the innate and acquired immune systems are "adaptive" in the physiological and evolutionary sense of allowing the organism to adapt to changing external circumstances (and both can be maladaptive if overactive, causing pathological inflammation and/or autoimmunity). Furthermore, the pathogen-receptors of innate and acquired immune mechanisms are both specific: the specificities of innate immunity have evolved over evolutionary time in response to highly conserved molecular features of the microbial world, whereas the specificities of acquired immunity mature in each organism. For this reason, the term "acquired" is generally preferred to "adaptive" or "specific".<sup>[*citation needed*]</sup>

## References

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