

Immune System

D Huw Davies, *University of California, Irvine, California, USA*

The immune system comprises an interacting assemblage of cells and soluble molecules whose primary function is to kill invading microorganisms that may cause damage to the body. Two interdependent kinds of immune system are present in most vertebrates, which together trigger one or more different killing mechanisms according to whether the microbes live within or outside the cells of the body. An innate system, mediated by receptors which recognize uniquely microbial structures, responds rapidly to the threat of invading organisms. This underlies an adaptive system, mediated by antigen receptors on lymphocytes, which produces a more sustained and comprehensive response. Only the adaptive system, found exclusively in vertebrates, retains a memory of exposure to each microbe and ensures the system is mobilized more rapidly upon a subsequent infection by the same pathogen.

Introduction

The human body is inhabited by a multitude of microorganisms that spend part or all of their life cycle on, or in, their human host. Many colonize the epithelial surfaces of the skin, and of the alimentary, genital and respiratory tracts and the majority are harmless commensal organisms, such as those that form the normal microbial flora of the gut. Normally, epithelium represents an impenetrable barrier to most microorganisms, blocking their entry into the body tissues. This mechanical barrier is aided by various antimicrobial chemicals and self-cleansing mechanisms (such as exfoliation and mucus) which together ensure that the colonization of our body surfaces by microorganisms is kept under control. **See also:** [Skin: Immunological Defence Mechanisms](#)

Despite these mechanical and chemical barriers, several species of microbes have evolved means to invade the body and colonize specific cells or tissues within. Other opportunists may simply gain entry if the epithelium becomes punctured or damaged in some way. If left unchecked, invading microorganisms would be disseminated by the circulatory system and may replicate rapidly within the body, causing an infection. Infection by many species, called pathogens, causes cell and tissue damage as they replicate which leads to disease. Such infections might cause fatal disease unless there is some form of active defence that can be mobilized against the invading microbes. **See also:** [Immune Response: Evasion and Subversion by Pathogens](#)

ELS subject area: Immunology

How to cite:

Davies, D Huw (December 2008) Immune System. In: *Encyclopedia of Life Sciences (ELS)*. John Wiley & Sons, Ltd: Chichester.
DOI: 10.1002/9780470015902.a0000898.pub2

Introductory article

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Online posting date: 15th December 2008

Blood clotting (coagulation) serves primarily to seal haemorrhages in punctured epithelium. However, it also serves to entrap and prevent the dispersal of any microorganisms that gain entry. Behind this lies the immune system whose role is to kill any invading microbes. In this section we will examine the variety of ways in which this is achieved. In addition to clearing away the infection, the immune system also retains a 'memory' of the exposure so that subsequent encounters to the same microbe elicit a more rapid response. Despite its importance, mobilization of the immune system is dependent on an additional type of reaction called inflammation. This is a rapid and complex physiological response to injury of the tissues that causes increased blood flow and permeability of the local capillaries. This allows the cells and soluble molecules of the immune system to infiltrate the site of injury and gain access to any invading microorganisms. Together these three systems form a complex and interdependent network of reactions that are triggered whenever there is a risk of tissue damage from microbial infection. **See also:** [Blood Coagulation](#); [Immunological Memory](#); [Inflammation: Acute](#)

Components of the Immune System

The immune system consists of specialized cells and soluble molecules (**Table 1**). The main cells are the white blood cells (leucocytes), which along with red cells (erythrocytes) are manufactured from stem cells in the bone marrow (a process called haematopoiesis). **See also:** [Haematopoiesis](#)

Leucocytes are a heterogeneous population of cells that play several active roles in killing microbes (see **Table 1**). They can be broadly classified into granulocytes and mononuclear cells. Granulocytes contain prominent granules in their cytoplasm and can be further subclassified into neutrophils, basophils and eosinophils, whereas mononuclear cells have a less granular appearance and comprise the monocytes and lymphocytes. Unlike the erythrocytes,

Table 1 Components of the immune system

Component	Main function in immune system
<i>Leucocytes</i>	
Neutrophils	Abundant, phagocytic, granulocytes that migrate to sites of inflammation to ingest invading microorganisms
Eosinophils	Phagocytic granulocytes that have Fc receptors for immunoglobulin E (IgE). IgE triggers degranulation over the surface of helminth worms and causes muscular contractions to aid in their expulsion
Basophils	Nonphagocytic granulocytes that have Fc receptors for IgE. IgE triggers degranulation and release of vasoactive substances and is thought to play a role in immunity to helminth worms
Monocytes	Precursors of tissue macrophages and dendritic cells which enter sites of inflammation wherein they undergo maturation
Lymphocytes	Cells of the adaptive immune system that recognize pathogens using antigen receptors; subclassified as follows:
B lymphocytes	Manufacture antibodies in the adaptive immune response
T lymphocytes	Multifunctional cells that respond to antigen presented to them on the surface of antigen presenting cells; subclassified as follows:
Cytotoxic T lymphocytes (CTLs or T _C)	CD8 ⁺ T lymphocytes that kill virus-infected cells and tumour cells
T helper 1 lymphocytes (T _{H1} cells)	CD4 ⁺ T lymphocytes that promote inflammation and immunity to intracellular microbes
T helper 2 lymphocytes (T _{H2} cells)	CD4 ⁺ T lymphocytes that provide cytokines and co-stimulation to B lymphocytes to enable them to produce antibodies
T helper 17 (T _{H17}) cells	CD4 ⁺ T lymphocytes that promote inflammation and immunity to extracellular microbes
T regulatory cells (Tregs)	Heterogeneous population of T lymphocytes that suppress the immune response after pathogen is cleared
Natural killer (NK) cells	Related to cytotoxic T lymphocytes, but which lack antigen receptors; effector cell of the innate immune system
Dendritic cells	Potent antigen-presenting cells able to activate naive T lymphocytes. Found in the blood, lymph (veiled cells) and secondary lymphoid tissues (interdigitating dendritic cells), and in an immature form in the skins (Langerhan's cells). A dendritic morphology maximises the surface area that is available for interaction with their surroundings
<i>Other components</i>	
Macrophages	Large phagocytic cells found throughout the body tissues involved in ingesting extracellular debris, effete cells and invading microbes
Mast cells	Granulated tissue cells that degranulate in response to tissue injury and initiate inflammatory reactions through the vasoactive properties of histamine
Professional antigen-presenting cells	Dendritic cells, macrophages and activated B lymphocytes; cells that enzymatically digest antigens ('antigen processing') and display the peptide fragments ('antigen presentation') within MHC class II molecules at the cell surface to CD4 ⁺ T lymphocytes
Antigen-presenting cell	Any nucleated cell in the body that bears class I MHC molecules; process and present antigens in the context of MHC class I molecules to CD8 ⁺ T lymphocytes; particularly important for clearance of virus infections
Primary lymphoid tissues	The tissues where antigen receptor gene rearrangements occur; i.e. thymus (T lymphocytes) and bone marrow (B lymphocytes)
Secondary lymphoid tissues	Sites through which naive lymphocytes circulate (traffic) and undergo antigen-stimulated activation; i.e. lymph nodes, spleen, Peyer's patches in gut, tonsils, etc.
Cytokines	Intercellular signalling molecules (interleukins, interferons, colony-stimulating factors, chemokines, etc.) that are released by cells during an immune response and which influence the behaviour of other cells

(Continued)

Table 1 Continued

Component	Main function in immune system
Complement	Enzymatic cascades consisting of plasma proteins that can be triggered spontaneously by microbial surfaces (alternative pathway), or indirectly by bound lectins (lectin pathway) or antibodies (classical pathway); the cascades generate chemotactic factors, opsonins, anaphylatoxins, all of which assist in the clearance of microorganisms by phagocytes
Antibodies	Soluble forms of B lymphocyte antigen receptors released during an immune response into blood and secretions (saliva, mucus, milk, etc.); adaptor molecules that bind to and neutralize extracellular microbes and toxins directly, or coat them for recognition by cells with Fc receptors such as phagocytes or NK cells, or trigger complement by classical pathway
Antigen	Any substance that can be recognized by an antigen receptor (an antigen receptor is defined as the product of rearranging genes and expressed only on T and B lymphocytes)

which function exclusively in the blood, leucocytes perform their immune functions within the tissues, and use the cardiovascular system as a means of transit between tissue sites. Exit from the blood into the tissues occurs at sites of inflammation, although lymphocytes are also able to migrate into secondary lymphoid tissues such as lymph nodes and spleen by a similar process. Lymphocytes are a particularly important subset of leucocytes as they underlie the adaptive immune response and immunological memory. Other important cells are described in **Table 1**. **See also:** [Cells of the Immune System](#)

In addition to this cellular component of the immune system, there is a 'humoral' component consisting of a variety of diffusible molecules (**Table 1**). Chemical signalling molecules called cytokines are released by cells involved in immune responses. These regulate the behaviour of neighbouring cells bearing the appropriate cytokine receptor, and can cause the target cell to proliferate, undergo differentiation into a cell with a new function or to undergo apoptosis. Other soluble molecules have antimicrobial properties. These include the complement cascade, and antibodies which are produced by B lymphocytes. **See also:** [Antibodies](#); [Complement](#); [Cytokines](#); [Immunological Cytotoxic Factors](#)

Together, these cellular and humoral components operate as the immune system. The complexity of the system is reflective of the numerous niches in the body that can be exploited by microorganisms. Many occupy extracellular environments, so several killing (so-called 'effector') mechanisms have evolved to cope with them. Other microbes, such as viruses and some species of bacteria, can hide by living inside cells and are consequently eliminated by different effector mechanisms. Before these effector mechanisms are discussed it is first necessary to introduce two kinds of immune response.

Two kinds of immunity

Whatever the niche exploited by a particular microorganism, effector mechanisms of the immune system are

potentially harmful to other cells in the body. Therefore, the immune system depends on specific receptors to selectively recognize and trigger responses to microbes while ignoring normal cells in the body. Two fundamentally different forms of recognition have evolved, and it is customary to classify immune responses into innate and adaptive, according to the kind of recognition system used. However, the two systems are closely interrelated and one rarely operates without the other. **See also:** [Immunological Discrimination Between Self and Nonself](#)

Most organisms that breach the mechanical and chemical barriers of the epithelium are recognized and destroyed within a few hours by innate mechanisms. Recognition in the innate system is mediated by receptors that recognize structures on microbes but which are absent from the body's own cells. These molecular structures are collectively termed 'pathogen associated molecular patterns' (PAMPs), and the receptors for them in the innate system are called 'pattern recognition receptors' (PRRs). The best characterized PRRs are the family of toll-like receptors (TLRs). There are at least 10 TLRs in the human innate system, which recognize various bacterial components (such as lipopeptides, glycolipids, lipopolysaccharide, peptidoglycan and flagellin), yeast components (zymosan) and double stranded RNA (ribonucleic acid) which is found only in virus-infected cells. Invertebrate animals depend entirely on pattern recognition for protection from infection, suggesting the innate system is phylogenetically more ancient than the adaptive system found only in vertebrates. **See also:** [Innate Immune Mechanisms: Nonself Recognition](#); [Pattern Recognition Receptor](#); [Toll-like Receptors](#)

In contrast, adaptive (or acquired) immunity is mediated by antigen receptors, which are expressed only on lymphocytes. Although the function of antigen receptors is also to recognize microbes and trigger effector mechanisms, it is conventional to term the ligand to which they bind simply as 'antigen'. The adaptive system has evolved recently than the older pre-existing innate system, and for this reason there are several instances where the same effector mechanisms can be triggered by either innate or antigen receptor

routes. **See also:** [Antibody Function](#); [B Lymphocytes: Receptors](#); [T-cell Receptors](#)

Although innate receptors operate by recognizing patterns unique to microorganisms, antigen receptors work on a fundamentally different principle. Several billion different antigen receptors are generated by a more-or-less random process of antigen receptor gene rearrangement. This endows each lymphocyte with a different receptor with a unique antigen specificity. This vast repertoire enables us to recognize any microbial antigen that we may encounter during our lifetimes. It also means that antigen receptors have no inherent capacity to discriminate between antigens from potentially harmful microbes, and normal 'self' antigens in the body. Therefore, before lymphocytes can enter circulation, those that are autoreactive are weeded from the repertoire in the primary lymphoid tissues. This helps prevent the immune system responding to self-antigens which may cause autoimmune disease. **See also:** [Immunoglobulin Gene Rearrangements](#)

Newly manufactured lymphocytes have short life spans and most die without ever encountering their specific antigen. In contrast, lymphocytes that encounter their specific antigen become activated and differentiate into an effector cell. In addition to antigen, lymphocyte activation requires additional signals that are produced only during inflammation. Because of the size of the repertoire, lymphocytes specific for a given antigen are rare and must first proliferate before sufficient numbers of effector cells are generated. Because each population is derived from a single activated cell, it is called a clone. The adaptive system is therefore initially much slower than the innate system to mount a response to a pathogen. However, unlike the innate system, an adaptive response leaves behind a pool of previously activated memory lymphocytes and preformed antibodies that can act immediately upon a subsequent infection. This ensures that an individual becomes protected, or 'immune', to a particular pathogen. Immunological memory, as this phenomenon is called, is also the basis of vaccination, in which a harmless preparation of a pathogen is administered to engender immunity to the pathogen but without eliciting disease. We will now examine the effector mechanisms of these two forms of immunity. **See also:** [Lymphocytes: Antigen-induced Gene Activation](#); [T-lymphocyte Activation](#)

Innate Immune Responses

Inflammation, outlined in [Figure 1](#), is an essential prerequisite for attracting the various cells and molecules of the immune system into the site of infection. Indeed, several microbes can persist in the body with impunity simply by avoiding triggering an inflammatory response. Inflammation is triggered by tissue damage, either by physical trauma such as cuts and burns, or by damage caused by replicating microorganisms that gain entry to the tissues. The immediate or 'acute' symptoms are dilation of the local capillaries (vasodilation). Stretching of the vascular

endothelium increases its permeability to fluid causing swelling, and the increased blood flow leads to redness and heat. Also during the acute phase, neutrophils in the blood attach to the vascular endothelial cells and migrate between them into the tissue. Once within the tissue their migration is guided to the site of injury by chemical signals released by the mast cells (chemotaxis). This helps the neutrophils locate and ingest any microorganisms that may have gained entry. **See also:** [Chemoattraction: Basic Concepts and Role in the Immune Response](#); [Inflammation: Acute; Neutrophils](#)

The process is triggered by tissue cells called mast cells. These cells are packed with granules that contain several pharmacologically active substances. One of these is histamine which causes vasodilation and activates vascular endothelial cells. Mast cells are fragile cells and degranulate in response to physical trauma directly. Alternatively, degranulation can be triggered by the cellular contents spilled by burst cells. This increases the acidity of the extracellular fluid and activates an enzymatic cascade that culminates in the production of bradykinin, which then binds to receptors on mast cells and triggers degranulation. **See also:** [Histamine Biosynthesis and Function](#); [Mast Cells](#)

Also involved are the tissue macrophages, which are amoeboid cells that are normally found moving through tissues throughout the body ingesting extracellular debris and effete cells. Macrophages are also attracted by the chemotactic factors released by mast cells and can help neutrophils clear away any invading microorganisms. Macrophages are important for propagating the inflammatory reaction. As they ingest microorganisms they become activated and release the inflammatory cytokines interleukin 1 (IL-1), IL-6 and tumour necrosis factor α (TNF α). Like histamine, these cytokines act on vascular endothelium to increase its permeability and to increase the expression of adhesion molecules. Macrophages therefore play an important part in recruiting more neutrophils. **See also:** [Interleukins](#); [Macrophages](#); [Tumour Necrosis Factors](#)

In addition to these local effects, the inflammatory cytokines also have systemic or endocrine effects on the body, such as acting on the hypothalamus of the brain to cause an elevation of the body temperature (fever). This is thought to retard the growth of some microbes that grow optimally at a normal body temperature. Another systemic effect acts on the hepatocytes of the liver to release acute-phase proteins (e.g. C-reactive protein and mannose-binding protein) into the blood. These enhance phagocytosis by opsonization, and also trigger the complement cascade (discussed later). **See also:** [Acute-phase Proteins](#); [Cytokines](#)

Phagocytosis

Phagocytosis is a form of endocytosis in which particulate material such as cellular debris and other cells is ingested. The major phagocytes in the body are neutrophils and macrophages which, as we have seen, play a major role

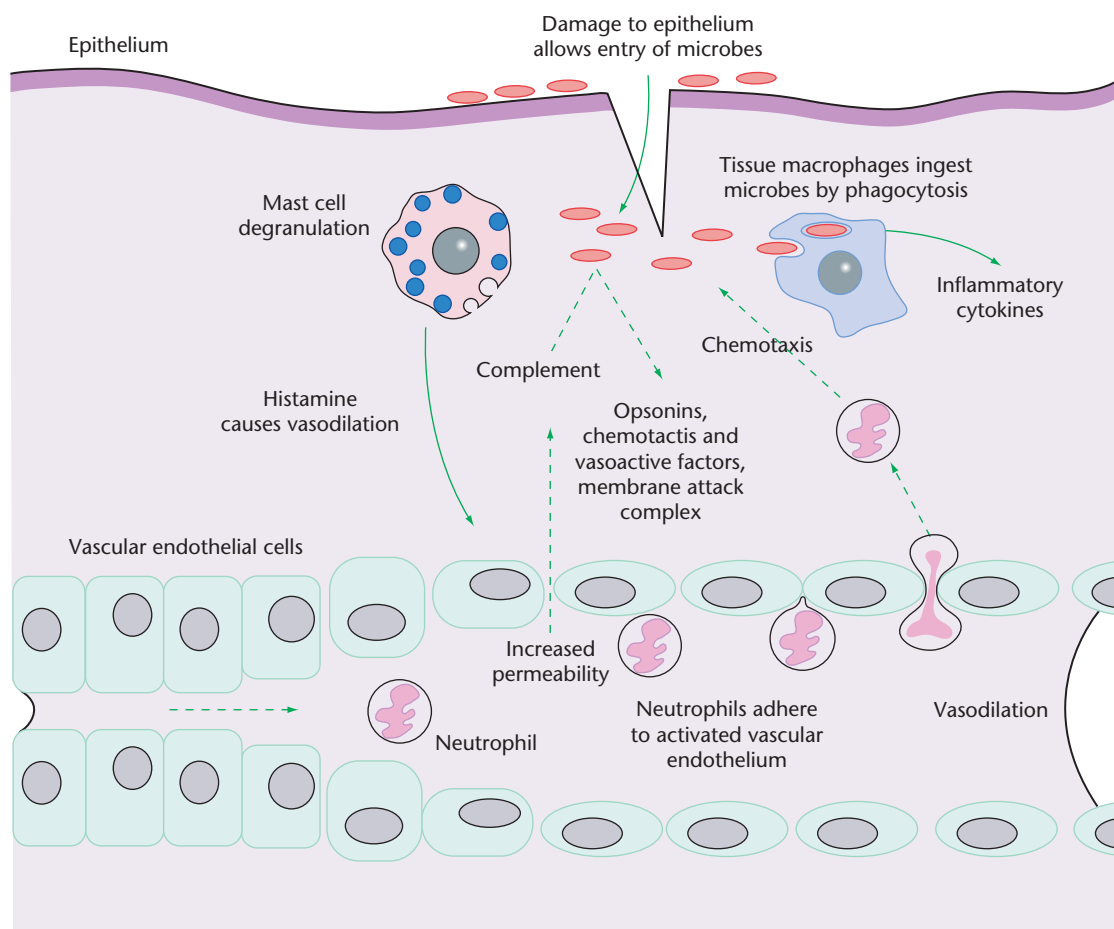


Figure 1 Overview of the acute phase of inflammation. Tissue damage causes mast cell degranulation in the tissues, either directly or via the bradykinin cascade (not shown), thereby releasing histamine and chemotactic factors. Histamine is vasoactive (causes vasodilation and increased vascular permeability) and increases the expression of adhesion molecules, enabling phagocytic neutrophils to adhere and cross into the tissue. Innate immune responses are triggered first. Neutrophils, guided by chemotactic factors, ingest microorganisms by phagocytosis. Increased vascular permeability allows components of the complement cascade to enter which generates a variety of antimicrobial and proinflammatory substances. Meanwhile tissue macrophages ingest any microorganisms and in so doing, release inflammatory cytokines. These also cause vasodilation, increased permeability and increased expression of adhesion molecules. Inflammatory cytokines also cause Langerhans cells (not shown) to migrate to draining lymph nodes where they activate T lymphocytes and initiate an adaptive immune response.

in clearing away microorganisms during inflammation. Phagocytosis is one of the most primordial of all effector mechanisms and probably has its evolutionary roots in the feeding mechanisms of unicellular organisms such as amoebae. **See also:** [Phagocytosis](#)

A key step in the process is the adhesion of the microbe to the surface of the phagocyte. Many microbes can be recognized directly by phagocytes by virtue of innate-type receptors on their surfaces that bind directly to components in microbial cell walls. However, the process is enhanced by several orders of magnitude if the surface of the microbe is first coated with a substance (termed an opsonin) for which a phagocyte has appropriate opsonin receptors. Once the microorganism has become attached to the phagocyte surface it becomes surrounded and eventually enclosed within a membrane-bound compartment called the phagosome. This undergoes fusion with smaller vesicles that deliver a

cocktail of enzymes and other microbicidal substances that help to kill and digest the ingested material. The phagosome also becomes more acidic which provides the optimum pH for the digestive enzymes. Phagocytosis also triggers a respiratory burst in which several very microbicidal byproducts of the metabolism of nitrogen and oxygen are produced and delivered into the endosome. **See also:** [Phagocytosis: Techniques](#)

Some of the digested material is regurgitated into the extracellular environment by exocytosis. In addition, larger microorganisms that are too big to be ingested by phagocytes may be digested extracellularly by enzymes released by phagocytes onto the surface of the organism. Either way, digested material is liberated into the extracellular environment. This is important both because it tends to exacerbate the inflammatory process and because it allows antigen-presenting cells (APCs) to ingest this

material. These are important prerequisites for exposing antigen to the adaptive immune response (discussed later). **See also:** [Antigen-presenting Cells](#)

The complement cascade

A second important innate defence mechanism is complement, so-called because it was first discovered for its role in complementing the activities of antibodies in the immune system. Complement is in fact an enzymatic cascade consisting of 30 or more proteins found predominantly in the plasma (**Figure 2**). During inflammation these components enter the site of infection owing to the increased permeability of vascular endothelium. The cascade can be triggered in three ways: by the lectin pathway, by the alternative pathway or by the classical pathway. In the initial stages of infection the cascade is triggered directly by the cell walls of microorganisms (the alternative pathway) or via the binding of acute-phase proteins (the lectin pathway) which enter through the vascular endothelium. These represent innate responses. The cascade can also be triggered by antibodies bound to microbial surfaces (the classical pathway). Antibodies are part of the adaptive response and appear later in the immune response during a primary exposure to a particular antigen. Pre-existing antibody

remaining from a previous exposure will ensure a more rapid activation of complement via this pathway upon a subsequent infection. **See also:** [Complement: The Alternative Pathway](#); [Complement](#); [Complement: Classical Pathway](#); [Complement: Terminal Pathway](#); [Lectins](#)

Once the cascade is triggered, a sequence of enzymatic reactions follows. At each stage, inactive substrates are cleaved to produce two or more cleavage products. Some have enzymatic properties of their own and activate the downstream component, whereas other complement products have useful antimicrobial properties. These include:

- **Opsonins:** these become deposited on microbes and enhance their uptake by phagocytes bearing complement receptors.
- **Chemotactic factors:** these attract phagocytes towards the microorganisms.
- **Anaphylatoxins:** these are substances that cause mast cells and basophils to degranulate and release vasoactive substances.
- **Membrane attack complexes (MACs):** MACs assemble into pores in accessible cell membranes and disrupt the membranes of certain bacteria, enveloped viruses and other microbes.

Natural killer (NK) cells

The NK cell is a cytotoxic cell whose role is to contact tumour cells and virally infected cells and cause them to undergo apoptosis. NK cells are related in many ways to the cytotoxic T lymphocyte (CTL) of the adaptive immune response, discussed later. Both differentiate from a common progenitor cell and both use similar effector mechanisms to kill infected cells and tumour cells. However, NK cells lack antigen receptors and instead use an innate receptor that recognizes certain sugar residues (i.e. is a lectin) found only on infected cells and tumour cells. NK cells can also identify target cells tagged by antibodies by a process called antibody-dependent cell-mediated cytotoxicity (ADCC), and therefore represent another effector mechanism that can be activated via innate and adaptive means. NK cells are particularly effective at killing cells lacking class I major histocompatibility complex (MHC) molecules which, as we will see in the next section, are required by CTL for recognition. NK cells therefore supplement the activity of CTLs and provide early protection while the adaptive arm of the immune response is being mobilized. **See also:** [Antibody-dependent Cell-mediated Cytotoxicity \(ADCC\)](#); [Natural Killer \(NK\) Cells](#)

Adaptive Immune Responses

Most microorganisms that penetrate the body are recognized and destroyed within a few hours by the innate system. Only if a few organisms breach this innate line of defence is an adaptive immune response mounted. A key event in mobilizing lymphocytes and the adaptive immune

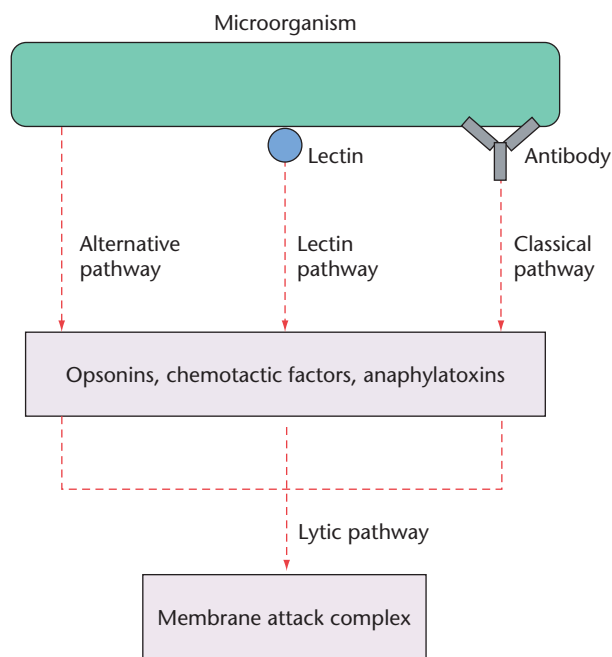


Figure 2 Complement cascades are enzymatic cascades that generate a variety of antimicrobial and pro-inflammatory substances that help phagocytes to clear away invading microorganisms. The innate or alternative pathway can be activated directly by the cell walls of microbes, or via bound lectins such as the acute-phase proteins generated during inflammation. The classical pathway is triggered by antibodies bound to the surface of microbes. Despite the nomenclature it is almost certain that the classical pathway has evolved recently than the innate pathways. It provides a good example of an effector mechanism that can be triggered by innate and adaptive forms of recognition. Thereafter, all pathways converge on a common, lytic pathway that culminates in the formation of a membrane attack complex.

response is the transport of microbial antigen to local secondary lymphoid tissues. These are the sites through which T and B lymphocytes constantly traffic and where activation of clones bearing the appropriate antigen receptors are activated (discussed in the next section). Antigen is carried back to the lymphoid tissues via the lymphatic system, either suspended in the fluid (lymph) that drains the tissues, or carried by dendritic cells. **See also:** [Dendritic Cells \(T-lymphocyte Stimulating\)](#); [Lymphatic System](#); [Mucosal Lymphoid Tissues](#)

Anatomy and the Circulation in the Immune System

Primary lymphoid tissues are defined as the anatomical sites where lymphoid stem cells differentiate into mature lymphocytes and acquire their antigen receptors. In humans, these tissues are the *bone marrow* for B lymphocytes, and the *thymus* for T lymphocytes. The genes for antigen receptors are inherited by all lymphocytes as the same non-functional gene fragments. During development in the primary lymphoid tissues, each immature lymphocyte rearranges its gene fragments into a single functional gene. Although the genes for T and B cell antigen receptors are different, the rearrangement process is very similar. It is an essentially random process that produces a T or B receptor with an antigen specificity that is essentially unique to each lymphocyte. Collectively, the population of lymphocytes becomes a vast repertoire of different antigen receptors able to recognize any antigen. A cost of this process is that some lymphocytes will randomly generate antigen receptors for self-antigens. These lymphocytes may cause *autoimmune disease* if allowed to emerge as mature cells into the peripheral circulation. Thus, the repertoire is first weeded of strongly autoreactive lymphocytes before it is then allowed to enter the periphery. This weeding process is known as *self-tolerance*, and results in a population of mature lymphocytes heavily skewed towards recognizing nonself- (i.e., foreign) antigens. **See also:** [Autoimmune Disease](#); [Immunological Tolerance: Mechanisms](#); [The Thymic Niche and Thymopoiesis](#)

The final repertoire that emerges into the periphery is so vast that it has the capacity to recognize any foreign antigen that may gain entry to the body. This is a hallmark of the adaptive immune system. A consequence is that the actual number of lymphocytes bearing any given antigen receptor is very low in the repertoire. If left to chance, the encounter between antigen receptor and its specific antigen during an infection would be a very inefficient process. For this reason the body uses *secondary lymphoid tissues* to trap antigens entering the body through which mature lymphocytes traffic via the circulatory (blood) system. This increases the likelihood that foreign antigen will be recognized by the appropriate lymphocytes. Antigens are collected in secondary lymphoid tissues either by passive filtering of antigen-antibody complexes (*immune*

complexes) and other particulate material that is carried in the blood or lymph, or by the active immigration of *phagocytes* and *dendritic cells* carrying antigen acquired in the skin or other tissues. The main secondary lymphoid tissues comprise the *lymph nodes*, the *spleen* and *Peyer's patches*. Lymph nodes are scattered throughout the body and collect the interstitial fluid between cells that drains from the tissues (the *lymph*). Antigens in the blood and gut are collected by the spleen and Peyer's patches, respectively. Thus for example, an infection in the skin would yield antigens and immune complexes that would be trapped by draining lymph nodes nearby. In addition, *Langerhans' cells* efficiently ingest debris, including microbial antigens, and migrate along the lymphatics to the draining lymph node. Circulating T lymphocytes that enter from the blood may encounter their specific antigen presented to them on the surface of the specialized APCs called dendritic cells, causing them to become activated (dendritic cells are discussed later). Lymphocyte activation is associated with maturation into an effector phenotype able to deal with the microbial infection, and often accompanied by proliferation to expand the number of effector cells. This accounts for swelling of the lymph nodes associated with infections (*lymphadenopathy*). **See also:** [Lymphatic System](#); [Lymphoid System](#)

Lymphocytes

Lymphocytes are at the heart of the adaptive immune response. T and B lymphocytes have different, although homologous, antigen receptors through which activation of the cell occurs. The B-lymphocyte receptor is also called immunoglobulin (Ig), and is used by the B cell to bind free antigen in solution. In response to cytokines produced by helper T lymphocytes these B cells then proliferate and differentiate into plasma cells, which manufacture large quantities of soluble immunoglobulin (antibodies). Antibodies can bind to microbes and neutralize them before they infect cells, or agglutinate (clump) microbes by virtue of having two identical antigen-binding sites per molecule. However, antibodies have no intrinsic antimicrobial properties of their own. Instead they coat the microbial surface. Macrophages with Fc-receptors may be able to ingest the antibody-coated (opsonised) microbe. The bound antibodies can also trigger the complement cascade via the classical pathway. **See also:** [B Lymphocytes](#); [B Lymphocytes: Receptors](#); [Complement: Classical Pathway](#); [Fc Receptors](#)

In contrast, the antigen receptor of T lymphocytes is the T-cell receptor (TCR) which only exists in a membrane-bound form. While immunoglobulin can bind to free antigen, the TCR binds instead to a peptide fragment of the antigen that is presented to it on the surface of another, 'antigen-presenting' cell within the cleft of a molecule encoded by the major histocompatibility complex (MHC). There are several subtypes of T lymphocytes whose different functions correlate with different phenotypes and the types of cytokine they release upon activation. T cells

bearing the CD8 co-receptor molecule differentiate into cytotoxic T lymphocytes (CTLs or T_C) whose function, like NK cells, is to kill cells in the body that have become cancer cells or have become infected by viruses. However, T cells bearing CD4 differentiate into helper T cells (T_H). There are two main subsets of $CD4^+$ T lymphocytes: T_H1 cells and T_H2 . Broadly speaking, the main functions of T_H1 cells is to produce cytokines that help macrophages, NK cells and CTLs to eliminate intracellular microbes, whereas the main function of T_H2 cells is to help B cells to produce antibodies which in turn provide various forms of protection to extracellular pathogens. This is an oversimplification, as some cytokines produced by T_H1 cells help antibody class-switching in B cells. However, once a response develops, the expanding T-cell population polarizes into a T_H1 or T_H2 direction, according to the type of pathogen needing to be eliminated. This is in part because cytokines from T_H1 cells suppress the development of T_H2 , and vice versa. **See also:** T Lymphocytes: Cytotoxic; T Lymphocytes: Helpers

Recently, two other major T-cell subsets have been described. Suppressor or regulatory T cells (T_{regs}) play a role in dampening down the immune response after the pathogen has been cleared (the contraction phase). These cells secrete immunosuppressive cytokines such as IL-10 and transforming growth factor beta ($TGF\beta$). IL-10 downregulates the expression of MHC class II and co-stimulatory molecules on professional APCs, and downregulates the expression of cytokines by T_H1 cells, whereas $TGF\beta$ restricts lymphocyte proliferation and induces apoptosis (cellular 'suicide'). The other subset is T_H17 cells, which are pro-inflammatory T lymphocytes whose main function in the immune system appears to be defence against extracellular pathogens. **See also:** T Lymphocytes: Regulatory

All of the above have a TCR comprising an α and a β chain. There are in addition, a smaller population of T cells that bear a $\gamma\delta$ receptor. This receptor is encoded in a different pair of genes that is less diverse than the $\alpha\beta$ receptor. These ' $\gamma\delta$ T cells' are found mostly in intestinal epithelium and recognize pyrophosphate molecules generated by bacteria and parasites. These cells produce anti-bacterial compounds and kill infected cells. **See also:** T-cell Receptors

Dendritic cells and other antigen-presenting cells

Before antigen recognition by T lymphocytes, the antigen is first enzymatically digested into peptides by an APC and then displayed at the APC surface within a molecule encoded by a gene within the MHC (Figure 3). There are two types of MHC molecules involved in antigen presentation to T cells, and the antigens that are presented by them are processed within different intracellular compartments inside APCs. Class I MHC molecules present peptides to $CD8$ -bearing T cells, whereas class II MHC molecules present peptides to $CD4$ -bearing T cells. All nucleated cells in the body bear class I MHC molecules, which ensures

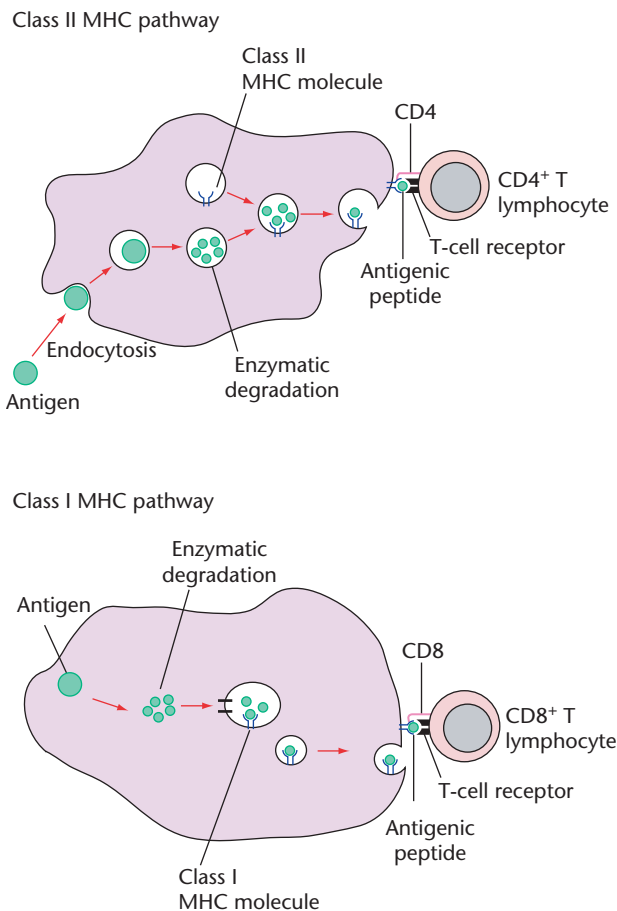


Figure 3 Antigen processing and presentation by antigen-presenting cells (APCs). Class II major histocompatibility complex (MHC) molecules are found only on all professional APCs (dendritic cells, macrophages and B lymphocytes). As a general rule, antigens ingested from outside the APC enter this pathway and are processed into peptide fragments by enzymatic degradation in endosomal compartments. These peptides are picked up by class II MHC molecules and presented to $CD4$ ('helper') T lymphocytes. In contrast, class I MHC molecules are found on all nucleated cells in the body (including APCs). These molecules present processed peptides to $CD8$ (cytotoxic) T lymphocytes (CTLs), and antigens presented by this pathway usually originate from within the cell (as is the case in viral infection) and are processed in the cytosol. By this means, all cells have the capacity to be recognized and killed by CTLs should they become infected. There is evidence that dendritic cells can also load class I from antigen derived from outside the cell.

they can be killed by CTLs if necessary. Class II MHC molecules are more restricted in their distribution, being found mainly on professional APCs (dendritic cells, macrophages and activated B lymphocytes). In addition to antigen, other co-stimulatory signals are also required for full T-cell activation. Dendritic cells are particularly potent APCs because they can deliver both signals to T lymphocytes. **See also:** Antigen-presenting Cells; Major Histocompatibility Complex: Human

Dendritic cells are the primary APC in initiating an adaptive immune response. During inflammation, immature dendritic cells (called Langerhans' cells) ingest

extracellular debris, apoptotic cells and microorganisms, and then migrate via the lymphatic system to draining lymph nodes. During this time these cells undergo maturation, characterized by a huge increase in the surface expression of class I and II MHC molecules, and of T-cell co-stimulatory molecules. Mature dendritic cells have a unique ability to activate naive T cells, and are regarded as the sentinels at the interface between the microbial world and the adaptive immune response. In recent years, a number of different dendritic cell subsets have been described, each with distinct locations, function and phenotype. **See also:** [Dendritic Cells \(T-lymphocyte Stimulating\)](#)

The following is a listing of the functions and effector mechanisms mediated by lymphocytes. These are considered hallmarks of the adaptive immune response.

Macrophage activation

An important effector function of T_H1 cells is macrophage activation, which is mediated predominantly by a cytokine secreted by T_H1 cells called interferon γ ($IFN\gamma$). $IFN\gamma$ has many immunomodulatory functions, but in macrophages it triggers a dramatic increase in the respiratory burst. This plays an important role in killing ingested bacteria, particularly those such as *Mycobacterium* that have become adapted to living inside the phagosomes of macrophages. Macrophages obtain this help from T_H1 cells because of their capacity as APCs to process ingested material and present antigenic peptides at their surface in the context of class II MHC molecules. **See also:** [Interferons](#); [Macrophages](#)

Antibodies

Antibodies or immunoglobulins (Ig) are soluble forms of the B-cell antigen receptor. To differentiate into antibody secreting cells, B cells require 'help' (in the form of cytokines from T_H2 cells). Like macrophages, B cells are APCs that bear class II MHC molecules. B cells use their surface immunoglobulin to capture and ingest extracellular antigen. Once inside, the antigen is processed and the peptides exported back out and displayed by class II MHC molecules (top panel in [Figure 3](#)). In this way the B cell can solicit help from a passing activated T_H cell bearing the appropriate antigen receptor (TCR). Upon binding the peptide–MHC complex the T cell undergoes further differentiation into a T_H2 cell which releases cytokines, notably IL-4, IL-5 and IL-6, that instruct the B cell to proliferate. As the clone of B lymphocytes expands, the cells differentiate into plasma cells whose function is to manufacture large quantities of antibody. Thus as an immune response develops the concentration of antibody (titer) in the blood and other extravascular fluids increases. Also, the affinity of the antibody for its specific antigen gradually increases during the course of an immune response (a process called affinity maturation) that is caused by somatic hypermutation of the antibody genes.

There are five main classes of antibodies: IgG, IgA, IgM, IgD and IgE. These molecules possess no toxic or antimicrobial properties of their own but instead bind to the surface of microorganisms. This can lead to a number of different effector mechanisms, according to the class of antibody: **See also:** [Antigen–Antibody Binding](#); [Antibody Function](#)

- **Neutralization:** One of the simplest functions of antibodies is to neutralize viruses, bacterial toxins and other potentially harmful substances by blocking their interaction with cell surface receptors.
- **Agglutination:** Another useful property of antibodies, which occurs by virtue of their possession of two identical antigen-binding sites, is antigen crosslinking. In this way microbes can be agglutinated into mesh-like structures called immune complexes which are more readily ingested by phagocytes or captured by secondary lymphoid tissues.
- **Activation of complement:** Antibodies bound to the surface of microbes also trigger the activation of the classical pathway of the complement cascade. As we saw earlier, this cascade generates a variety of opsonins, chemotactic factors, pro-inflammatory mediators and culminates in the production of a membrane attack complex.

In addition, there are antibody-mediated effector mechanisms that require accessory cells bearing receptors which bind to a part of the antibody away from the antigen-binding site called the Fc region. These include:

- **Opsonization:** Phagocytes such as macrophages and neutrophils bear Fc receptors that enhance their ability to ingest microorganisms coated by bound antibody.
- **Antibody-dependent cell-mediated cytotoxicity (ADCC):** Fc receptors on NK cells enable them to identify and kill antibody-tagged tumour cells and virus-infected cells.
- **Degranulation of mast cells, basophils and eosinophils:** These cells play an important role in immunity to helminth worms which are too large to be ingested by individual phagocytes. Their Fc receptors recognize antibodies bound to the worms which trigger their release of inflammatory mediators and substances that cause muscle contractions which are thought to aid expulsion of the worms from the gut. **See also:** [Fc Receptors](#)

Cytotoxic T lymphocytes (CTLs)

While NK cells are important during the early stages of infections by viruses, CTLs are required for their complete elimination. CTLs recognize virus-infected or tumour cells by the complexes of processed peptides and class I MHC molecules displayed at the surface of the transformed cell. Engagement of the TCR by the peptide–MHC activates the CTL and triggers the release of preformed substances from granules. CTL and NK cells both release perforins which, like the complement membrane attack complex,

assemble into pores in the plasma membrane of the target cell. They also release enzymes called granzymes which enter the cell through the perforin pores and trigger the cell to undergo apoptosis. CTLs can also trigger apoptosis by stimulating a cell-surface receptor called CD95 found on most cells. **See also:** T Lymphocytes: Cytotoxic

Memory

A key feature of the adaptive immune system is memory. During the response to pathogens, T- and B-cell clones expand by proliferating and differentiating into short-lived effector cells and long-lived memory cells. This is followed by a contraction phase after the pathogen is cleared during which most of the effector cells are gradually destroyed, mainly by apoptosis, leaving a population of memory cells with a distinct phenotype from naïve cells. Antibody memory to an antigen is maintained by memory B cells and/or long-lived plasma cells.

Memory T lymphocytes are heterogeneous, and include T 'central' and more T 'effector' memory cell subsets. T central-memory cells are long-lived, quiescent cells found predominantly in lymphoid organs that may provide a reserve of memory cells. T effector-memory cells are found mainly in the tissues and are shorter-lived than T central-memory and more readily re-activated by antigen. Other types of memory cells have been described that promote inflammation, help antibody production or regulate other immune responses.

Memory cells are more readily activated by antigen than naïve cells, which ensures that the secondary response to a particular antigen is much more rapid than a primary response by naïve cells. Indeed, the secondary response is often so rapid that disease symptoms never occur when we are re-exposed to a particular pathogen. Memory against infectious agents such as influenza and smallpox can persist for decades after initial exposure and it is this state of

immunity that is exploited by vaccines, as discussed earlier. **See also:** Immunological Memory; Vaccination

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