**Cellular Components of the Immune System**

The immune system consists of cellular components and [molecular components](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/molecular-components-of-the-immune-system) that work together to destroy antigens.

## Antigen-Presenting Cells

Although some antigens (Ags) can stimulate the immune response directly, T cell–dependent acquired immune responses typically require antigen-presenting cells (APCs) to present antigen-derived peptides within major histocompatibility complex (MHC) molecules.

**Intracellular antigens** (eg, viruses) can be processed and presented to CD8 cytotoxic T cells by any nucleated cell because all nucleated cells express class I MHC molecules. By encoding proteins that interfere with this process, some viruses (eg, cytomegalovirus) can evade elimination.

**Extracellular antigens** (eg, from many bacteria) must be processed into peptides and complexed with surface class II MHC molecules on professional APCs (which specialize in presenting antigens to T cells) to be recognized by CD4 helper T (Th) cells. The following cells constitutively express class II MHC molecules and therefore act as professional APCs:

* Dendritic cells
* Monocytes
* Macrophages
* [B cells](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/cellular-components-of-the-immune-system#v992166)

**Dendritic cells** are present in the skin (as Langerhans cells), lymph nodes, and tissues throughout the body. Dendritic cells in the skin act as sentinel APCs, taking up antigen, then traveling to local lymph nodes where they can activate T cells. Follicular dendritic cells are a distinct lineage, do not express class II MHC molecules, and therefore do not present antigen to Th cells. They are not phagocytic; they have receptors for the crystallizable fragment (Fc) region of immunoglobulin (Ig) G and for complement, which enable them to bind with immune complexes and present the complex to B cells in germinal centers of secondary lymphoid organs.

**Monocytes** in the circulation are precursors to tissue macrophages. Monocytes migrate into tissues, where over about 8 hours, they develop into macrophages under the influence of macrophage colony-stimulating factor (M-CSF), secreted by various cell types (eg, endothelial cells, fibroblasts). At infection sites, activated T cells secrete cytokines (eg, interferon-gamma [IFN-gamma]) that induce production of macrophage migration inhibitory factor, preventing macrophages from leaving.

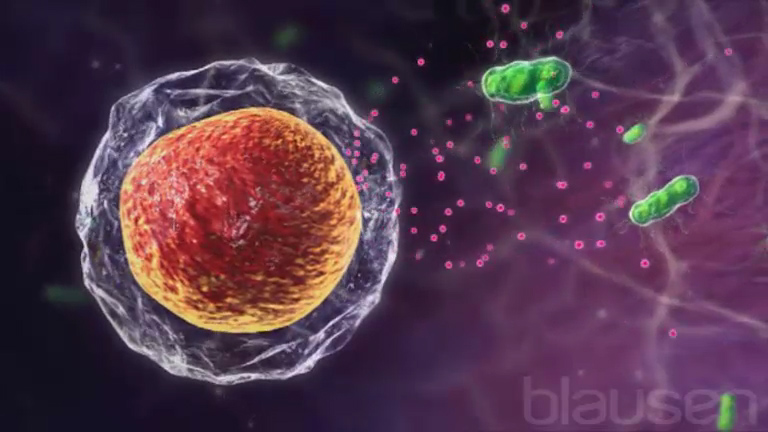
**Macrophages** are activated by cytokines (eg, IFN-gamma, interleukin (IL)-4, IL-13) and by various microbial components (eg, lipopolysaccharide). Activated macrophages kill intracellular organisms and secrete cytokines (eg, tumor necrosis factor-alpha (TNF-alpha), IL-10. Based on different gene expression profiles, subtypes of macrophages.

## Lymphocytes

The 2 main types of lymphocytes are

* B cells (which mature in bone marrow)
* T cells (which mature in the thymus)

The main types of lymphocytes are morphologically indistinguishable but have different immune functions. They can be distinguished by antigen-specific surface receptors and molecules called clusters of differentiation (CDs), whose presence or absence define some subsets. More than 300 CDs have been identified. Each lymphocyte recognizes a specific antigen via surface receptors.



### B cells

About 5 to 15% of lymphocytes in the blood are B cells; they are also present in the bone marrow, spleen, lymph nodes, and mucosa-associated lymphoid tissues.

B cells can present antigen to T cells and release cytokines, but their primary function is to develop into plasma cells, which manufacture and secrete [antibodies](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/molecular-components-of-the-immune-system#v28603680).

Patients with B-cell immunodeficiencies (eg, [X-linked agammaglobulinemia](https://www.msdmanuals.com/professional/immunology-allergic-disorders/immunodeficiency-disorders/x-linked-agammaglobulinemia)) are especially susceptible to recurrent bacterial infections.

After random rearrangement of the genes that encode immunoglobulin (Ig), B cells collectively have the potential to recognize an almost limitless number of unique antigens. Gene rearrangement occurs in programmed steps in the bone marrow during B-cell development. The process starts with a committed stem cell, continues through pro‒B and pre‒B cell stages, and results in an immature B cell. At this point, any cells that interact with self antigen (autoimmune cells) are removed from the immature B cell population via inactivation or apoptosis. Elimination of these cells ensures that the immune system is less likely to recognize these antigens as foreign (immune tolerance). Cells that are not removed (ie, those that recognize nonself antigen) continue to develop into mature naive B cells, leave the marrow, and enter peripheral lymphoid organs, where they may encounter antigens.

Their response to antigen has 2 stages:

* **Primary immune response:** When mature naive B cells first encounter antigen, they become lymphoblasts, undergo clonal proliferation, and differentiate into memory cells, which can respond to the same antigen in the future, or into mature antibody-secreting plasma cells. After first exposure, there is a latent period of days before antibody is produced. Then, only IgM is produced. After that, with the help of T cells, B cells can further rearrange their Ig genes and switch to production of IgG, IgA, or IgE. Thus, after first exposure, the response is slow and initially provides limited protective immunity.
* **Secondary (anamnestic or booster) immune response:** When memory B and Th cells are reexposed to the antigen, the memory B cells rapidly proliferate, differentiate into mature plasma cells, and promptly produce large amounts of antibody (chiefly IgG because of a T cell–induced isotype switch). The antibody is released into the blood and other tissues, where it can react with antigen. Thus, after reexposure, the immune response is faster and more effective.

### T cells

T cells develop from bone marrow stem cells that travel to the thymus, where they go through rigorous selection. There are 3 main types of T cell:

* Helper
* Regulatory (suppressor)
* Cytotoxic

In selection, T cells that react to self antigen presented by self MHC molecules or to self MHC molecules (regardless of the antigen presented) are eliminated by apoptosis, limiting the likelihood of autoimmunity. Only T cells that can recognize nonself antigen complexed to self MHC molecules survive; they leave the thymus for peripheral blood and lymphoid tissues.

Most mature T cells express either CD4 or CD8 and have an antigen-binding, Ig-like surface receptor called the T-cell receptor (TCR). There are 2 types of TCR:

* Alpha-beta TCR: Composed of TCR alpha and beta chains; present on most T cells
* Gamma-delta TCR: Composed of TCR gamma and delta chains; present on a small population of T cells

Genes that encode the TCR, like Ig genes, are rearranged, resulting in defined specificity and affinity for antigen. Most T cells (those with an alpha-beta TCR) recognize antigen-derived peptide displayed in the MHC molecule of an antigen-presenting cell. Gamma-delta T cells recognize protein antigen directly or recognize lipid antigen displayed by an MHC-like molecule called CD1. As for B cells, the number of T-cell specificities is almost limitless.

For alpha-beta T cells to be activated, the TCR must engage with antigen-MHC (see figure [Two-signal model for T cell activation](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/cellular-components-of-the-immune-system#v992206)). Costimulatory accessory molecules must also interact (eg, CD28 on the T cell interacts with CD80 and CD86 on the antigen-presenting cell); otherwise, the T cell becomes anergic or dies by apoptosis. Some accessory molecules (eg, CTLA-4 [cytotoxic T-lymphocyte antigen 4] on the T cell, which also interacts with CD80 and CD86 on the antigen-presenting cell, PD-1 [programmed cell death protein 1] on the T cell, which interacts with PD-L1 [programmed cell death protein ligand 1] on the antigen-presenting cell) inhibit previously activated T cells and thus dampen the immune response. Molecules such as CTLA-4 and PD-1, and their ligands, are termed checkpoint molecules because they signal that the T cell needs to be restrained from continuing its activity. Cancer cells that express checkpoint molecules may thus be protected from the immune system by restraining the activity of tumor-specific T cells.

Monoclonal antibodies that target checkpoint molecules on either T cells or on tumor cells (termed checkpoint inhibitors, see table [Some Immunotherapeutic Agents in Clinical Use](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/immunotherapeutics#v992868)) are used to prevent downregulation of antitumor responses and effectively treat some heretofore resistant cancers. However, because checkpoint molecules are also involved in other types of immune response, checkpoint inhibitors can cause severe immune-related inflammatory and autoimmune reactions (both systemic and organ specific).

Polymorphisms in the CTLA-4 gene are associated with certain autoimmune disorders, including [Graves disease](https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/thyroid-disorders/hyperthyroidism#v981625) and [type I diabetes](https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/diabetes-mellitus-and-disorders-of-carbohydrate-metabolism/diabetes-mellitus-dm#v988029).

### Two-signal model for T-cell activation

| The alpha (α) and beta (β) chains of the T-cell receptor (TCR) bind to antigen (Ag)–major histocompatibility complex (MHC) on an antigen-presenting cell (APC), and CD4 or CD8 interacts with the MHC. Both actions stimulate the T cell (1st signal) through the accessory CD3 chains. However, without a 2nd (coactivation) signal, the T cell is anergic or tolerant.  The TCR is structurally homologous to the B-cell receptor; the α and β (or gamma [γ] and delta [δ]) chains have constant (C) and variable (V) regions. (1) = 1st signal; (2) = 2nd signal.  Two-signal model for T-cell activation |
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**Helper T (Th) cells** are usually CD4 but may be CD8. They differentiate from Th0 cells into one of the following:

* Th1 cells: In general, Th1 cells promote cell-mediated immunity via cytotoxic T cells and macrophages and are thus particularly involved in defense against intracellular pathogens (eg, viruses). They can also promote the production of some antibody classes.
* Th2 cells: Th2 cells are particularly adept at promoting antibody production by B cells (humoral immunity) and thus are particularly involved in directing responses aimed at extracellular pathogens (eg, bacteria, parasites).
* Th17 cells: Th17 cells promote tissue inflammation.

Each cell type secretes several [cytokines](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/molecular-components-of-the-immune-system#v28603723) (see table [Functions of T Cells](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/cellular-components-of-the-immune-system#v992227)). Different patterns of cytokine production identify other Th-cell functional phenotypes. Depending on the stimulating pathogen, Th1 and Th2 cells can, to a certain extent, downregulate each other's activity, leading to dominance of a Th1 or a Th2 response.

The distinction between the different Th cells is clinically relevant. For example, a Th1 response dominates in tuberculoid [leprosy](https://www.msdmanuals.com/professional/infectious-diseases/mycobacteria/leprosy#v1011501), and a Th2 response dominates in lepromatous leprosy. A Th1 response is characteristic of certain autoimmune disorders (eg, type 1 [diabetes](https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/diabetes-mellitus-and-disorders-of-carbohydrate-metabolism/diabetes-mellitus-dm), [multiple sclerosis](https://www.msdmanuals.com/professional/neurologic-disorders/demyelinating-disorders/multiple-sclerosis-ms)), and a Th2 response promotes IgE production and development of allergic disorders, as well as helps B cells produce autoantibodies in some autoimmune disorders (eg, [Graves disease](https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/thyroid-disorders/hyperthyroidism), [myasthenia gravis](https://www.msdmanuals.com/professional/neurologic-disorders/peripheral-nervous-system-and-motor-unit-disorders/myasthenia-gravis)). Th17 cells, via their role in inflammation, may also contribute to autoimmune disorders such as [psoriasis](https://www.msdmanuals.com/professional/dermatologic-disorders/psoriasis-and-scaling-diseases/psoriasis) and [rheumatoid arthritis](https://www.msdmanuals.com/professional/musculoskeletal-and-connective-tissue-disorders/joint-disorders/rheumatoid-arthritis-ra). Patients with immunodeficiencies characterized by defective Th17 cells (eg, hyper-IgE [Job] syndrome) are especially susceptible to infection with [Candida albicans](https://www.msdmanuals.com/professional/infectious-diseases/fungi/candidiasis-invasive) and [Staphylococcus aureus](https://www.msdmanuals.com/professional/infectious-diseases/gram-positive-cocci/staphylococcal-infections).

**Regulatory (suppressor) T (Treg) cells** mediate suppression of immune responses and usually express the Foxp3 transcription factor. They comprise functional subsets of CD4 or CD8 T cells that develop either within the thymus (natural Treg) or from conventional T cells upon encounter with antigen in the periphery (induced Treg). Regulatory T cells secrete cytokines such as transforming growth factor (TGF)-beta and interleukin (IL)-10 with immunosuppressive properties, or suppress the immune response by mechanisms that require cell-to-cell contact and involve cell surface molecules such as CTLA-4 and CD25. Patients with functional mutations in Foxp3 develop the autoimmune disorder [IPEX syndrome](https://www.msdmanuals.com/professional/endocrine-and-metabolic-disorders/polyglandular-deficiency-syndromes/ipex-syndrome)  (*i*mmunodysregulation, *p*olyendocrinopathy, *e*nteropathy, *X*-linked syndrome).

**Cytotoxic T (Tc) cells** are usually CD8 but may be CD4; they are vital for eliminating intracellular pathogens, especially viruses. Tc cells play a role in organ transplant rejection.

Tc-cell development involves 3 phases:

* A precursor cell that, when appropriately stimulated, can differentiate into a Tc cell
* An effector cell that has differentiated and can kill its appropriate target
* A memory cell that is quiescent (no longer stimulated) but is ready to become an effector when restimulated by the original antigen-MHC combination

Fully activated Tc cells, like natural killer (NK) cells, can kill an infected target cell by inducing apoptosis.

Tc cells can secrete cytokines and, like Th cells, have been divided into types Tc1 and Tc2 based on their patterns of cytokine production.

Tc cells may be

* Syngeneic: Generated in response to self (autologous) cells modified by viral infection or other foreign proteins
* Allogeneic: Generated in response to cells that express foreign MHC products (eg, in organ transplantation when the donor’s MHC molecules differ from the recipient’s)

Some Tc cells can directly recognize foreign MHC (direct pathway); others may recognize fragments of foreign MHC presented by self MHC molecules of the transplant recipient (indirect pathway).

**Natural killer T (NKT) cells** are a distinct subset of T cells. Activated NKT cells secrete IL-4 and interferon-gamma and may help regulate immune responses. NKT cells differ from [NK cells](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/cellular-components-of-the-immune-system#v28603593) in phenotype and certain functions.

## Mast Cells

Mast cells are tissue-based and functionally similar to basophils circulating in the blood.

Mucosal mast cell granules contain tryptase and chondroitin sulfate; connective tissue mast cell granules contain tryptase, chymase, and heparin. By releasing these mediators, mast cells play a key role in generating protective acute inflammatory responses; basophils and mast cells are the source of type I hypersensitivity reactions associated with [atopic allergy](https://www.msdmanuals.com/professional/immunology-allergic-disorders/allergic,-autoimmune,-and-other-hypersensitivity-disorders/overview-of-allergic-and-atopic-disorders#v994890). Degranulation can be triggered by cross-linking of IgE receptors or by the anaphylatoxin complement fragments C3a and C5a.

## Natural Killer (NK) Cells

Typical natural killer (NK) cells belong to a category of cells collectively referred to as innate lymphoid cells (which also includes ILC1, ILC2, and ILC3). NK cells constitute 5 to 15% of peripheral blood mononuclear cells and have a round nucleus and granular cytoplasm. They induce apoptosis in infected or abnormal cells by a number of pathways. Like other innate lymphoid cells, they lack antigen-specific receptors; however, recent evidence suggests that some NK cells have a form of immunologic memory.

NK cells are best characterized by CD2+, CD3-, CD4-, CD8+, CD16+ (a receptor for IgG-Fc), and CD56+ surface markers.

Typical NK cells are thought to be important for tumor surveillance. NK cells express both activating and inhibitory receptors. The activating receptors on NK cells can recognize numerous ligands on target cells (eg, MHC class I–related chain A [MICA] and chain B [MICB]); the inhibitory receptors on NK cells recognize MHC class I molecules. NK cells can kill their target only when there is no strong signal from inhibitory receptors. The presence of MHC class I molecules (normally expressed on nucleated cells) on cells therefore prevents destruction of cells; their absence indicates that the cell is infected with certain viruses that inhibit MHC expression or has lost MHC expression because cancer has changed the cell.

NK cells can also secrete several cytokines (eg, IFN-gamma, IL-1, TNF-alpha); they are a major source of IFN-gamma. By secreting IFN-gamma, NK cells can influence the acquired immune system by promoting differentiation of type 1 helper T (Th1) cells and inhibiting that of type 2 (Th2) cells.

Patients with NK-cell deficiencies (eg, some types of [severe combined immunodeficiency](https://www.msdmanuals.com/professional/immunology-allergic-disorders/immunodeficiency-disorders/severe-combined-immunodeficiency-scid)) are especially susceptible to [herpesvirus](https://www.msdmanuals.com/professional/infectious-diseases/herpesviruses/overview-of-herpesvirus-infections) and [human papillomavirus infections](https://www.msdmanuals.com/professional/infectious-diseases/sexually-transmitted-diseases-stds/human-papillomavirus-hpv-infection), while an excess of NK cells may contribute to the development of [autoimmune disease](https://www.msdmanuals.com/professional/immunology-allergic-disorders/allergic,-autoimmune,-and-other-hypersensitivity-disorders/autoimmune-disorders).

## Polymorphonuclear Leukocytes

Polymorphonuclear leukocytes, also called granulocytes because their cytoplasm contains granules, include

* Neutrophils
* Eosinophils
* Basophils

Polymorphonuclear leukocytes occur in the circulation and have multilobed nuclei.

### Neutrophils

Neutrophils constitute 40 to 70% of total circulating white blood cells; they are a first line of defense against infection. Mature neutrophils have a half-life of about 2 to 3 days.

During acute inflammatory responses (eg, to infection), neutrophils, drawn by chemotactic factors and alerted by the expression of adhesion molecules on blood vessel endothelium, leave the circulation and enter tissues. Their purpose is to phagocytose and digest pathogens. Microorganisms are killed when phagocytosis generates lytic enzymes and reactive oxygen compounds (eg, superoxide, hypochlorous acid) and triggers release of granule contents (eg, defensins, proteases, bactericidal permeability-increasing protein, lactoferrin, lysozymes). DNA and histones are also released, and they, with granule contents such as elastase, generate fibrous structures called neutrophil extracellular traps (NETs) in the surrounding tissues; these structures facilitate killing by trapping bacteria and focusing enzyme activity.

Patients with immunodeficiencies that affect the phagocytes' ability to kill pathogens (eg, [chronic granulomatous disease](https://www.msdmanuals.com/professional/immunology-allergic-disorders/immunodeficiency-disorders/chronic-granulomatous-disease-cgd)) are especially susceptible to chronic bacterial and fungal infections.

### Eosinophils

Eosinophils constitute up to 5% of circulating white blood cells.

They target organisms too large to be engulfed; they kill by secreting toxic substances (eg, reactive oxygen compounds similar to those produced in neutrophils), major basic protein (which is toxic to parasites), eosinophil cationic protein, and several enzymes.

Eosinophils are also a major source of inflammatory mediators (eg, prostaglandins, leukotrienes, platelet-activating factor, many cytokines).

### Basophils

Basophils constitute < 5% of circulating white blood cells and share several characteristics with [mast cells](https://www.msdmanuals.com/professional/immunology-allergic-disorders/biology-of-the-immune-system/cellular-components-of-the-immune-system#v28603588), although the 2 cell types have distinct lineages. Both have high-affinity receptors for IgE called Fc-epsilon RI (FcεRI). When these cells encounter certain antigens, the bivalent IgE molecules bound to the receptors become cross-linked, triggering cell degranulation with release of preformed inflammatory mediators (eg, histamine, platelet-activating factor) and generation of newly synthesized mediators (eg, leukotrienes, prostaglandins, thromboxanes).