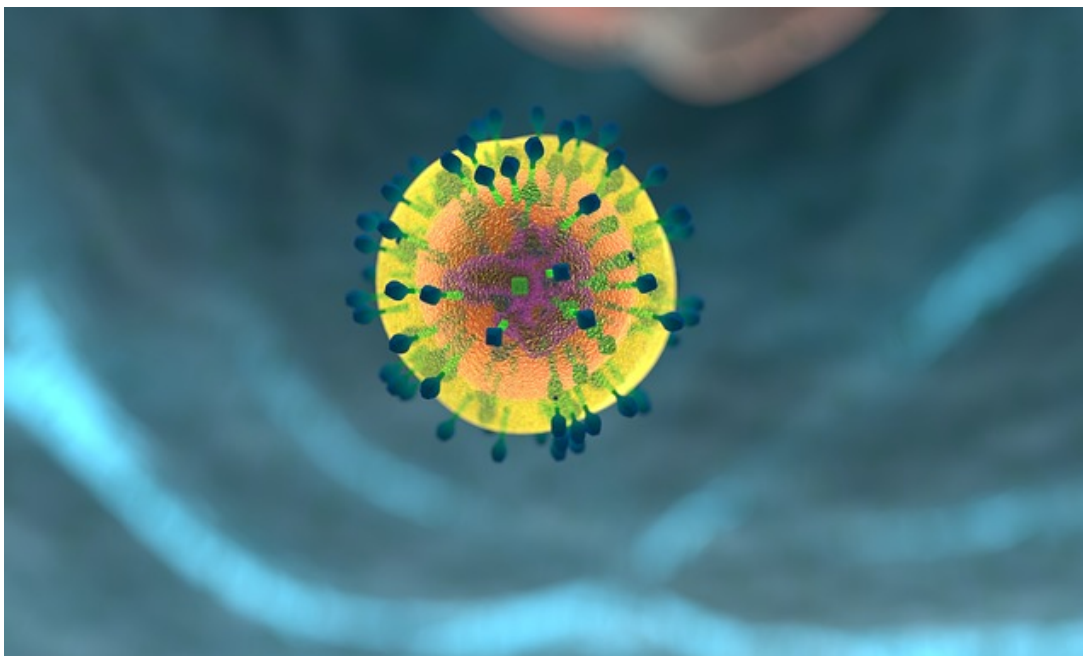


Lymphocyte Activation — B- and T-Cell Activation, Germinal Center and Co-stimulation

[See online here](#)

The adaptive or acquired immune system is the body's main line of defense against ever-evolving pathogens. This subsystem of over all immune system comprises of specialized cells to eliminate lethal organisms which otherwise may lead to death. Read on to find where the cells of the adaptive immune system reside, and what their mechanisms of action are.



Primary Immune Response

When antigen exposure occurs for the first time (**priming dose**), our body gives the primary immune response. There is a latent period, wherein immediately after the priming dose, no antibodies are detected in the serum. This is followed by a **log phase** in which active biosynthesis of antibodies takes place.

During the **plateau, or steady-state**, the serum concentration of antibodies remains constant. Finally, a **decline phase** is observed, during which **catabolism** is greater than synthesis. Thus, the primary response is slow, sluggish and short-living. It has a long lag phase of 5 to 7 days. Low titers of antibodies (IgM) are persistent for short duration. The primary response may take 14 days to resolve and generates memory cells.

Secondary Immune Response

A secondary immune response is observed when the same antigen enters the body for a second time (i.e., **booster dose**). It can occur after weeks, months or even years.

Following a booster dose, there is a markedly enhanced response characterized by an accelerated appearance of immunocompetent cells and antibodies.

It has a very short and negligible latent phase of 2 to 3 days and high levels of antibodies (IgG) lasting for a long period. Thus, the secondary response is prompt, powerful and with a prolonged anamnestic or recall response.

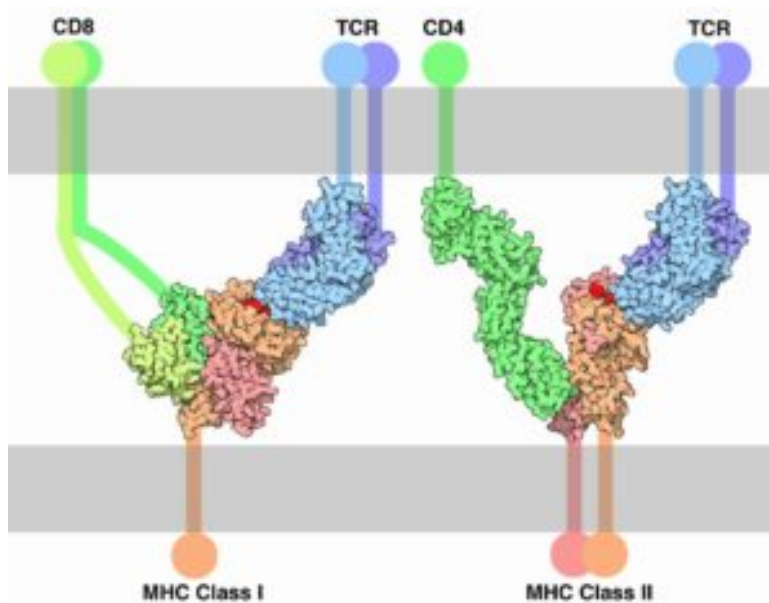


Image: "T Cell receptor complexed with MHC I and II." by David Goodsell - RCSB Molecule of the Month doi: 10.2210/rcsb_pdb/mom_2005_3. License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

Lymphoid Organs

Lymphoid organs are divided into primary and secondary depending on their functions.

Primary lymphoid organs include the thymus, bursa of fabricius, bone marrow and intestinal epithelium, wherein there is **antigen-independent proliferation and differentiation of lymphocytes**.

Secondary lymphoid organs include lymph nodes, [spleen](#), and mucosa-associated lymphoid tissue, wherein antigenic stimuli initiate immune responses in lymphocytes. These are tactically positioned so that foreign antigens that enter through the bloodstream, peripheral tissues, and mucosal sites are skillfully trapped.

The structure of the secondary lymphoid tissues is such that it helps in the initiation of adaptive responses. This is because of better interactions between **dendritic cells** that bear the antigen, the **B-cells** and **T-cells**.

However, routes of antigen transport, trafficking of lymphocytes and distinctive cell populations decide the task of a specific secondary lymphoid tissue during immune responses to different foreign antigens (including transplanted organs).

Thymus

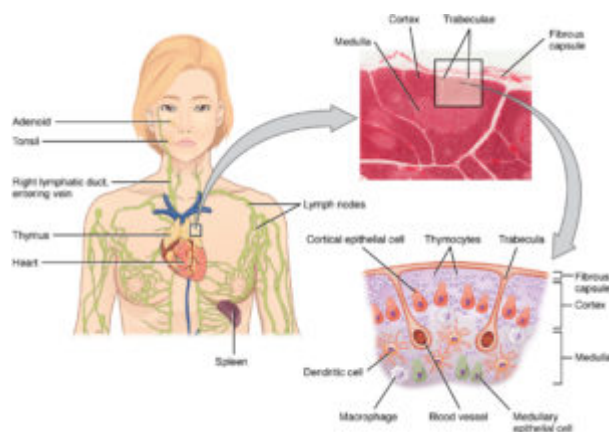


Image: "The thymus lies above the heart. The trabeculae and lobules, including the darkly staining cortex and the lighter staining medulla of each lobule, are clearly visible in the light micrograph of the thymus of a newborn. LM \times 100. (Micrograph provided by the Regents of the University of Michigan Medical School \copyright 2012)" by OpenStax College in Anatomy of the Lymphatic and Immune Systems at <https://legacy.cnx.org/content/m46563/1.4/>, License: [CC BY 3.0](https://creativecommons.org/licenses/by/3.0/)

This **lymphoepithelial bilobed structure** is located behind the upper part of the sternum. It acquires a characteristic lymphoid appearance by the 3rd month of gestation and increases in size during fetal development. It reaches maximum size at birth, gradually decreases in size with age and finally atrophies.

It is made of **lobules**, which are differentiated into an **outer cortex** and **inner medulla**. The immature lymphocytes from the yolk sac, fetal liver and bone marrow travel to the thymus. Within the cortex of the thymus, they undergo changes such as **maturation** and **attainment of specific surface characteristics**. Furthermore, they move into the medulla of the thymus where lymphocytes **complete their maturation process** and **exit into the blood**.

Mature T-cells are further seeded into secondary lymphoid organs. It is a major site for **lymphocyte proliferation** and **production of T-lymphocytes**, wherein lymphocytes acquire new surface antigens.

The thymus confers immunological competence to lymphocytes by the hormone-like humoral factors **thymosin**, **thymopoetin**, etc. (which are secreted by thymic epithelium), so that lymphocytes become capable of mounting CMI.

Spleen

Spleen

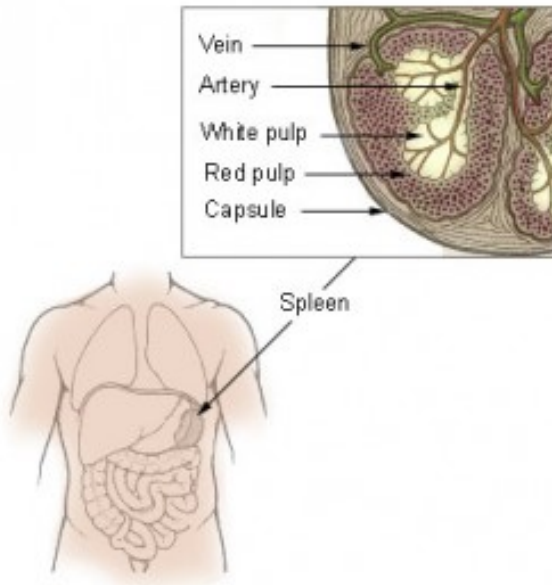


Image: "Red and white pulp in the spleen." by DooFi. License: Public Domain

The **spleen** is the largest lymphovascular organ; it consists of red and white pulp separated by a marginal zone. The **white pulp** is rich in lymphoid tissue, while the **red pulp** is abundant in sinuses and contains large quantities of RBCs.

White pulp is composed primarily of T-lymphocytes. The external lymphoid area is a B-cell dependent area, i.e., **germinal center/mantle layer**. Approximately 30 – 40 % of the cells in the spleen are T-cells, and 50% are B-cells.

Periarterial lymphoid collections in the white pulp are known as **Malpighian corpuscles or follicles**. Following antigenic stimulation, germinal centers are produced in the white pulp; they are composed of large numbers of rapidly dividing cells. The spleen is the only lymphatic organ specialized to filter blood (in the form of dendritic cells and **macrophages**). It is a major site for **antibody synthesis** against **bloodborne pathogens**.

Mucosa associated lymphoid tissue (MALT)

MALT is a potentially important collection of lymphocytes (both B and T lymphocytes) in the form of isolated cells or small cell clusters. They mainly produce IgA present throughout the mucosal lining of the alimentary, respiratory, genitourinary and other surfaces.

Such lymphoid tissues of the gut are called **gut-associated lymphoid tissue (GALT)**; those in the respiratory tract are called **bronchus-associated lymphoid tissue (BALT)**. Main GALT structures in humans are tonsils, appendix, Peyer's patches and the lamina propria of the intestine.

MALT contains a **mixture of B-cells, T-cells, phagocytic cells, plasma cells and APCs**. Secretory IgA is the main Ig produced by MALT. IgG, IgM, and IgE are also produced locally. It mainly provides immunity against pathogens invading local tissues.

Memory B-cells and plasma cells are the building blocks of the immunological memory. Both of these cells are part of the **humoral immune system** and are mainly produced in

the **germinal centers (GCs)**.

High-affinity Abs are produced in the GCs as a result of an amalgamation of the following processes – **clonal expansion of B-cells, somatic hypermutation** and **selection based upon affinity**. Cytokine interleukin factor (IL-21) has been recently recognized as a key factor that can directly influence the B-cell fate by modulating these processes within the GCs. There are various types of immune cells involved in the GC B-cell responses.

GCs arise 7–10 days post preliminary exposure to a thymus-dependent antigen. B-cells that are activated undergo intense proliferation throughout the first stage of GC formation. A well-marked dark zone is formed by proliferating B-cells (centroblasts) in the GC.

Over a period of time, **centroblasts** mature into **centrocytes** that migrate into the region containing **follicular dendritic cells**, i.e., the light zone of the GCs. Within the light zone, Ag-Ab complexes are present, and the centrocytes thus come in contact with the Ags.

B- and T-Cell Activation

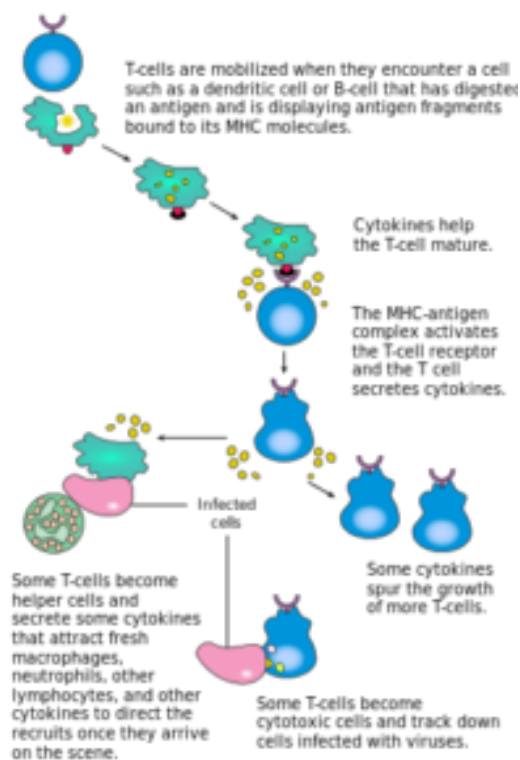


Image: “The T-lymphocyte activation pathway is triggered when a T-cell encounters its cognate antigen, coupled to an MHC molecule, on the surface of an infected cell or a phagocyte.” Derivative work by Hazmat2. License: Public Domain

Igs present on the B-cell surface behaves as **specific receptors for antigens**. When an antigen enters our body, it reacts with the B-cells of appropriate specificity. This interaction stimulates B-cells to undergo **blastoid transformation**, converting them into plasmablasts (**clone formation**) and finally into **plasma cells**.

Each B-cell possesses **genetic instructions** to produce an antibody of unique antigen

specificity as a **membrane receptor**. Once the signal is received, B-cells are differentiated into **plasma cells**, which produce and secrete antibodies.

An antigen present over **MHC molecules** leads to the **activation of T-lymphocytes**. The role of various **co-stimulatory molecules** is to bring about the **proliferation and differentiation of T-lymphocytes**. APCs assist the co-stimulatory molecules in this task. Only protein antigens loaded over MHC molecules are recognized by T-cells.

Contact sensitivity reactions are those wherein there is an induction of T-lymphocytes by chemicals that gain entry into our body through the skin. After **antigen sensitization**, an effectual immune response is produced by the differentiated effector T-cells.

Co-stimulatory Molecules

Co-stimulatory molecules are generated from naive T-cells by their proliferation and differentiation into **effector cells**. APCs help them in this transition. Co-stimulation is vital for an effective immune response presented by T-lymphocytes that are antigen-sensitized.

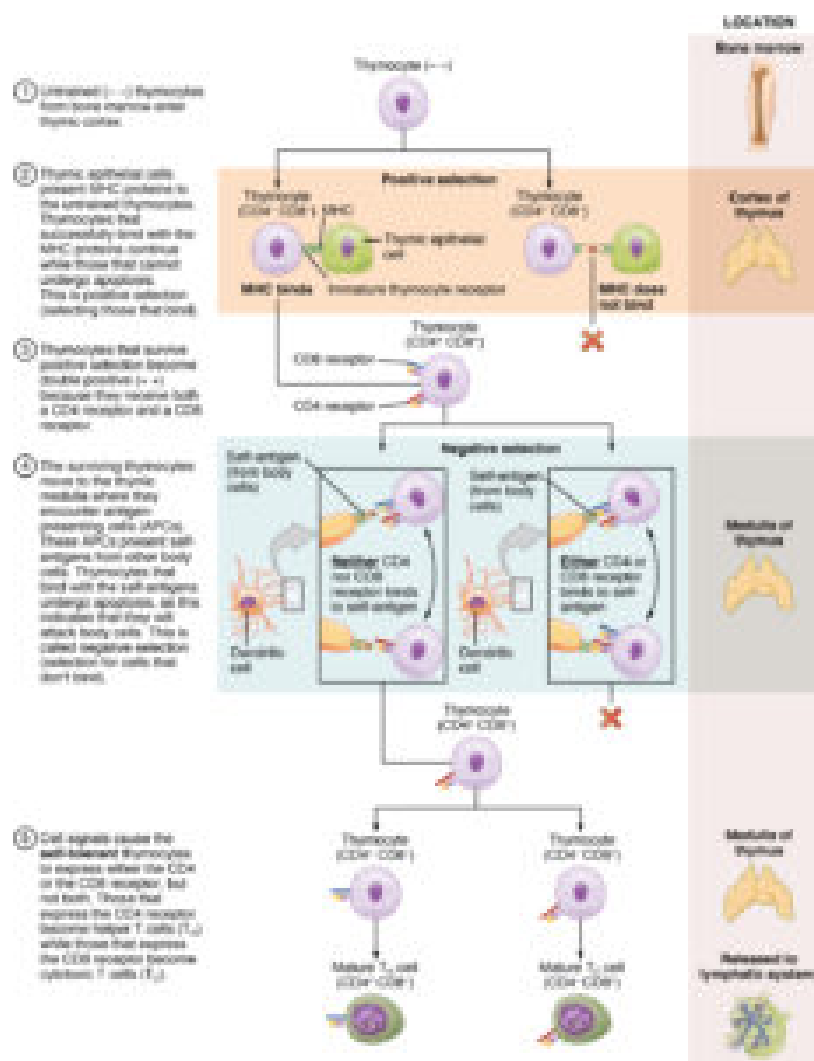


Image: "Thymocytes enter the thymus and go through a series of developmental stages that ensure both function and tolerance before they leave and become functional components of the adaptive immune response." by Heather Ketchum, Eric Bright on cnx.org (Download for free at <http://cnx.org/contents/a7fa09d4-b7d6-4ae8-a6fa-71037b392af9@1.>), License: [CC BY 4.0](https://creativecommons.org/licenses/by/4.0/)

Co-stimulatory molecules that are well known are **B7-1(CD80) and B7-2(CD86)**. There is an expression of co-stimulatory molecules on APCs that are activated. Their ligands, known as **CD28**, are present on the T-cell surface.

Activated T-cells also express **CD40 ligands** which bind with CD40 on the APCs. A cascade follows during activation of the T-cells. The binding of CD40L and CD40 leads to expression of co-stimulatory molecules (B7-1 and B7-2), which further bind to TCR (CD28). Additionally, cytokines (IL-12) secreted by the APCs **stimulate T-lymphocyte proliferation and differentiation**.

Activation of **mitogen-activated protein (MAP)** is essential for the activation of T-cells that are brought about by CD28. Expression of **antiapoptotic Bcl-x and Bcl-2** is stimulated by **MAP kinase** that causes prolonged cell survival. **CTLA-4 (cytotoxic T-lymphocyte antigen-4) and PD1 (Programmed Death 1)** are inhibitors of CD28 that cause modulation of T-lymphocyte activation. Access to co-stimulatory molecules is totally inhibited when CTLA-4 is activated as it has a high affinity for those molecules.

B-lymphocytes that are newly formed in the bone marrow migrate to the periphery to be stimulated or excluded from the immune system. On activation, B-cells will proliferate into clones of cells, some of which form **effector cells** secreting Igs at a higher rate, while others form a long-term memory cell.

Thus, part of the immune system represents a **one-way differentiation pathway**, the endpoint of which is a plasma cell. This is unique in the sense that clonal specificity relevant for a given antigenic epitope regulates the amplification of a given B-cell clone. This is the basis of the **clonal selection theory** proposed by Jerne in 1955 and Burnet in 1957.

According to this theory, Ig molecules are present on the surfaces of B-cells and work as specific receptors for specific antigens. When an Ag is introduced, it combines with *that* Ig molecule on the surface, which is a complementary fit for it. This interaction results in proliferation of that lymphocyte to form a clone of cells producing an antibody of the same specificity as that on the surface of the parent lymphocyte. Some of the **progeny cells** are converted into **memory cells**. Hence, an Ag selects a specific B-cell and stimulates it to proliferate into a clone of cells producing a specific antibody.

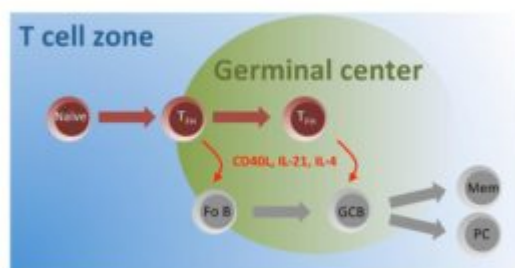


Image: "The function of TFH cells: A subset of naive T-cells in the T-cell zone is activated by an antigen. They migrate to the follicles where they differentiate into TFH cells which interact with and instruct Follicular B (Fo B) cells. Thus they undergo isotype switching, somatic hypermutation, and rapid cellular division to seed germinal centers (GC). Within these germinal centers, TFH cells continue to provide help to GC B-cells to facilitate their production of high-affinity antibody-producing plasma cells (PC)

Germinal centers (GC) are the places where the important steps of B-cell differentiation occur. These steps include **affinity maturation**, **class switching**, **plasma B-cells** and **memory cells formation**. The GCs are significant for the first two of these steps, while the remainder takes place outside the GCs.

E2A, **EBF**, and **Pax5** are **transcription factors** that influence the differentiation of B-cells from **pleuripotent hematopoetic cells**. They help in the development of B-cells by transcribing certain genes and bringing about their recombination. B-cells are developed in the following order: **pleuripotent hematopoetic stem cells to Pro B-cells, to follicle B-cells, to marginal B-cells, to B1 B-cells**.

Following the B-cells' selection, there is differentiation into plasma and memory cells. Usually, there is a lack of detectable membrane-bound immunoglobulin in plasma cells. Because of this lack of membrane-bound Ig in the plasma cells, there is a synthesis of secreted antibodies.

Ig producing plasma cells synthesize immunoglobulins at a very high rate of about 1000 Ig molecules per cell per second. **Plasma cells** are formed from the mature B-cells because of an alteration in the processing of RNA. **Memory cells** are formed from the B-cells that are not selected in the light zone of the GCs. As a result of class switching, the naive B-cells co-express IgM and IgD only, while all Igs are expressed by memory cells. Different Igs have different characteristics. For example, IgG enhances phagocytosis, and IgA prevents absorption of Ag. IgM is the first antibody produced as a result of a primary immune response.

Dendritic cells (DCs) are a type of APCs. They have the capacity to **prime T-lymphocyte responses**. They have to travel all the way to secondary [lymphoid organs](#) for the presentation of foreign Ags to naive T-cells.

This migration of DCs is a multi-step process that is closely regulated. **Chemokines** play a significant role in this process. Related chemokine receptors are expressed after their production.

TLR (Toll like receptor) is a chemokine expressed on effector cells and stimulates DC migration. For the process of migration, specific **selectin** molecules on high endothelial valves are expressed, and the stimulated lymph nodes also undergo physical changes. Whenever DCs are activated, the chemokine response is lessened, which helps in their migration towards the draining lymph nodes.

DCs are capable of not only Ag processing but also acquiring the Ag. They indirectly lead to naive T-lymphocyte activation by expression of co-stimulatory molecules. DCs can pass on specific information to T-cells. Depending on the information passed on, the result could be the **formation of Th1, Th2, Th17 effectors and memory cells**.

Common lymphoid progenitor cells are generated from **pleuripotent hematopoetic cells**. **Transcriptional factors** play a major role in the formation of NKCs or Pro-T-cells from the common lymphoid progenitor cells.

There is a **notch receptor** that is activated by lymphoid progenitor cells. On cleavage, the notch receptor travels to the nucleus. This leads to activation of **GATA 3**, which is a transcription factor generating Pro-T-cells. IL-7 is produced by both the bone marrow as well as the thymus and is an important influence for differentiation of Pro-T-cells.

Lymphocyte Activation

Two independent signals are required by lymphocytes for a complete activation. A preliminary **antigen-specific signal** is sent through antigen receptors: T-cell receptor (TCR) on T-cells and surface Ig on B-cells.

A second signal is known as **co-stimulation** that is independent of the antigen receptor and is imperative for a complete activation. It also assists in the sustenance of cell proliferation, prevention of energy and/or [apoptosis](#), induction of differentiation to effector and memory status and allows cell-cell cooperation. Regulation of co-stimulation is, in turn, done by expression of **inhibitory receptors** after lymphocyte activation.

References

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Notes