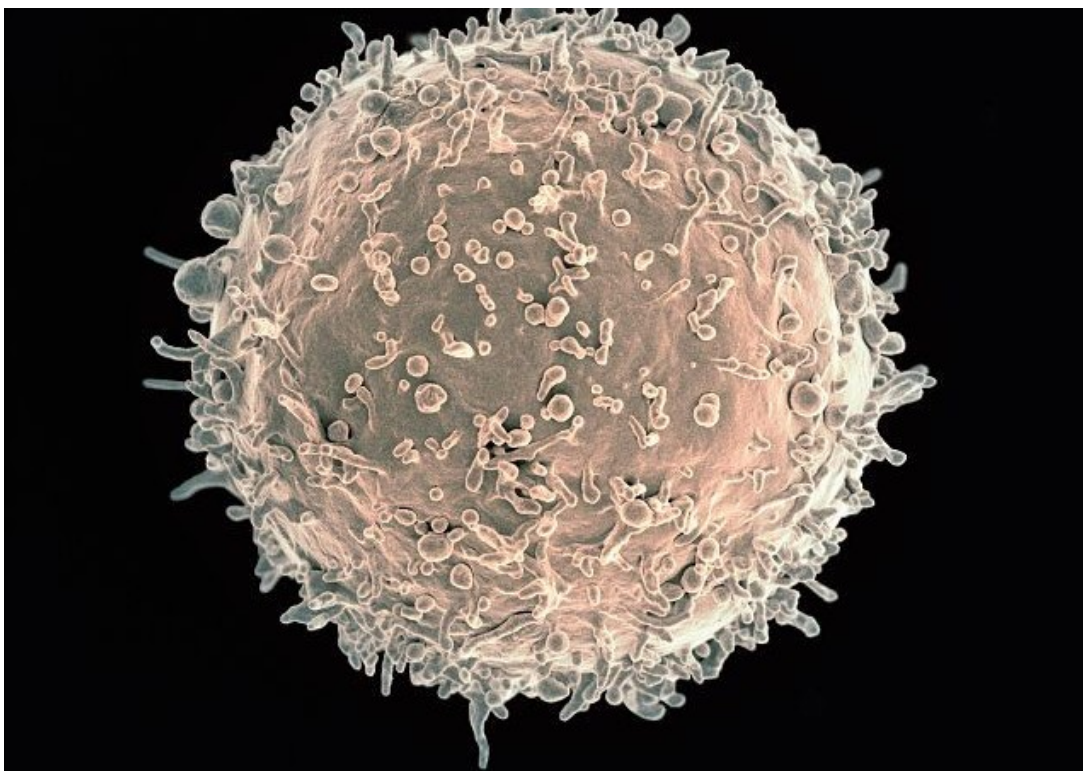


Lymphocyte Development — B- and T-Cell Development

[See online here](#)

Lymphocytes are the cornerstone of the adaptive immune system and afford the body a diverse protection against all kinds of pathogens. In this article, we explore the different types of lymphocytes and the processes involved in their development.



Adaptive Immune System

Antigens and antibodies

Adaptive immunity specifically recognizes and destroys pathogens because lymphocytes carry specialized cellular receptors and produce specific antibodies. Any substance that is recognized by our body as a potential pathogen or harmful substance is known as an **antigen** (Ag).

To limit these antigens, certain substances (proteins), known as **antibodies** (Abs), are produced by our body as a response. The physiological function of these antibodies is to defend the body against **extracellular microbes** (including **viruses**) and **microbial exotoxins**. Adaptive immunity can be transferred to other individuals by the transfer of

serum (as antibodies).

Lymphopoiesis

Lymphopoiesis is a process wherein production of new lymphocytes takes place in the **central lymphoid tissues**, i.e., **bone marrow** for B-cells and the **thymus** for T-cells. The fetal **liver** and **spleen** are further sites for the development of B lymphocytes.

Some T-cells develop as specialized populations in '**cryptopatches**' (below the intestinal epithelial crypts). In children, the production of new lymphocytes takes place in the central lymphoid tissues. They, then, travel to the **secondary lymphoid organs**. In adults, generation of new B lymphocytes continues in the bone marrow whereas generation of new T lymphocytes becomes slow.

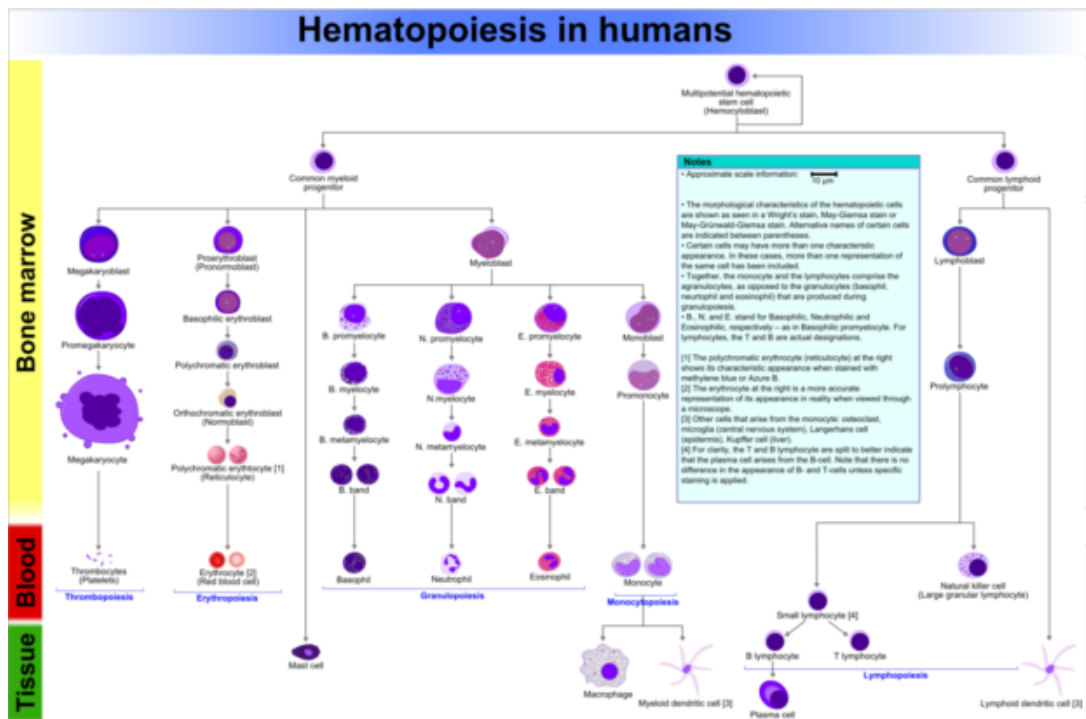


Image: "This diagram shows the lymphopoiesis as part of hematopoiesis as it occurs in humans." by A. Rad - Own work. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

B-Cell Development

All types of blood cells arise from the **pluripotent hematopoietic cells**. For the development of B-cells, external signals are generated by **stromal cells**. Several factors are secreted by the bone marrow each of which plays a role in B-cell development. B-cell development takes place in the following stages:

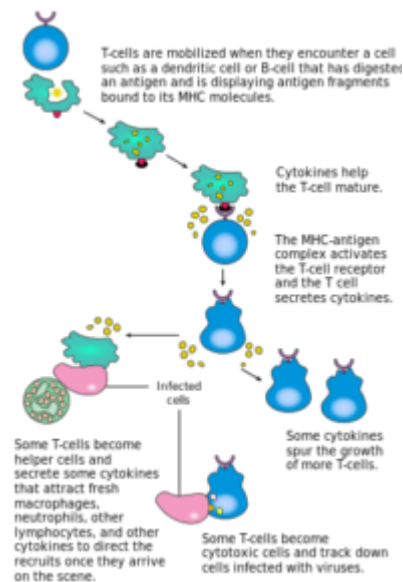


Image: "The T lymphocyte activation pathway is triggered when a T-cell encounters its cognate antigen, coupled to a MHC molecule, on the surface of an infected cell or a phagocyte." Derivative work by Hazmat2. License: Public Domain

1. Early Pro-B-cell - D-J joining, expresses CD45 and MHC II
2. Late Pro-B-cell - V-DJ joining
3. Large Pre-B-cell - VDJ rearranged
4. Small Pre-B-cell - RAG and TdT expression
5. Mature B-cell - Ig $\alpha\beta$ expression

T-Cell Development

Hematopoietic stem cells are present in the **bone marrow**. These cells, upon reaching the thymus, are differentiated into **Pro-T-cells**, which on recombination with **β -chain** further differentiate into **Pre-T-cells**.

Pre-T-cells can express only the β -chain of TCR, but when this Pre-T-cell differentiates into a **double positive T-cell**, it can express on its surface both the α - and β -chains. Immature T-cells differentiate into mature T-cells only on reaching the circulation.

T- and B-Cell Receptors

The specificity of T- and B-cells is attributed to the expression of precise receptors (for **MHC class molecules**) on their surface. After rearrangement of T- and B-cells during embryonic life, **functional Ag receptor genes** are produced on these cells. Even before these cells come across an Ag, Ag receptor genes are expressed on the immature lymphocytes. Antigen receptors on both these cells are thought to initiate signalling in comparable ways.

Rearrangement of genes in B and T lymphocytes

Arrangement of various gene segments gives rise to certain genes that constitute the B- and T-cell Ag receptors. Various gene segments consist of Variable (V), Diversity (D) and Joining (J) regions. Rearrangements within these segments is known as the **V(D)J**

recombination. The diversity of our immune system cells is attributable to this.

Organization of immunoglobulin (Ig) and T-cell receptor (TCR) gene

Receptors for antigens are also present on T-cells which are composed of **2 dissimilar polypeptide chains** having constant and variable regions analogous to immunoglobulins. The structure and organization of immunoglobulins and TCR are comparable.

An immunoglobulin molecule has heavy and light chains, out of which the **heavy chain** is encoded by chromosome 14, while the **light chain** is encoded by two different chromosomes.

Chromosome 2 encodes the κ light chain, and chromosome 22 encodes the λ light chain. The variable segment is about 300 bp long and present at the 5' end of the gene. The joining region is about 30-50 bp long and starts after the variable region. The space between the variable and joining regions is occupied by the diversity region.

For the TCR, chromosome 14 encodes α and δ chains, while chromosome 7 encodes the β and γ chains. The **T-cell loci** are comparable to those of Ig. **T-cell receptor diversity** is also produced in the same way as antibody diversity (e.g., by VJ and VDJ joining of gene segments and combinatorial association). However, **no somatic mutation** has been observed in T-cells.

In humans, the vast diversity of B-cells is due to three distinctive genomic alterations, namely **class-switch recombination (CSR)**, **V(D)J recombination** and **somatic hypermutation (SHM)**. All of these processes work together to bring about the most efficient immune response.

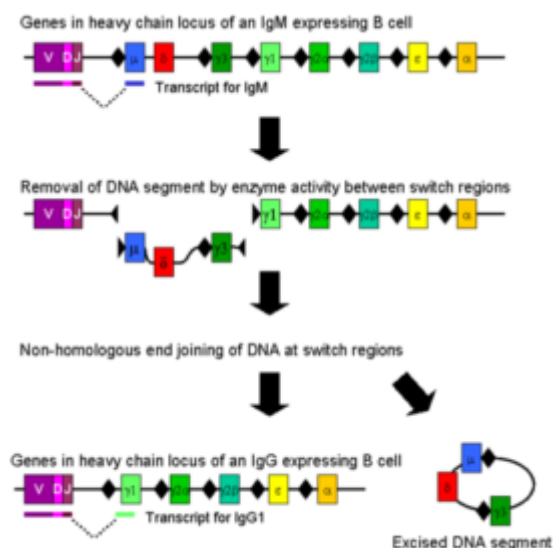


Image: "Class switching recombination." by EN:User:Ciar - made by English Wikipedia User, EN:User:Ciar. License: Public Domain

Class switching is the biological mechanism wherein the B-cell production of Igs changes from one class to another, i.e., IgM to other Igs namely IgG, IgE or IgA. The constant region of Ig heavy chain is changed, but the variable region remains unchanged. Class switching does not affect Ag specificity.

CSR is a unique process that occurs as a result of a combination of processes. There is **excision of exons** that encode for the C_{μ} segment of the Ig heavy-chain. This is further replaced by new constant gene segments that are known as C_n genes (namely C_{γ} , C_{ϵ} or C_{α}). Thus, the expression of B-cells changes from IgM to those producing IgG, IgE or IgA. So basically, CSR is a reaction based on **DNA deletion-recombination**.

DNA double-strand breaks (DSBs) are generated in recurring switch (S) sequences that are present in every C_n gene. End-joining among donor S_{μ} and acceptor S regions completes the process. Inimitable ability of T- and B-(predominantly) cells, for somatically altering their genomes, leads to the diversity of antigen receptors.

CSR causes relocation of already rearranged V/D/J complex from the earlier position near C_{μ} gene to a position close to the other heavy-chain C-regions. Therefore, a new transcription unit is created, and heavy chain with the same V-region, but a new C-region, is synthesized.

Two of the key features of class switching are that the **VH-region** remains the same, and that **class switching is unidirectional and irreversible**. As the light chains are not changed by switching, specificity of the antibody (and its idiotype) cannot change.

Secondly, there can be switching of a cell from one C-region to another situated to the right of the first ($5' > 3'$ direction) but not backwards ($3' > 5'$ direction). Thus, the order of heavy chain constant region genes on the chromosome defines the order of switching.

Single antigenic specificity of B-cells is ensured by **allelic exclusion**. The B-cell is diploid yet rearranged heavy-chain genes and rearranged light-chain genes from only one chromosome are expressed by it, and this is accomplished by allelic exclusion.

That more than one VHDHJH and one VLJL unit is not contained by B-cells is ensured by allelic exclusion. **Allelic exclusion** intends that after productive VH-DH-JH and VL-JL rearrangement, the recombination process is stopped.

G. D. Yancopoulos and F. W. Alt proposed that once productive rearrangement is done, its encoded protein is expressed; the presence of this protein acts as a signal to prevent further gene rearrangement. According to their model, heavy chains signal maturing B-cells to stop the rearrangement of other heavy-chain alleles and also to start rearrangement of the light-chain genes.

A complete antibody molecule is formed on productive rearrangement when light chains are produced and paired with heavy chains. Presence of this antibody stops further light-chain rearrangement. If the rearrangement of both the alleles is non-productive, then the rearrangement of chain genes begins again. If neither allele rearranges productively, the B-cell, presumably, does not mature and dies by [apoptosis](#).

Sources of vast multiplicity in variable regions began to come forward as the organization of immunoglobulin genes was understood. In mice and humans, 7 means of **antibody diversification** have been recognized:

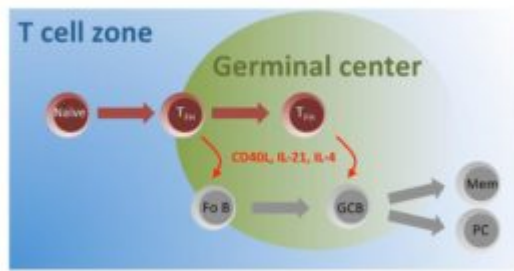


Image: "The function of TFH cells: A subset of naive T-cells in the T-cell zone are activated by antigen and migrate to the follicles where they differentiate into TFH cells which interact with and instruct Follicular B-(Fo B) cells to undergo isotype switching, somatic hypermutation and rapid cellular 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) and long-lived memory (Mem) B-cells." by Science boy83. License: [CC BY-SA 3.0](https://creativecommons.org/licenses/by-sa/3.0/)

1. Multiple germ-line gene segments
2. Combinatorial V-(D)-J joining
3. Junctional flexibility
4. P-region nucleotide addition (P-addition)
5. N-region nucleotide addition (N-addition)
6. Somatic hypermutation
7. Combinatorial association of light and heavy chains.

There are inaccuracies in recombination between V-J and V-D-J, and the diversity produced by V-J and V-D-J joining is tripled. Diversity produced by these mechanisms occurs in 3rd hypervariable region and is therefore directly affecting the combining site of the Ab.

There is often an insertion of a series of nucleotides at the junction between D and J segments that is catalyzed by the enzyme **terminal transferase** which leads to further diversity in the 3rd hypervariable region. There is evidence that **somatic hypermutations** occur in V gene, mainly where the 2nd hypervariable region is coded.

Cells that have not encountered an Ag are called **naïve B-cells**. They contain IgM and IgD on their cell surface and the same binding VDJ regions yet a different constant region. They depart the bone marrow with single specificity and go to the lymph nodes or [spleen](#). IgM and IgD are co-expressed on naive B-cells by a process called **alternative mRNA splicing**.

Signalling via B-cell receptor (BCR) is necessary for maturation, maintenance, activation and silencing of peripheral B lymphocyte. A minimum of two light chains and two heavy chains are present in functional Ig protein.

Ig is compulsorily associated with two other membrane proteins, **CD79-a and CD79-b (Ig- α and Ig- β , respectively)** in its membrane-bound form. These proteins function as a chaperone for facilitation of membrane expression and also couple BCR to membrane-proximal signalling elements. Further development of B-cell is regulated by signals from this BCR complex. **BCR signalling** controls the following:

- **Expansion** of only those B-cells that have undergone productive V(D)J rearrangements during early development;
- **Deletion** of self-reactive B-cell clones;
- **Survival** of B-cells by representing a maintenance signal in periphery;
- **Activation** of B-cells on encountering an Ag, or specific deactivation in the absence of appropriate costimulation that results in apoptosis or a state called '**anergy**';
- **Induction of differentiation** into memory cell
- **Terminal differentiation** into antibody-secreting plasma cell that is closely linked with down-regulation of Ig membrane expression.

There are two types of B cells – **B1 and B2**. B2 is the main set of cells in human beings, but B1 cells arise before B2.

B1 cells appear during fetal life and express surface IgM with little or no IgD. B1 cells arise in the bone marrow but renew their population by proliferation in the spleen and lymph nodes. They respond poorly to protein Ags and better to carbohydrates. B1 cells do not undergo much class switch and thus the antibodies have a low affinity. Many chronic **leukemias** arise from the B1 population.

There is class switching in B2 cells, and they have a greater affinity for Ags. They proliferate in the stem cells and not in the secondary organs.

Natural Killer Cells

NKs were first described in 1976. It was found that our body contains a small population of large, granular lymphocytes which display cytotoxic activity against a wide range of tumor cells in the absence of any past immunization.

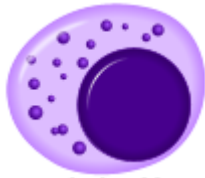


Image: "Natural killer cell." by) Arcadian.
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NK cells play a significant role in the host defense both against **tumor** cells and some virus infected cells. These cells constitute around 5%–10% of lymphocytes in the peripheral blood. They do not express membrane molecules and receptors that characterize the T- and B-cell lineages.

There are no T-cell receptors or Ig incorporated in plasma membranes of NK cells, but they can identify potential target cells in two different ways. **NK cell receptors** can recognize certain **abnormalities** such as **reduced MHC class I molecules display**.

They can also reveal the tumor and virus infected cells that have **surface Ags with abnormal profiles**. Another way by which NK cells identify potential target cells depends on the fact that tumor cells and virus infected cells show antigens against which the immune system has made an antibody response. Thus, **antitumor or antiviral antibodies** are bound to their surfaces.

NK cells express **CD16**, which is a membrane receptor for carboxyl-terminal end of IgG

molecule, called the Fc region. Therefore, they can attach to these antibodies and then destroy the targeted cells. This process is known as **antibody-dependent cell mediated cytotoxicity (ADCC)**. Also, NK cells play an important role in the host's defense against tumors.

References

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