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قسم الميكروبيولوجياو الكيمياء الحيوية

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شهادة موافقة علمية على مطبوعة بيداغوجية
للأستاذة: فاطمي أحلام –أستاذة محاضرة- ب

يشهد رئيس اللجنة العلمية لقسم المكروبيولوجيا والكيمياء الحيوية بجامعة محمد بوضياف-المسيلة ، أنه بعد الاطلاع على تقارير الخبرة الواردة من طرف الخبراء:

-الأستاذة : بن الشيخ دليلة أستاذة محاضرة –أ- بجامعة محمد بوضياف-المسيلة.

-الأستاذة : سعدي وئام أستاذة محاضرة –أ- بجامعة الجيلالي بونعامة خميس مليانة.

و المعينين من طرف اللجنة العلمية لقسم المكروبيولوجيا والكيمياء الحيوية في الاجتماع المنعقد في دورته العادية يوم : **2026/03/09** لإجراء الخبرة للمطبوعة البيداغوجية الخاصة بالأستاذة فاطمي أحلام –أستاذة محاضرة- ب بقسم المكروبيولوجيا والكيمياء الحيوية والمعنونة ب " Cellular and Molecular Immunology" والمقررة في برنامج التكوين : لطلبة الليسانس L3 المفتوح بقسم المكروبيولوجيا والكيمياء الحيوية، قد تمت الموافقة عليها شكلا ومضمونا .

رئيس اللجنة العلمية لقسم المكروبيولوجيا
والكيمياء الحيوية
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Objectives

1- Know the immune response, the development of the immune system and lymphocyte repertoires. 2- Establish the physiological and molecular bases of the development and functioning of the immune system. 3- Address the signals and cellular functions in this unit, as well as the theories of immunity and regulation 4- Analyze and interpret pathological cases of the immune system

1- Know the immune response, the development of the immune system and lymphocyte repertoires.

2- Establish the physiological and molecular bases of the development and functioning of the immune system.

3- Address the signals and cellular functions in this unit, as well as the theories of immunity and regulation

4- Analyze and interpret pathological cases of the immune system

Introduction

Cellular and molecular immunology is the scientific study of the immune system at the cellular and molecular levels. It is a comprehensive analysis of the mechanisms that protect organisms from infections and maintain homeostasis. In addition, it offers a detailed discussion of how malfunctions in these mechanisms can lead to a variety of diseases, including autoimmune disorders, allergies, and cancer.

- At the cellular level, the field of immunology is concerned with the study of immune cells in immune response pathways. Such pathways include the activation of T cells, B cell activation, immune tolerance and autoimmunity, and immunological memory.
- At the molecular level, the field of immunology is concerned with the biochemical processes and interactions that regulate the immune system. These include antibodies (also known as immunoglobulins), major histocompatibility complex (MHC) molecules, cytokines, and chemokines.

The following areas of research are considered to be of particular importance within the field of cellular and molecular immunology:

Immunogenetics: The present study will examine the genetic basis of immune responses.

Host-pathogen interactions: The present study will explore the manner in which pathogens and the immune system influence each other.

Immunodeficiency diseases: It is imperative to comprehend the genetic or acquired conditions that result in immune function impairment, such as HIV/AIDS.

Research into autoimmunity and allergies: The present study aims to investigate the aetiology of inappropriate immune responses and to develop new treatments to combat these.

Cellular and molecular immunology is an area of research that is undergoing rapid development. Advancements in this field are continually enhancing our understanding of disease mechanisms and generating novel therapeutic strategies.

General Information on Immune Responses

1. Organs of the Immune System

The immune system is a complex network comprising cells, tissues, organs, and proteins. These work in concert to protect the body from harmful invaders such as bacteria, viruses, fungi, and toxins. It is imperative to note that this process plays a crucial role in the identification and neutralisation of foreign substances. In addition, it is equally important to highlight its ability to distinguish these substances from the body's own healthy cells.

The classification of the organs can be undertaken on the basis of their function.

The classification of the subject is into two primary groups. The primary lymphoid organs provide the appropriate microenvironments for the development and maturation of lymphocytes. It is represented by **Bone Marrow** and **Thymus**.

Secondary lymphoid organs have been identified as the sites where antigen from defined tissues or vascular spaces is trapped. It has been demonstrated that these organs are also sites where mature lymphocytes can interact effectively with the antigen. It is evident that a symbiotic relationship exists between the organs, with blood vessels and lymphatic systems playing a pivotal role in integrating these vital functions. It is **Lymph Nodes, Mucosa-Associated Lymphoid Tissues (MALT)**, and **Spleen.**

2. Primary Lymphoid Organs

2.1. Bone Marrow

Bone marrow (BM)is a semi-solid tissue found within the spongy portions of bones. It consists of hematopoietic cells, marrow adipose tissue, and supportive stromal cells. Bone marrow comprises approximately 5% of total body mass in healthy adult humans.

It is important to note that bone marrow is not the site of B-cell development in all species. In birds, a lymphoid organ is present, which is known as the bursa of Fabricius.

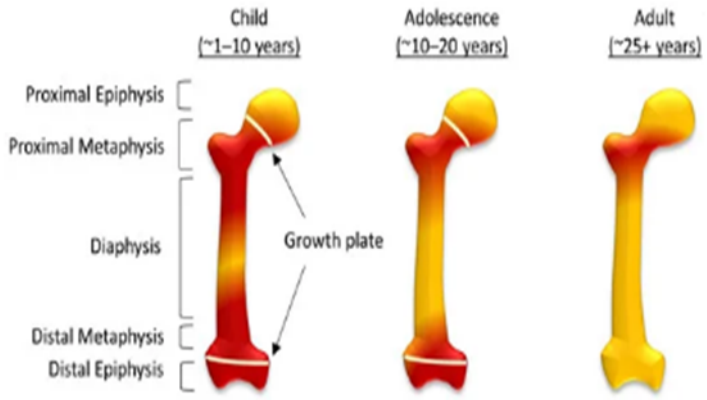


Image 1 BN Structure

a) Structure of Bone marrow

- Is present in different quantities and compositions depending on species and age. Two forms of bone marrow have been described: yellow bone marrow, mainly composed of adipocytes, and red hematopoietic bone marrow.
- Cellular components.
- Hematopoietic stem cells (HSCs): Pluripotent cells are capable of giving rise to all blood cell types, including red cells, white cells, and platelets.
- Myeloid and lymphoid progenitors, Mature blood cells: This includes erythrocytes, leukocytes (neutrophils, lymphocytes, monocytes, etc.), and thrombocytes (platelets).
- Stromal and supportive in nature: These elements constitute the bone marrow microenvironment and regulate the process of hematopoiesis. The following cell types have been identified: mesenchymal stem cells (osteoblasts,chondrocytes, or adipocytes); fibroblasts; macrophages; adipocytes; osteoblasts and osteoclasts; and endothelial cells.

b) Bone Marrow Function

Central hematopoietic and antigen-responsive organ

Importance for storage and long-term survival of memory B and memory T cells

Bone marrow barrier and Lymphatic role

2.2. Thymus

The thymus is the site of T-cell development and maturation. It is a flat, bilobed organ situated above the heart. It has been demonstrated that there is a concomitant increase in the total fat content of the organ. The mean weight of the thymus is 70 g in infancy; however, its age-dependent involution results in an organ with a mean weight of only 3 g in the elderly.

a) Structure of Thymus

The bilobed organ is located in the superior region to the heart. Each lobe is enveloped by a capsule and is subdivided into lobules, which are separated from each other by strands of connective tissue known as trabeculae. Each lobule is composed of two distinct compartments. The cortex is distinguished by a dense accumulation of immature T cells, scientifically termed 'thymocytes'. In contrast, the inner compartment, designated as the medulla, exhibits a comparatively sparse population of thymocytes.

The cortex and medulla of the thymus are both composed of epithelial cells, dendritic cells, and macrophages. This network provides the framework for the organ and contributes to the growth and maturation of thymocytes.

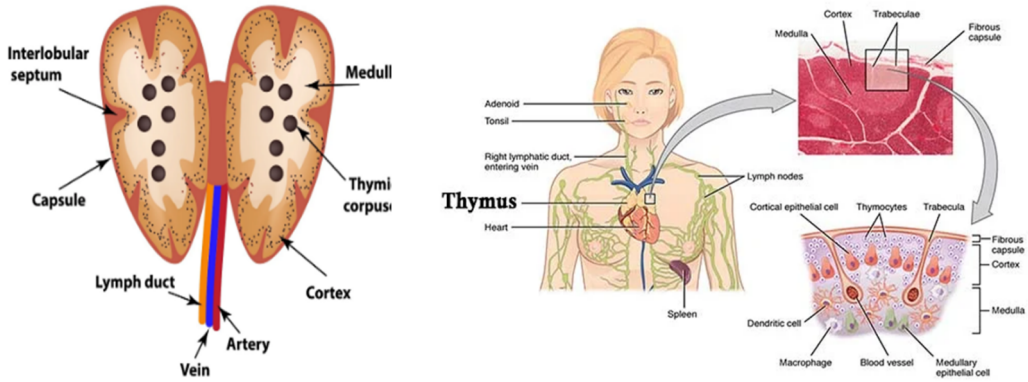


Image 2 Thymus Structure

b) Thymus Function

1. T cell maturation: T cells begin from the bone marrow as thymocytes to maturate in the thymus
2. Positive selection: Based on the acquisition of TCR. the T cell receptor interacts with the MHC molecules on the surface of epithelial cells. A mature T cell expresses only CD4 or CD8, but not both.
3. Negative selection: Eliminate T cells that attack the body's proteins in the thymus. Thymocytes that react strongly to self-antigens die by apoptosis. Some CD4-positive T cells exposed to self-antigens persist as T regulatory cells.

3. Secondary Lymphoid Organs

The lymph nodes and the **spleen** are the most highly organised secondary lymphoid organs. They comprise not only lymphoid follicles, but also distinct regions of T-cell and B-cell activity. They are surrounded by a fibrous capsule. The body has various sites where it contains less-organized lymphoid tissue, collectively called **mucosal-associated lymphoid tissue (MALT)**. MALT includes Peyer's patches. These are found in the small intestine. MALT also includes the tonsils and the appendix. Numerous lymphoid follicles are present within the lamina propria of the intestines. The same is true for the mucous membranes lining the upper airways, bronchi and genital tract.

3.1. Lymph Nodes

Lymph nodes are the organs in which adaptive immune responses occur. These small nodular aggregates of lymphocyte-rich tissue are situated along lymphatic channels throughout the body. Each lymph node consists of an outer cortex and an inner medulla. Each node is surrounded by a fibrous capsule pierced by numerous afferent lymphatics that empty lymph into a subcapsular or marginal sinus.

the outer cortex contains follicles, which are aggregates of cells. Some of these follicles contain central areas known as germinal centres in this caseare called secondary follicles. Follicles without germinal centres are called primary follicles. The cortex surrounding the follicles is organised into cords containing lymphocytes, dendritic cells, and mononuclear phagocytes arranged around lymphatic and vascular sinusoids. Below the cortex is the medulla contain macrophages and plasma cells.

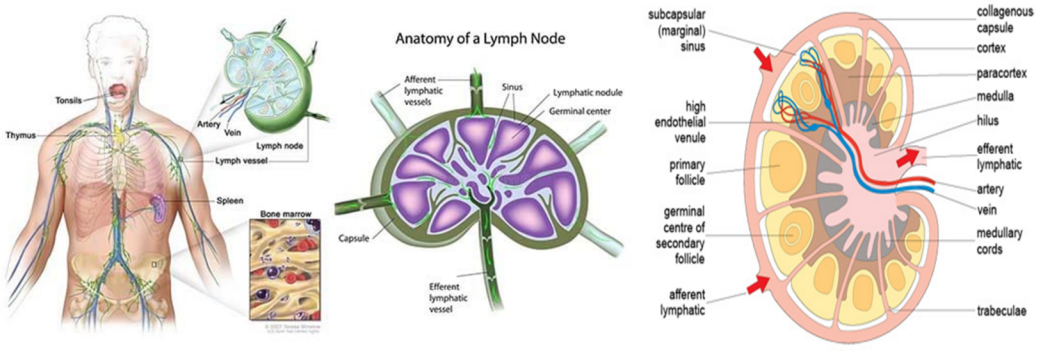


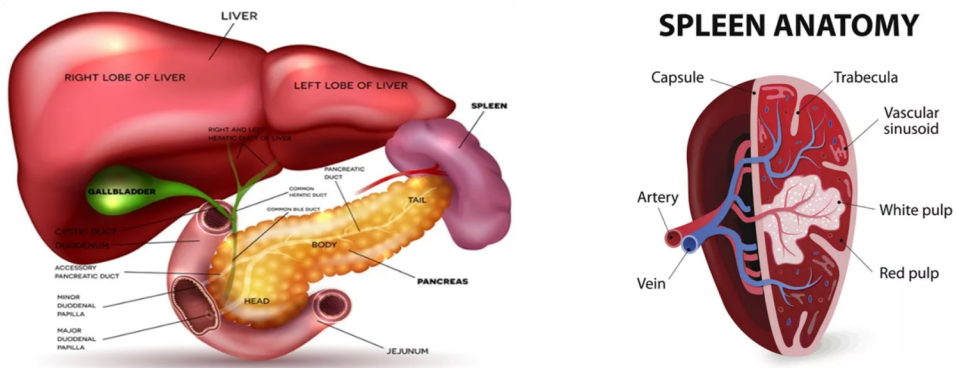
Image 3 Lymph Node Sturcture

3.2. Spleen

It is located in the upper part of the left abdominal cavity. Lymph nodes are responsible for trapping antigen from local tissues, while the spleen is responsible for filtering blood and trapping blood-borne antigens. Consequently, the spleen is able to respond to systemic infections.

The spleen is enveloped by a capsule that extends a series of projections (trabeculae) into its interior, consequently forming a compartmentalised structure. The compartments are of two types: red pulp and white pulp, which are separated by a diffuse marginal zone. The splenic red pulp constitutes a

network of sinusoids populated by macrophages and a substantial number of red blood cells (erythrocytes), with a comparatively lower number of lymphocytes. This area is the site at which old and defective red blood cells are destroyed and removed. The splenic white pulp envelopes the branches of the splenic artery, thereby forming a periarteriolar lymphoid sheath (PALS), which is predominantly populated by T lymphocytes. The rencontre with the Ag effected in the marginal zone, The initial activation of B and T cells occurs in the T cell-rich PALS.



Position and sturcture of Spleen

3.3. Mucosal-associated Lymphoid Tissue

The mucous membranes lining the digestive, respiratory, and urogenital systems have a combined surface area of about 400 m2 and are the major sites of entry for most pathogens.

Structurally, these tissues range from loose, barely organized clusters of lymphoid cells in the lamina propria of intestinal villi to well-organized structures such as the familiar tonsils and appendix, as well as Peyer's patches, which are found within the submucosal layer of the intestinal lining.

Different systems can be identified:

- In the nasopharynx: NALT (Nasopharyngeal Associated Lymphoid Tissue)
- In the upper airways: BALT (Bronchus Associated Lymphoid Tissue).
- In the digestive tract: GALT (Gut Associated Lymphoid Tissue).

The functional importance of MALT in the body's defense is attested to by its large population of antibody-producing plasma cells, whose number far exceeds that of plasma cells in the spleen, lymph nodes, and bone marrow combined.

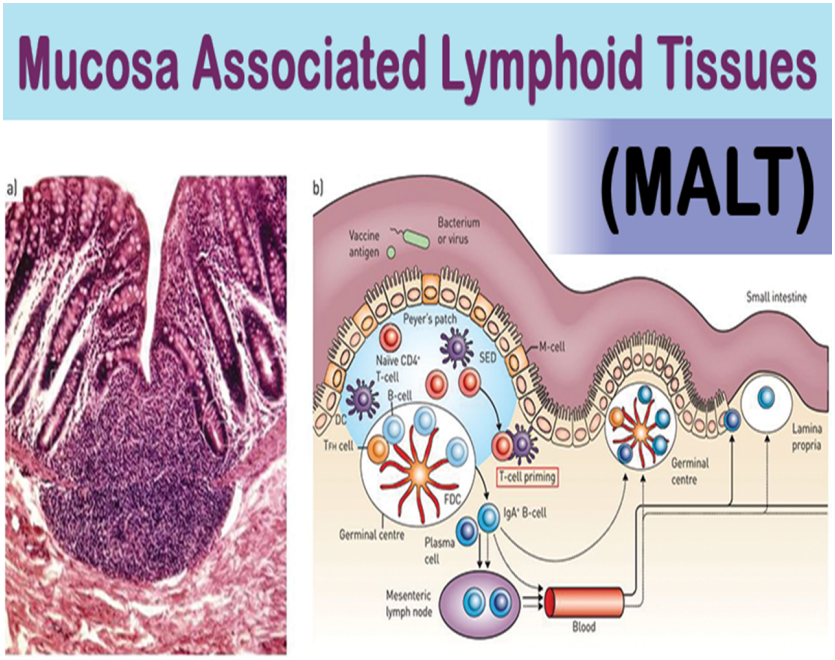


Image 4 Mucosa-associated lymphoid tissues (MALT)

4. Antigen-presenting cells (APCs and others)

It is essential to acknowledge that all nucleated human cells can present peptide fragments of endogenous proteins via the MHC class I pathway and display them on the cell surface for recognition by CD8+ cytotoxic T lymphocytes. However, only professional APCs are characterized by the ability to present exogenous antigens using MHC class II molecules and to present them to CD4+ helper T cells (TH cells), together with the requisite costimulatory molecules, such as CD86 and CD83. Recent studies show that the three main granulocyte subsets (neutrophils, eosinophils and basophils) possess the ability to present exogenous antigens to naïve T helper cells via MHC class II.

4.1. Dendritic cells "Professional APCs"

Dendritic cells have been shown to play important roles in antigen capture and the induction of T lymphocyte responses to protein antigens. Dendritic cells are located beneath epithelia, and in the majority of organs. These cells have a key function in capturing foreign antigens, which they subsequently transport to peripheral lymphoid organs. The majority of dendritic cells are derived from the monocyte lineage and thus are designated as '**Myeloid Dendritic Cells**'.

Follicular dendritic cells (FDCs) are cells characterised by the presence of membranous projections. They are found in the germinal centres of lymphoid follicles, which are located in the lymph nodes, spleen, and mucosal lymphoid tissues. The vast majority of FDCs are not derived from precursors in the bone marrow and are not related to the dendritic cells that present antigens to LT. FDCs have been shown to trap antigens complexed to antibodies or complement products and display these antigens on their surfaces for recognition by LB. It is imperative to consider this factor when selecting activated B lymphocytes, as their antigen receptors exhibit a high degree of binding affinity for the displayed antigens.

a) DC Functions

- It plays a role in the innate inflammatory response to pathogens.
- Efficient and effective priming of immature T cells.
- Activation and generation of immune memory T cells.
- Inducing the activation of B cells.
- Immune tolerance by maintaining a stable immune homeostasis through continuous presentation of tissue-derived self-antigens to CD4+ and CD8+ T cells.
- Development of an effective adaptive immune response.
- Provides a critical link between innate and adaptive immune responsiveness.
- It is now used in dendritic cell-based immunotherapies, such as those used to treat cancer.

4.2. Macrophages "professional APCs"

The migration and differentiation of a monocyte into a tissue produces a macrophage, characterised by the following: the cell expands five- to tenfold; its intracellular organelles increase in number and complexity; and it acquires an increased ability to phagocytose, produces higher levels of hydrolytic enzymes, and begins to secrete a variety of soluble factors.

Macrophages can take up residence in particular tissues as "fixed macrophages", or remain motile and be called "free" or "wandering". According to their tissue location, macrophages are called:

- Alveolar macrophages are found in the lungs.
- histiocytes in connective tissue;
- Kupffer cells in the liver.

- Mesangial cells are found in the kidney.
- Microglial cells in the brain.
- Osteoclasts in bone.

a) Phagocytosis

Macrophages have the capacity to ingest and digest exogenous antigens, such as whole microorganisms and insoluble particles, as well as endogenous matter, including injured or dead host cells, cellular debris, and activated clotting factors.

1. The initial phase of phagocytosis is characterised by the attraction and subsequent movement of macrophages towards the Ag, a process known as chemotaxis.
2. The subsequent stage in this process is the binding of the antigen to the macrophage cell membrane.
3. The process of adhesion is known to induce the extension of membrane protrusions, termed pseudopodia, around the attached material.
4. The fusion of the pseudopodia results in the enclosure of the material within a membrane-bounded structure known as a phagosome.
5. The phagosome progresses towards the cell interior and undergoes fusion with a lysosome, thereby forming a phagolysosome.
6. The contents of the phagolysosome are subsequently expelled during a process referred to as exocytosis.

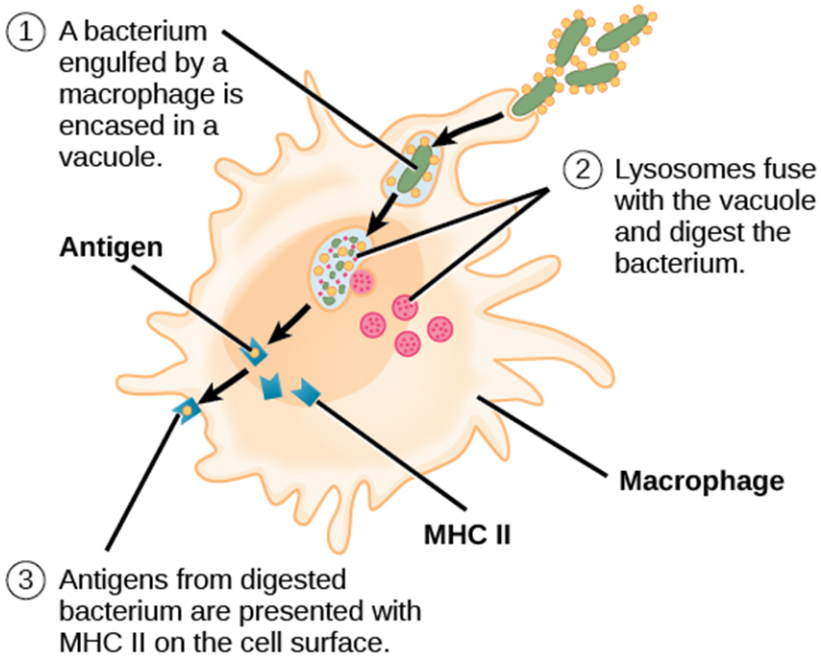


Image 5 Phagocytosis

b) Types of Macrophages

1- M1 Macrophage

in pro-inflammation and pathogen clearance

- M1 Increased phagocytic activity
- Antigen presenting capacity
- Increased synthesis and release of pro-inflammatory cytokines

2- M2 Macrophage

in anti-inflammation

- M2 Angiogenesis
- Neovascularization
- Stromal activation and remodeling
- Tissue repair
- Fibrosis Quite anti-inflammatory

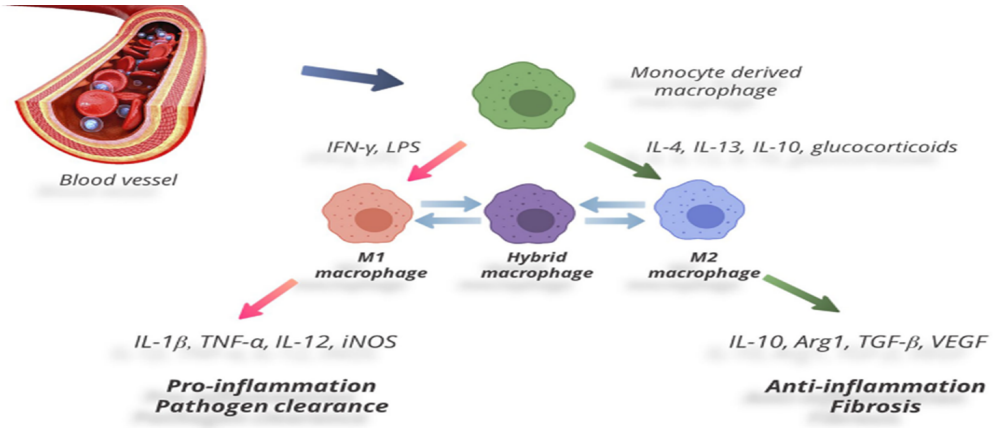


Image 6 Types of Macrophages

4.3. B cells

It is evident that B cells frequently operate in a manner that is not as widely recognised as their role in antibody production. However, it is evident that they meet the criteria for being considered competent APCs, particularly under specific circumstances.

The function of B cells as professional antigen-presenting cells (APCs) is as follows:

- MHC Class II Expression: B cells have been observed to constitutively express MHC II molecules, enabling them to present exogenous antigens to CD4+ T cells.
- Antigen Uptake via BCR: In contrast to dendritic cells, B cells internalise antigens specifically via their B cell receptor (BCR), a property that renders them highly selective.
- Co-stimulatory Molecules: Upon activation, B cells upregulate CD80, CD86, and CD40, which are critical for effective T cell priming.

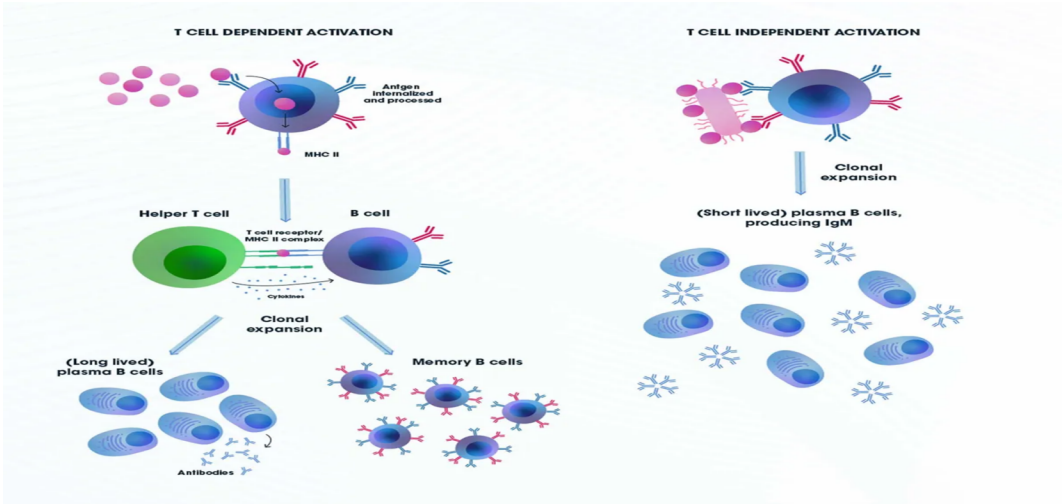


Image 7 B cells activation

Note

Mechanisms of Antigen Presentation

Feature	B Cells	Dendritic Cells	Macrophages
Antigen uptake	BCR-mediated (specific)	Phagocytosis, macropinocytosis	Phagocytosis
MHC II expression	Constitutive	High (especially after activation)	Inducible
Co-stimulation	Moderate (↑ upon activation)	High	Moderate
T cell activation	$CD4^+$ T cells (especially memory)	Naïve and memory T cells	Mostly memory T cells

Hematopoiesis

1. Introduction

Hematopoiesis, the formation of blood components, including red blood cells, white blood cells, and platelets. It is a process that occurs during embryonic development and continues throughout adulthood, ensuring the production and replenishment of the blood system. All blood cells are derived from a single type of cell, known as the **haematopoietic stem cell** (HSC).

The rationale behind the study of haematopoiesis is as follows: Beyond its physiological importance, hematopoiesis is central to our understanding of both **normal blood development** and **hematological disorders** such as leukemia, aplastic anemia, and bone marrow failure syndromes.

2. HSC characteristics

1. **Self-renewal** refers to the capacity of HSCs to proliferate while preserving their biological characteristics.
2. **Multipotency** is defined as the ability of HSCs to generate all mature cell types that comprise the blood and immune system.
3. **Quiescence** is defined as the ability of the HSC to remain inactive and unresponsive to external stimuli.

Reminder

Cellular Components of the Niche

- **Mesenchymal stromal cells (MSCs):** Provide structural support and secrete growth factors.
- **Endothelial cells:** Regulate HSC trafficking, homing, and mobilization.
- **Osteoblasts and osteoclasts:** Influence HSC localization near the endosteal region of bone marrow.
- **Adipocytes and fibroblasts:** Modulate the metabolic environment and cytokine secretion.
- **Immune cells (macrophages, T cells):** Contribute to signaling and niche remodeling.

3. Hematopoietic Formation and Development

- The onset of this phenomenon occurs during the early stages of embryonic development, specifically within the first weeks after conception. In this particular instance, yolk sac stem cells undergo a process of differentiation, resulting in the formation of primitive red cells that are characterised by the presence of fetal haemoglobin.
- In the third month of pregnancy, the process of migration of hematopoietic stem cells from the yolk sac to the fetal liver and then to the spleen is observed. These two organs are instrumental in the process of hematopoiesis from the third to the seventh month of pregnancy.

- Subsequently, the process of differentiation of HSCs in the bone marrow becomes the primary factor in the process of haematopoiesis.
- Subsequent to parturition: A salient observation is the paucity of hematopoiesis in the liver and spleen, with marrow hematopoiesis being exclusive to life in all bones up to 4 years of age, and thereafter, in short and flat bones (sternum, vertebrae, ribs, and iliac bones).
- In the early phase of hematopoiesis, the multipotent stem cells differentiate to a common lymphoid progenitor cell or a common myeloid progenitor cell, a process dictated by its microenvironment.
- During the development of the lymphoid and myeloid lineages, stem cells differentiate into progenitor cells, which have lost the capacity for self-renewal and are committed to a particular cell lineage.
- Common lymphoid progenitor cells give rise to B-cells, T-cells, natural killer (NK) cells, and some dendritic cells.
- Myeloid stem cells have been shown to generate progenitors of red blood cells (erythrocytes), as well as many of the various white blood cells (neutrophils, eosinophils, basophils, monocytes, mast cells, dendritic cells), and platelets.

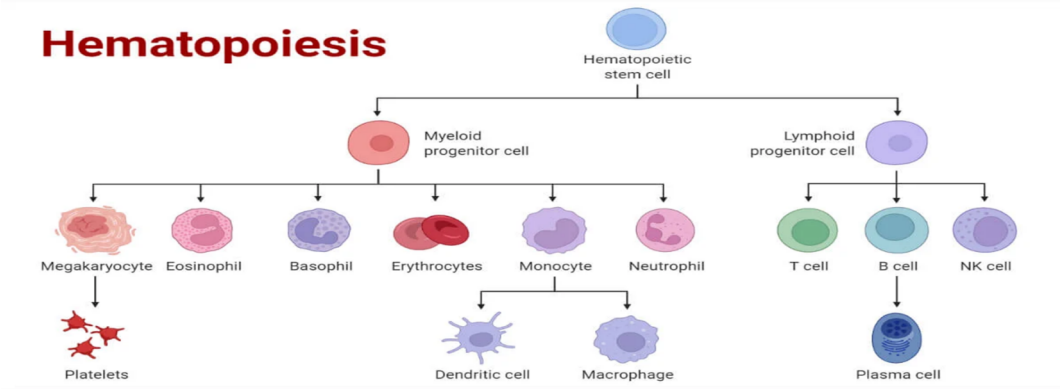


Image 8 Hematopoiesis

4. Cytokines that Stimulate Hematopoiesis

Cytokines are necessary for normal hematopoiesis in the bone marrow and provide a means of fine-tuning bone marrow function in response to stimulation. Several cytokines generated during innate and adaptive immune responses stimulate the growth and differentiation of bone marrow progenitor cells. Thus, immune and inflammatory reactions, which consume leukocytes, also elicit the production of new leukocytes.

Granulocyte-monocyte colony-stimulating factor (**GM-CSF**), monocyte colony-stimulating factor (**M-CSF**), and granulocyte colony-stimulating factor (**G-CSF**) are cytokines made by activated T cells, macrophages, endothelial cells, and bone marrow stromal cells that act on bone marrow progenitors to increase production of inflammatory leukocytes.

GM-CSF promotes the maturation of bone marrow cells into dendritic cells and monocytes.

G-CSF is generated at sites of infection and acts as an endocrine hormone to mobilize neutrophils from the marrow to replace those consumed in inflammatory reactions.

Recombinant **GM-CSF** and **G-CSF** are used to stimulate bone marrow recovery after cancer chemotherapy and bone marrow transplantation. These are some of the most successful clinical applications of cytokines.

IL-9 is a cytokine that supports the growth of some T cell lines and of bone marrow-derived mast cell progenitors. Its physiologic role is unknown.

IL-11 is produced by bone marrow stromal cells. It stimulates megakaryocytopoiesis and is in clinical use to treat patients with platelet deficiencies resulting from cancer chemotherapy

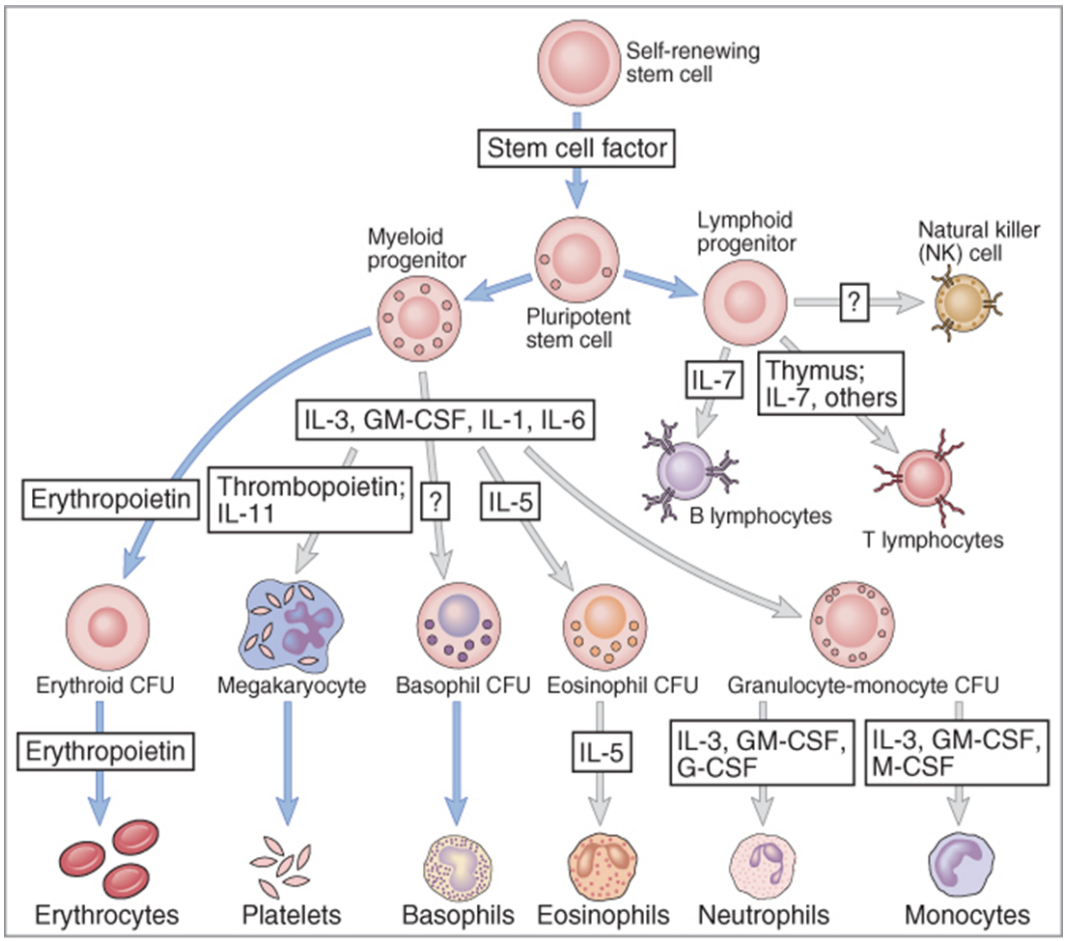


Image 9 Cytokines that stimulate Hematopoiesis

5. Hematopoietic Homeostasis Involves Many Factors

Steady-state regulation of hematopoiesis is accomplished in various ways, which include:

- Control of the levels and types of cytokines produced by bone-marrow stromal cells
- The production of cytokines with hematopoietic activity by other cell types, such as activated T cells and macrophages
- The regulation of the expression of receptors for hematopoietically active cytokines in stem cells and progenitor cells
- The removal of some cells by the controlled induction of cell death

6. Lymphopoiesis "Ontogenesis of T and B Lymphocytes"

Common Lymphoid Progenitor cells (CLP) are the earliest lymphoid progenitor cells derived from hematopoietic stem cells, giving rise to T-lineage, B-lineage, and natural killer (NK) cells. lL-7 plays a significant role at specific stages in the development of these cells.

Lymphopoiesis can be divided into two phases

Central phase

•Rearrangement and expression of antigen receptors (BCR and TCR)

•Selection / elimination of autoreactive lymphocytes (MHC-peptide/TCR, Ag /BCR)

Peripheral phase

•Differentiation into “effector” lymphocytes

•Activator signal and costimulatory molecules

How IL-7 and their receptors influence the lymphopoiesis

Warning

IL-7R signal transduction is important in directing the differentiation, proliferation, and survival of immune cells including B, T, and natural killer (NK).

IL-7 and its cell-surface receptor-α heterodimer consisting of the IL-7Rα and the common γ chain (γc)—form a ternary complex that engages the JAK-STAT pathway. The subsequent downstream activation of PI3K, bcl-2, and src kinases leads to gene transcription.

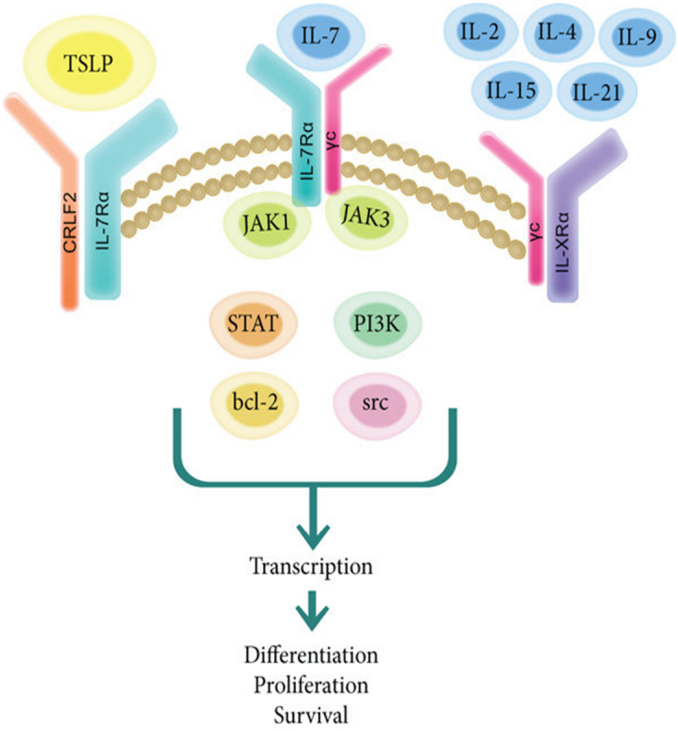


Image 10 how IL-7 and their receptors influence the lymphopoiesis

6.1. B Lymphocyte Ontogenesis "B Lymphopoiesis"

B cells originate in the bone marrow and circulate in the peripheral blood until they recognise an antigen. There are various stages in the development of B lymphocytes: stem cell (HSC), common lymphoid progenitor (CLP), pro-B cell, pre-B cell, immature B cell and mature B cell.

Once mature, the naive IgM+IgD+ B cell can recognize antigens and activate upon engagement with T lymphocytes and stimuli within the microenvironment. The activated, antigen-specific, effector cells can undergo class switching and affinity maturation, improving the capacity to identify and bind to an identified antigen.

The development of B lymphocytes is a process that occurs in two distinct phases. Firstly, there is an antigen-independent phase, which takes place in the bone marrow. Secondly, there is an antigen-dependent phase, which occurs in peripheral lymphoid tissues, such as the spleen, lymph nodes and MALT.

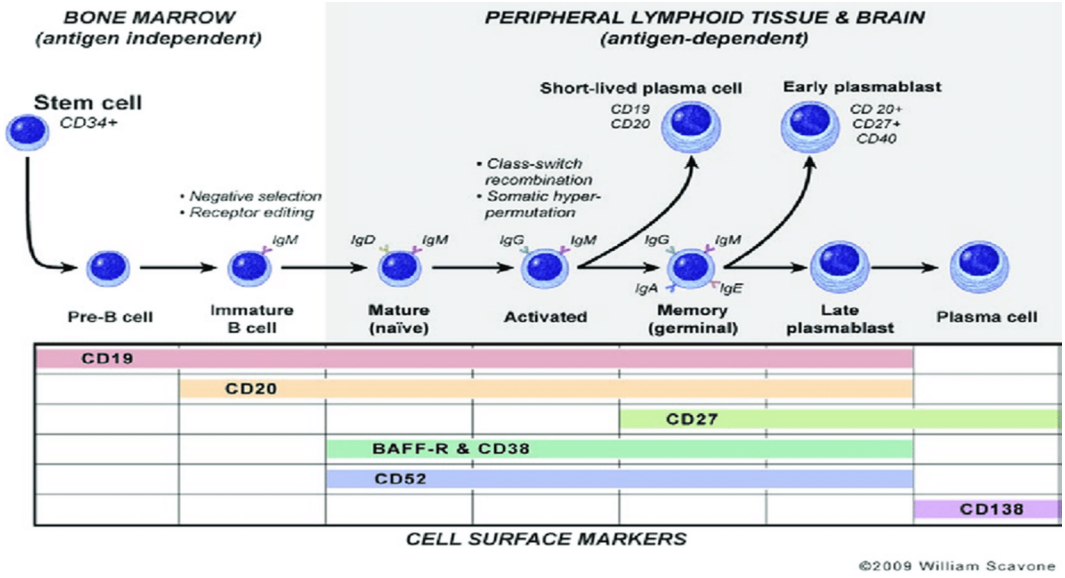


Image 11 B cells Development

a) An antigen-independent phase

takes place in the bone marrow from pluripotent stem cells under the effect of signals given by stromal cells (soluble cytokines, intercellular contact).

i) Stage of Progenitor B cell (pro-B)

is the first stage of B cell development.

- Pro-B cells are capable of self-renewal
- express stem cell-associated antigens (CD34 and CD117)
- express the B lineage-specific antigens CD 19 and CD22 (the latter restricted to the cytoplasm).

ii) The pre-B cells stage

- In this stage the synthesis of immunoglobulin begins.
- The heavy chains of the IgM immunoglobulins (u chain) then become detectable in the cytoplasm of the pre-B cells.

iii) Immature B cells stage

- These cells express whole IgM molecules on their surface.
- Immature cells perish by apoptosis when their immunoglobulins bind self-antigens that are probably presented by bone marrow stromal cells (clonal deletion or clonal anergy).

b) An antigen-dependent phase

i) Mature B cells stage

- These cells are called naïve B cells (virgin B cells) since the cells have not yet encountered foreign antigens.
- They leave the marrow and migrate first to the T cell-rich areas of the peripheral lymphoid organs for a new selection now takes place: all cells that do not obtain a survival signal from the T cells are eliminated by apoptosis.
- The remaining B cells migrate to the lymph nodes expressing on their surface immunoglobulins IgD as well as the differentiation antigens CD21, CD22, CD23 and CD37.

- The B cells then differentiate into plasma cells producing IgM (primary B cell response). The affinity for the antigen of these IgM antibodies remains low.

ii) Activated B cells stage

- When immune complexes are encountered, which have been fixed by follicular dendritic cells, B cells undergo an additional specific development in the lymph nodes (a process termed the 'germinal centre reaction'). The purpose of this reaction is to produce higher quality antibodies.
- The process of germinal centre reaction (GCR) facilitates the generation of antibodies of diverse classes (referred to as 'switching') by B cells.

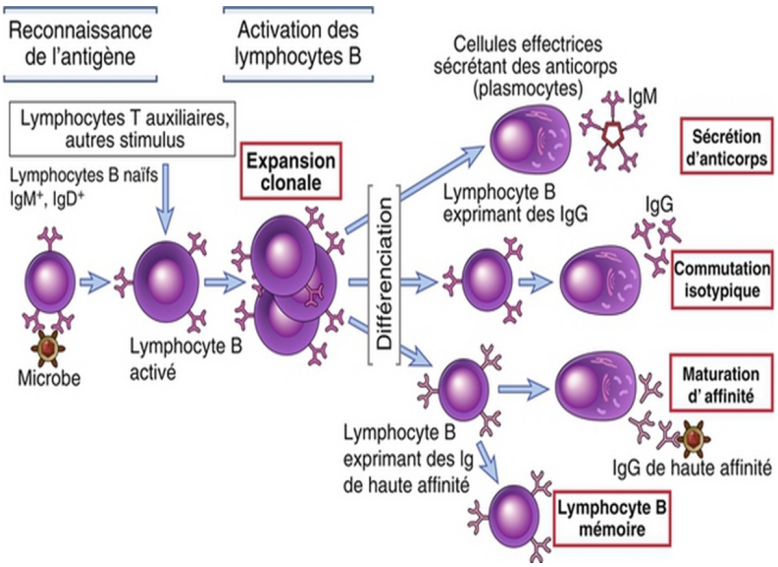


Image 12 Bcells activated

6.2. T Lymphocyte Ontogenesis "T Lymphopoiesis"

T progenitors (CD34+, CD71+) originate from the bone marrow and penetrate the thymus, where they proliferate and differentiate to create functionally distinct mature T cell subpopulations. This process necessitates a close interaction between thymocytes and the thymic stroma.

The differentiation of LT is characterised by the emergence of two significant phenomena, which enable the distinction of three distinct stages of thymic maturation and differentiation.

- The arranged appearance/disappearance of surface markers, some of which will be preserved throughout the life of LT.
- The acquisition of a functional TCR that is capable of recognising a specific type of antigen is a prerequisite for the subsequent processes.

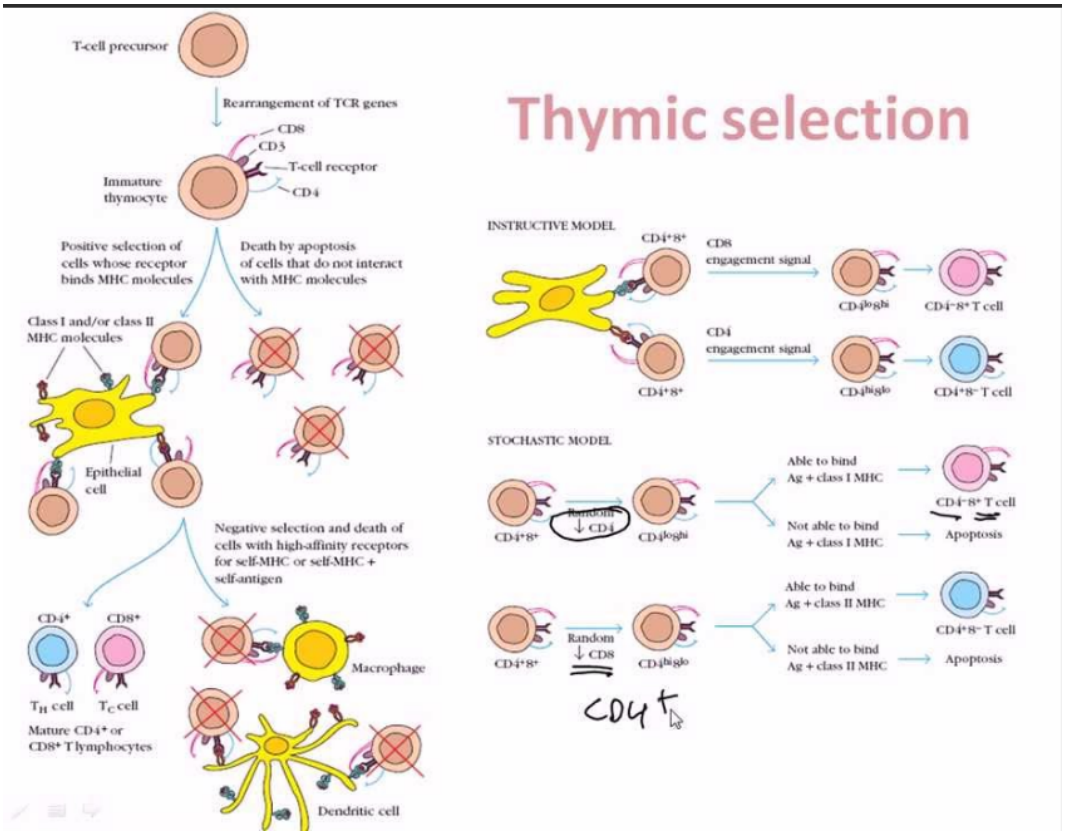


Image 13 Thymic Selection

a) The double negative stage (DN)

- T progenitors in the cortical zone of the thymus acquire lineage markers including the CD3 molecule, and express neither CD4 nor CD8, nor a functional TCR.
- This DN stage is subdivided into 4 stages (DN1, DN2, DN3, DN4). Each stage is characterized by a decisive event for the life of LT, essentially, concerning the rearrangement of the genes that encode the TCR.
- From the DN3 stage, the rearrangement of the TCR genes begins first with the γδ genes, if it is productive the cell becomes Tγδ and leaves the thymus to reach the epithelia if not, it continues its differentiation by trying the rearrangement of the β and α genes.
- A productive rearrangement leading to the expression of TCRαβ allows the cell to continue its differentiation.
- Otherwise, it will be eliminated by apoptosis.

b) Double positive stage (DP)

- At this stage, thymocytes express both markers (CD4 and CD8) as well as an αβ TCR, and are localized in the cortex in contact with epithelial cells that express MHC I and II molecules.
- If the cell loses expression of the CD8 molecule and therefore becomes an LTCD4+ when the CD4 molecule and the TCR of a thymocyte interact with an intermediate affinity with the HLA class II molecule.
- If the CD8 molecule and the TCR of thymocyte interact with an intermediate affinity with the HLA class I molecule, the thymocyte loses expression of the CD4 molecule and becomes an LTCD8+.

c) The single positive stage (SP)

- Single-positive cells undergo another selection process called negative selection in the medulla during which a large part of the SP cells are eliminated, to create self-tolerant LTs.
- It tends to eliminate all lymphocytes whose TCR recognizes with high affinity or does not recognize or only very weakly the self peptides presented by these cells.

6.3. Natural Killer NK

NK cells are a third population of lymphocytes whose receptors are different from those of B and T cells and whose major function is in innate immunity. NK cells secrete cytokines like IFN-γ, TNF-α, chemokines, and other factors that modulate the functions of other immune cells.

NK cell	CD56	CD16	Cytotoxicity	Cytokines production
10 %	+++	+	+	+++
90 %	+	+++	+++	+

NK1-T cells exhibit characteristics of both T cells and NK cells. Similar to T cells, NK1-T cells possess T cell receptors (TCRs).However, in contrast to the majority of T cells, the TCRs of NK1-T cells interact with MHC-like molecules, termed CD1, rather than with class I or class II MHC molecules. Similar to natural killer (NK) cells, they exhibit variable expression levels of CD16 and other receptors characteristic of NK cells, and possess the capacity to execute cell death. A population of triggered NK1-T cells has the capacity to secrete large quantities of the necessary cytokines with the purpose of supporting antibody production by B cells, in addition to inflammation and the development and expansion of cytotoxic T cells. This cell type can be regarded as a kind of rapid response system that has evolved in order to provide assistance at an early stage while conventional TH responses are still developing.

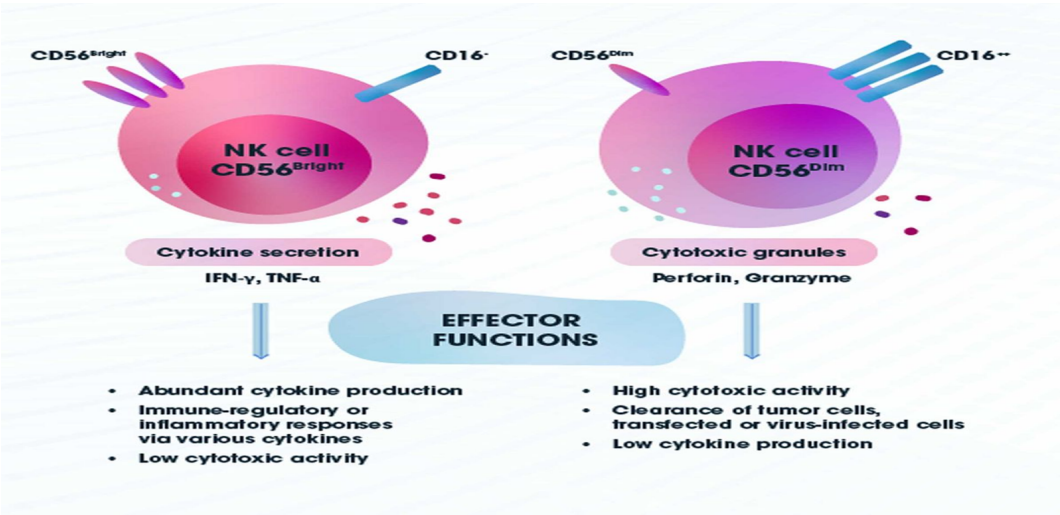


Image 14 NK classes

Lymphocyte Classes *Fundamental*

Class	Functions	Antigen receptor	Selected phenotype markers	Percent of total lymphocytes		
T lymphocytes				Blood	Lymph node	Spleen

$CD4^+$ (Helper T lymphocytes)	Stimuli for B cell growth and differentiation (humoral immunity) Macrophage activation by secreted cytokines (cell-mediated immunity)	αβ heterodimers	$CD3^+$, $CD4^+$, $CD8^-$	50-60*	50-60	50-60
$CD8^+$ (Cytolytic T lymphocytes)	Killing of virus-infected cells, tumor cells; rejection of allografts (cell-mediated immunity)	αβ heterodimers	$CD3^+$, $CD4^-$, $CD8^+$	20-25	15-20	10-15
B lymphocytes	Antibody production (humoral immunity)	Surface antibody (immunoglobulin)	Fc receptors; class II MHC; CD19; CD21	10-15	20-25	40-45
Natural killer cells	Killing of virus-infected cells, tumor cells; antibody-dependent cellular toxicity	Killer cell Ig-like receptor	Fc receptor for IgG (CD16)	~10	Rare	~10

Activation of Lymphocytes (T and B)

1. Introduction

LT represent the majority of cells of the lymphoid lineage in the blood and constitute the support of cell-mediated immune responses. In contrast to LB represent the support of humoral immune responses.

The process of expansion and differentiation of naive T and B cells, as well as the effector functions of differentiated lymphocytes, is initiated by the binding of antigens to antigen receptors. This process is influenced by additional stimuli. So, T and B cells are different types of cells in the body, right? And they have different needs when it comes to being switched on and how they react.

After activation (recognizing an antigen) LT contribute to eliminate it either directly “cytotoxic potential”, or indirectly, by cooperating with other cell lines via synthesize soluble molecules “cytokines”. While LB can differciated to plasma cells produce of specific antibodies or presented the antigens (CPA) to LTh cells,

2. T Cell Activation and Proliferation

LTCD4+ and LTCD8+ cells leave the thymus and enter the circulation as resting cells in the G0 phase of the cell cycle. This recirculation of LT naive cells increases the chances of encountering appropriate antigens.

All T cells that didn't encounter antigen (naive T cells) are characterized by:

- Condensed chromatin
- Very little cytoplasm
- Little transcriptional activity

2.1. From naive LT to effector LT

1. Protein antigens that enter the body through the epithelium and enter the bloodstream are captured by 'professional APCs, primarily dendritic cells, and transported to the lymph nodes and spleen.
2. Naive T cells continuously recirculate through lymph nodes. A T cell is activated when it finds an antigen in the form of peptide-MHC complexes.
3. This recognition induces the expansion and differentiation of these cells into effector and memory lymphocytes.
4. Effector T cells can migrate to any site of infection or inflammation and respond in ways that eliminate the antigens.
5. CD4+ helper T cells express membrane molecules and secrete cytokines that activate macrophages to kill microbes that have been phagocytosed and help B cells to differentiate into plasma cells that secrete antibodies.
6. The effector cells of the CD8+ subset kill infected and tumour cells that display class I MHC-associated antigens.

7. Memory T cells are an expanded population of antigen-specific T cells that can respond rapidly to a subsequent encounter with the same antigen, differentiating into effector cells that eliminate it.

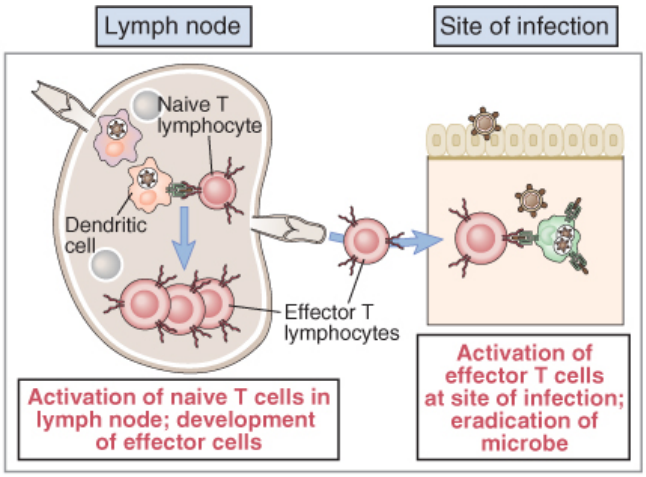


Image 15 Activation of naive and effector T cells by antigen

2.2. Stimulation Signals of LT

The activation of T cells requires the recognition of antigens displayed on APCs as a stimulation signal, and costimulatory ("second signals"), and cytokines produced by the APCs and by the T cells themselves.

a) Stimulation Signal

- The first signal involves a peptide-MHC complex present on the surface of DCs as APC and the TCR of LT.
- This first signal is insufficient to ensure complete activation of LTs.
- This signals induced anergy state of LT.

b) Costimulation Signal

- It involves the interaction of the B7 family costimulatory molecules: CD80 (B7-1) and CD86 (B7-2) expressed by activated DCs with the CD28 receptor expressed by LTs.
- This CD28/CD80 or CD86 interaction results in the formation of the immunological synapse at the center of which is the TCR linked to the MHC and, on the periphery, the costimulatory molecules (CD80 and CD86) and adhesion molecules (Intercellular Adhesion Molecule 1/Lymphocyte Function-Associated Antigen-1 [ICAM-1/LFA-1] and LFA-3/CD2).
- Other costimulatory molecules also participate in this process such as CD40L, OX40L and 4-1BB (CD137).

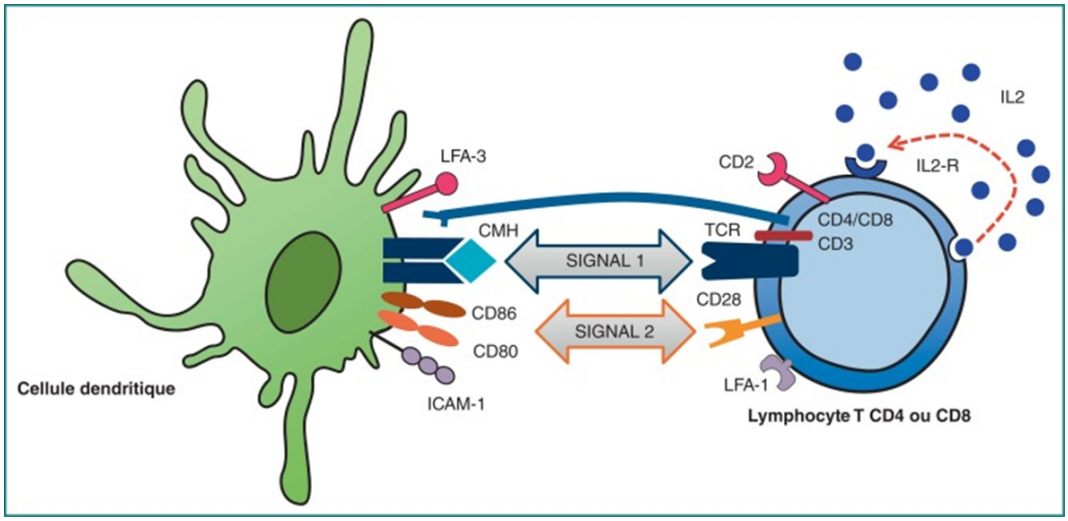


Image 16 Signals of LT activation

Note

The formation of the immunological synapse induces:

1. Optimal activation of LTs
2. Secretion of cytokines such as IL-2
3. Clonal expansion
4. Differentiation of LT into effector cells

2.3. Signal Transduction Cascade

Two phases can be recognized in the antigen-mediated induction of T-cell responses

Initiation:

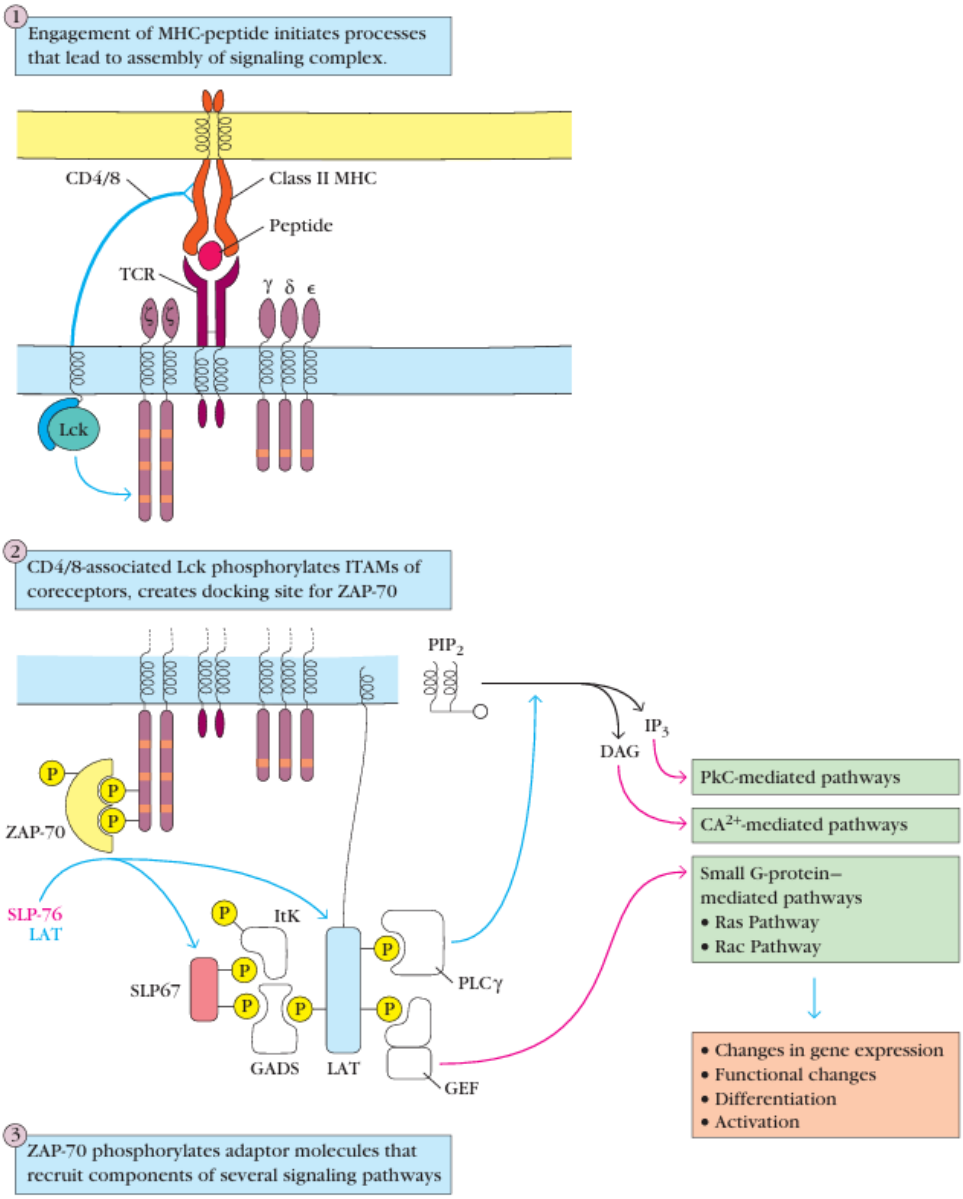
The process of engagement of MHC-peptide by the TCR results in clustering with CD4 or CD8 coreceptors. This is due to the binding of these coreceptors to invariant regions of the MHC molecule (step 1). Lck, a protein tyrosine kinase linked to the cytoplasmic tails of the coreceptors, is brought into close proximity with the cytoplasmic tails of the TCR complex, where it phosphorylates the immunoreceptor tyrosine-based activation motifs (ITAMs).

As outlined in step 2, the phosphorylated tyrosines in the ITAMs of the zeta chain provide docking sites. At these sites, a protein tyrosine kinase called ZAP-70 attaches and becomes active.

As outlined in step 3, ZAP-70 catalyses the phosphorylation of a number of membrane-associated adaptor molecules. These molecules act as anchor points for the recruitment of several intracellular signal transduction pathways.

The generation of multiple intracellular signals:

As illustrated in the figure below, the initiation phase activates numerous signalling pathways, which in turn trigger changes in gene expression, functional changes, differentiation and activation.



Graphic 1 Signal Transduction Cascade

2.4. Chronological course of gene expression after LT activation

1. **Immediate genes:** expressed within half an hour after antigen recognition; they encode many transcription factors, including c-Fos, c-Myc, c-Jun, NF-AT, and NF-κB.
2. **Early genes:** expressed within 1-2 h after antigen recognition; they encode IL-1, IL-2R (the IL-2 receptor), IL-3, IL-6, IFN-γ, and many other proteins.
3. **Late genes:** expressed more than 2 days after antigen recognition; increased expression of MHC molecules (on some cells) and adhesion proteins is observed.

2.5. The regulation of LT activation

In order to ensure T lymphocyte homeostasis, there are "immunological" brakes consisting of inhibitory receptors expressed by activated T cells, the best known of which are:

1. **Cytotoxic T lymphocyte Antigen-4** (CTLA-4) predominates in secondary lymphoid organs (central brake). The CTLA-4 receptor interacts with high affinity with its ligands CD80 and CD86, thus taking the place of the activating receptor CD28
2. **Programmed Cell Death-1 Protein** (PD-1) interacts with two ligands PD-L1 (B7-H1) and PD-L2 (B7-DC), leading to the inhibition of effector T cells, particularly in peripheral tissues.

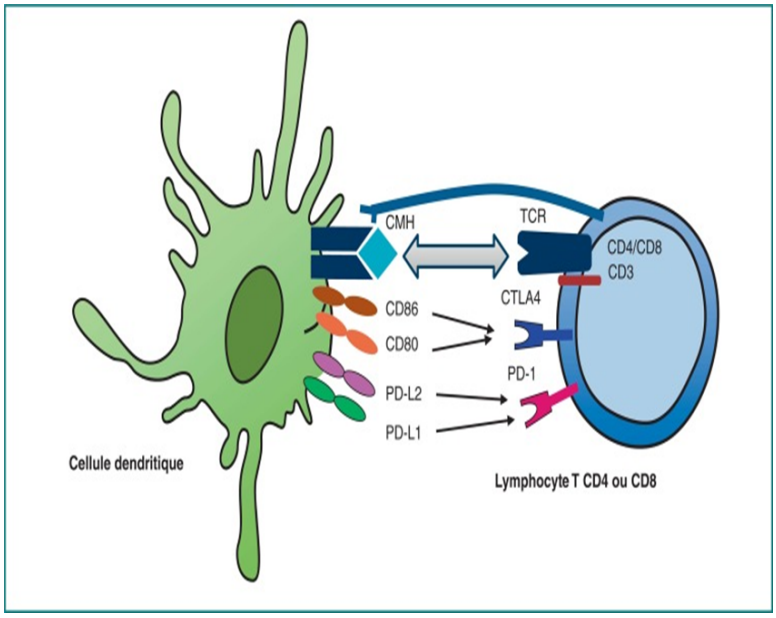


Image 17 Regulation of LT activation

3. B cell Activation and Proliferation

Humoral immunity is a process that is mediated by secreted antibodies, which are produced by cells of the B lymphocyte. Antibodies bind to the antigens of extracellular microbes, neutralising and eliminating them. The destruction of various types of microbes necessitates multiple effector mechanisms, which are facilitated by distinct classes, otherwise referred to as isotypes, of antibodies.

Antigen-triggered activation and clonal selection of naive B cells lead to the generation of plasma cells and memory B cells.

In the absence of antigen-induced activation, naive B cells in the periphery are short-lived, and die by apoptosis.

Depending on the nature of the antigen and the involvement of T lymphocytes, B lymphocyte activation leading to antibody production occurs through two different pathways:

1. Thymus-independent activation: some antigens can induce an antibody response even in the absence of a thymus; these are of two types: thymus-independent antigens type I and thymus-independent antigens type II.
2. Thymus-dependent activation: most antigens require direct involvement of T lymphocytes

3.1. Thymus-Independent Activation of B cells

Antibody responses to non-protein antigens, for instance polysaccharides and lipids, are not contingent upon antigen-specific helper T lymphocytes.

The response to Thymus-independent antigens is generally weaker, no memory cells are formed, and IgM is the predominant antibody secreted, reflecting a low level of class switching.

a) Type I thymus-independent antigens

- Cause polyclonal activation of LBs
- Activate both mature and immature B cells
- This activation does not go through the BCR but through receptors common to all LBs
- As is the case with bacterial LPS (lipopolysaccharides) activated LB via TLR4, knowing that LB can be activated by a BCR specific to LPS

b) Type II Thymus-independent antigens

- Lead to monoclonal stimulation of LB
- Only activate mature B cells
- Passes the BCR which recognizes antigenic determinants with repetitive epitopes such as polymeric proteins (e.g., bacterial flagellin) or pneumococcus polysaccharides

3.2. Thymus-dependent Activation of B cells

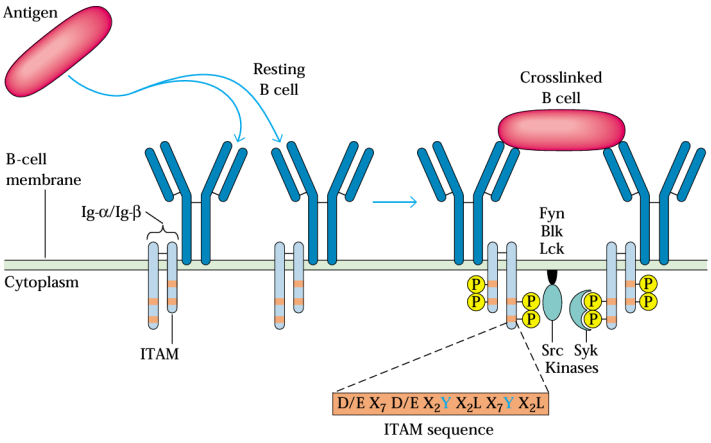
a) Stimulation Signals of LB

i) The activation signals

- Internalization (endocytosis) of the Ag-BCR complex, thus allowing the degradation of the antigen in the endosomal system.
- The peptide fragments obtained will be associated with MHC-II molecules, providing the B lymphocyte with the status of antigen-presenting cell.
- The activation of tyrosine kinases that will phosphorylate the ITAM motifs of the intra-cytoplasmic regions of the Igα-Igβ dimer (CD79a-CD79b) associated with the BCR, thus leading to the activation of transcription factors that will allow the expression of many molecules.

ii) The co-stimulation signals

- Via co-receptors (CD19, CD21 and CD81) that will amplify the signal.
- CR1 (CD35) and CR2 (CD21) are receptors for the C3 fragment or products resulting from its activation. The fixation of complement on antigens allows their opsonization via these receptors which are functionally coupled to the CD19 molecule.



B cell activation

b) TH Cells and B-Cell Responses

The binding of a protein antigen to a B-cell mIg is ineffective on its own in inducing an effective competence signal without additional interaction with membrane molecules on the TH cell. Furthermore, it is necessary to consider the role of cytokines in the process of B-cell proliferation.

i) The Formation of the T-B Conjugate

Following the binding of the antigen by mIg on B cells, the antigen is internalised by receptor-mediated endocytosis and processed within the endocytic pathway into peptides. Concurrently, a number of cell-membrane molecules, including class II MHC molecules and the co-stimulatory ligand B7, are up-regulated. The increased expression of both of these membrane proteins enhances the ability of the B cell to function as an antigen-presenting cell in T-cell activation.

Following internalisation, the process takes between 30 and 60 minutes. The two cells then interact to form a T-B conjugate.

ii) Contact-Dependent help mediated by CD40/CD40L Interaction

The formation of a T-B conjugate results in the release of TH-cell cytokines and up-regulation of CD40L (CD154). CD40L then interacts with CD40 on B cells, providing an essential signal for T-cell–dependent B-cell activation.

The interaction of CD40L with CD40 on the B cell delivers a signal (signal 2) to the B cell. This, in combination with the signal generated by mIg crosslinkage (signal 1), drives the B cell into G1. CD40 signals are transduced by several intracellular signalling pathways, which ultimately result in changes in gene expression.

iii) Signals provided by Th-Cell Cytokines

Following the activation of B cells, the expression of membrane receptors for various cytokines, including IL-2, IL-4, IL-5 and others, begins. These cytokines are then produced by T helper (TH) cells. Cytokine receptor interactions produce signals that promote B-cell growth and can trigger the formation of plasma cells and memory B cells, along with class-switching and affinity maturation.

Synthesis of Antibodies and their Diversity

1. Introduction

Antibodies are antigen-binding proteins found on B cells that have the ability to bind to specific antigens.

They can also be secreted by plasma cells and circulate in the bloodstream, where they play a role in humoral immunity. Their main functions include neutralizing antigens and marking them for elimination.

Despite their shared structural characteristics and ability to bind to antigens, antibodies have a limited number of effector functions. When produced in response to a particular antigen. Antibodies are heterogeneous this is because most antigens are complex and contain multiple antigenic determinants.

Any antibody binds to only a portion of the macromolecule, which is called a determinant or an epitope.

2. Structure of Antibodies

Antibodies are known to possess a heterodimeric structure, comprising four peptide chains. The structure comprises two identical light (L) chains (with a molecular weight of approximately 25,000) and two identical heavy (H) chains (with a molecular weight of 50,000 or more).

Each light chain is bound to a heavy chain by a disulfide bond, and by non-covalent interactions such as salt linkages, hydrogen bonds, and hydrophobic bonds, to form a heterodimer (H-L).

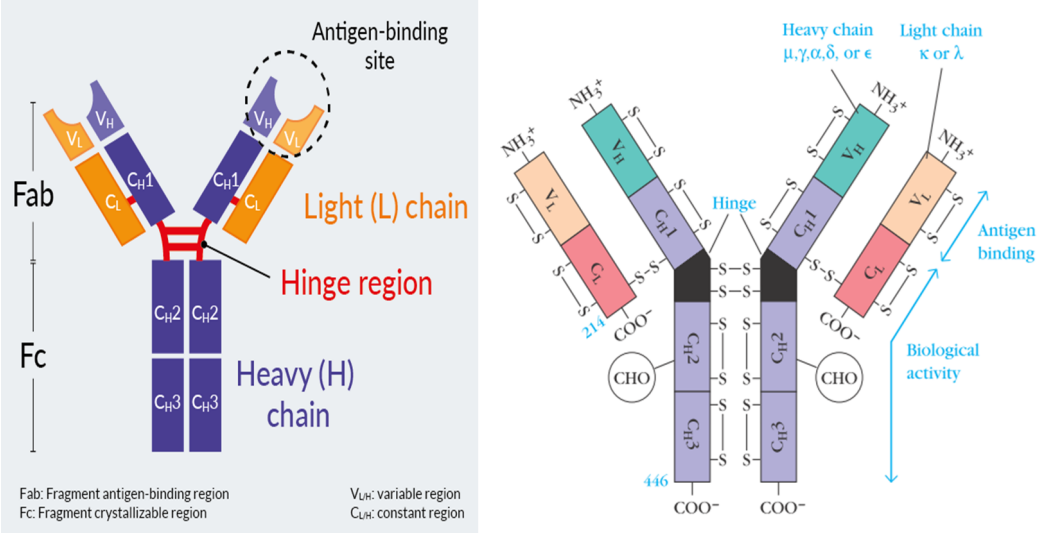
It is evident that non-covalent interactions and disulfide bridges play a pivotal role in linking the two identical heavy and light (H-L) chain combinations to each other. This process is instrumental in forming the fundamental four-chain (H-L) 2 antibody structure.

The first 110 amino acids of the amino-terminal region of an L or H chain vary greatly among antibodies of different specificity. These segments are known as V regions.

The majority of antibody differences are found in the V regions, specifically in the complementarity-determining regions (CDRs). These CDRs, present on both the light and heavy chains, are crucial for the antibody's antigen-binding site.

The regions beyond the variable regions have been designated C regions. The antigen-binding activity in these regions has been termed Fab fragments, which stands for "fragment antigen binding".

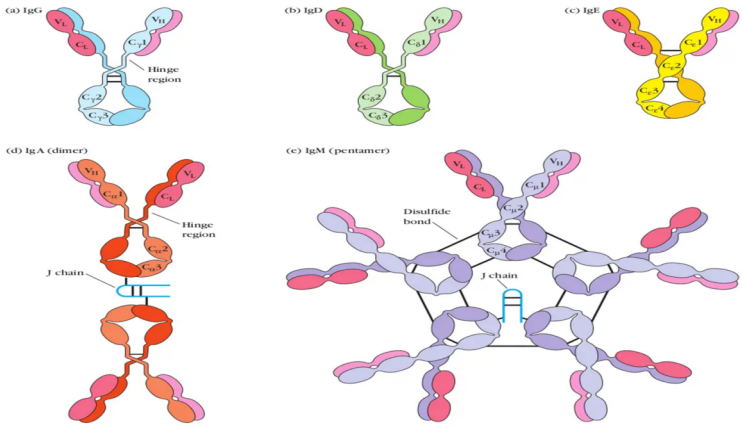
It is evident that the other fragment exhibits no antigen-binding activity whatsoever. Following the discovery that the substance crystallised during the storage process, it was designated the Fc fragment (i.e. 'fragment, crystallizable'). This fragment is responsible for the class specificity of the antibody.



Antibody Structure

3. Antibody Classes and Biological Activities

The classification of these antibodies is predicated on the presence of distinct amino acid sequences within the heavy-chain constant region, which impart class-specific structural and functional characteristics.



Classes of Antibodies

3.1. Immunoglobulin G (IgG)

IgG is the most common type of antibody in the blood. It makes up 80% of all the antibodies in the serum. The IgG molecule is made up of two heavy chains and two light chains. There are four types of human IgG. They are different because of differences in the -chain sequence. They are numbered according to how much is in the blood: IgG1, IgG2, IgG3 and IgG4

IgG1, IgG3 and IgG4 can easily cross the placenta and are important in protecting the developing baby.

IgG3 is the best at activating complement, with IgG1 next best. IgG2 is less efficient, and IgG4 is the least effective.

It can't activate the complement.

IgG1 and IgG3 stick tightly to Fc receptors on phagocytic cells, which helps to target them for removal.

IgG4 has an average level of binding to Fc receptors, and IgG2 has a very low level.

3.2. Immunoglobulin M (IgM)

IgM accounts for 5%–10% of the total serum immunoglobulin, with an average serum concentration of 1.5 mg/ml. It is found in very low concentrations in the intercellular tissue fluids.

Monomeric IgM is expressed as membrane-bound antibody on B cells. IgM is secreted by plasma cells as a pentamer, in which five monomer units are held together by disulfide bonds.

IgM is the first immunoglobulin class produced in a primary response to an antigen, and it is also the first immunoglobulin to be synthesised by the neonate. IgM has a higher valency than the other isotypes. Pentameric IgM is more efficient than other isotypes in binding antigens with many repeating epitopes, such as viral particles. IgM has been shown to be more efficient than IgG in terms of activating complement.

3.3. Immunoglobulin A (IgA)

Although IgA constitutes only 10–15% of the total immunoglobulin in serum, it is the predominant immunoglobulin class in external secretions, such as breast milk, saliva, tears and the mucus of the bronchial, genitourinary and digestive tracts. In serum, IgA primarily exists as a monomer, but also in polymeric forms (dimers, trimers and some tetramers). There are two subclasses: IgA1 (dominant in serum) and IgA2 (dominant in secretions).

IgA binds to pathogens and toxins, preventing their attachment to epithelial cells. IgA traps antigens in mucus and facilitates their removal. It can also neutralise viruses inside epithelial cells. Unlike IgG, IgA does not strongly activate the complement system, reducing inflammation at mucosal sites.

3.4. Immunoglobulin E (IgE)

IgE can be detected in serum, despite its extremely low average serum concentration (0.3 g/ml). IgE antibodies are responsible for the immediate hypersensitivity reactions that cause the symptoms of hay fever, asthma, hives, and anaphylactic shock. IgE is known to bind to Fc receptors present on the membranes of blood basophils and tissue mast cells. Cross-linkage of receptor-bound IgE molecules by antigen (allergen) induces basophils and mast cells to translocate their granules to the plasma membrane and degranulate. Consequently, a range of pharmacologically active mediators are released, leading to allergic manifestations. Localised mast-cell degranulation induced by IgE may also result in the release of mediators that facilitate the accumulation of various cells necessary for antiparasitic defence.

3.5. Immunoglobulin D (IgD)

IgD has a serum concentration of 30 g/ml and constitutes approximately 0.2% of the total immunoglobulin in serum. IgD, along with IgM, is the main membrane-bound immunoglobulin expressed by mature B cells, and its role in the physiology of B cells is currently being investigated. To date, no biological effector function has been identified for IgD.

Property/Activity	IgG1	IgG2	IgG3	IgG4	IgA1	IgA2	IgM‡	IgE	IgD
Molecular weight†	150,000	150,000	150,000	150,000	150,000–600,000	150,000–600,000	900,000	190,000	150,000
Heavy-chain component	γ1	γ2	γ3	γ4	α1	α2	μ	ε	δ
Normal serum level (mg/ml)	9	3	1	0.5	3.0	0.5	1.5	0.0003	0.03
In vivo serum half life (days)	23	23	8	23	6	6	5	2.5	3
Activates classical complement pathway	+	+/−	++	−	−	−	+++	−	−
Crosses placenta	+	+/−	+	+	−	−	−	−	−
Present on membrane of mature B cells	−	−	−	−	−	−	+	−	+
Binds to Fc receptors of phagocytes	++	+/−	++	+	−	−	?	−	−
Mucosal transport	−	−	−	−	++	++	+	−	−
Induces mast-cell degranulation	−	−	−	−	−	−	−	+	−

Properties and biological activities of classes and subclasses of human serum immunoglobulins

4. Genetic Rearrangements at the Germinal Center

The synthesis of immunoglobulin-based genes expression, with consideration for the properties of antibodies.

- The substantial heterogeneity of antibody specificities is a notable phenomenon.
- The presence of a variable region at the amino-terminal end and a constant region at the carboxyl-terminal end in Ig heavy and light chains has been observed.
- The existence of isotypes with the same antigenic specificity has also been demonstrated.

The human immunoglobulin genes are located on different chromosomes. The λ light chain genes are located on chromosome 22, the kappa light chain genes on chromosome 2, and the heavy chain genes on chromosome 14.

The diversity of these Ig is due to a process known as V(D)J recombination, which is a type of somatic gene rearrangement that occurs during the development of B cells in the bone marrow. There are multiple copies of each segment (e.g., ~40 V, 23 D, 6 J for heavy chains in humans), which are randomly selected and then joined together to form each category.

For heavy chains: The process of converting V + D + J → VDJ exon.

For light chains: V + J → VJ exon

In addition to the rearrangement of the C genes responsible for the constant part of Ig.

Somatic hypermutation is a process that adds diversity to already-rearranged gene segments. This process involves the replacement of individual nucleotides in VJ or VDJ units with alternatives. This can potentially alter the specificity of the encoded immunoglobulins. This process occurs in the germinal centres of secondary lymphoid organs. The process is initiated by Activation-Induced Cytidine Deaminase (AID), within a week or so of immunization with an antigen that activates a T-cell-dependent B-cell response.

Class switching, also known as **isotype switching,** among constant-region genes has been shown to induce changes in the antibody isotype (e.g., IgM to IgG, IgA, or IgE) without altering antigen specificity. Further research has revealed that the heavy-chain DNA can undergo a rearrangement in which the VHDHJH unit can combine with any CH gene segment, influenced by factors such as:

- IL-4 → IgE
- IFN-γ → IgG
- TGF-β → IgA

It is important to note that the heavy and light chains are synthesised on separate polyribosomes (polysomes). The assembly of the chains to form the disulfide-linked immunoglobulin molecule occurs as the chains pass through the cisternae of the rough endoplasmic reticulum (RER) into the Golgi apparatus and then into secretory vesicles.

5. Antibody-Mediated Effector Functions

It is important to note that antibodies do not generally kill or remove pathogens by binding to them directly. Instead, they trigger responses – called **'effector functions '**– that lead to the removal of the antigen and, ultimately, the death of the pathogen.

The **heavy-chain constant region** is responsible for a variety of collaborative interactions with other proteins, cells, and tissues. These interactions are what result in the effector functions of the humoral response.

5.1. Opsonization

This is a key component of antibacterial defenses. As outlined in the report, the process occurs via FcR, which is present on the surfaces of macrophages and neutrophils.

The binding of phagocyte Fc receptors with multiple antibody molecules that are complexed with a singular target, such as a bacterial cell, produces an interaction that results in the binding of the pathogen to the phagocyte membrane. This initiates a signal-transduction pathway that leads to the phagocytosis of the antigen-antibody complex.

Within the phagocyte, the pathogen is subject to a range of destructive processes, including enzymatic digestion, oxidative damage and the membrane-disrupting effects of antibacterial peptides.

5.2. Antibodies Activate Complement

It has been established that, in the case of human subjects, the majority of IgG subclasses, and IgM have the capacity to activate the complement system. These proteins have the ability to perforate cell membranes. The collaboration between antibodies and the complement system is vital for the inactivation and removal of antigens and the elimination of pathogens.

A significant byproduct of the complement activation pathway is a protein fragment known as C3b, which binds nonspecifically to cell- and antigen-antibody complexes in the proximity of the site at which the complement was initiated.

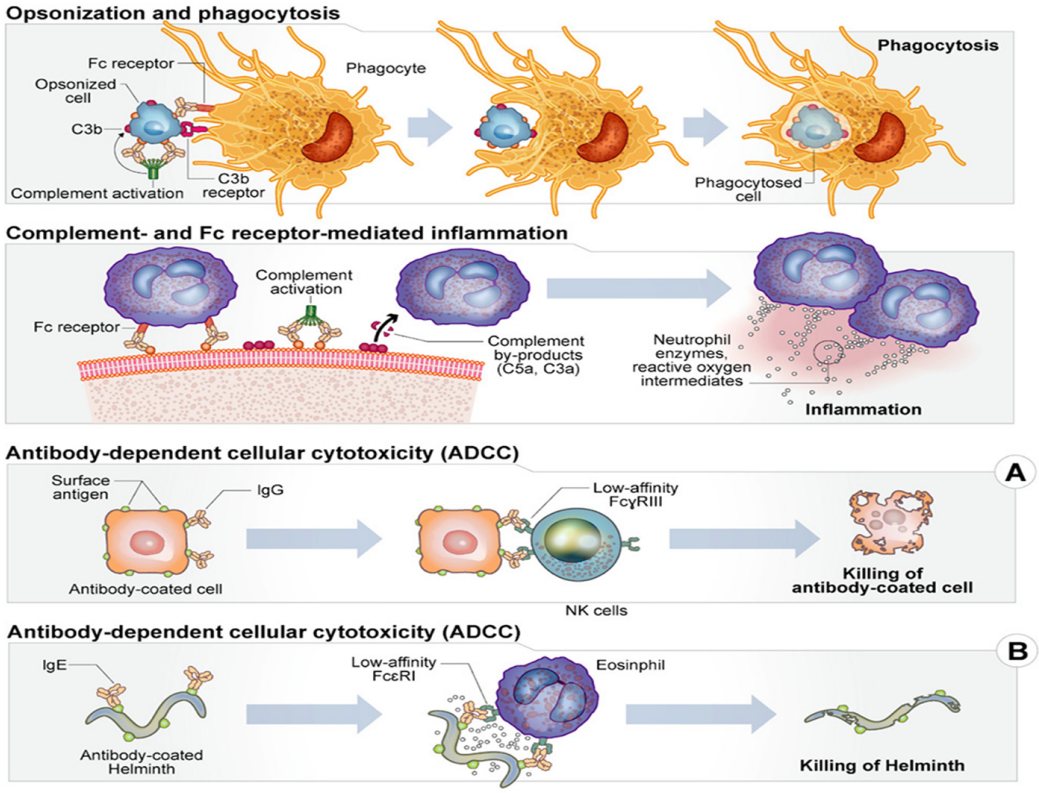
The binding of antigen-antibody complexes by the C3b receptors of a red blood cell enables the erythrocyte to deliver the complexes to the liver or spleen, where resident macrophages remove them without destroying the red cell.

5.3. Antibody-Dependent Cell-Mediated Cytotoxicity (ADCC) Kills Cells

The binding of antibodies to target cells (i.e. virus-infected host cells) is associated with the Fc receptors of various cell types, particularly natural killer (NK) cells. This binding facilitates the direct targeting of the effector cell's cytotoxic activities towards the target cell.

5.4. Some Antibodies Can Cross Epithelial Layers by Transcytosis

The delivery of antibody to mucosal surfaces, as well as its export to breast milk, requires the movement of immunoglobulin across epithelial layers. This process is known as **transcytosis** and is dependent on the properties of the constant region, particularly IgA and IgM. As maternal and fetal circulatory systems are separate, antibodies must be transported across the placental tissue that separates mother and foetus. This process is known as **passive immunization**.



Antibody-Mediated Effector Functions

6. The Immunoglobulin Superfamily

It has been demonstrated that a significant proportion of membrane proteins are characterised by the presence of one or more regions that bear a striking similarity to an immunoglobulin domain.

The term 'superfamily' is employed to denote proteins whose corresponding genes are derived from a common primordial gene encoding the basic domain structure. These genes have evolved independently of one another and do not share either genetic linkage or function.

The following proteins, in addition to the immunoglobulins themselves, are representative members of the immunoglobulin superfamily:

1. Ig-α /Ig-β heterodimer, part of the B-cell receptor
2. Poly-Ig receptor, which contributes the secretory component to secretory IgA and IgM
3. T-cell receptor
4. T-cell accessory proteins, including CD2, CD4, CD8, CD28, and chains of CD3
5. Class I and class II MHC molecules
6. Various cell-adhesion molecules, including VCAM-1,ICAM-1, ICAM-2, and LFA-3

7. Antigenic Determinants on Immunoglobulins

There are three major categories of antigenic determinants, or epitopes, that fall within immunoglobulin molecules: isotypic, allotypic and idiotypic determinants, which are located in specific portions of the molecule.

Determinate type	Definition	Location	Biological Significance
Isotypic	Antigenic differences that define the class and subclass of immunoglobulins (e.g., IgG, IgA, IgM, etc.)	Constant region of heavy and light chains	Shared by all individuals of a species; recognized as foreign when transferred between species
Allotypic	Minor allelic variations in the constant regions of immunoglobulin chains	Constant region, but varies between individuals of the same species	Basis for genetic polymorphism; can be immunogenic in transfusions or maternal-fetal incompatibility
Idiotypic	Unique antigenic determinants formed by the variable region, especially the complementarity-determining regions (CDRs)	Variable region of heavy and light chains	Reflects the antigen specificity of the antibody; can be targeted in anti-idiotype therapies or regulatory networks

Cellular Immunity

1. Introduction

It is important to note that both antigen-specific and -nonspecific cells have the capacity to contribute to the cell-mediated immune response. The specific cells in question comprise CD8+ cytotoxic T lymphocytes (CTLs) and cytokine-secreting CD4+ T H cells. Nonspecific cells include natural killer (NK) cells and non-lymphoid cell types, such as macrophages, neutrophils, and eosinophils. The functionality of both specific and nonspecific components is generally contingent upon the effective local concentrations of various cytokines.

The following cell types have been identified as the most prominent source of the cytokines responsible for orchestrating and sustaining cell-mediated immunity: T cells, NK cells, and macrophages.

2. Properties of Effector T Cells

2.1. The Activation Requirements of T Cells Differ

So, what happens when T cells are activated is that they start to multiply and then they go through a process of becoming what are called effector T cells. And for this to happen, they need two things: first, a kind of signal that tells them to get going, and this happens when the TCR complex and the CD4 or CD8 coreceptor have a bit of a chat with a foreign peptide–MHC molecule complex. And then, they need a second signal, which is kind of like a boost, and this is provided by certain molecules on the T cell and the APC, interacting with each other.

By way of contrast, antigen-experienced effector cells and memory cells are capable of responding to TCR-mediated signals with minimal, if any, co-stimulation.

2.2. Cell-Adhesion Molecules Facilitate TCR-Mediated Interactions

CD2 and the integrin LFA-1 are cell-adhesion molecules on the surfaces of T cells that bind, respectively, to LFA-3 and ICAMs on APC and various target cells. The level of LFA-1 and CD2 is twofold to fourfold higher on effector T cells than on naive T cells, enabling the effector T cells to bind more effectively to APC and to various target cells that express low levels of ICAMs or LFA-3.

2.3. Effector T Cells Express a Variety of Effector Molecules

In contrast to naive T cells, effector T cells express specific effector molecules, which can be membrane-bound or soluble. Each of these molecules plays an important role in various T-cell effector functions.

CTLs are known to secrete cytotoxins, including perforins and granzymes, as well as two cytokines: IFN-γ and TNF-β.

It is evident that the Th1 and Th2 subsets secrete largely non-overlapping sets of cytokines.

For instance, FasL, perforins and granzymes mediate target-cell destruction by the CTL. Membrane-bound TNF-β and soluble IFN-γ and GM-CSF promote macrophage activation by the Th1 cell. Membrane-bound CD40 ligand and soluble IL-4, IL-5 and IL-6 all play a role in B-cell activation by the Th2 cell.

3. T Cell (LT CD4+)

3.1. T Cell (LT4) Activation

1. Antigen Recognition: CD4+ T cell receptor (TCR) binding to antigen presented on MHC class II of an antigen-presenting cell (APC), e.g. a dendritic cell, is the process known as antigen recognition.

2. Co-stimulation: represent the second signals. that is the process by which the CD28 receptor on a T cell binds to the B7 (CD80/CD86) receptor on an antigen-presenting cell (APC).

3. Cytokine Signalling: APC secretes cytokines that guide T cell differentiation (see the next subtitle for more information).

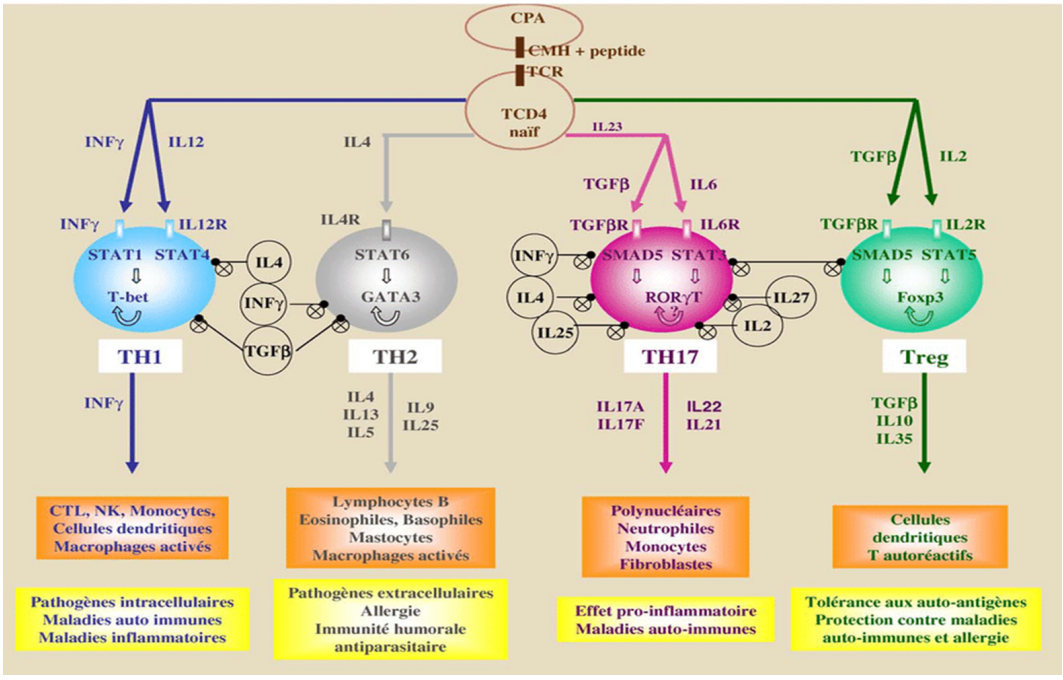
4. Clonal Expansion: Activated CD4+ T cells proliferate and differentiate by IL-2 (an autocrine growth factor) is involved in this process. Only T cells with the correct TCR specificity expand, ensuring a targeted immune response. Regulatory T cells modulate this expansion to prevent overactivation and autoimmunity

5. Effector Function: "differentiated T cells" are a type of white blood cell that plays a crucial role in the body's immune system. These cells have the ability to activate other immune cells, such as macrophages and B cells, or to suppress inflammation through the secretion of cytokines. Some examples of cytokines produced by differentiated T cells include IFN-γ, IL-4, IL-17, and IL-1.

3.2. Differentiation of CD4+ T lymphocytes

The process of activation of the CD4+ T lymphocyte commences immediately upon the binding of the TCR to the MHC-peptide complex of the antigen-presenting cell. The process of differentiation is initiated under the influence of various cytokines, resulting in the formation of one of four distinct CD4+ T cell subpopulations.

The relevant details can be found in the illustration provided below:



LT CD4+ Differentiation

3.3. Role of CD4⁺ T Cells in Cellular Immunity

Activation of macrophages: $CD4^+$ T cells (especially Th1 subtype) release cytokines like IFN-γ that enhance macrophage killing of intracellular pathogens.

Support for cytotoxic T cells ($CD8^+$): They help activate $CD8^+$ T cells by producing IL-2 and presenting antigens via MHC class II, indirectly boosting cytotoxic responses.

Cytokine secretion: $CD4^+$ T cells secrete a variety of cytokines (e.g., IL-2, IL-12, IFN-γ) that shape the immune response toward cellular immunity.

Recruitment of immune cells: They promote inflammation and recruit neutrophils, monocytes, and other immune cells to the site of infection.

4. Cytotoxic T Cells

Cytotoxic T lymphocytes (CTLs) are generated by immune activation of T cytotoxic cells that have lytic capability and are critical in the recognition and elimination of altered self-cells (e.g., virus-infected cells and tumor cells) and graft-rejection reactions, generally activated via class I-MHC restricted.

The immune response mediated by CTL can be divided into two phases, reflecting different aspects of the reaction:

- The first phase activates and differentiates naive T C cells into functional effector CTLs.
- In the second phase, effector CTLs recognize antigen–class I MHC complexes on specific target cells, which leads them to destroy the target cells.

4.1. The Transition of CTL Precursors to Effector CTLs

Naive T C cells cannot kill target cells and are therefore referred to as CTL precursors (CTL-Ps) to denote their functionally immature state.

for CTL-Ps activation requires at least three sequential signals:

1. An antigen-specific signal 1 transmitted by the TCR complex upon recognition of a peptide–class I MHC molecule complex
2. A co-stimulatory signal transmitted by the CD28-B7 interaction of the CTL-P and the APC
3. A signal induced by the interaction of IL-2 with the high-affinity IL-2 receptor

After a CTL-P activation, it can be differentiated into a functional CTL with cytotoxic activity.

IL-2 and activated CTL-P *Fundamental*

- IL-2 is the principal cytokine required for the proliferation and differentiation of activated CTL-Ps into effector CTLs.
- Antigen activation induces a CTL-P to begin expressing the IL-2 receptor and to a lesser extent IL-2.
- The most activated CTL-Ps require additional IL-2 produced by proliferating T h1 cells to proliferate and differentiate into effector CTLs.
- After clearance of antigen, the level of IL-2 declines, which induces Th1 cells and CTLs apoptosis. In this way, the immune response is rapidly terminated, lessening the likelihood of nonspecific tissue damage from the inflammatory response.
- In some cases, the amount of IL-2 secreted by an antigen-activated CTL-P may be sufficient to induce its proliferation and differentiation; this is particularly true of memory CTL-Ps, which have lower activation requirements than naive cells do.

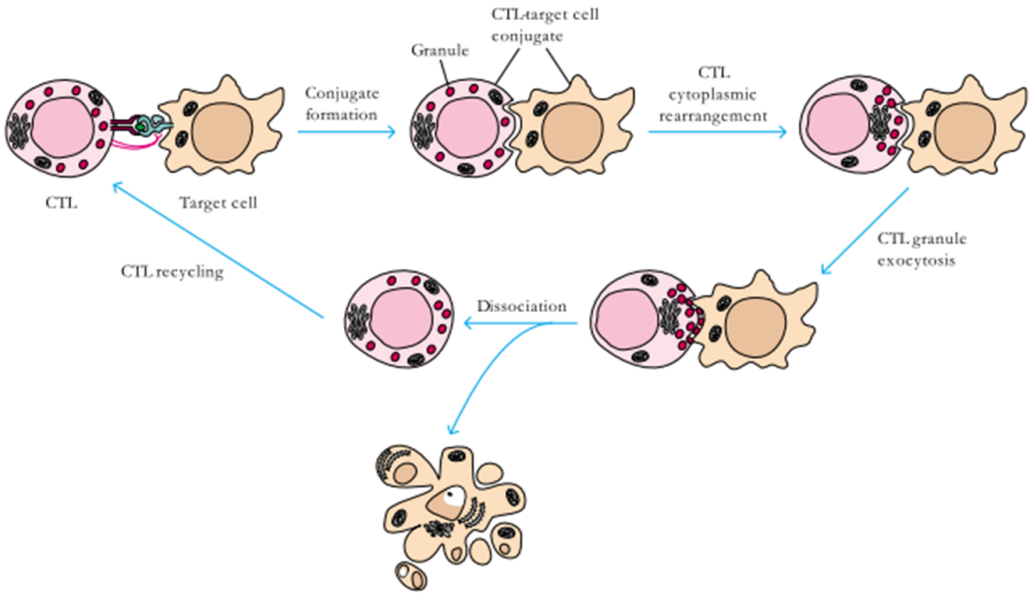
4.2. Effector CTLs

The effector phase of a CTL-mediated response involves a carefully orchestrated sequence of events that begin with the embrace of the target cell by the attacking cell.

CTL can kill the target cells in two ways the perforin/granzyme and Fas-mediated pathways and the final result is the activation of dormant death pathways that are present in the target cell « apoptosis ».

The primary events in CTL-mediated death are:

1. Conjugate formation
2. Membrane attack
3. CTL dissociation
4. Target-cell destruction



Steps of Effector CTLs

a) Perforin-Dependent killing

•After this antigen-specific recognition TCR-CD3 on a CTL recognizes antigens in class I MHC molecules on a target cell, the integrin receptor LFA-1 on the CTL membrane binds to ICAMs on the target-cell membrane.

•After the formation of a CTL–target cell conjugate, the perforin, and the granzyme proteases are released from the granules by exocytosis into the junctional space between the two cells. As the perforin contacts the target-cell membrane forms cylindrical pores mediates granzyme entry; another is the perforin-assisted pathway.

•Once it enters the cytoplasm of the target cell, granzyme B initiates a cascade of reactions that result in the fragmentation of the target-cell DNA into oligomers of 200 bp; this type of DNA fragmentation is typical of apoptosis.

• Within 5 min of CTL contact, target cells begin to exhibit DNA fragmentation. Interestingly, viral DNA within infected target cells has also been shown to be fragmented during this process.

b) Fas-mediated killing

•Some potent CTL lines have been shown to lack perforin and granzymes. In these cases, cytotoxicity is mediated by Fas.

• This transmembrane protein, which is a member of the TNF-receptor family, can deliver a death signal when crosslinked by its natural ligand, a member of the tumor necrosis family called Fas ligand.

•FasL is found on the membrane of CTLs, and the interaction with Fas on a target cell triggers apoptosis.

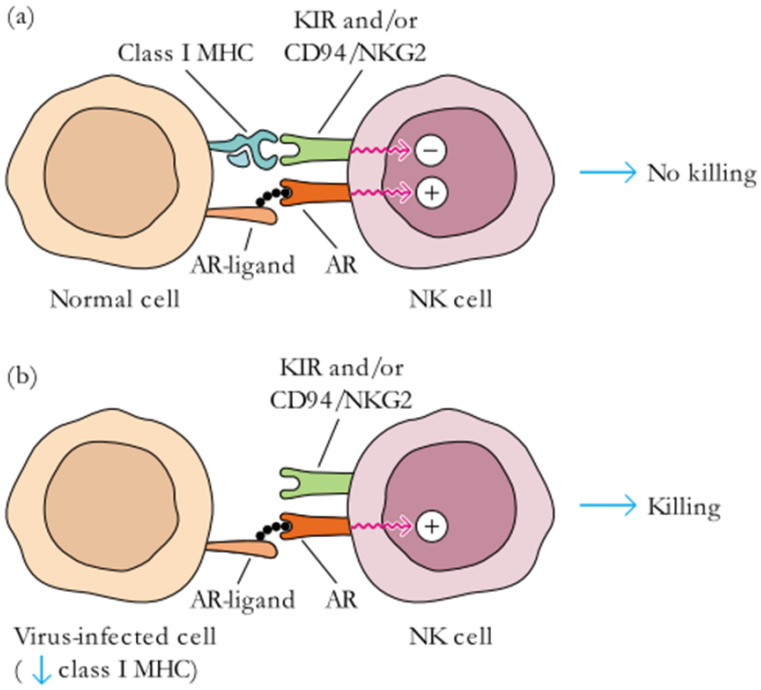
5. Natural Killer Cells

5.1. Natural Killer cells activation

Engagement of inhibitory NK cell receptors such as KIR and CD94/NKG2 by class I MHC molecules delivers an inhibitory signal that counteracts the activation signal.

However, an activation receptor (AR) on NK cells interacts with its ligand on normal and altered self-cells, inducing an activation signal that results in killing.

Expression of class I molecules on normal cells thus prevents their destruction by NK cells. Because class I expression is often decreased on altered self-cells, the killing signal predominates, leading to their destruction.



NK Activation

5.2. NK-Mediated Killing

Natural killer cells appear to kill target cells by processes similar to those employed by CTLs.

NK cells bear FasL on their surface and readily induce death in Fas-bearing target cells. Their cytoplasm contains numerous granules containing perforin and granzymes.

Unlike CTLs, which need to be activated before granules appear, NK cells are constitutively cytotoxic, always having large granules in their cytoplasm.

After an NK cell adheres to a target cell, degranulation occurs by releasing perforin and granzymes at the junction of the interacting cells.

5.3. Role of NK in Infection

- NK cells are involved in the early response to infection with certain viruses and intracellular bacteria. NK activity is stimulated by IFN-α, IFN-β, and IL-12.
- In the course of a viral infection, the level of these cytokines rapidly rises, followed closely by a wave of NK cells that peaks in about 3 days.
- NK cells are the first line of defense against virus infection, controlling viral replication during the time required for activation, proliferation, and differentiation of CTL-P cells into functional CTLs at about day 7.

6. Antibody-Dependent Cell-Mediated Cytotoxicity

Some cells are nonspecific for antigens and have cytotoxic potential to express membrane receptors for the Fc region of the antibody molecule.

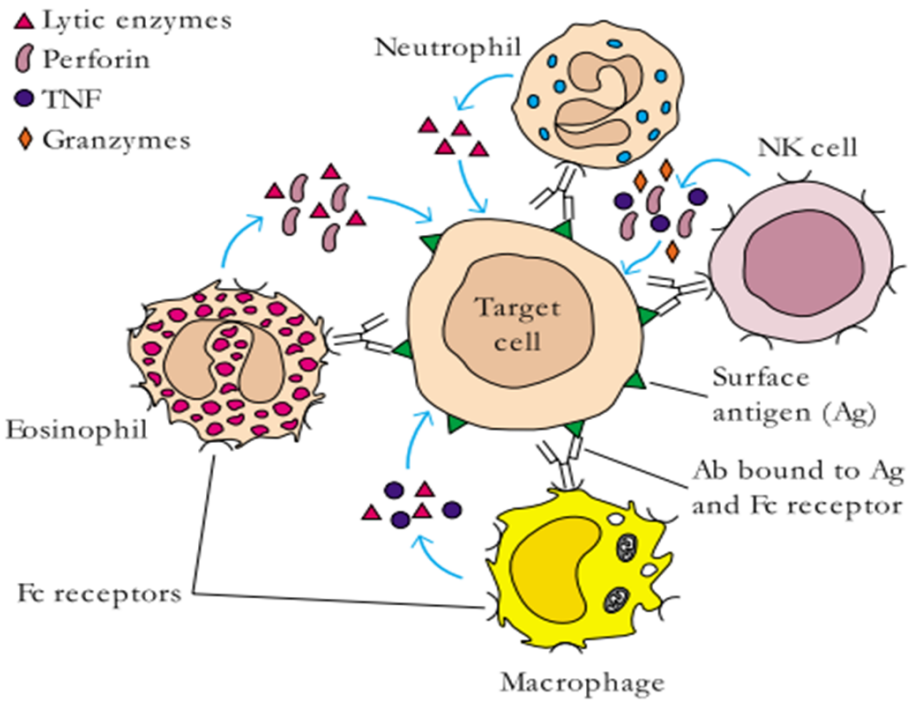
When antibody is specifically bound to a target cell, these receptor-bearing cells can bind to the antibody Fc region, and thus to the target cells, and subsequently cause lysis of the target cell. This type of cytotoxicity is referred to as Antibody-dependent Cell-mediated Cytotoxicity (ADCC).

The principal cells that have this power are NK cells, macrophages, monocytes, neutrophils, and eosinophils.

6.1. Mechanisms of Target-cell killing by ADCC

Target-cell killing by ADCC appears to involve several different cytotoxic mechanisms, but not complement-mediated lysis.

1. After macrophages, neutrophils, or eosinophils bind to a target cell by way of the Fc receptor, lytic enzymes lysosomes or granules increase. Release of these lytic enzymes at the site of the Fc-mediated contact may result in damage to the target cell.
2. Activated monocytes, macrophages, and NK cells have been shown to secrete TNF, which may have a cytotoxic effect on the bound target cell.
3. NK cells and eosinophils contain perforin in cytoplasmic granules, their target-cell killing also may involve perforin-mediated membrane damage.



Antibody-Dependent Cell-Mediated Cytotoxicity

T-B Interaction

1. Introduction

T-helper lymphocytes play a key role in stimulating various processes in B cells. These processes include clonal expansion, isotype switching, affinity maturation, and differentiation into memory B cells.

The activation of T-dependent B cells occurs in different areas of the peripheral lymphoid organs. The early phase of this activation occurs at the border of T-cell-rich areas and primary follicles. During this phase, B-cell proliferation, initial antibody secretion, and some isotype switching occur.

In contrast, the late phase of T-cell-dependent humoral immune responses takes place in the germinal centers within lymphoid follicles. This phase involves affinity maturation, the generation of memory B cells, and further isotype switching. These different phases occur in distinct anatomical regions and contribute to the development of a robust and effective immune response.

2. Functional consequences following antigen recognition

The initial encounters between antigen-stimulated B and T lymphocytes occur at the interface of the follicules and the T cell zones.

The cytokines and molecules present on the membrane of activated helper T cells have been shown to facilitate the proliferation and differentiation of B cells into antibody-secreting cells.

Consequently, between three and seven days following antigen exposure, antibody-producing B cells are observed in close proximity to activated LT.

The T-B cell interaction is known as a cognate interaction, as it is contingent on the specific recognition of antigen and several other surface molecules on the two cells.

3. Early events in humoral immune responses to T cell-dependent protein antigens

Anatomically, the activation of naive B and T cells leads to their migration toward each other.

Naïve CD4+ T cells are able to recognize antigens presented by APCs after a period of more than two days. Following this, the T cells become activated and reduce their expression of CCR7 in order to leave these areas.

Concurrently, B lymphocytes recognize and activate antigens in the primary follicles. This activation contributes to an increase in their expression of CCR7, a chemokine receptor that promotes cell migration to T cell areas in lymphoid organs.

Molecules that play a key role in the stability of B-T interactions.

Integrins represent a key component of most leukocyte cell-to-cell interactions and migratory processes, playing a crucial role in maintaining the stability of B-T interactions. Integrin LFA1 on helper T cells has been shown to engage both ICAM1 and ICAM2 on B cells, thereby significantly enhancing the capacity of lower-affinity B cells to enter responses.

The quantity of MHC-peptide presented by the B cell plays a key role in stabilizing these interactions. In addition to actin regulatory proteins.

3.1. Early events in T cell signaling: Recognition and priming

1. Antigen recognition

The TCR is capable of recognizing a peptide presented by MHC I or II. This interaction is stabilized by CD4 (MHC II) or CD8 (MHC I).

2. Activation of the CD3/ζ complex

The TCR is associated with CD3 (ε, δ, γ) and ζ (zeta), which contain ITAM motifs.

These motifs are phosphorylated by Lck, a tyrosine kinase associated with CD4/CD8.

3. The recruitment and activation of ZAP-70

The ZAP-70 protein has been shown to bind to phosphorylated ITAMs, which in turn leads to the phosphorylation of LAT (Linker for Activation of T cells) and SLP-76.

These adapters recruit key enzymes: PLC-γ1, Grb2, Gads, Vav1.

3.2. Early events in B cell signaling: Detection and signaling

1. Antigen recognition

BCR (IgM/IgD) is capable of recognizing the native antigen. Activation of Igα/Igβ co-receptors (CD79a/b) leads to the phosphorylation of ITAMs by Lyn.

2. Signaling cascade

The recruitment of Syk is followed by the activation of BLNK, PLC-γ2, PI3K and Btk. The production of IP_3 and DAG leads to the activation of the Ca^{2+}/NFAT, PKC/NF-κB and MAPK/AP-1 pathways.

Importance of Signaling Pathways *Fundamental*

Pathway	Key Molecules	Main Function	Outcome in T Cells
Ca^{2+}/NFAT	Calcium ions, Calcineurin, NFAT (Nuclear Factor of Activated T cells)	Calcium influx activates calcineurin, which dephosphorylates NFAT, allowing its translocation to the nucleus	Initiates transcription of IL-2 and other cytokines essential for T cell proliferation and differentiation
PKC/NF-κB	Protein Kinase C, IKK complex, NF-κB	PKC activates IKK, which phosphorylates IκB, releasing NF-κB to enter the nucleus	Promotes survival, cytokine production (e.g., IL-2, TNF-α), and anti-apoptotic gene expression

MAPK/AP-1	Ras/Raf, MEK, ERK/JNK/p38, AP-1 (Fos/Jun)	Sequential phosphorylation cascade leads to activation of AP-1 transcription factor	Regulates genes involved in cell cycle progression, cytokine expression, and effector functions

4. Late Events in T Cell-Dependent Antibody Responses: Germinal Center Reactions

The late events of immune responses are dependent on T helper cells, which contribute to the affinity maturation of B cells and the formation of memory B cells in the germinal centres of lymphoid follicles.

Following activation, some B cells migrate to the depths of the follicle within 4 to 7 days, where they proliferate rapidly to form the central zone of the follicle (germinal centre), as indicated by light staining. It is estimated that central cell proliferation takes between six and twelve hours. As a result, within five days, a single lymphocyte can produce approximately five thousand daughter cells, which are smaller cells known as central cells.

The undivided small cells produced by B cells migrate to a nearby dark basal zone, where they come into close contact with the processes of follicular dendritic cells (FDCs). It is here that subsequent selection events occur.

4.1. Late events in T cells: Amplification and transcription

resumed in the table below:

-

Pathway	key molecules	effect
PLC-γ1 Phospholipase C gamma 1	Cleaved into IP_3 and DAG	Triggers two major pathways
IP_3 Inositol 1,4,5-trisphosphate	Releases Ca^{2+} from the ER	Activates calmodulin → calcineurin → NFAT
DAG Diacylglycerol	Activates PKCθ	Activates NF-κB via CARMA1/Bcl10/MALT1
RasGRP Ras Guanyl-Releasing Protein	Activates Ras → Raf → MEK → ERK	Activates AP-1

These three transcription factors (NFAT, NF-κB, AP-1) cooperate to induce the expression of IL-2, CD25, cyclins, etc.

Ca^{2+} binds to calmodulin, which activates calcineurin. Calcineurin dephosphorylates NFAT, allowing its nuclear translocation.

Pharmacological inhibitors: Cyclosporine and tacrolimus are immunosuppressive drugs that work by inhibiting calcineurin and thereby blocking T-cell activation.

G proteins: Certain TCR pathways activate G proteins, regulate the cytoskeleton via Rho/Rac/Cdc42, and influence lymphocyte migration, adhesion, and polarization.

a) Regulatory molecules

Regulatory molecules are a key component control the LT activation:

CD2: Adhesion via LFA-3, represent secondary co-stimulation signal.

CD28: is vital for co-stimulation via CD80/CD86, which stabilizes the secretion of IL-2.

CD45: is a phosphatase that plays a regulatory role in the Lck/Fyn pathway, controlling the activation threshold.

4.2. Late events in B cells: Functional response

Gene transcription: proliferation, differentiation, isotype switching. The BCR-antigen complex is internalized, and then presented via MHC II to CD4+ T lymphocytes.

a) Regulatory molecules

CD19: has been shown to amplify the signal via PI3K.

CD21 (CR2): is a complement co-receptor that facilitates activation.

CD80 (B7-1): assure the interaction between CD80 (B7-1) and CD28/CTLA-4 on CD4+ T cells.

CD40: The process of binding to CD40L by CD40 results in activation, isotype switching and memory.

5. Transduction of Activating Signals

Crosslinking of BCRs has been demonstrated to induce numerous signal-transduction pathways and activate the B cell. A significant number of parallels have been identified between B-cell and T-cell activation, including the following:

5.1. Compartmentalization of function within receptor subunits

Both the B-cell and T-cell pathways commence with antigen receptors, which consist of an antigen-binding and a signalling unit. The antigen-binding unit is responsible for specificity, however its cytoplasmic tails are too short to transduce signals to the cell's cytoplasm. The signalling unit possesses long cytoplasmic tails that function as the receptor complex's signal transducers.

5.2. Activation by membrane-associated Src protein tyrosine kinases

The early phases of signal transduction are accompanied by a series of crucial phosphorylations catalysed by receptor-associated protein tyrosine kinases (PTKs). These include Lck in T cells and Lyn, Blk and Fyn in B cells, which are essential for the formation of a signalling complex capable of eliciting a functional response in the receptor.

5.3. Signaling complex with protein tyrosine-kinase activity:

The phosphorylation of tyrosines within the ITAM motifs of the BCR and TCR has been demonstrated to facilitate the binding of molecules that confer tyrosine kinase activity upon these receptors. In the context of T cells, this process is governed by ZAP-70, while in B cells, it is regulated by Syk.

5.4. Recruitment of other signal-transduction pathways

The production process is initiated by signals from the BCR and TCR. The second messengers IP3 and DAG are of particular significance. IP3 has been shown to induce the release of Ca^{2+} from both intracellular stores and DAG. This substance has been shown to activate PKC. A third important set of signaling pathways are those governed by the small G proteins Ras and Rac that are also activated by signals received through the TCR or BCR.

5.5. Changes in gene expression

Following the engagement of the BCR or TCR, the signal activates transcription factors that are responsible for stimulating or inhibiting the transcription of specific genes. This process takes place in the nucleus.

6. Feedback control

Negative Regulation of T and B Cell Activation proved by :

6.1. CTLA-4

CTLA-4 (Cytotoxic T-Lymphocyte Antigen 4): is a T-cell receptor found on the surface of T cells. Expressed on activated CD4+ and CD8+ T cells, and constitutively on Tregs. It competes with CD28 for binding to CD80/CD86 on APCs, but with higher affinity. Instead of co-stimulation, CTLA-4 delivers inhibitory signals:

- Recruits phosphatases like SHP-2.
- The product has been shown to inhibit the PI3K/Akt and Zap-70 pathways.
- It is essential for peripheral tolerance and immune checkpoint control.
- This product is used in immunotherapy (e.g. ipilimumab) to enhance T cell responses in cancer.

6.2. FcγRIIB – B Cells:

This is an inhibitory Fc receptor that is expressed on B cells, dendritic cells, and mast cells. The product contains an ITIM (Immunoreceptor Tyrosine-based Inhibitory Motif). When co-engaged with BCR (e.g., by immune complexes), it recruits:

- SHIP (SH2-containing inositol phosphatase) is responsible for the hydrolysis of PIP3, thereby inhibiting PI3K signalling.
- SHP-1 has been shown to dephosphorylate Syk and other signalling intermediates.
- It has been demonstrated that the substance in question has the capacity to suppress B cell activation, proliferation, and antibody production.
- It is imperative for preventing autoimmunity and maintaining immune homeostasis.

Memory Acquisition Specialty of Acquired Immunity Vaccination

1. Introduction

Many infectious diseases are only encountered once in an individual's lifetime, despite repeated exposure to the same pathogens. This initial exposure triggers a response from the immune system, enabling it to eliminate the pathogens and generate memory immune cells.

This memory is a fundamental aspect of adaptive immunity. The secondary response is typically faster, more intense, and more effective than the initial response. It has been a crucial foundation for the development of vaccination concepts by physicians and researchers.

2. General characteristics of a memory response

- Their immunoreceptor has a high affinity.
- They have a lower threshold for activation and require fewer costimulation signals.
- Various cytokines, such as IL-2, IL-7 and IL-15 for memory T cells, BAFF (B cell-activating factor belonging to the TNF family) and APRIL (apoptosis-related interleukin-like protein) for memory B cells, can stimulate their proliferation. This is due to the expression of the corresponding receptors on memory cells.
- The effector function is operational at a rapid or immediate rate.
- The effector function is operational at a rapid or immediate rate.
- Resident memory cells, these cells are present in the peripheral tissues (skin and mucous membranes). This enables them to act immediately against the aggressor.
- Memory T cells have been found to be capable of altering Th1/Th2 functional polarity. This phenomenon is known as 'plasticity'.
- Memory B cells are capable of undergoing new isotype switching and BCR mutations during the proliferation phase.

3. B Cell Memory

Following the formation of memory B cells during the primary response, they cease to divide and enter the G0 phase of the cell cycle. These cells have a variable lifespan, with some persisting throughout an individual's lifetime. In B cell responses, there are two forms of memory:

Firstly, the long-term production of antibody is initiated by long-lived plasma cells (LLPCs).

Secondly, a pool of relatively quiescent memory B cells (Bmems) is generated, which can be reactivated by subsequent antigen exposures.

3.1. B Cell Memory Location

The location of Bmems to antigen encounter is important. Most B cells appear to be recirculating, but some are tissue-resident, for example in the lung.

Within lymph nodes, B cells appear to be positioned in a subcapsular niche, enabling them to encounter antigen-bearing subcapsular sinus macrophages and T follicular helper (Tfh) cells rapidly.

3.2. B Cell Memory Formation

Memory B cell (Bmem) formation is influenced by both intrinsic factors, such as the B cell receptor (BCR) isotype, and extrinsic cues, including CD40 engagement and cytokine signaling. Recent findings suggest a potential role for interleukin-9 (IL-9) in this process. Within the germinal center (GC), elevated expression of the transcription factor Bach2 appears to bias B cell differentiation towards the Bmem lineage rather than long-lived plasma cells (LLPCs). When the body is exposed to antigen once more, the ability of Bmems to become activated is governed by their BCR affinity and epitope specificity. This is because they must compete not only with other memory B cells, but also with circulating antibodies secreted by LLPCs.

Following re-exposure to antigen, Bmems have the capacity to differentiate into GC B cells or plasma cells. Furthermore, specific subsets of IgM versus IgG Bmems, defined by surface markers such as CD73, CD80, and PDL2, demonstrate different propensities to undergo particular differentiation programs.

It is thought that GC B cells give rise to a significant proportion of the Bmem pool, yet there are also GC-independent Bmems that appear very early in the immune response.

3.3. Comparison of Naive and Memory B Cells

The difference between primary and secondary B cell response resumed in the table below:

Property	Primary response	Secondary response
Responding B cell	B cell Naive (virgin)	Memory B cell
Lag period following antigen administration	Generally 4–7days	Generally 1–3days
Time of peak response	7–10days	3–5days
Magnitude of peak antibody response	Varies depending on antigen	Generally 100–1000times higher response than primary response
Isotype produced	IgM predominates early in the response	IgG predominates
Antigens	Thymus-dependent and thymus-independent	Thymus-dependent
Antibody affinity	Lower	Higher
Membrane markers Immunoglobulin	IgM, IgD	IgM, IgG, IgA, IgE
Complement receptor	Low	High

Anatomic location	Spleen. lymph node	Bone marrow, lymph node, spleen
Life span	Short-lived	May be long-lived
Recirculation	Yes	Yes
Receptor affinity	Lower average affinity	Higher average affinity due to affinity maturation
Adhesion molecules	Low ICAM-1	High ICAM-1

4. T Cell Memory

With the exception of thymus-independent antigens, any primary immune response is comprised of three distinct stages.

Firstly, there is the recruitment of antigen-specific T clones.

Secondly, there is their more or less intense clonal expansion.

Thirdly, there is the disappearance of a part of the generated cells, or clonal contraction, which is accompanied by the persistence of memory T lymphocytes.

Three fates are possible for the activated T cell:

Death by Active Apoptosis: death induced by cell activation is caused by the re-engagement of the TCR on the presenting cells, favored by cellular promiscuity at the very site of clonal expansion. It prevents uncontrolled runaway clone growth,

Passive Apoptosis Due to Cytokine Deficiency: the majority of activated T cells migrate to inflammatory sites where they are less threatened by an active apoptosis process, but where they are exposed to a deficiency in growth factors, particularly IL-2.

Survival as memory T cells: for cells that survive these apoptosis processes.

4.1. T cell Memory Formation

The quality of the primary response and the degree of clonal contraction determine the size and qualities of the memory T cell pool. These qualities depend on many factors

- The nature of the antigen: live pathogen or, at the extreme, synthetic peptides.
- The initial dose and route of administration of the antigen, which determine the intensity of the initial proliferation.
- The intensity of the inflammatory response at the initial phase of T cell activation.
- The amount of growth cytokines produced.
- In the case of CD8+ T cells, cognitive assistance from CD4+ T cells.

the only element established to date is a survival advantage for cells that preserve a strong membrane expression of the IL-7 receptor (IL-7Ra or (D127) They represent 5 to 15% of activated T cells These activated CD127" T cells could constitute the precursors of memory T cells

4.2. Differentiation into Memory Subsets

A classification based on the presence or absence of the molecules CCR7 (chemokine receptor interacting with CCL19 and CCL21), CD62L (or L-Selectin) and CD45RA on the surface of circulating T cells allows us to identify three major categories of cells that have escaped the clonal contraction phase.

a) Central Memory T cells

Reside in lymphoid organs, CCR7+ /CD45RA- cells have been shown to predominantly express CD62L, and thus possess a high proliferative potential. Furthermore, it has been demonstrated that these cells constitute a reserve for the rapid generation of new effector T cells in the event of re-exposure to the antigen. CCR7 and CD62L facilitate their return to secondary lymphoid organs, where they are poised to engage rapidly with antigen-presenting cells.

b) Effector Memory T cells

These cells are known to circulate within peripheral tissues, are characterized by a lack of expression of both CCR7 and CD45RA, and typically do not express CD62L. In the event of reinfection, a prompt response is observed. These cells are present in the blood and lymphatic circulation, as well as in non-lymphoid tissues, a property that facilitates rapid action in close proximity to the source of infection. These cells possess a high proliferative capacity and secrete cytokines rapidly upon activation. It is possible that these cells already contain cytotoxic granules.

c) Terminally Differentiating T cells

Or tissue-resident memory T cells, which have been shown to permanently reside in non-lymphoid tissues such as skin or mucosa, providing localized protection. These cells are characterized by the expression of CCR7 and CD45RA, and have been found to exhibit immediate effector capacities, albeit limited proliferative capacity. These cells, which constitute an exceedingly small proportion of CD4+ T lymphocytes, are predominantly present within the CD8+ memory T compartment in adults and the elderly.

4.3. Function of Memory T cells

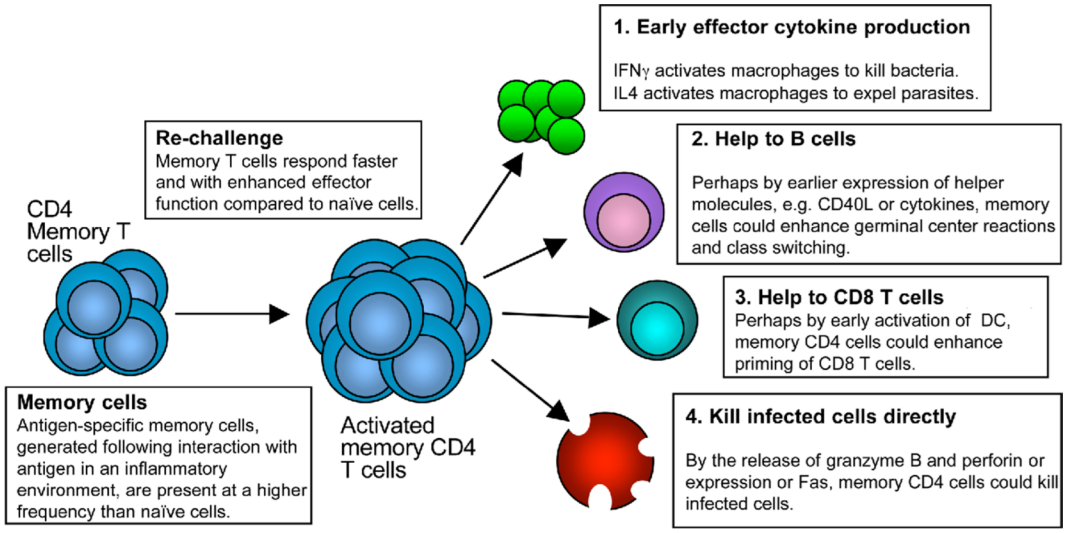
The mean role of T memory cells :

Rapid Response: Following a secondary infection, the proliferation and activation of memory T cells can lead to a reduction in disease severity.

Long-Term Protection: These cells have the capacity to persist for extended periods, often spanning multiple decades, in a state of immune surveillance.

Support Vaccination: Vaccines are designed to stimulate the production of memory T cells (and B cells) to prevent future illness.

Tissue-Resident Memory T Cells (Trm): These are located in specific tissues (e.g. the lungs, gut or skin) and provide localized protection.



function of memeory T cells

5. Vaccination

5.1. Active and Passive Immunization

Immunity to infectious microorganisms can be achieved by active or passive immunization. It is evident that immunity can be acquired in a number of ways. Firstly, it can be acquired through natural processes, such as the transfer of antibodies from the mother to the foetus, or through previous infection by the organism. Secondly, it can be acquired through artificial means, such as the injection of antibodies or vaccines.

The agents employed for the induction of passive immunity encompass antibodies derived from both humans and animals. Conversely, active immunization is accomplished through the inoculation of microbial pathogens that elicit immunity without inducing disease, or by the administration of antigenic components derived from these pathogens.

5.2. Principal Factors in Designing Vaccines

In order to ensure the successful development of a vaccine, it is imperative to consider several factors.

Firstly, it is imperative to acknowledge that the development of an immune response does not necessarily imply the attainment of a state of protective immunity. It is imperative to ascertain the branch of the immune system that is activated, as this is of critical importance. Consequently, vaccine designers must recognise the significant differences between the humoral and cell-mediated branches.

A secondary factor that must be considered is the development of immunological memory. For instance, a vaccine that elicits a protective primary response may fail to stimulate the formation of memory cells, leaving the host unprotected after the primary response to the vaccine subsides.

5.3. Types of Vaccines

1. Live-attenuated vaccines are vaccines that utilise a weakened form of the virus or bacteria that causes the disease. It is imperative to stimulate a robust and enduring immune response.

Examples: The following vaccines are available: measles, mumps, rubella (MMR), and BCG (for tuberculosis).

2. Inactivated vaccines are composed of killed versions of the pathogen. It is generally accepted that this is a safer option than live vaccines, however it should be noted that booster shots may be required.

Examples include: The following vaccines are administered: polio (IPV), hepatitis A and rabies.

3. The following vaccines are characterised by the use of specific pathogen components: subunit, recombinant, polysaccharide and conjugate vaccines. These components may be proteins or sugars, for example. The medication is targeted and safe, even for individuals with compromised immune systems.

Examples: Vaccines are available for the prevention of hepatitis B, HPV, pneumococcal and meningococcal infections.

4. Toxoid vaccines are designed to protect against toxins produced by bacteria; they do not protect against the bacteria itself.

The utilisation of inactivated toxins (toxoids) has been demonstrated to facilitate the development of immunity.

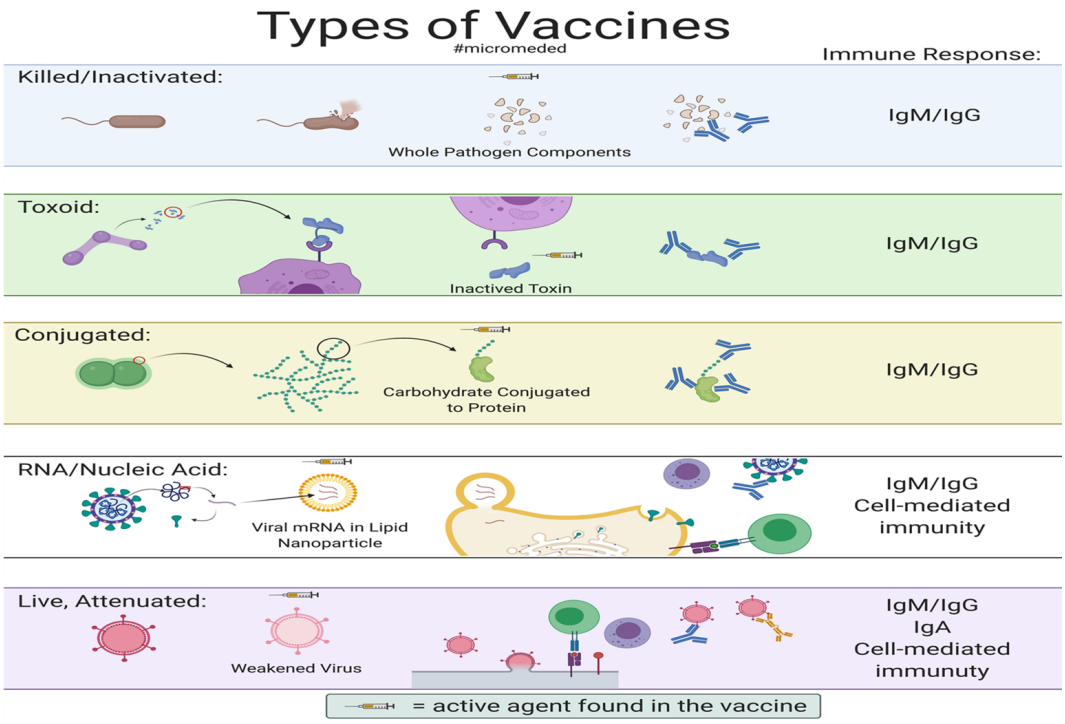
Examples: Tetanus and diphtheria.

5. The fifth point pertains to the mechanism of mRNA vaccines, which are designed to utilise genetic instructions, or mRNA, to instruct cells in the production of a harmless fragment of the pathogen. It is possible to trigger a robust immune response without the need to utilise the live virus.

Examples: Pfizer-BioNTech and Moderna vaccines have been developed for the prevention of the effects of the SARS-CoV-2 virus.

6. Viral vector vaccines are a form of immunological intervention that employ a harmless virus to deliver genetic material from the pathogen. The human body produces a protein that serves to trigger the immune system.

Examples include: Johnson & Johnson COVID-19 vaccine, Ebola vaccine.

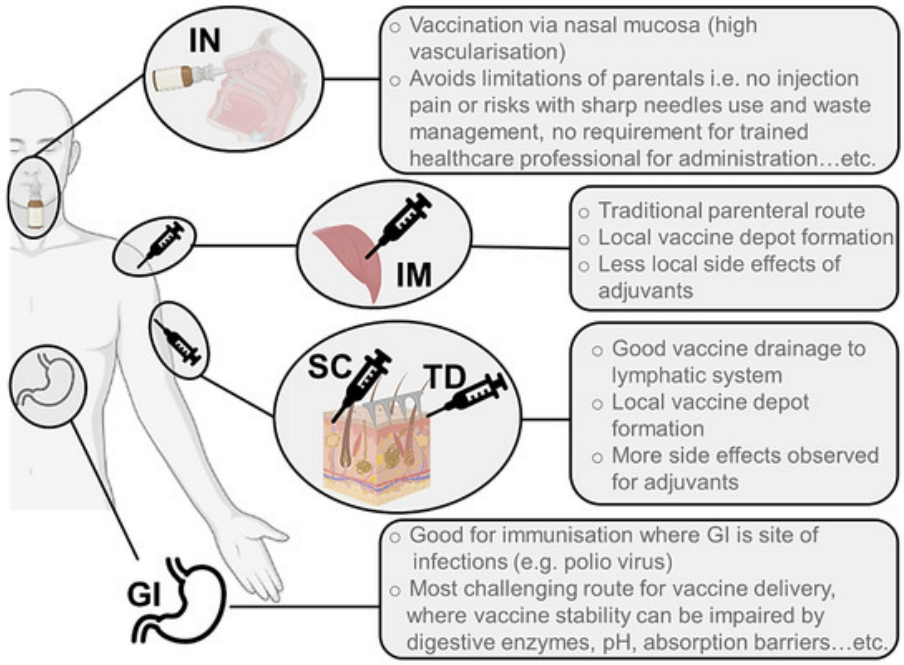


5.4. Route of Administration of Vaccines

The ideal vaccine is defined as a live attenuated vaccine administered via the mucosal route. This type of vaccine has been shown to stimulate the production of secretory IgA, thereby protecting individuals against natural infection.

Vaccines are typically administered via subcutaneous, intramuscular or intradermal injection. The selection of the route of administration was initially informed by empirical data derived from clinical practices and clinicobiological findings, with the objective of enhancing antibody levels.

Recent advances in the characterization of dendritic cells have demonstrated that the injection site (epidermis, superficial dermis, deep dermis or hypodermis) exerts a significant influence on the type of dendritic cells (Langerhans cells, dermal dendritic cells) involved, with the potential to generate distinct adaptive responses (antibodies, CD4 or CD8 T responses).



Route of Administration of Vaccines

5.5. Concept of Adjuvants

- In the context of vaccines, the concept of immunological adjuvants encompasses any agent introduced to enhance, extend, or fortify the immune response specific to the antigen targeted by the vaccine, when employed in conjunction with the adjuvant.
- The nature of these substances (i.e. mycobacteria, oils, aluminium salts, microparticles, squalanes, PRR ligands) and their mechanisms of action can vary significantly, resulting in variable efficacy.
- The adjuvant concentration is of pivotal significance. Indeed, it has been demonstrated that an increase in the immunogenicity of the vaccine is associated with an increase in the concentration of aluminium. However, a concentration that is excessively high can reduce this immunogenicity by covering and completely masking the vaccine antigens.

Hybridomas and Monoclonal Antibodies

1. Introduction

It is notable that the majority of antigens manifest multiple epitopes, thereby inducing the proliferation and differentiation of a diverse array of B cell clones. This, in turn, results in the production of heterogeneous antibodies in serum, each specific for a distinct epitope.

As previously discussed, the response of polyclonal antibodies following binding to the antigen localises it, thus facilitating its phagocytosis and degradation by complement. This process offers clear advantages to the organism. However, the heterogeneity of antibodies, which enhances immune protection in the living environment, frequently diminishes the effectiveness of antiserum in various laboratory applications. For the majority of research, diagnostic and therapeutic purposes, it is preferable to use monoclonal antibodies, which are derived from a single copy and are therefore specific to a single site. It has been established that the direct biochemical purification of a monoclonal antibody from a polyclonal antibody preparation is not a possibility.

2. Mechanism of action of AMCs

1. Blocking the action of specific molecules/receptors:

Monoclonal antibodies are utilized to selectively inhibit the activity of growth factors, cytokines, and other soluble mediators. This blocking is achieved through two mechanisms: direct binding to the factor itself, or to its receptor.

For instance, monoclonal antibodies have been shown to impede the interaction and activation of immune cells by obstructing the binding of ligands to receptors. This mechanism elucidates the therapeutic efficacy of specific monoclonal antibodies in autoimmune and inflammatory diseases. In addition, the binding of an antibody can also be sufficient to neutralize certain toxins and viruses.

2. Targeting specific cells:

In the field of oncology, monoclonal antibodies are utilized for the targeted elimination of tumor cells. Two mechanisms have been identified: Antibody-dependent cellular cytotoxicity (ADCC) and complement-dependent cytotoxicity (CDC) are two distinct mechanisms that can be investigated in relation to the study of cell death.

3. Functioning as signaling molecule:

The binding of membrane receptors by signaling monoclonal antibodies has been demonstrated to generate transmembrane signals that regulate tumor cell growth and apoptosis. An alternative mechanism involves the binding of antibodies to the receptor, effectively mimicking the natural ligand and thereby impeding the associated signaling functions.

The utilization of signaling antibodies has been observed to result in deregulation of targeted expression. This phenomenon has been linked to modifications in intracellular signaling.

3. Hybridoma Technology Step

The following is a step-by-step guide to hybridoma technology:

3.1. Immunization

Immunization involves the injection of a target antigen into a mammal, typically a mouse, to stimulate an immune response. It is possible for the antigen injection to be administered over a period of several weeks. The next step is to harvest the mouse's spleen in order to obtain B cells that produce the desired antibody.

3.2. Cell Fusion

In a professional setting, the process of fusing antibody-producing B cells with myeloma cells in a cell culture involves the use of Polyethylene Glycol (PEG) or electrofusion techniques. These methods are employed to facilitate the fusion of both cells' plasma membranes, resulting in the formation of a single hybridoma cell that contains two or more nuclei.

Method

Polyethylene Glycol (PEG) is a key agent in hybridoma technology, used to fuse antibody-producing B cells with myeloma cells to create hybridomas capable of producing monoclonal antibodies. PEG is added briefly to induce fusion. It acts by:

- Removing water from the cell surface.
- Destabilizing lipid bilayers.
- Promoting membrane coalescence.

3.3. Hybridoma Cell Growth

The process of cell fusion is a complex one, and it is only in less than 1% of cases that the initial cells fuse to form hybridoma cells. In the culture, unresponsive B cells cease to divide spontaneously, while the process of chemotherapy effectively eradicates the myeloma cells that have not yet undergone fusion. Researchers use a specialised medium called HAT (hypoxanthine-aminopterin-thymidine) to enable the selective proliferation of immortal monoclonal antibody-producing cell lines.

Method

HAT medium plays a critical role in the selection of hybridoma cells by exploiting differences in DNA synthesis pathways and enzyme deficiencies. The process of cell fusion is thus controlled to ensure the survival of only those hybridoma cells that have undergone the desired fusion.

The composition of HAT Medium:

Hypoxanthine: This purine base is utilized within the salvage pathway for the purpose of nucleotide synthesis.

Aminopterin: functions by obstructing the de novo pathway of DNA synthesis through the inhibition of dihydrofolate reductase.

Thymidine: It is evident that a pyrimidine nucleoside is utilized within the salvage pathway.

The mechanism of selection:

Following the fusion of B lymphocytes and myeloma cells, three distinct cell types are present.

Unfused myeloma cells: These cells have been engineered to lack HGPRT (hypoxanthine-guanine phosphoribosyltransferase), thus preventing them from utilizing the salvage pathway.

Unfused B cells: These cells possess a limited lifespan and are unable to proliferate within a culture setting.

Fused hybridoma cells: The combination of immortality from myeloma cells and functional salvage enzymes from B cells is a significant development in the field.

Aminopterin has been demonstrated to impede the de novo pathway, thereby compelling cells to depend on the salvage pathway for their survival. It has been established that the only cells capable of surviving and proliferating in HAT medium are hybridomas, due to the presence of the necessary enzymes (HGPRT and thymidine kinase).

3.4. Screening

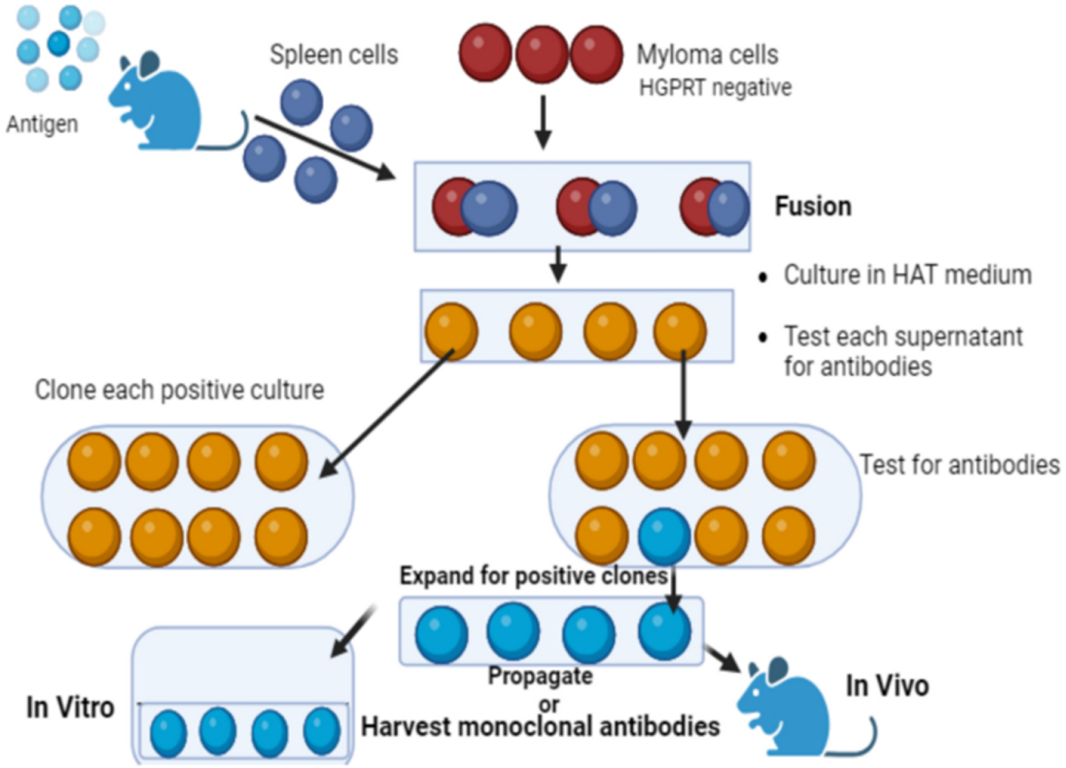
The monoclonal antibody of interest should be screened for using ELISA, indirect ELISA, western blot, flow cytometry, or immunoprecipitation-mass spectrometry.

3.5. Hybridoma Expansion

The objective of the Hybridoma Expansion Cloning process is to obtain a stable cell population of desired hybridoma cells, which are capable of producing monoclonal antibodies. There are two methods to achieve this.

The in vitro growth of hybrid cells in tissue culture.

The in vivo growth of hybridoma cells, following inoculation into a mouse's abdomen.



Hybridoma Technology Step

4. Classification of Monoclonal Antibodies

We can produce monoclonal antibodies (mAbs) using different methods, which results in four main types based on their origin:

Murine, chimeric, humanised and fully human.

4.1. Murine Monoclonal Antibodies

These antibodies are fully derived from mice. The variable regions of both the heavy and light chains are of mouse origin. Murine mAbs are named using the prefix “o-” or “-omab” at the end of the generic name.

Example: “rituximab” is a chimeric antibody that contains murine variable regions and is used to treat certain types of lymphoma and autoimmune diseases.

4.2. Chimeric Monoclonal Antibodies

Chimeric antibodies are constituted of human constant regions and mouse variable regions. It has been established that the antibody's effector functions are determined by the constant regions, while it is the variable regions which are responsible for antigen specificity. Chimeric mAbs are designated with the suffix "-ximab" appended to the generic name.

Example: infliximab is a chimeric antibody that targets tumour necrosis factor-alpha (TNF-α) and is utilised in the treatment of inflammatory diseases, including rheumatoid arthritis.

4.3. Humanised Monoclonal Antibodies

Humanised antibodies are characterised by a predominance of human sequence, with only a minor contribution of mouse sequence in the complementarity-determining regions (CDRs). The process of humanising the mAbs in question has been shown to reduce the immunogenicity that is typically associated with murine mAbs. Humanised monoclonal antibodies (mAbs) are designated with the suffix "-zumab" appended to the generic name.

Example: trastuzumab is a humanised antibody utilised in the treatment of HER2-positive breast cancer.

4.4. Fully Human Monoclonal Antibodies

Fully human antibodies are derived entirely from human sequences, both in the constant and variable regions. The objective of their design is twofold: firstly, to minimise immunogenicity, and secondly, to maximise compatibility with the human immune system. Fully human mAbs are designated with the suffix "-umab" appended to the generic name.

Example: adalimumab is a fully human antibody that targets TNF-α and is utilised in the treatment of various autoimmune diseases, including rheumatoid arthritis and psoriasis.

5. Hybridoma Benefits and Limitations

5.1. Hybridoma Benefits

1. The product's key benefits are its high specificity and affinity. Hybridoma-derived monoclonal antibodies (mAbs) exhibit precise antigen targeting, enabling accurate detection and neutralisation of specific epitopes.
2. A consistent and sustainable supply is essential for the smooth running of our business. Once established, hybridoma cell lines can be cultured indefinitely, ensuring a stable and reproducible source of identical antibodies.
3. In Vitro Production: This product reduces reliance on animal models for antibody generation, aligning with established ethical standards and the 3Rs (Replacement, Reduction, Refinement).

4. Versatile Applications:

- In the field of cancer immunotherapy, mAbs such as rituximab and trastuzumab are employed to target and combat tumours. They are also used to treat autoimmune diseases and infectious diseases, playing a crucial role in the management of these conditions.
- I am an expert in ELISA, immunohistochemistry, and rapid diagnostic tests.
- Vaccine Development: I am able to assist with epitope mapping and immune response monitoring.
- Targeted Drug Delivery: Antibody-drug conjugates (ADCs) employ mAbs to deliver cytotoxic agents directly to tumour cells.

5.2. Hybridoma Limitations

1. The process is time-consuming and requires a significant amount of resources, resulting in high costs.
2. There is an absence of stable myeloma cells for human antibody production.
3. It is not suitable for generating short peptides and fragment antigens.
4. There is a risk of contamination and poor cell viability.
5. There is a risk of virus contamination and disease transmission.

Control of The Immune Response

1. Introduction

T and B cells are key components of the adaptive immune system. Through their immunological roles, they build a complex network to achieve immune tolerance and maintain homeostasis in the body. This is achieved through central and peripheral tolerance mechanisms, both associated with advantages and disadvantages. For this reason, the immune system is tightly regulated, and their dysregulation can result in the subsequent initiation of various diseases. In this course, we will summarize the roles played by T cells and B cells within immune tolerance.

The immune response control involves a sequence of activation, amplification, and resolution phases that are meticulously regulated to ensure effective defence while preventing excessive inflammation or autoimmunity. In previous courses, we have covered all the steps except the final one. This course will provide the necessary learning.

2. Immune Tolerance

Immunological tolerance is defined as a complex series of immunological mechanisms which have the capacity to impair the normal immune system responses against self-antigens. These mechanisms involve a series of checkpoints, at which the immune system identifies and responds to the presence of autoreactivity. Thereafter, it endeavors to either eliminate or neutralize it.

Fundamental

The definition of Immunological tolerance varies according to the type of disease.

- In the context of transplantation, tolerance is defined as the acceptance of the graft without the need for ongoing immunosuppressive therapy.
- In the context of allergies, tolerance is characterised by an extended period of unresponsiveness to allergen challenges following desensitisation therapy.
- In the context of autoimmune disease, tolerance is defined as the long-term improvement of symptoms, alongside a reduction in the necessity for disease-modifying therapy.
- In the context of cancer, tolerance is defined as the ability of tumor cells to evade the immune system, leading to uncontrolled cell proliferation and metastasis.

2.1. Mechanisms of Immune Tolerance

The regulation in question is achieved through both central and peripheral immune mechanisms targeting T and B lymphocytes.

Central Tolerance: is defined as a process that eliminates autoreactive lymphocytes. This process occurs in either the bone marrow or the thymus. During central tolerance, autoreactive cells are efficiently eliminated by apoptosis.

Peripheral Tolerance : In certain instances, autoreactive T and B cells have been observed to penetrate the periphery, thus demonstrating peripheral tolerance. Unwanted peripheral immune activation is inhibited by peripheral tolerance mechanisms, including deletion and anergy.

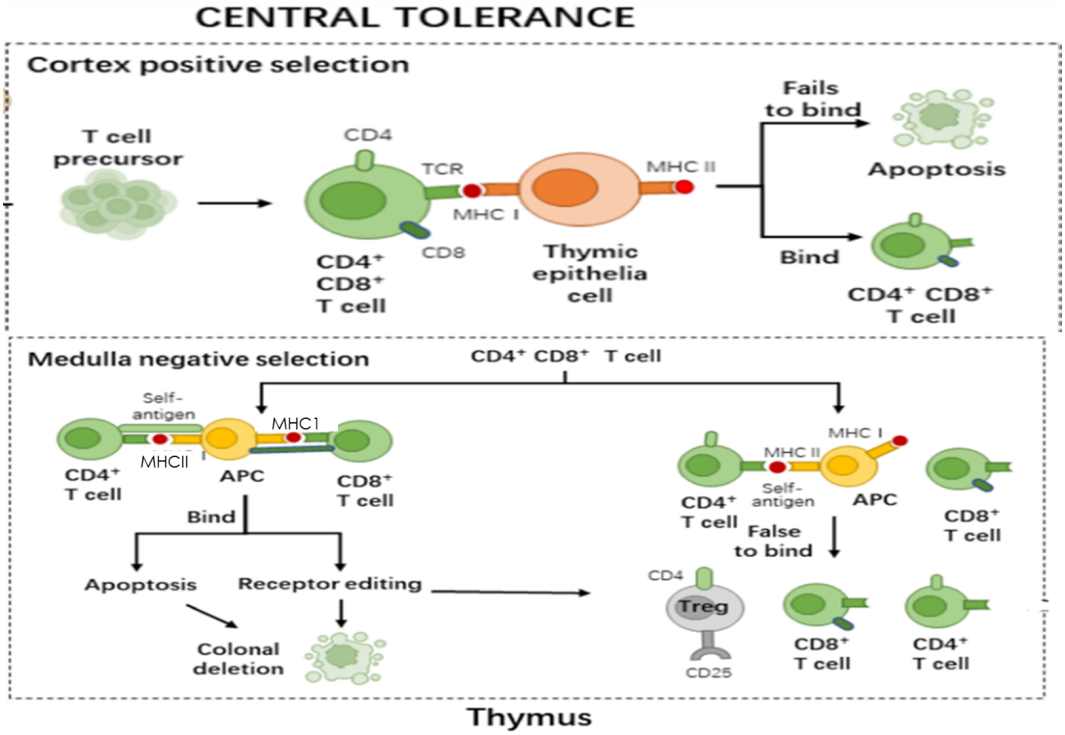
In the event of the peripheral tolerogenic balance being lost, a range of diseases may ensue.

3. T Cell Tolerance

There are central and peripheral T cell tolerance

3.1. Central Tolerance of T Cell

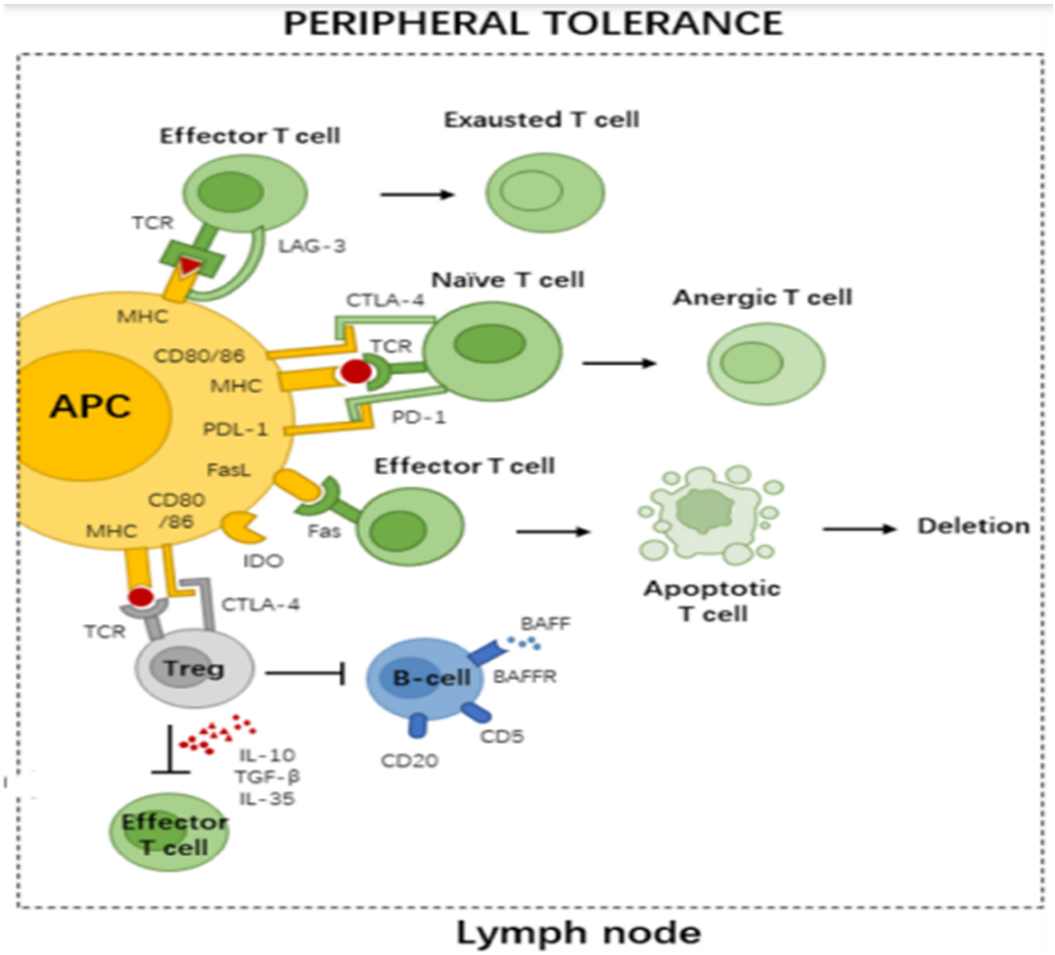
Hematopoietic lymphoid progenitors migrate to the cortex, where they are screened by thymic epithelial cells and develop into CD4+CD8+ double-positive (DP) thymocytes expressing the T-cell antigen receptor (TCR). Furthermore, DP cells have been observed to migrate to the medulla. Following screening for the capacity to bind to self-peptide-associated MHC-I or MHC-II molecules on the antigen-presenting cell (APC) surface, DP cells undergo a developmental process that results in the formation of CD4+CD8+ DP thymocytes that express the TCR.



Central Tolerance of T Cells

3.2. Peripheral Tolerance of T Cell

Peripheral tolerance of T cells can be considered a safety net that ensures escaped autoreactive T cells do not result in the onset of autoimmune disease. The fundamental mechanisms by which this process occurs are the elimination, deletion and suppression of energy by Tregs.



Peripheral Tolerance of T Cell

3.3. Tolerance Mechanisms of T cells

These described below:

a) Exhaustion

T cell exhaustion is an important mechanism of tolerance in certain immunological situations. Phenotypically, exhausted T cells (TEx) display reduced functional and proliferative capacities, as well as elevated levels of inhibitory receptor expression. This includes Programmed Cell Death Protein 1 (PD-1), Cytotoxic T-Lymphocyte-Associated Protein 4 (CTLA-4) and Lymphocyte Activation Gene 3 (LAG-3), among others. So, the exhausted phenotype may describe cells that are more resistant to activation, not that they cannot be activated at all.

b) Anergy

T cell anergy is defined by the state of hyporesponsiveness of naïve T cells to TCR stimuli following antigen exposure. Anergy is characterised by the activation of intracellular pathways initiated by the interaction between the TCR and pMHC in the absence of costimulation.

T cell anergy is regarded as a peripheral tolerance mechanism. The term "clonal anergy" refers to a state in which T cells do not proliferate, yet they still secrete a modest amount of effector cytokines, thereby exhibiting a state of functional impairment. The maintenance of its function is achieved without the need for continuous antigen exposure, and this form of T cell anergy can be reversed by interleukin (IL)-2.

Anergy has been demonstrated to play a pivotal role in the modulation of the immune system, preventing it from attacking healthy tissues. In the event of low-affinity TCR interaction with pMHC, anergy can be induced in CD4+ T cells, resulting in a lack of capacity for proliferation or IL-2 production.

Furthermore, the alteration of the timing of the TCR-pMHC interaction has been demonstrated to result in CD4+ T cell anergy, for example, a short-duration TCR-pMHC interaction or low TCR signaling.

c) Deletion

Deletion in tolerance is the process by which self-reactive or excess lymphocytes are apoptotic removed, with this being mediated by death receptor pathways (Fas/FasL) and suppression of survival signals (such as BCL-2). It is central to both thymic negative selection and peripheral immune regulation.

d) Regulation: Tregs

Regulation is an important mechanism of T cell tolerance, primarily mediated by Tregs. These cells are characterised by the expression of CD25 and CD4, in addition to the specific expression of the transcription factor Foxp3.

Tregs have been observed to inhibit the function of both autoreactive T cells that have evaded central deletion and T cells that cross-react with self-antigens as a consequence of molecular similarity with microbial antigens.

The loss of Treg function can result in a range of systemic immune diseases or infections, including type I diabetes, allergies, and inflammatory bowel disease.

The classification of regulatory T cells (Tregs) can be divided into various subsets based on their developmental pathway.

- The thymus-derived Tregs (tTregs).
- Peripherally-derived (pTregs) are a subset of Tregs that are located in the periphery.
- In vitro-induced Tregs (iTregs) are a subset of Tregs that are induced in a laboratory setting.

The specific TCR of pTreg is capable of recognising both infectious and harmless microbial antigens, a process that is of significant importance to the establishment of mucosal tolerance.

The immunosuppressive mechanisms that are induced by Tregs can be achieved through the actions of humoral factors, such as anti-inflammatory cytokines (IL-2, IL-10, transforming growth factor-β [TGF-β], and IL-35), or secreted/intracellular molecules (granzyme).

3.4. Inhibitory Molecules

a) Interleukin-10

IL-10 is a significant anti-inflammatory cytokine that plays a crucial role in regulating immune responses and maintaining immune homeostasis. However, it has been observed that IL-10 can, in certain circumstances, result in inflammation and tissue damage.

The production of this molecule is initiated by various cells of the immune system, including T cells, B cells, macrophages, and DCs. The molecule exerts its function by means of several mechanisms, including the inhibition of T cell proliferation and activation, the acceleration of depletion, the suppression of the antigen-presenting function of APC cells, and the induction of iTreg cells. In addition, it redirects the differentiation of naïve T cells to a regulatory phenotype, leading to the development of Treg and the promotion of immune tolerance. IL-10 can convert naïve T cells into Treg cells and IL-10-secreting type-1 regulatory CD4+ T cells (Tr1). In addition, they can also suppress immunogenic CD4+T cells.

b) Transforming Growth Factor-β

TGF-β is a multifunctional cytokine that plays a pivotal role in the regulation of immune responses (can act as both **anti-inflammatory** and **pro-inflammatory**,), including T cell tolerance.

The production of this molecule is initiated by a variety of immune cells, including Tregs, DCs, and macrophages.

It has been demonstrated that this agent exerts its effects on T cells and APCs, thereby inhibiting their activation and differentiation. It thus plays a pivotal role in the induction and maintenance of T cell tolerance.

Furthermore, TGF-β has been demonstrated to promote the differentiation of Th17 cells to Tregs. The function and survival of APCs is inhibited by transforming growth factor-beta (TGF-β), which consequently prevents the activation of self-reactive T cells and promotes their deletion or anergy in the thymus and peripheral tissues.

c) Interleukin-35

IL-35 is a member of the IL-12 family of cytokines, which are potent anti-inflammatory agents.

The production of this molecule is primarily undertaken by Treg, endothelial cells, smooth muscle cells, and monocytes.

IL-35 has been shown to play a protective role in autoimmune diseases, transplant rejection, and allergic diseases.

Research has demonstrated that the substance in question can inhibit the activity of autoreactive T cells and promote the activity of Treg cells. This, in turn, has been shown to suppress the activity of pro-inflammatory immune cells and to promote the production of anti-inflammatory cytokines. Furthermore, IL-35 has been shown to inhibit apoptosis, adhesion, migration, and activation of eosinophils.

4. B Cell Tolerance

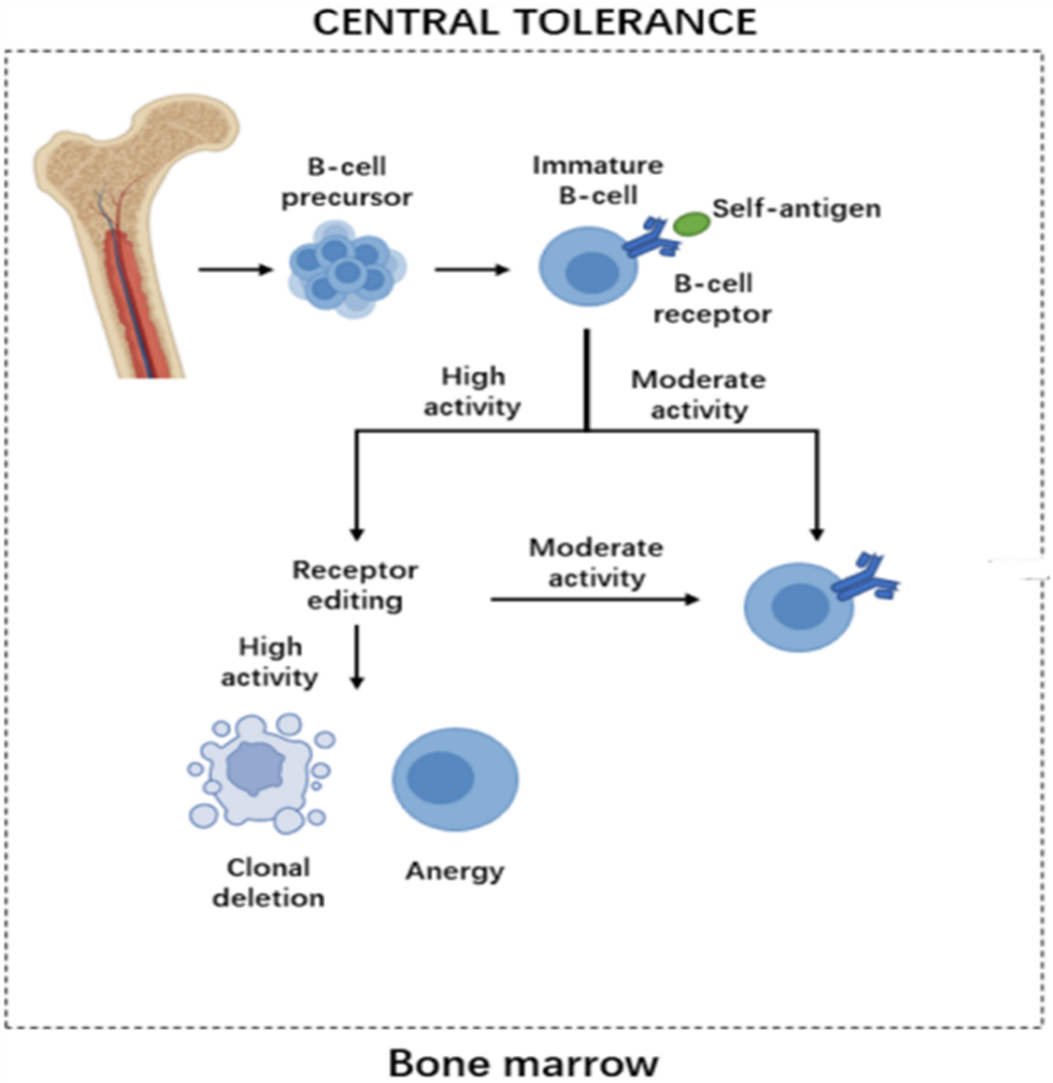
B cells are renowned for their ability to differentiate into antibody-secreting plasma cells, which protect against invading pathogens.

B cells also have significant antigen-presenting capacity, a field that has received less attention than other professional APCs, such as DCs.

4.1. Central Tolerance of B Cell

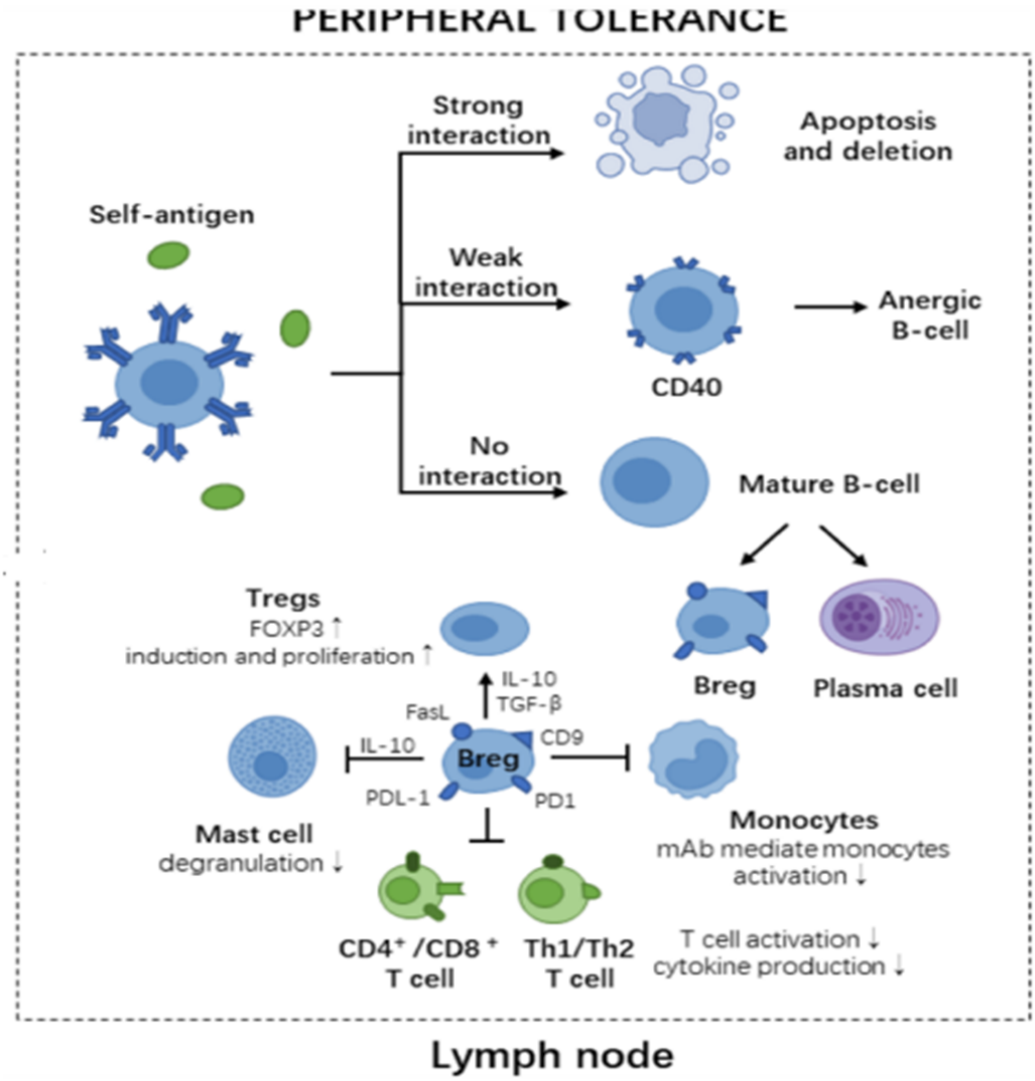
The process by which undifferentiated B cells become tolerant in the bone marrow is known as central tolerance. The central tolerance process is primarily achieved through deletion, anergy, and BCR editing of B cells.

When there is a strong binding of a self-antigen to the BCR, it results in the clonal deletion of the B cell. However, if the self-antigen has a lower binding strength to the BCR, this can lead to the inactivation of the B cell without deletion, which is known as 'anergy.'



Central Tolerance of B Cell

4.2. Peripheral Tolerance of B Cell



Peripheral Tolerance of B Cell

a) Regulatory B (Breg)

Regulatory B cells (Bregs) play a key role in maintaining peripheral tolerance, limiting persistent immune responses, and restoring immune balance. In addition, they have a key role in the suppression of diseases associated with exacerbated inflammatory responses in autoimmunity and persistent transplant rejection, as well as infections, allergies, cancer, and chronic metabolic diseases. At present, the isolation of Breg cells in a laboratory setting is challenging, where the capacity to secrete IL-10 is a primary factor in their identification. Bregs promote tolerance through their secretion of inhibitory cytokines. These cytokines traditionally include IL-10 and, more recently, IL-35 and TGF-β.

b) Interleukin-10

IL-10 is responsible for the conversion of naïve T cells into Treg cells and other functions. In people with immune diseases, these functions are dysregulated due to a reduced proportion of IL-10+ Breg cells and impaired function. However, these functions are enhanced in patients with chronic viral disease. Furthermore, IL-10 Breg cells have been shown to play a crucial role in promoting tolerance to the foetus during pregnancy in both mice and humans. This involves the generation of tolerogenic DCs and Tregs, as well as the reduction of Th17 cells, which have been demonstrated to be essential for maintaining homeostasis and ensuring successful pregnancy outcomes.

c) Transforming growth factor-β

It is evident that the primary source of TGF-β is Treg cells; however, there is also evidence to suggest that Breg cells are capable of producing this cytokine. The production of TGF-β by Breg has been shown to induce naïve CD4+ T cells to differentiate into Treg, thereby limiting T cell-related immune responses. TGF-β+ Breg cells have been identified as pivotal modulators in the suppression of Th2-driven inflammation, through the influence of Tregs. In addition, TGF-β+ Breg cells have been shown to induce immature DCs to differentiate into tolerogenic DCs, which in turn reduces their antigen-presentation capacity, consequently limiting inflammatory responses.

d) Interleukin-35

IL-35 can induce the conversion of B cells into the Breg subsets. These highlight the importance of IL-35 and its potential use as a therapeutic target for multiple diseases.Studies in human have demonstrated that IL-35+ Bregs play a key role in promoting tumor growth with their levels being upregulated in late-stage gastric cancer and pancreatic cancer.

Development of The Immune System

1. Introduction

Over the last two decades, there have been major advances in our understanding of the immune system at different stages of life. Numerous research tools have provided deeper insight into phenomena that were previously poorly understood. The continuous growth in the field of functional and molecular research into the immune system will allow us to gain a deeper understanding of the interactions between mother and foetus in the womb. This research will also help us to understand how maternal microbiota interact with the foetus and newborn, and how immune competence is acquired in both health and disease. In addition to its development in older people, who have lost a significant part of their immune system functions.

2. Development of the Fetal Immune System

2.1. The Yolk Sac

The yolk sac constitutes an early extra-embryonic structure that plays a crucial role in embryonic development, especially in the first trimester. The formation of the yolk sac occurs from the endoderm of the embryonic disc, with the process being surrounded by extra-embryonic mesoderm.

The mesodermal mesenchymal cells undergo a process of differentiation, resulting in the formation of hematopoietic cells. By the first days of gestation, the yolk sac is responsible for the production of nascent erythrocytes, which represent the predominant hematopoietic output at this stage. In addition, primitive macrophages and megakaryocytes are occasionally produced. Since the fourth week of gestation, haematopoietic stem cell (HSC)-like progenitors, natural killer (NK) cell progenitors, erythroid cells, mast cells (MCs), and innate lymphoid cell (ILC) progenitors could be observed in the yolk sac. The fetal yolk sac has also been identified as one of the sources of macrophages that subsequently give rise to the macrophages in the brain, liver, lung, and epidermis. Concurrently, at the 6-week gestational stage, the embryonic pancreas is populated by macrophages.

2.2. The Liver Development

The first production of dendritic cells (DCs) was recorded among the HSC-dependent macrophages, monocytes, and DCs in the fetal liver at 6 weeks of gestation, during the developmental period of the human embryo. which in turn stimulates T-cell differentiation, propagation, and activation. Consequently, the pivotal functions of DCs in sustaining the tolerance of human fetuses are evident.

The initial appearance of B cell lineage as precursors and mature B cells is observed in the foetus's liver from 7 and 9 weeks of gestation, respectively. Consequently, prior to birth, the liver assumes a pivotal function in the process of haematopoietic differentiation and the proliferation of HSCs.

2.3. The Bone Marrow Development

The development of bone marrow is closely associated with the process of blood vessel invasion of cartilaginous bone and subsequent bone ossification. The formation of BM is randomly marked at 8 weeks of gestation, and it is seeded with HSCs.With the growth, the BM develops as the key source of B cells, which become abundantly enriched in the spleen at mid-gestation. Intestinal B cells encompass both follicular and transitional B cells, which are formed from second-trimester foetuses to infants.

2.4. Spleen Development

The spleen manifests at 6 weeks of gestation. During the second trimester, the body produces both red and white blood cells. The spleen has been demonstrated to initiate T-cell-dependent immunity with the assistance of dendritic cells. To date, the developmental process of splenic DC in fetuses has not been the subject of investigation. The circulating monocytes have been shown to give rise exclusively to mucosal DC, rather than splenic DC.

2.5. Thymus Development

Early lymphoid progenitors migrate into the thymus from the fetal liver at 8 weeks of gestation, where the development of naive T cells occurs. Early thymic progenitors undergo a process of differentiation, ultimately becoming naive T cells, and subsequently migrate to other tissues. The development of the thymus and the production of circulating T cells are observed to occur at 10–11 weeks of gestation. A regulatory T (Treg) cell is generated from the naive T cells of the foetus, which in turn suppress the multiplication and secretion of cytokines from other foetal T cells. Memory T cells have been observed to respond to foreign antigens, which are identified in the fetal intestine, while intestinal CD4+ T cells have been shown to play a part in the expression of TNF-α.

2.6. Lymph Node Development

The initial lymph node originates from mesenchymal cells that condense at the base of the lymph sac, a process that occurs between 8–11 weeks of gestation. It is important to note the significant functions of lymph nodes. These include immune surveillance for pathogens and antigens, and the boosting of immune responses through their capture within the lymph nodes.

2.7. T Lymphocyte Development

The stem cells from which T cells arise in the thymus, known as thymic progenitor cells, can be seen in the fetal liver from the seventh week of pregnancy. By the tenth week of pregnancy, the CD3 membrane is clearly distinguishable.

Thymus development commences in the eighth week, with the initial colonization of the periphery by primary T cells and the clear appearance of regulatory T cells (Treg) in weeks 12-14. Regulatory T cells have been shown to be capable of suppressing the activation, proliferation, and effector functions of a wide range of immune cells. The presence of self and maternal antigens leads to rapid T cell growth, suggesting that the immune system is actively tolerant of the developing foetus. Therefore, T cells in the foetus are strongly suppressed by Tregs, suggesting a complex regulatory loop in foetal immune responses.

2.8. B Lymphocyte Development

B cells were primarily detected in the fetal liver at week 8 and in the spleen at weeks 13–23 of gestation, while CD5+ B cells, indicative of the pleural and peritoneal cavities, appeared at week 15 of gestation. Significant expression of the M chain, surface IgM, IgD, and CD20 has been identified in the fetal liver at 8-13 weeks of gestation. B cells are present in the fetal peripheral circulation at 12 weeks of gestation and are found in the bone marrow at 16-20 weeks of gestation. The cells were found to be positive for

CD19, CD20, CD21, CD22, HLA-DR, IgM, and IgD. In comparison to adults, a higher proportion of CD5+ B cells was identified in the foetus, which are believed to represent the initial line of defense in newborns.

2.9. Immunoglobulin Production

The spleen begins producing large amounts of IgG and IgM early on, at 10 weeks of pregnancy. Serum IgG levels begin to rise from week 5.5 to week 22 of pregnancy, then rise significantly until delivery. IgG is transferred from the placenta throughout pregnancy, with a peak increase in regulation from week 32 of pregnancy. IgE production commences at week 11 of pregnancy in the fetal liver and lungs, and at week 21 in the spleen.

3. Immune System Mechanisms in the Neonatal Period

Divided in innate and adoptive immunity

3.1. Innate Immune System Mechanisms in the Neonatal Period

The innate immune system in newborns consists of granulocytes (mainly neutrophils), antigen-presenting cells, natural killer cells, and γδ T cells. These cells are immediately ready to act effectively against a wide range of pathogens. Newborns are reliant on their innate immune response for protection against infection due to limited exposure to antigens in the intrauterine environment and the immaturity of the adaptive immune response.

Neutrophils are the main component of the innate immune system and are responsible for destroying pathogens during infection. Neutrophils in newborns are quantitatively and qualitatively deficient compared to adults. Decreased cell surface expression of TLR-4 and L-selectin has been demonstrated to reduce the migration of cells to sites of infection by 50%.

The components of the complement system are expressed during pregnancy and in early childhood, reaching adult levels in the first 12-18 months of life. Newborns express C3 and C4 fractions and total hemolytic complement.

NK cell counts are higher in newborns than in adults, with increased expression of the inhibitory receptor. However, neonatal NK cells typically exhibit a diminished functional capacity in comparison to adult NK cells.

Neonatal γδ T cells generally display a low capacity for proliferation and production of cytokines when stimulated. Furthermore, they produce lower proportions of perforin and granzyme.

3.2. Adaptive Immune System Mechanisms in the Neonatal Period

Following birth, maternal antibodies are known to decline. Research on the half-life of total serum IgG has produced variable results, but on average it ranges from 24 to 30 days.Total IgG concentrations begin to rise around the fourth month of life, marking the point when the child's IgG production exceeds the maternal IgG consumption. However, it should be noted that the IgG concentrations of children will not reach those of adults until approximately eight years of age.

a) Breastfeeding

Breastfed infants have been shown to have a 47% reduction in the risk of death from infectious diseases, 63% in the risk of death from acute diarrhoeal disease, and 57% in the risk of death from hospitalisation due to respiratory diseases.The immune system is influenced by several components present in breast milk. The following are of particular interest: immunoglobulins, human milk oligosaccharides, lactose, lactalbumin, long-chain polyunsaturated fatty acids, vitamins (A, E, C), interleukins, lactoferrin, lysozyme, lactoperoxidase, TNF-β, food antigens from the maternal diet,

soluble CD14 receptors, TLR2, tumor necrosis factor (TNF-α), defense cells (macrophages, neutrophils), and probiotics. While all classes of immunoglobulins are present in breast milk, IgA is widely regarded as the most significant.

Colostrum is the initial milk produced by the nursing mother and offered to the newborn. The substance is produced during the initial stages of life, with low levels being produced in the first few days. It contains a high concentration of immunoglobulins, especially IgAs, and trophic factors for the gastrointestinal tract, such as TGF-β, in addition to proteins. This differentiated composition is essential for ensuring the continuity of the transfer of passive maternal immunity to the newborn.

Over time, the milk changes, becoming mature milk, which includes changes in the factors that contribute to mucosal immunity. The specific alterations in the gut microbiota of mothers can vary, influenced by health, microbiota, and maternal diet, as well as by genetic and environmental factors.

b) The Microbiota of Breast Milk

During the final stages of pregnancy and the immediate postnatal period, there is a significant increase in the translocation of microorganisms from the oral cavity and gastrointestinal tract. Breast milk contains hundreds of different bacterial species, with approximately 1,000 colony-forming units per millilitre. It is a well-established fact that the most common species found in breast milk are Streptococcus and Staphylococcus, along with Bifidobacterium, Lactobacillus, Propionibacterium, Enterococcus, and members of the Enterobacteriaceae family.

c) Exosomes

Extracellular vesicles (EVs) or exosomes, recently identified as components of breast milk, also impact the immune system of young infants. The secretion of EVs by the mammary gland occurs in the form of fat envelopes, which carry various components involved in cell signaling.

These components include messenger RNA, micro-RNAs, cytosolic and membrane proteins. Breast milk exosome research has revealed that these particles have a number of biological functions, including roles in cell maintenance, DNA synthesis, glucose metabolism and immunological processes.

4. Immunological Ageing

The well-established theory defines ageing as an accumulation of errors. It is important to note that the gradual build-up of damage caused by routine errors will eventually have a negative impact on the ability to work effectively. Over time, this will lead to a decline in performance. The immune system's components experience gradual deterioration due to daily stress. Consequently, immunosenescence can exacerbate the adverse effects of the ageing process by introducing these errors.The innate immune system is responsible for combating bacteria and viruses. It does this by producing reactive oxygen and nitrogen species, which are produced by a process called the respiratory burst. Absent organelle barriers and antioxidants, this could prove detrimental to the host. It is an inevitable consequence of the ageing process that there is a reduction in the respiratory burst. The harmful factors that are produced during dysfunctional respiratory bursts can directly cause aging.

4.1. Different Mechanisms observed during Ageing

- Thymus involution
- Dominance of a different cytokine profile that causes chronic inflammation
- Low rate of programmed T cell death
- Reduction in naïve T cells
- The presence of higher number of memory cells are of the implicated mechanisms
- Increasing immunogenetic diversity of cells as the organism ages is another culprit as well

- Accumulated DNA damages in nuclei of immune cells, rescheduling of metabolism and inducing cell-specific sustained distress signals contribute to long-standing immunogenic diversity
- Throughout the aging process, the capability of T and B cells in mediating immune response decreases while the frequency of autoreactive cells increases.
- When the immune system fails to preserve certain checkpoints, tolerance mechanisms will not be successful and age-related clinical problems, including autoimmunity, will arise.

4.2. Immune Cells in Ageing Persons

Resymed in the table below:

cells	function
Monocytes	Increased abundance in the blood Increased abundance of non-classical CD14+CD16+ cells in the blood
DCs	Decreased abundance of pDCs in the blood
B cells	Decreased abundance of B1 cells (CD19+CD20+CD27+CD38low/midCD43+) in the blood Decreased abundance of the ZBTB32+ (CD27+CD38low/mid) subset in the blood
MAIT	cells Decreased abundance in the blood
γδ T cells	Decreased abundance in the blood Decreased abundance of Vδ2+Vγ9+ cells in the blood Decreased abundance of SOX4+ cells in the blood
CD4+ T cells	Decreased abundance of naive cells in the blood Increased abundance of TEM cells in the blood Decreased abundance of recent thymic emigrants in the blood Decreased abundance of an interferon-activated subset in the blood Increased abundance of the cytotoxic subset in the blood (supercentenarians)
CD8+ T cells	Decreased abundance of naive cells in the blood Increased abundance of TEM cells in the blood Increased abundance of the GZMK+(CD28+CD57–) subset of TEM cells in the blood Increased abundance of the CD57+ subset in the blood

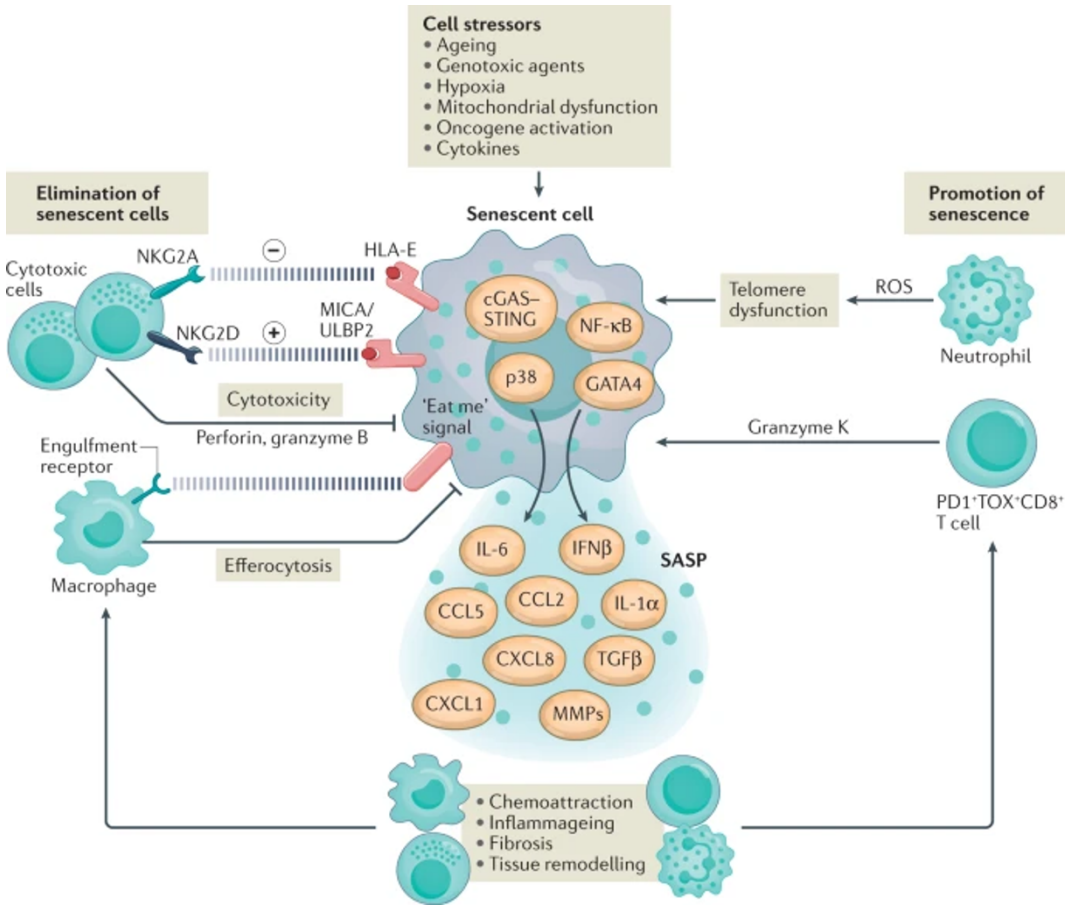
4.3. Role of Non-Immune Cells (stromal cells) in Immune Ageing

It is important to note that a variety of mesenchymal and epithelial cells are capable of performing immune functions. This is due to the fact that they are equipped to respond to pathogens and participate in immune homeostasis. Fibroblasts are vital structural components of most tissues and have been extensively researched in the context of disease and ageing. Human skin fibroblasts displayed elevated levels of genes associated with low-grade inflammation in specific groups of aged fibroblasts. Additionally, there was a decrease in communication between fibroblasts and other cell types in aged skin.

Aging has been shown to cause significant alterations to the inflammatory transcriptional profiles of endothelial cells in different tissues. For example, the altered inflammation and cytokine signalling pathways in endothelial cells are associated with neurodegenerative diseases. It is important to note that communication between endothelial cells and various types of immune cells (including macrophages and T cells) changes significantly in aged tissues, including the liver and adipose tissue.

4.4. Senescent Cell Contribution to Inflammageing

In aging, senescent cells gradually accumulate throughout the body in their final stage of differentiation, often occurring in damaged or stressed cells, leading to permanent withdrawal from the cell cycle and transformation into a distinctive senescence. This secretome involves the secretion of numerous chemokines, cytokines, and growth factors and contributes to low-grade systemic inflammation in aging. Interestingly, senescent cells include various cell types that are concentrated in the liver lining and the proximal and distal tubule epithelium in the kidneys. Elimination of these senescent cells reduces immune infiltration in a model of metabolic liver disease.



Senescent cell contribution to inflammageing

Anti-Infectious Immunity

1. Introduction

In the case of infection by various pathogens such as bacteria, viruses, fungi, and parasites, anti-infective immunity is the body's defense system, including innate immunity and adaptive immunity. They work together to ensure a coordinated response to infection, including recognizing and eliminating pathogens and preventing reinfection. The efficiency of anti-infective immunity is critical for survival in a microbe-rich environment, with research continuing to explore its therapeutic potential in vaccines and treatments for infectious diseases.

2. Strategies of Pathogens to Escape the Immune System

It is evident that a significant number of pathogens have the capacity to reduce their antigenicity through various mechanisms.

- The cells are able to grow within their host cells and shed their membrane antigens.
- The product's surface replicates that of the host cells.
- Some pathogens have the ability to suppress the immune response selectively or regulate it in such a way that a branch of the immune system is activated, which is ineffective against the pathogen.
- There is ongoing variation in surface antigens.

3. Viral Infections

3.1. Innate Immune Response

The innate immune response to viral infection depends primarily on the stimulation of type I interferons (IFN-α and IFN-β) and the activation of natural killer cells. Double-stranded RNA produced during the viral life cycle has been found to stimulate the expression of IFN-α and IFN-β by infected cells, as well as macrophages, monocytes, and fibroblasts. It is well established that the activity of natural killer cells is significantly boosted by IL-12, a cytokine that is produced during the early stages of the body's response to viral infection.

3.2. Adoptive Immune Response

Response type	Effector molecule or cell	Activity
Humoral	Antibody (especially, secretory IgA)	Blocks binding of virus to host cells, thus preventing infection or reinfection
	IgG, IgM, and IgA antibody	Blocks fusion of viral envelope with host-cells plasma membrane
	IgG and IgM antibody	Enhances phagocytosis of viral particles (opsonization)
	IgM antibody	Agglutinates viral particles
	Complement activated by IgG or IgM antibody	Mediates opsonization by C3b and lysis of enveloped viral particles by membrane-attack complex
Cell-mediated	IFN-γ secreted by T_H or T_C cells	Has direct antiviral activity
	Cytotoxic T lymphocytes (CTLs)	Kill virus-infected self-cells
	NK cells and macrophages	Kill virus-infected cells by antibody-dependent cell-mediated cytotoxicity (ADCC)

Adoptive immune in viral infection

4. Bacterial Infections

There are four primary steps in bacterial infection:

1. Attachment to Host Cells: Bacteria use specialized surface structures such as pili (fimbriae), adhesins, or glycoproteins to bind to receptors on host cell membranes.

2. Proliferation (Colonization and Growth): Once attached, bacteria begin to multiply locally. The immune system tries to limit growth via phagocytosis, complement activation, and antimicrobial peptides.

3. Invasion of Host Tissue: Some bacteria secrete enzymes (e.g. hyaluronidase, collagenase) that degrade the extracellular matrix, allowing them to penetrate deeper tissues.

Intracellular invasion: Certain pathogens (e.g. Salmonella, Listeria) have the ability to enter host cells, evade immune surveillance, and spread.

4. Toxin-Induced Damage to Host Cells: Toxins have the capacity to kill cells, impair immune function and cause widespread tissue damage.

Exotoxins are a type of toxin that are produced by some types of bacteria. They are proteins that are secreted, and their function is to directly damage host cells or disrupt physiological processes. For instance: Clostridium botulinum is responsible for the production of botulinum toxin, which interferes with the release of neurotransmitters.

Endotoxins: Lipopolysaccharides (LPS) from Gram-negative bacteria have been shown to trigger strong inflammatory responses, which can sometimes lead to septic shock.

Infection process	Host defense	Bacterial evasion mechanisms
Attachment to host cells	Blockage of attachment by secretory IgA antibodies	Secretion of proteases that cleave secretory IgA dimers (*Neisseria meningitidis, N. gonorrhoeae, Haemophilus influenzae*)
		Antigenic variation in attachment structures (pili of *N. gonorrhoeae*)
Proliferation	Phagocytosis (Ab- and C3b-mediated opsonization)	Production of surface structures (polysaccharide capsule, M protein, fibrin coat) that inhibit phagocytic cells
		Mechanisms for surviving within phagocytic cells
		Induction of apoptosis in macrophages (*Shigella flexneri*)
	Complement-mediated lysis and localized inflammatory response	Generalized resistance of gram-positive bacteria to complement-mediated lysis
		Insertion of membrane-attack complex prevented by long side chain in cell-wall LPS (some gram-negative bacteria)
Invasion of host tissues	Ab-mediated agglutination	Secretion of elastase that inactivates C3a and C5a (*Pseudomonas*)
Toxin-induced damage to host cells	Neturalization of toxin by antibody	Secretion of hyaluronidase, which enhances bacterial invasiveness

Steps of Bacterial Infection

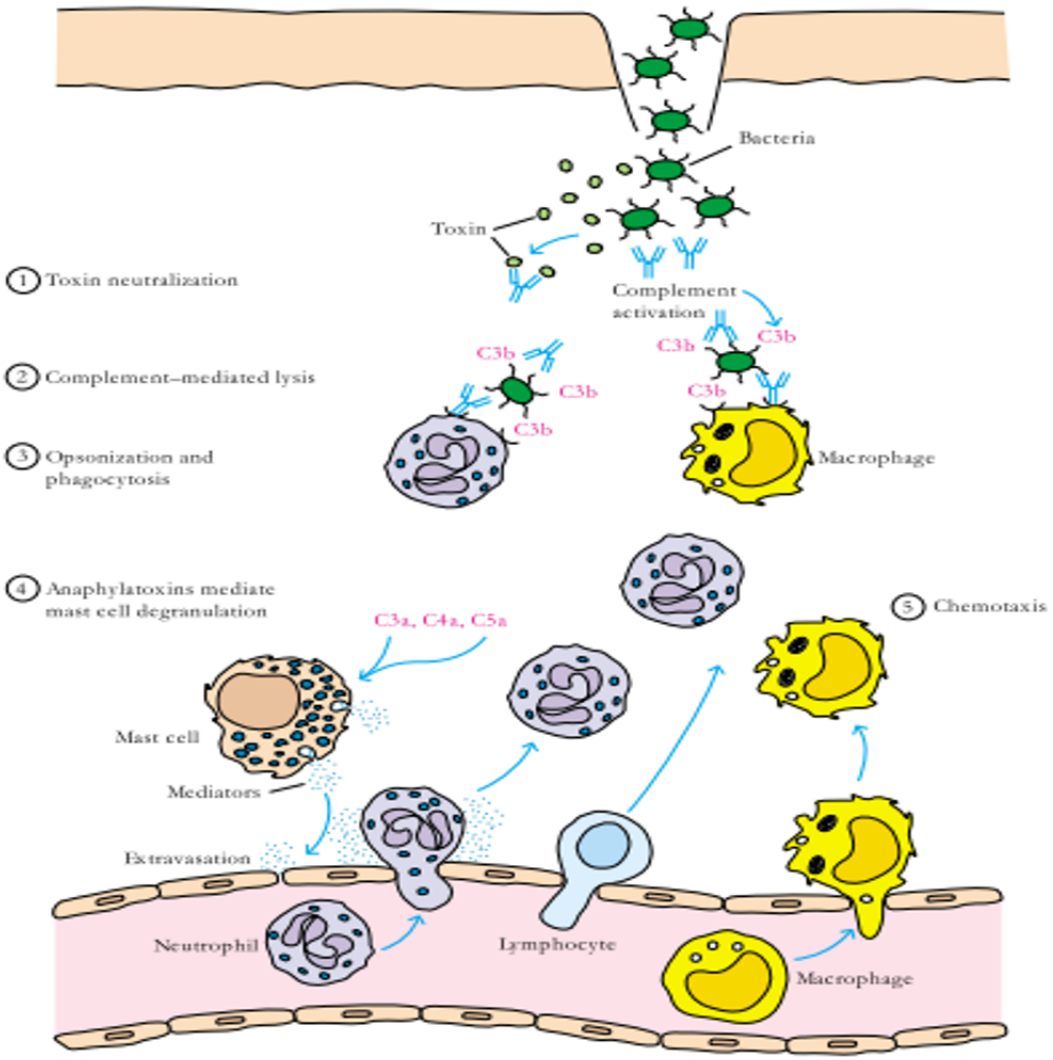
4.1. Immune Responses to Extracellular and Intracellular Bacteria

The humoral immune response is the primary protective response against extracellular bacteria. These antibodies protect the host from invading organisms, including removing bacteria and neutralizing bacterial toxins. Antibodies have been shown to activate the C3b component of complement, which acts as an opsonin to increase phagocytosis and thus remove bacteria. In the case of some bacteria, particularly Gram-negative organisms, complement activation can directly lead to the lysis of the organism.

Activation of the complement system by antibodies leads to the local production of effective immune molecules that help develop an amplified and more effective inflammatory response. Research indicates that other complement cleavage products act as chemotactic agents for neutrophils and macrophages, causing phagocytic cells to accumulate at the site of injury.

The antibody to the bacterial toxin can also bind to the toxin and neutralize it; it is then removed by phagocytes in the same way that any other antigen-antibody complex is removed.

Although innate immunity is not especially effective against intracellular bacterial pathogens, it has been demonstrated that intracellular bacteria can activate NK cells. These cells, in turn, provide an early defense against such bacteria. Intracellular bacterial infections have been observed to induce a cell-mediated immune response, specifically of the delayed-type hypersensitivity variety. In this response, the secretion of cytokines by CD4+ T cells is of significance, with IFN-γ being particularly noteworthy in its capacity to effectively activate macrophages, thus facilitating the more efficient elimination of ingested pathogens.



Bacterial Infections

5. Fungi Infection

The principal mediators of innate immunity against fungi are neutrophils and macrophages. Patients suffering from neutropenia are acutely vulnerable to opportunistic fungal infections. It is hypothesized that the release of fungicidal substances, such as reactive oxygen intermediates and lysosomal enzymes, and the subsequent phagocytosis of fungi by neutrophils leads to the intracellular killing of the latter. Virulent strains of Cryptococcus neoformans have been observed to inhibit the production of cytokines such as TNF and IL-12 by macrophages and to stimulate production of IL-10, thus inhibiting macrophage activation.

Cell-mediated immunity represents the predominant mechanism of adaptive immunity in the context of fungal infections.

Histoplasma capsulatum, a facultative intracellular parasite that resides within macrophages, is eradicated by the same cellular mechanisms that are effective against intracellular bacteria.

The cooperation of CD4+ and CD8+ T cells is pivotal in the elimination of the yeast forms of *C. neoformans*, which have a tendency to colonize the lungs and brain in immunodeficient hosts. It is widely accepted that the onset of Candida infections typically occurs at mucosal surfaces. Cell-mediated immunity is considered to play a pivotal role in preventing the dissemination of these fungi into deeper tissue layers.

In all these situations, Th1 responses are protective, while Th2 responses are detrimental to the host. As would be anticipated, granulomatous inflammation represents a significant cause of host tissue injury in certain intracellular fungal infections, a prime example of which is histoplasmosis. Fungi frequently provoke specific antibody responses that are beneficial for serologic diagnosis. Nevertheless, the protective efficacy of humoral immunity remains to be substantiated.

6. Protozoan Infections

Protozoans are defined as unicellular eukaryotic organisms. It has been determined that these organisms are responsible for the causation of several serious diseases in humans, including amoebiasis, Chagas' disease, African sleeping sickness, malaria, leishmaniasis and toxoplasmosis.

The nature of the immune response that develops in response to protozoan infection, and the extent to which this response is effective, are contingent, at least in part, on the location of the parasite within the host organism. A significant proportion of protozoans possess life-cycle stages in which they are capable of traversing the bloodstream freely, and it is during these stages that humoral antibody is most effective. Furthermore, many of these pathogens are also capable of intracellular growth; during these stages, cell-mediated immune reactions are effective in host defense. In the development of vaccines for protozoan diseases, the branch of the immune system that is most likely to confer protection must be carefully considered.

Immunopathology and Immunotherapy

1. Introduction

Immunopathology is the scientific study of diseases caused by abnormal immune responses. Whilst the immune system is generally effective in protecting against infection, its dysregulation can result in damage to the body itself. Such dysregulation may lead to hypersensitivity reactions, autoimmune diseases, immunodeficiency disorders and chronic inflammation. Persistent immune activation can result in tissue damage. These conditions demonstrate how both innate and adaptive immunity can malfunction, leading to pathology. Immunotherapy, on the other hand, harnesses immune mechanisms to treat or prevent illness.

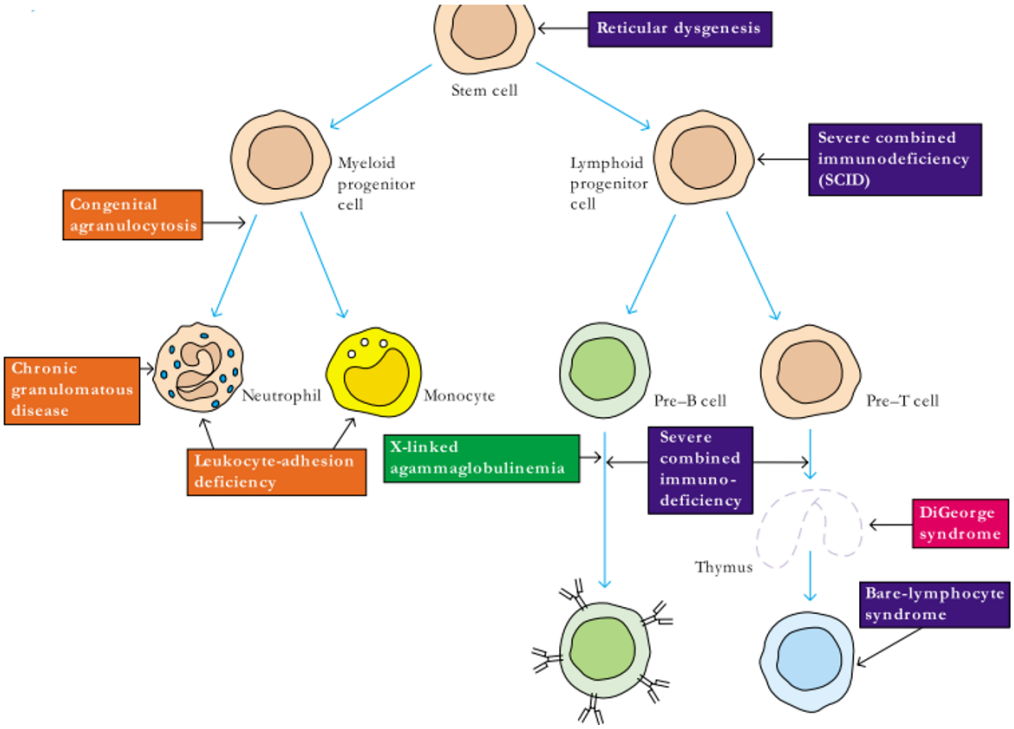
2. Immunodeficiencies

The immune system may fail in some or all of its components. Should this system lose its ability to sense itself, it will begin to attack the host's cells and tissues, resulting in **autoimmunity**. In instances where the system is unable to protect the host from pathogens or malignant cells, **immunodeficiency** can result.

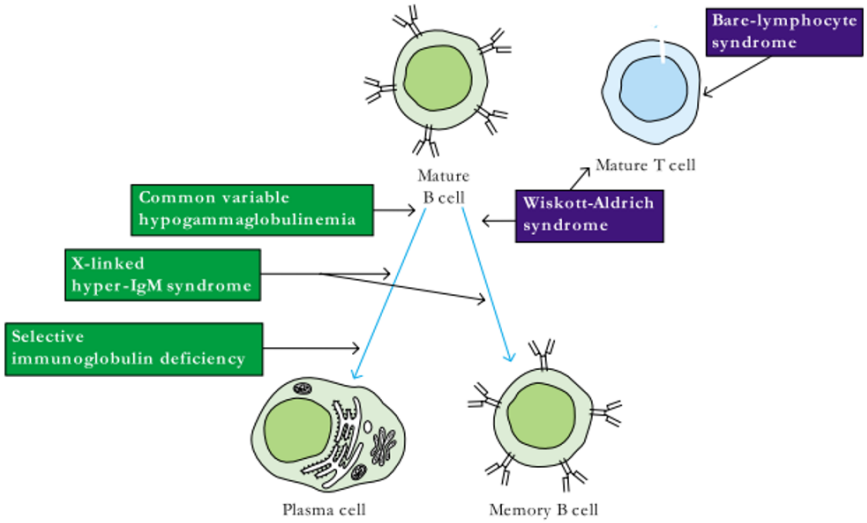
2.1. Primary Immunodeficiencies

Primary immunodeficiency is a term used to describe a genetic disorder or defect in the development of the immune system present from birth. Even if this is only evident at a later stage in life.

Primary immunodeficiencies have the potential to impact both adaptive and innate immune functions. The severity of these symptoms varies depending on the specific type of immune deficiency in question. For instance, deficiencies in components of adaptive immunity, such as T cells or B cells, can have different implications. It is also possible that the defect is present in non-specific mediators of innate immunity, such as phagocytes or complement.



Primary Immunodeficiencies part 1



Primary Immunodeficiencies part 2

2.2. Secondary immunodeficiency

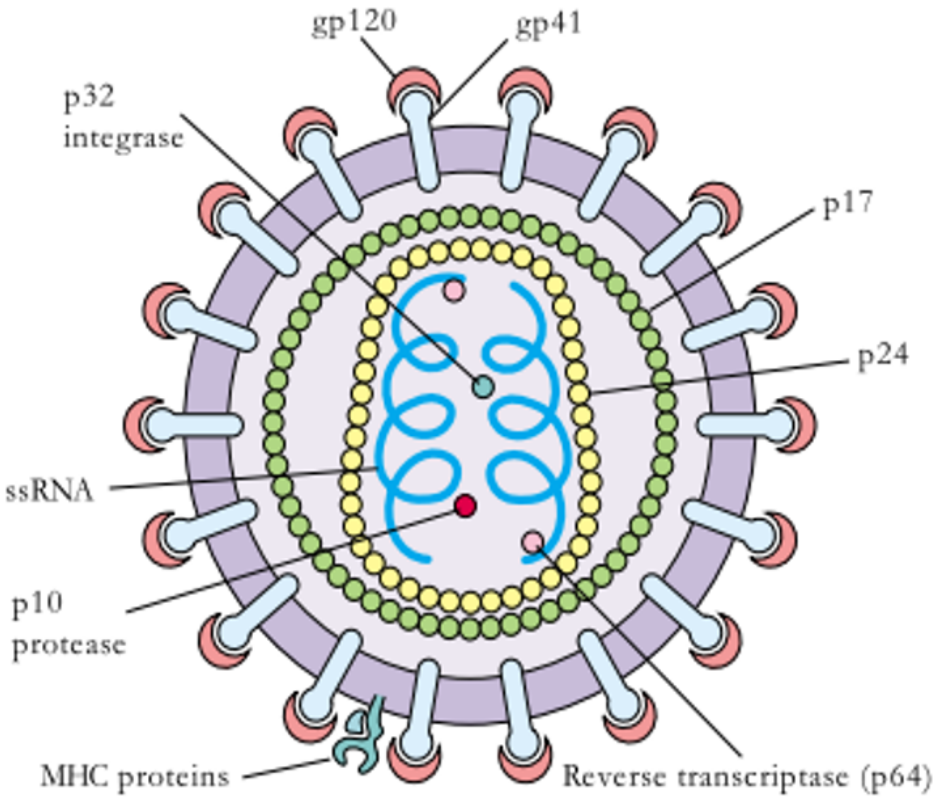
Secondary immunodeficiency, also known as acquired immunodeficiency, is the loss of immune function after exposure to various factors. The most prevalent form of secondary immunodeficiency is Acquired Immunodeficiency Syndrome (AIDS), which is caused by infection with the human immunodeficiency virus 1 (HIV-1).

a) AIDS (Secondary Immunodeficiencies)

Acquired Immunodeficiency Syndrome (AIDS) is the advanced stage of HIV infection. At this stage, the immune system becomes severely weakened, leaving the body vulnerable to opportunistic infections and certain cancers.

i) Structure of HIV

HIV is composed of 72 glycoprotein protrusions, which are composed of gp120 and gp41. The transmembrane molecule GP41 is capable of crossing the lipid bilayer of the viral envelope. The GP120 coating of the GP41 molecules enables it to act as a viral receptor for CD4 cells on host cells. The virus uses a part of the host cell membrane that contains major histocompatibility complex (MHC) class I and II molecules to form the viral envelope. The viral nucleus, otherwise known as the nucleocapsid, consists of an inner layer of p17 protein and an inner layer of p24 protein. The HIV genome consists of two copies of single-stranded RNA, linked by two molecules of reverse transcriptase (p64), nucleoprotein (p10), and protease and integrase (p32).



Structure of HIV

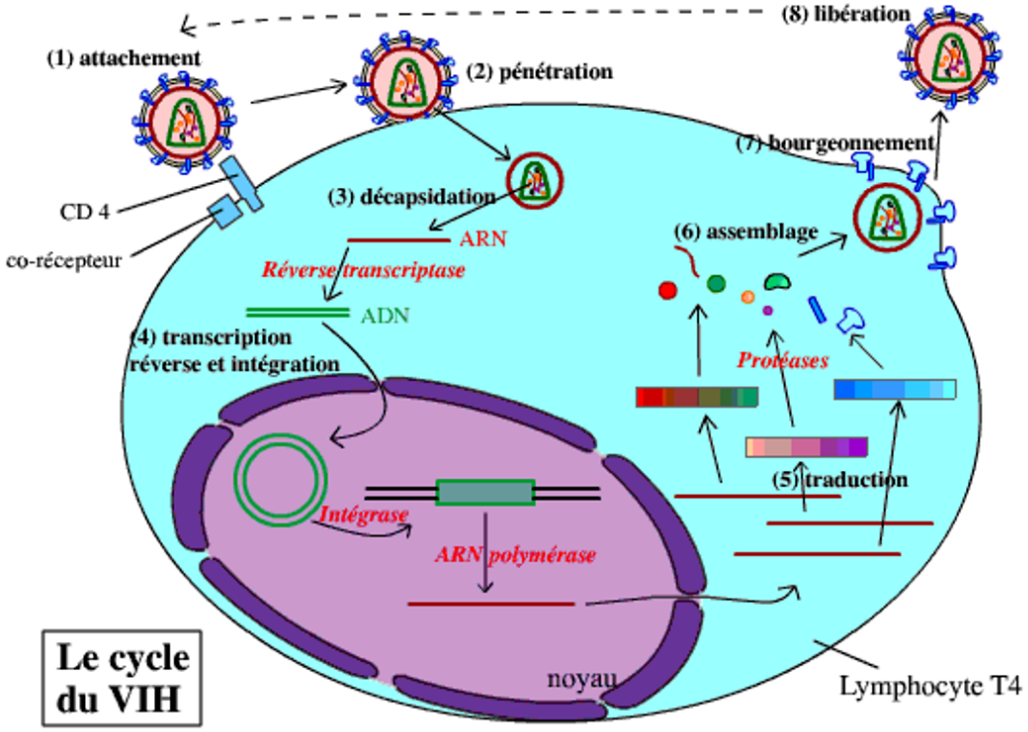
ii) HIV Cycle

The process of HIV gp120 binding to CD4 on the target cell is an essential step in the viral life cycle. The fusogenic domain in gp41, in conjunction with CXCR4, a G-protein–linked receptor located in the target cell's membrane, plays a crucial role in mediating fusion. Following binding, the nucleocapsid containing the viral genome and enzymes enters the cell. The release of the viral genome and enzymes is triggered by the removal of core proteins. The viral reverse transcriptase catalyzes the reverse transcription of ssRNA, resulting in the formation of RNA–DNA hybrids. The original RNA template experiences partial degradation by ribonuclease H, followed by the synthesis of a second DNA strand to yield HIV dsDNA. The viral dsDNA is then translocated to the nucleus and integrated into the host chromosomal DNA by the action of the viral integrase enzyme. Transcription factors stimulate the transcription of proviral DNA into genomic ssRNA and, after processing, several mRNAs. The viral RNA is exported to the cytoplasm, where host-cell ribosomes catalyze the synthesis of viral precursor proteins. The viral protease then cleaves these proteins. The process of viral proteins being formed is a key step in the life cycle of a virus.

The HIV ssRNA and proteins assemble beneath the host-cell membrane, where gp41 and gp120 are inserted.

The membrane buds out, forming the viral envelope.

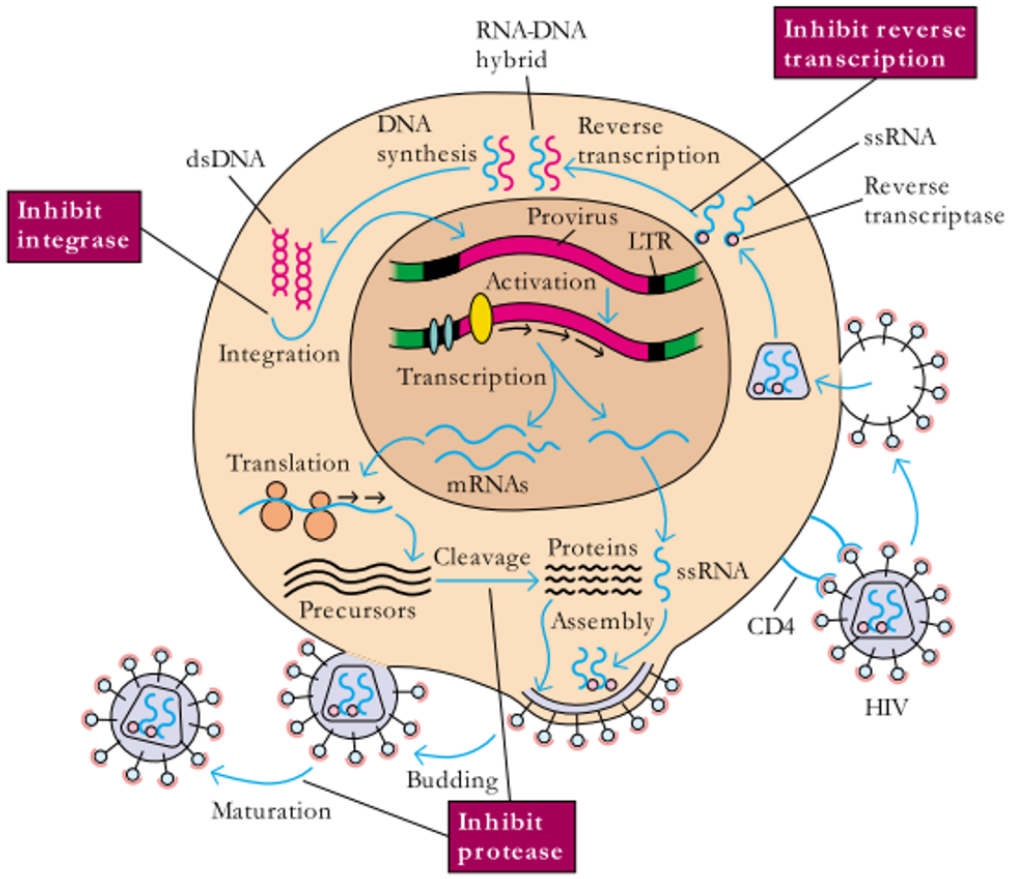
The released viral particles then complete maturation. The precursor proteins are cleaved by the viral protease present in the viral particles.



HIV Cycle

iii) Therapeutic Agents Inhibit Retrovirus Replication

Antiretroviral therapies are determined based on the viral replication cycle. Licensed drugs currently work by either inhibiting the virus's activity in the reverse transcription process of viral RNA to complementary RNA (cDNA), or by inhibiting the viral protease enzyme necessary for breaking down viral precursor proteins into the proteins required to form a new virus and complete its maturation into an infectious virus.



Therapeutic of HIV

3. Cancer

In certain cases, a group of cells may not respond correctly to the body's normal growth control mechanisms, which can sometimes lead to the formation of a tumor.

A tumor that grows in a limited way and does not extensively invade surrounding healthy tissue is considered benign.

A tumor that continues to grow and becomes progressively invasive is considered malignant; the term cancer specifically refers to a malignant tumor.

Uncontrolled growth can lead to malignant tumors metastasizing. In this process, small groups of cancer cells break away from the tumor, invade blood vessels or lymphatic vessels, and then spread to other tissues, where they continue to multiply. Consequently, a primary tumor in one location can potentially result in a secondary tumor in another location.

The classification of malignant tumors, or cancers, is based on the genetic origin of the tissue from which the tumor arises.

The majority of these cases (over 80%) are carcinomas, which are tumors that originate in endoderm or ectoderm tissues, such as the skin or the epithelial lining of internal organs and glands. The majority of colon, breast, prostate, and lung cancers are carcinomas.

Leukemias and lymphomas are malignant tumours that affect the blood-forming cells in the bone marrow and account for approximately 9% of cancer cases in the United States.

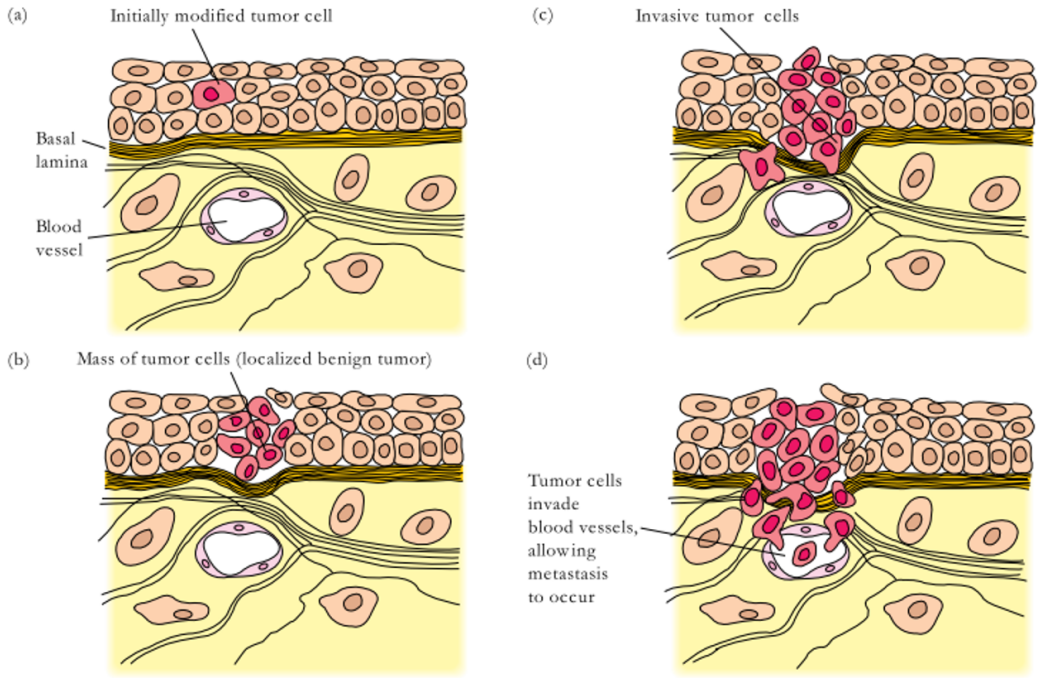
Leukemias are known to proliferate as single cells, while lymphomas tend to grow as tumor masses.

Sarcomas, which are less common (accounting for approximately 1% of cases in the United States), originate in mesodermal connective tissues, such as bone, fat, and cartilage.

3.1. Stages of Cancer Development

The following is a description of the various stages of cancer development:

- A - The initial stage is marked by the development of altered growth properties in a single cell at a specific tissue site.
- B - The altered cell proliferates, forming a mass of localized tumor cells, or benign tumor.
- C - The neoplastic cells exhibit an increasing degree of invasiveness, penetrating the underlying basal lamina. The tumor has now been re-classified as malignant.
- D - The process of metastasis in a malignant tumor is characterized by the dislodgement of small clusters of cancer cells from the primary site of the tumor. These cells are then transported via the blood or lymphatic system to distant sites within the body, where they can establish colonies and contribute to the development of new tumors.



Stage of Cancer Development

3.2. Cancer Immunotherapy

a) Manipulation of Co-Stimulatory Signals Can Enhance Immunity

The manipulation of co-stimulatory signals, which are molecules that provide the "second signal" for T cell activation, has been shown to enhance immunity by increasing T cell proliferation, survival, and effector functions. This strategy is not exclusively employed in the field of cancer research; its application is also extant in the domain of vaccine development and the treatment of infectious diseases.

b) Enhancement of APC Activity Can Modulate Tumor Immunity

Enhancing antigen-presenting cell (APC) activity can significantly modulate tumor immunity by improving T-cell priming, boosting immune checkpoint blockade efficacy, and overcoming tumor-induced immune suppression.

c) Cytokine Therapy

Cytokine Therapy Can Augment Immune Responses to Tumors: IFN-α , β, and ϒ; IL-1, IL-2, IL-4, IL-5, and IL-12; GM-CSF

Cytokine can enhance antitumor immunity by stimulating both innate and adaptive immune responses via the activation of T cells, NK cells and macrophages is crucial for enhancing immune surveillance and the body's ability to attack and destroy tumor cells. However, it is essential to carefully balance efficacy and toxicity when considering its clinical use.

d) Monoclonal Antibodies

Monoclonal antibodies (mAbs) have been shown to be an effective treatment for certain types of tumors. These drugs have the capacity to target specific proteins on cancer cells, helping the immune system to recognize and destroy them. In some cases, they are also able to block signals that tumors use to grow and spread.

4. Autoimmunity

The key difference between systemic autoimmune diseases and organ-based autoimmune diseases is the range and specificity of the immune system's attack.

4.1. Systemic Autoimmune Diseases

Systemic Autoimmune Diseases: These diseases have the potential to affect multiple organs or tissues throughout the body. The immune system attacks widespread antigens, often leading to inflammation and damage in various organs and tissues simultaneously.

Examples:

Systemic lupus erythematosus (SLE): The condition has the potential to impact the skin, kidneys, joints and other organs.

Rheumatoid arthritis (RA): This condition primarily affects the joints, but there is also a possibility of involvement of the lungs, heart and eyes.

4.2. Organ-Based Autoimmune Diseases

Organ-specific autoimmune diseases: The immune system is compromised in specific organs or tissues. It incorrectly identifies antigens that are specific to a particular organ as harmful, resulting in inflammation and localized damage.

Examples:

Type 1 diabetes is a condition that targets the insulin-producing beta cells in the pancreas.

Hashimoto's thyroiditis is an autoimmune disorder that affects the thyroid gland.

Multiple sclerosis (MS) is an autoimmune condition that affects the central nervous system.

4.3. Autoimmunity Therapy

In the case of autoimmune diseases, treatment strategies are aimed at managing symptoms, controlling an overactive immune system, and preventing long-term damage. Treatment varies depending on whether the disease is systemic or organ-specific. Common treatment strategies include:

1- Firstly, the recommended course of action is to administer **immunosuppressive therapy**. Corticosteroids (e.g., prednisone) are effective for rapidly controlling inflammation.

2- **Biologic agents**: including tumor necrosis factor inhibitors (e.g. infliximab) and interleukin-6 inhibitors.

In organ-specific cases, missing or damaged components are replaced.

- Insulin is a medication used to treat type 1 diabetes.
- Thyroid hormone therapy for Hashimoto's thyroiditis.

3. **Intravenous immunoglobulin (IVIG)**

4. It is recommended that patients suffering from this condition follow an **anti-inflammatory diet**, practice stress management techniques and arrange physical therapy appointments in order to reduce the frequency of disease flare-ups.

5. **Experimental therapies**: Stem cell transplantation and gene therapy are currently being explored in advanced research.

5. Hypersensitivity Diseases

Hypersensitivity diseases are the result of excessive or uncontrolled responses to foreign antigens, such as non-infectious environmental antigens. Hypersensitivity diseases are a clinically heterogeneous group of disorders.

The clinical and pathological manifestations of these diseases vary depending on the type of immune response causing tissue damage and the nature and location of the antigen targeted by this response.

Note

A notable similarity exists between the mechanisms of action in immune diseases and the mechanisms of humoral and cellular immunity against microbes and other foreign antigens.

5.1. Types of Hypersensitivity Diseases

Type I – Immediate (IgE-mediated)

The mechanism of action of allergens is as follows: IgE antibodies bind to mast cells and basophils, which, upon exposure to the allergen, trigger degranulation and the release of histamine.

Examples include: The following allergic reactions are of particular concern: anaphylaxis, hay fever, asthma and food allergies.

Timing: The duration of exposure is measured in seconds or minutes.

Type II – Cytotoxic (IgG/IgM-mediated)

Mechanism: Antibodies bind to antigens on cell surfaces, which results in complement activation or antibody-dependent cell-mediated cytotoxicity (ADCC). This, in turn, leads to cell lysis.

Examples: The following pathologies are to be considered: hemolytic anemia, and transfusion reactions.

The temporal parameters of the exposure are hours.

Type III – Immune Complex-Mediated

Mechanism: The deposition of antigen-antibody complexes within tissues subsequently results in complement activation, which, in turn, leads to inflammation and tissue damage.

Examples include: Systemic lupus erythematosus (SLE), and rheumatoid arthritis.

The temporal framework for the onset of symptoms is wide-ranging, extending from hours to days following exposure.

Type IV is classified as delayed-type (T-cell-mediated).

Mechanism: Sensitized T lymphocytes release cytokines, which in turn activate macrophages, resulting in tissue injury.

Examples: The following conditions have been observed: contact dermatitis (a reaction to poison ivy or nickel allergy), and type 1 diabetes.

The optimal timing for administration is between 48 and 72 hours following exposure.

Type of hypersensitivity	Pathologic immune mechanisms	Mechanisms of tissue injury and disease
Immediate hypersensitivity: Type I	IgE antibody	Mast cells and their mediators (vasoactive amines, lipid mediators, cytokines)
Antibody mediated: Type II	IgM, IgG antibodies against cell surface or extracellular matrix antigens	Opsonization and phagocytosis of cells Complement-and Fc receptor-mediated recruitment and activation of leukocytes (neutrophils, macrophages) Abnormalities in cellular functions, e.g., hormone receptor signaling
Immune complex mediated: Type III	Immune complexes of circulating antigens and IgM or IgG antibodies	Complement-and Fc receptor-mediated recruitment and activation of leukocytes
T cell mediated: Type IV	1. $CD4^+$ T cells (delayed-type hypersensitivity) 2. $CD8^+$ CTLs (T cell-mediated cytolysis)	1. Macrophage activation, cytokine-mediated inflammation 2. Direct target cell killing, cytokine-mediated inflammation

Types of Hypersensitivity

5.2. Immunotherapeutic of Hypersensitivity

The primary therapeutic approach for hypersensitivity diseases is the administration of anti-inflammatory medications, with corticosteroids being of particular significance. The pharmaceuticals in question are designed to target the reduction of tissue injury, with a particular focus on the effector phases of pathological immune responses. Research is underway to determine the efficacy of antagonists of proinflammatory cytokines, such as IL-1 and TNF, and agents that block leukocyte emigration into tissues, such as antibodies against integrins, in reducing inflammation.

Molecular Aspects of Transplantation and Graft Rejection

1. Introduction

Organ transplantation is defined as the process of transferring cells, tissues or organs (known as 'grafts') from one person to another. The person who provides the graft is called the donor, while the person who receives it is known as the recipient or host. Transplantation is used to correct a functional or anatomical defect in the recipient.

The type of graft can be determined based on its location. If the graft is placed in its normal anatomical location, the procedure is called an orthotopic transplantation; if it is placed in a different location, it is called an heterotopic transplantation.

Blood transfusions, which involve the transfer of blood cells or plasma from one person to another, are also considered organ transplants.

2. Types of Transplants

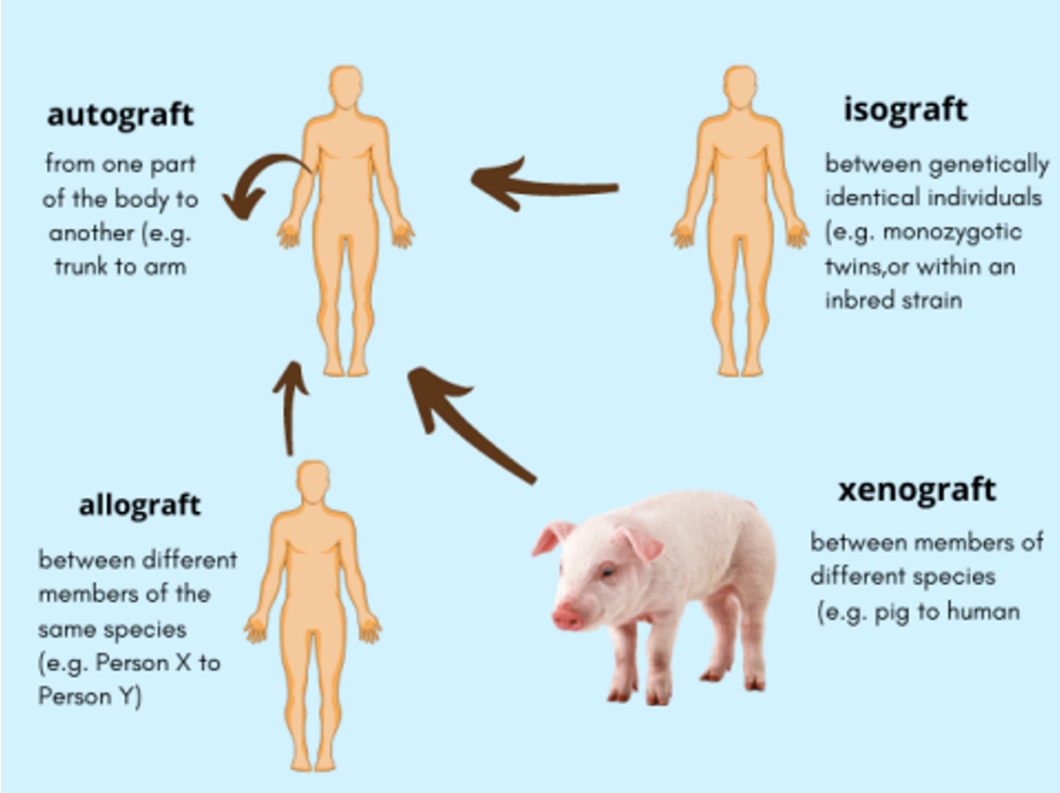
Organ transplants are classified into several main types based on the relationship between the donor and recipient. These include autografts, allografts, xenografts, isografts.

Autografts: In this case, the transplant is from within the same person (such as skin grafts from the thigh to the arm).

Isografts grafts: (homogenic transplants): These are performed between genetically identical individuals, such as identical twins.

Allografts grafts: The recipient and donor are of the same species but genetically different (this is the most common type of human organ transplant).

Xenografts grafts: The recipient and donor are of different species (such as pig heart valves transplanted into humans).



Types of Transplants

3. Immune Process of Graft Acceptance

In the case of acceptance of graft the recipient's immune system does not mount a destructive response against the graft. based to some factors promoting acceptance:

1- Genetic similarity: Closer match of donor and recipient HLA.

2- Immunosuppressive therapy: Drugs like cyclosporine or corticosteroids) reduce T-cell activation and antibody production and decrease immune response generally.

3- Immune regulation: Regulatory T cells help suppress graft-directed immune responses and augmented the tolerance.

4. Cell-Mediated Graft Rejection

4.1. Sensitization Stage

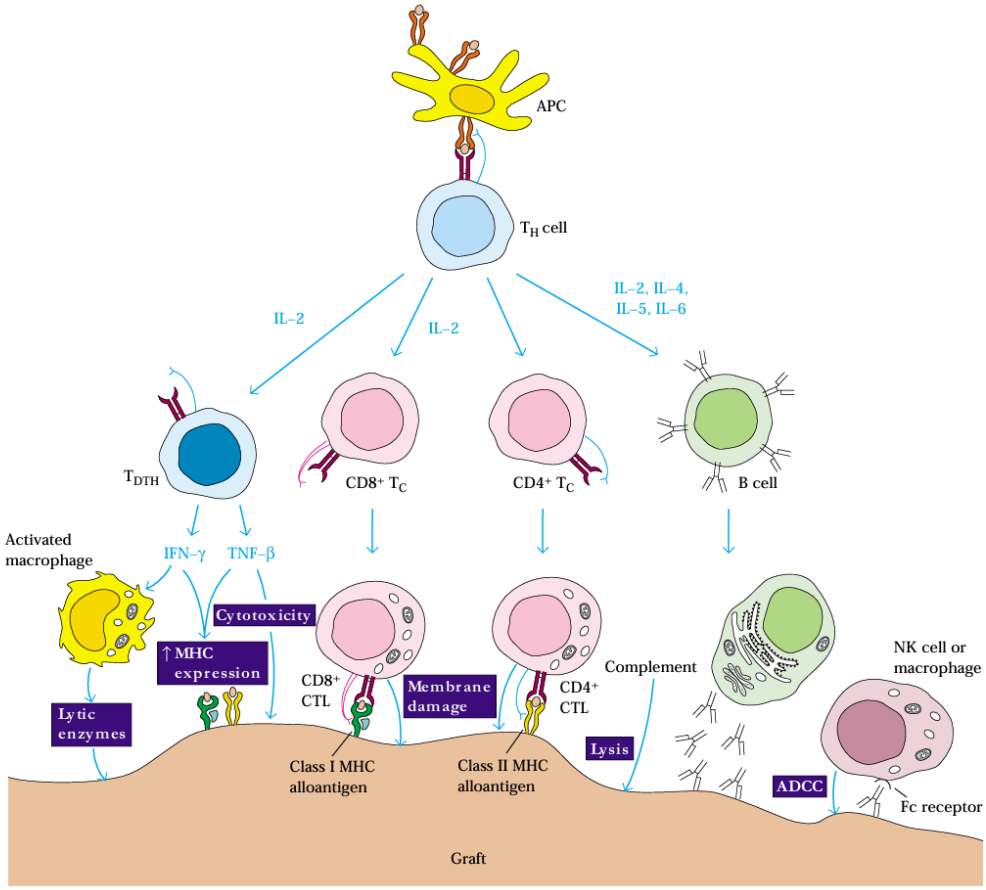
At this stage, a helper T (Th) cell is activated after interacting with an antigen-presenting cell (APC) expressing the appropriate MHC-antigen-binding molecule complex, providing the necessary signals. Dendritic cells are the main type of antigen-presenting cell in tissues. Therefore, CD4+ and CD8+ T cells recognize the foreign antigens expressed on the graft cells and proliferate in response.

4.2. Effector Stage

Graft rejection is characterised by a high influx of T cells and phagocytes into the graft. The most common cellular reactions are delayed hypersensitivity and cytotoxic T cell-mediated lysis; less common mechanisms include antibody and complement lysis and antibody-dependent cell-mediated toxicity (ADCC).

Activated T cells secrete several cytokines involved in graft rejection, most notably IL-2, IFN-γ, and TNF-β. IL-2 has been shown to promote T cell proliferation and is generally essential for the development of effective cytotoxic T cells.

IFN-γ has been shown to promote the development of a delayed hypersensitivity response, contributing to the influx of phagocytes into the graft and their subsequent activation into more destructive cells. TNF-β has a direct cytotoxic effect on the transplanted cells.



Mechanisms of Graft Rejection

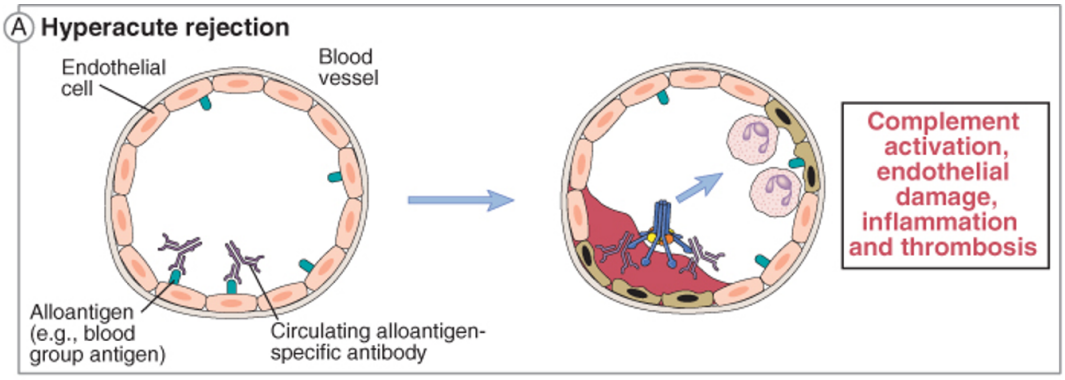
5. Effector Mechanisms of Allograft Rejection

Graft rejection based on" histopathologic features" or "the time course of rejection" after transplantation rather than "immune effector mechanisms" can be classified in : hyperacute, acute, chronic

5.1. Hyperacute Rejection

In acute rejection, thrombotic occlusion of the graft blood vessels begins within minutes to hours after the recipient's blood vessels are connected to the graft vessels. This is due to the presence of antibodies in the recipient's bloodstream, often mediated by IgM, and IgG, which bind to the donor's vascular endothelial antigens.

Following this binding, complement activation triggers a series of changes in the graft's vascular endothelium, promoting intravascular coagulation, damaging endothelial cells, and exposing subendothelial basement membrane proteins, which in turn activates platelets.

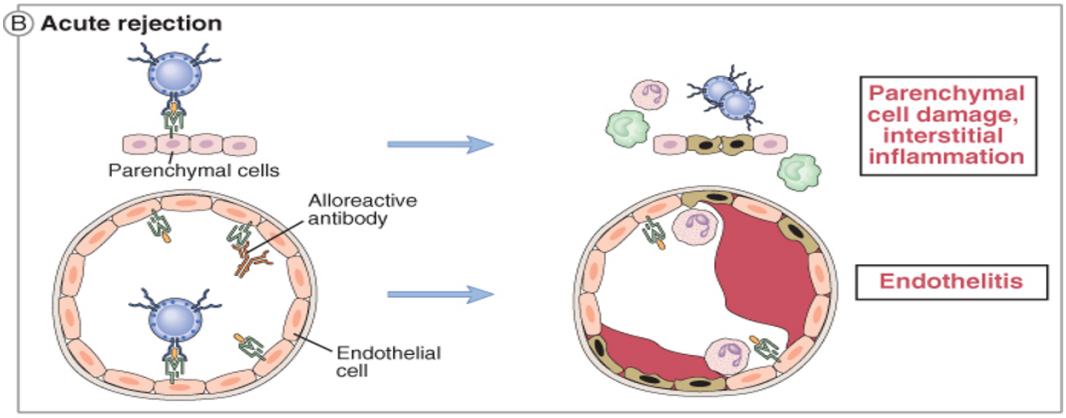


Hyperacute Rejection

5.2. Acute Rejection

Acute rejection typically manifests within the first week, affecting blood vessels and visceral tissues. This process involves helper T cells (CD4+), cytotoxic T cells (CD8+), and antibodies.

T cells (CD4+) have been shown to play a role by releasing cytokines and inducing delayed-onset hypersensitivity reactions in grafts. It is suggested by some evidence that helper T cells (CD4+) are sufficient to mediate acute rejection.



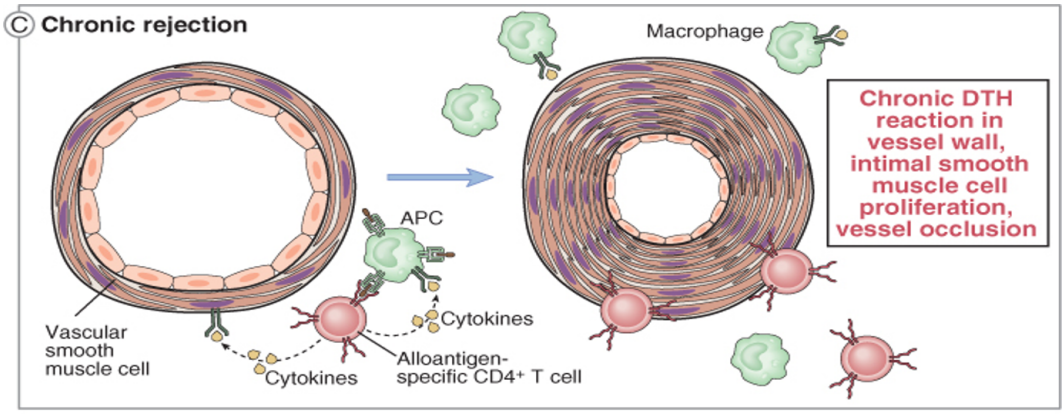
Acute Rejection

5.3. Chronic Rejection

Chronic rejection is characterized by fibrosis and vascular dysfunction, which can result in prolonged loss of function in the transplanted organ. Chronic rejection fibrosis may result from immune reactions and the production of cytokines that stimulate fibroblasts, or it may be a consequence of wound healing following necrosis of visceral cells in cases of acute rejection.

Chronic organ transplant rejection is most likely caused by arterial occlusion, resulting from smooth muscle cells multiplying in the artery lining. This process is known as accelerated atherosclerosis.

A common complication of heart and kidney transplants is atherosclerosis, which can develop within six months to a year post-transplant.



Chronic Rejection

6. General Immunosuppressive Therapy

There are two general cases in which an allograft may be accepted.

- One is when cells or tissue are grafted to a so-called privileged site that is sequestered from immune-system surveillance.
- The second is when a state of tolerance has been induced biologically, usually by previous exposure to the antigens of the donor in a manner that causes immune tolerance rather than sensitization in the recipient.

The dregs used in graft transplantation resumed in the table below

Drug	Mechanism of action
Cyclosporine and FK-506	Block T cell cytokine production by inhibiting activation of the NFAT transcription factor
Azathioprine	Blocks proliferation of lymphocyte precursors
Mycophenolate mofetil	Blocks lymphocyte proliferation by inhibiting guanine nucleotide synthesis in lymphocytes
Rapamycin	Blocks lymphocyte proliferation by inhibiting IL-2 signaling
Corticosteroids	Reduce inflammation by inhibiting macrophage cytokine secretion
Anti-CD3 monoclonal antibody	Depletes T cells by binding to CD3 and promoting phagocytosis or complement-mediated lysis (used to treat acute rejection)
Anti-IL-2 receptor antibody	Inhibits T cell proliferation by blocking IL-2 binding
CTLA4-Ig	Inhibits T cell activation by blocking B7 costimulator binding to T cell CD28; used to induce tolerance (experimental)
Anti-CD40 ligand	Inhibits macrophage and endothelial activation by blocking T cell CD40 ligand binding to macrophage CD40 (experimental)

Immunosuppressive Therapy In Graft Rejection

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