Ministry of Public Health of Ukraine
Poltava State Medical University
Department of biological and bioorganic chemistry

Biochemical principles of realization of immune processes. Immunodeficiency conditions.

Assoc. Prof. Bilets M.V.

Lectures plan

- General characteristics of the immune system; cellular and biochemical components.
- Immunoglobulins: structure, biological functions.
- Mediators and hormones of the immune system.
- Biochemical components of the complement system.
- Biochemical mechanisms of immunodeficiency states: primary (hereditary) and secondary immunodeficiencies.

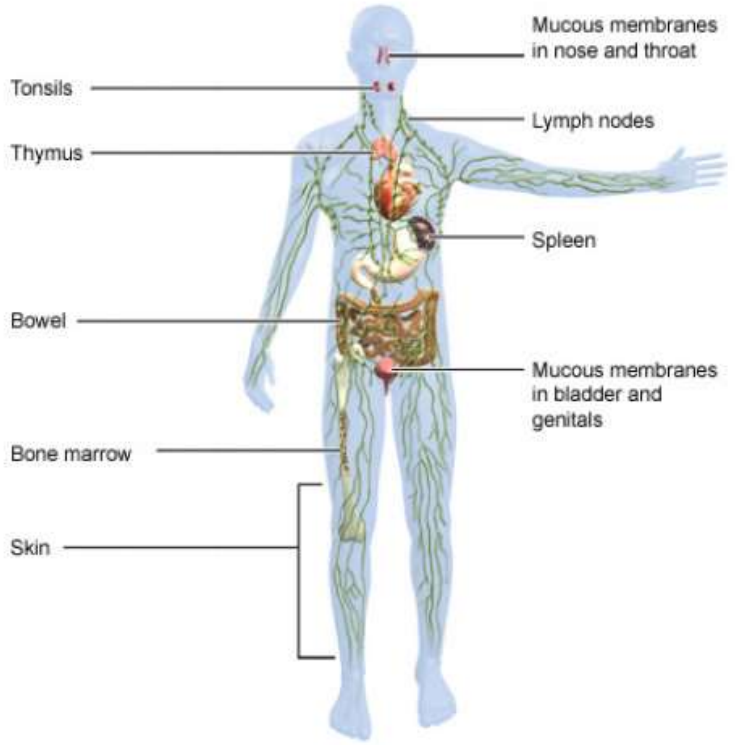
General characteristics of the immune system. Cellular and biochemical components.

- **The immune system** is a system of organs and tissues that protect the body from foreign agents: pathogens, foreign bodies, poisonous substances and degenerated cells of the body itself.
- **The immune system consists of**: ***central organs:*** bone marrow and thymus; and ***peripheral organs containing lymphoid tissue*** (lymphocytes of varying degrees of maturity): spleen; the lymph nodes; intestinal Peyer's patches; tonsils; the appendix, and the ***monocytic-macrophage system*** (monocytes, tissue macrophages, dendritic cells, microphages or polymornonuclear granulocytes: basophils, eosinophils, neutrophils).
- **The immune system includes levels:**

✓ ***Organ level***

✓ ***Cellular level*** (macrophages and microphages, T and B lymphocytes, monocytes, platelets and other cells)

✓ ***Humoral or molecular level*** (immunoglobulins or antibodies, cytokines, interferons, etc.).



What are the parts of the immune system?

https://www.ncbi.nlm.nih.gov/books/NBK279395/#:~:text=Primary%20lymphoid%20organs%3A%20These%20organs,for%20instance%20in%20the%20bowel).

- The **immune system** allows the formation of immunity - defense mechanisms that are aimed at recognizing, neutralizing and eliminating molecules from the body, parts of molecules that carry signs of foreignness (antigens).
- **Antigens** are substances that, when introduced into the body, activate the development of an immune response in the form of the production of specific antibodies and / or T-lymphocytes.
- Sources of antigens are **pathogens** - integral objects (bacteria, viruses, dust particles, etc.), which, when ingested, lead to pathological changes.

- **Antigen properties:**

✓ Molecular weight 1-10 kDa

✓ Antigens can be: proteins, polysaccharides, esters, polycyclic compounds, nucleic acids or complexes of these molecules.

✓ Molecules with antigenic properties should have a well-defined spatial structure.

✓ Antigens are not fully recognized by lymphocytes, but only by specific sites: an ***epitope*** (recognized by B-lymphocytes), an ***immunogenic peptide*** (recognized by T-lymphocytes).

✓ Recognition by lymphocytes occurs through binding to specific surface receptors:

✓ **B-cell receptor, BCR (B-cell antigen receptor, for B-lymphocytes)** is a membrane form of antibodies (immunoglobulins) synthesized by this B-lymphocyte, and has the same substrate specificity as secreted antibodies.

✓ **T-cell receptor TCR (B-cell antigen receptor for T-lymphocytes)** - a surface protein complex of T-lymphocytes, responsible for the recognition of processed antigens associated with molecules of the major histocompatibility complex on the surface of antigen-presenting cells (macrophages, B-lymphocytes and dendritic cells)

✓ **Haptens** are low molecular weight substances that induce an immune response only after binding to proteins.

Forms of immunity

- There are two main forms of immunity **- innate** and **adaptive** immunity.
- **Innate immunity** - the ability of the body to neutralize foreign and potentially dangerous microorganisms, transplants, toxins, tumor cells, cells infected with a virus, existing initially, before the first entry of this biomaterial into the body. Innate immunity is associated with the activation of inflammation, chemotaxis, the complement system, detection and removal of foreign bodies from organs and tissues using leukocytes.
- There is a classification of **adaptive immunity** depending on its origin, according to which it is subdivided into ***natural*** (not to be confused with natural immunity due to factors of nonspecific resistance) and ***artificial***.

✓ ***Natural adaptive immunity*** is formed naturally. Active natural adaptive immunity is formed as a result of a previous infection and is therefore called *post-infectious.* ***Passive natural adaptive immunity*** is formed due to maternal antibodies that enter the fetus through the placenta, and after birth - into the baby's body with breast milk.

✓ ***Active artificial immunity*** is formed as a result of vaccination and is therefore called post-vaccination. ***Passive artificial adaptive immunity*** is formed as a result of the administration of therapeutic and prophylactic sera and therefore is called post-serum.

✓ **Adaptive immunity can be**: ***humoral and cellular, systemic and local, in terms of focus - antibacterial, antiviral, antitoxic, antitumor, antitransplantation.***

Types of lymphocytes

Lymphocytes are of two classes: **B- and T-lymphocytes.**

B lymphocytes produce antibodies.

T-lymphocytes kill cells infected with the virus and regulate the activity of other leukocytes; cell maturation occurs in the thymus;

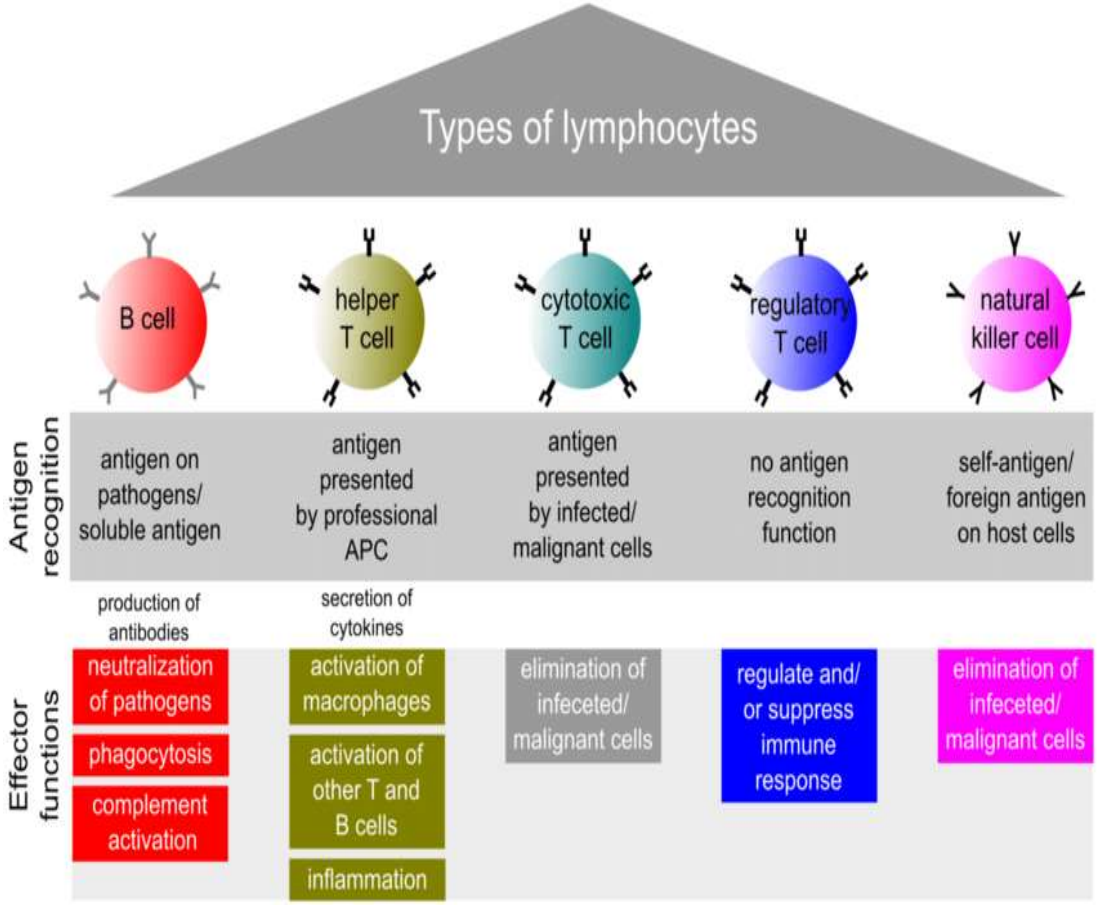
T-lymphocytes are classified into:

T-helpers that promote the development of an immune response;

T-suppressors that suppress the development of the immune response;

T-killers that destroy cells that carry antigens.

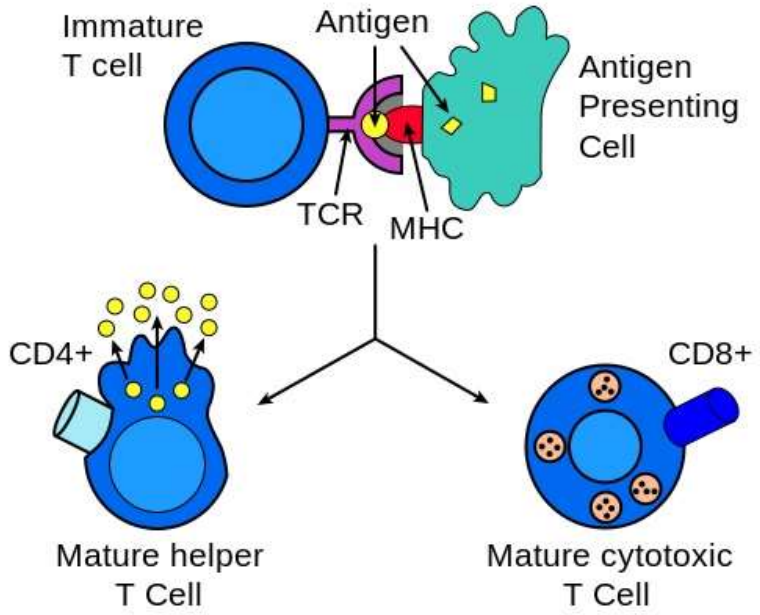
Normal (natural) killer cells destroy some types of tumor and virus-infected cells.



https://www.researchgate.net/figure/Types-of-lymphocytes-and-their-effector-functions-The-lymphocyte-family-includes_fig2_280663544

Major histocompatibility complex proteins

- For the normal functioning of T-lymphocytes, proteins of the **major histocompatibility complex (MHC)** play a very important role.
- Proteins of the MHC belong to leukocyte antigens - **HLA (human-leucocyte-associated antigens)**. MHC proteins are produced by all cells. The polymorphism of these proteins is so great that it seems unlikely that two individuals carry the same set of MHC proteins unless they are identical twins. MHC proteins bind small peptides presented by T cells on their variable part.
- ***MHC proteins are divided into two large classes.***
- **MHC class I** proteins are found on the surface of almost **all nuclear cells** in the body. It is these proteins that cause tissue rejection when transplanted from another individual. They consist only of an α-chain linked to β2-microglobulin by a small invariant protein. These proteins are involved in binding to T-killer receptors. To do this, T- killers contain surface markers **- CD8+**, which act as coreceptors.
- **MHC class II** protein molecules are built from two homologous peptide chains (α and β). They are located on the surface of the cells of the immune system and distinguish the latter from the rest of the body's cells. These proteins are involved in binding to T-helper receptors. To this end, T-helper cells contain surface markers – **CD4+**, which act as coreceptors.

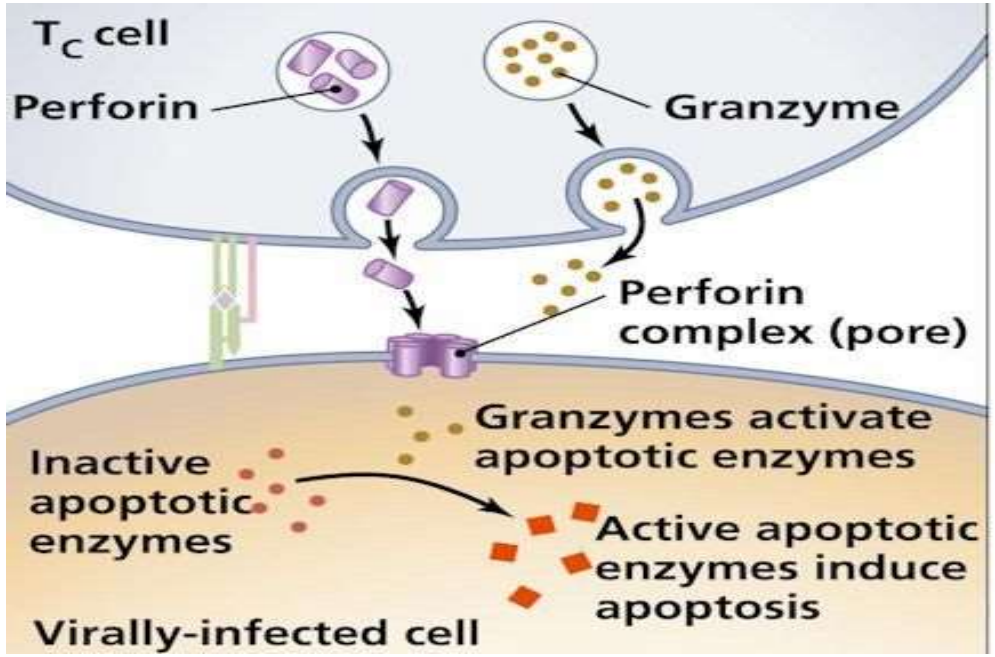


https://pediaa.com/what-is-the-difference-between-hla-and-mhc/

T-killers

- Many pathogens are located inside the affected cells, out of reach of humoral immunity factors (such as antibodies). To fight against intracellular parasites, a system of cellular adaptive immunity has emerged, based on the functioning of T-killer cells.
- T-killer cells come into direct contact with damaged cells and destroy them.
- T-killer cells specifically recognize a specific antigen and only kill cells with that antigen. There are tens of millions of T-killer clones, each of which is “tuned” to a specific antigen.
- Clone cells begin to multiply when the corresponding antigen enters the internal environment of the body after the activation of T-killers by T-helpers.
- **T lymphocytes can recognize a foreign antigen only if it is expressed on the cell surface.** They recognize the antigen on the cell surface in combination with a cellular marker: MHC class I molecules. In the process of recognizing the surface antigen, the cytotoxic T-lymphocyte comes into contact with the target cell and, if a foreign antigen is detected, destroys it before replication begins. In addition, it produces interferon gamma, which limits the penetration of the virus into neighboring cells.

Most cytotoxic T cells belong to the CD8 + subpopulation and recognize antigen presented in association with MHC class I molecules. Activated T-killers kill cells with a foreign antigen, to which they have a receptor, by inserting perforins (proteins that form a wide, non-closing opening in the membrane) into their membranes and injecting toxins (granzymes) inside. In some cases, T-killer cells trigger apoptosis of an infected cell through interaction with membrane receptors.



T-helpers

- **T-helpers** - their function is to enhance the adaptive immune response. Activate T-killers, B-lymphocytes, monocytes, NK-cells, presenting fragments of a foreign antigen to them during direct contact, as well as humoral, releasing cytokines. The main phenotypic feature of T-helpers is the presence of a CD4 molecule on the cell surface. T-helpers recognize antigens when their T-cell receptor interacts with an antigen associated with molecules of the major histocompatibility complex 2 class (MHC-II).
- **There are several subtypes of T-helpers:**

✓ **T-helpers 0 (Th0)** - "naive", undifferentiated T-helpers;

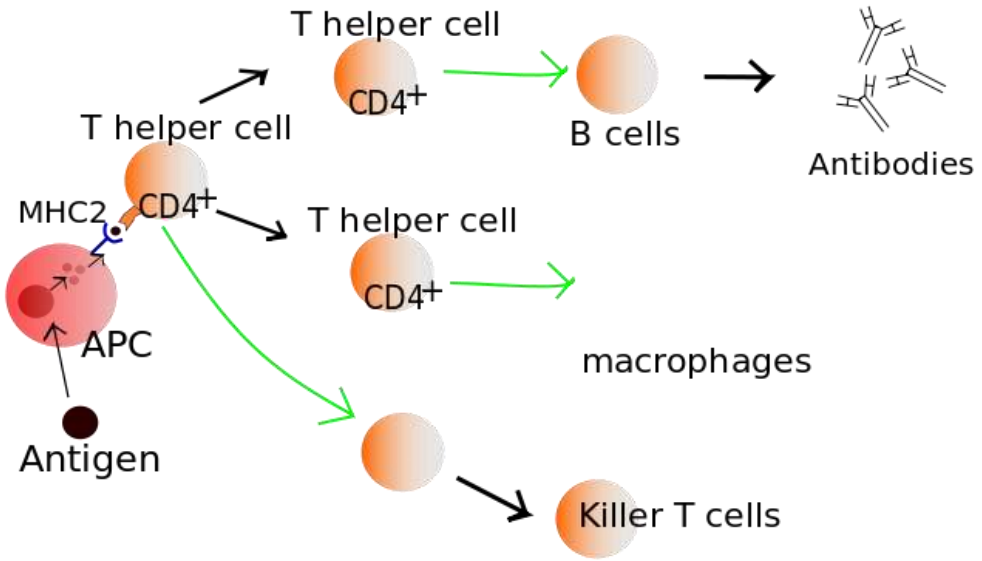
✓ **T-helpers 1 (Th1)** - predominantly promote the development of a cellular immune response by activating macrophages; the main secreted cytokine is interferon-gamma;

✓ **T-helpers 2 (Th2)** - activate B-lymphocytes, contributing to the development of a humoral immune response; produce interleukins 4, 5 and 13;

✓ **T-helpers 3 (T-reg, T-regulators, T-suppressors)** - express on the surface of the CD25 molecule and express the transcription factor Foxp3, secrete interleukin-10 and transforming growth factor-beta (TGF-beta) and suppress the immune response.

✓ **T-helpers 17 (Th17)** - a subtype of T-helpers, which in large quantities produces a pro-inflammatory cytokine - IL-17. The role of Th17 cells in the development of autoimmune pathology has been shown.

✓ **T-helpers 22 (Th22)** - identified in inflammatory skin diseases. Their role in the body's defense remains unclear because these cells have recently been characterized. They produce a pro-inflammatory cytokine, IL-22.



https://commons.wikimedia.org/wiki/File:Lymphocyte_activation_simple.svg

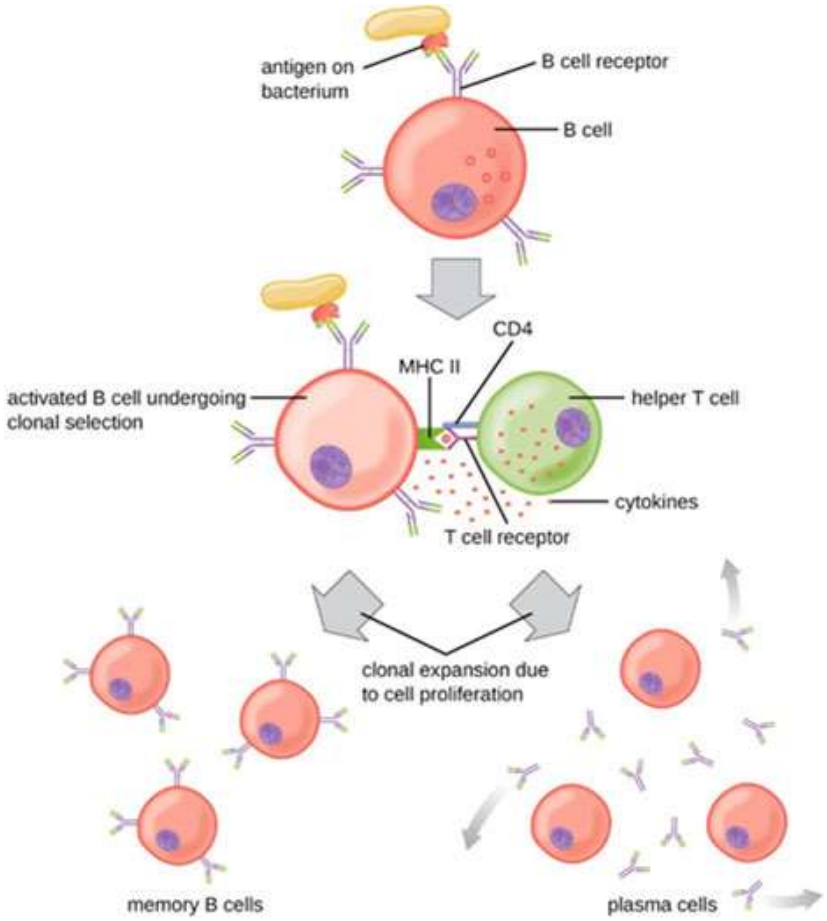
B-lymphocytes

- **B-lymphocytes** are formed in the red bone marrow, but differentiate in the lymphoid tissue of the intestine, process, palatine and pharyngeal tonsils. In the blood, they make up 20-30% of circulating lymphocytes.
- The main **function** of B-lymphocytes is to create **humoral immunity** by producing antibodies.
- After meeting with the antigen, B-lymphocytes migrate to the bone marrow, spleen and lymph nodes, where they multiply and turn into plasma cells, which are producers of antibodies - immune y-globulins.
- B-lone antigen and is responsible for the production of antibodies only against it.ymphocytes are very specific: each group (clone) reacts with only
- **Types of B-lymphocytes:**

✓ ***"Naive" B-lymphocytes*** - non-activated B-lymphocytes, not in contact with the antigen. They are multispecific and have low affinity for many antigens.

✓ ***Memory B-cells*** are activated B-lymphocytes, which have again passed into the stage of small lymphocytes as a result of cooperation with T-cells. They are a long-lived clone of B cells that provide a fast immune response and the production of a large amount of immunoglobulins when the same antigen is re-administered. Called memory cells, as they allow the immune system to "remember" an antigen for many years after its termination. Memory B cells provide long-term immunity.

✓ ***Plasma cells*** are the last stage in the differentiation of antigen-activated B cells. Unlike other B cells, they carry few membrane antibodies and are able to secrete soluble antibodies. They do not live long (2-3 days) and are quickly eliminated in the absence of the antigen that caused the immune response.



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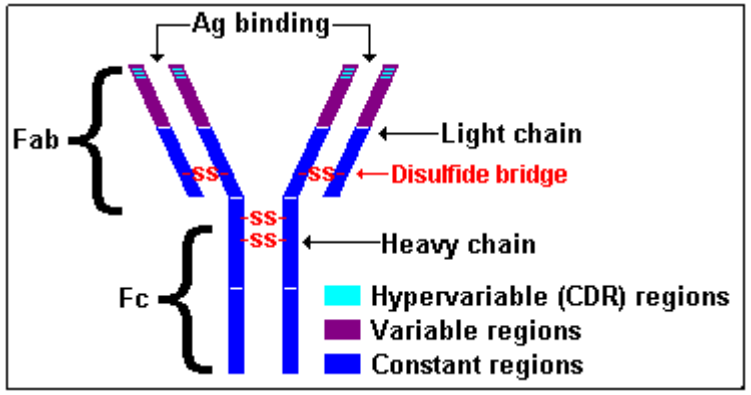
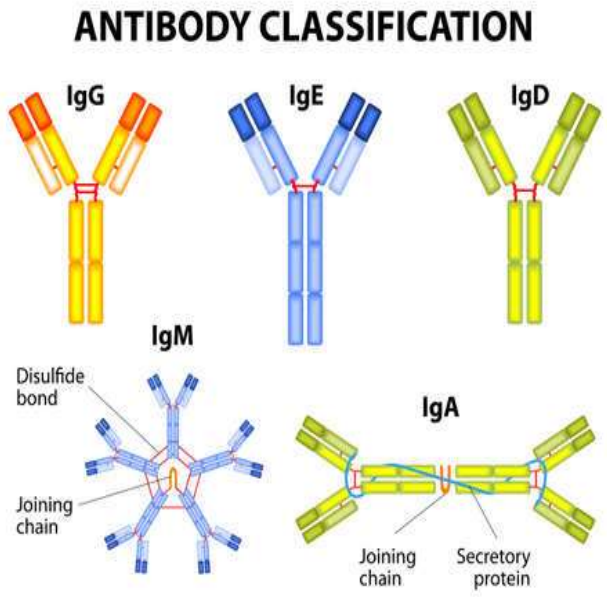
Immunoglobulins





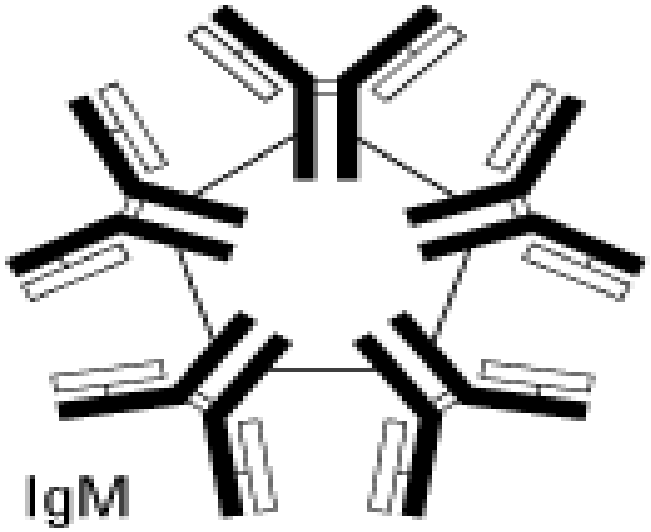
- The immunoglobulin monomer consists of two heavy chains (H) and two light chains (L), linked by disulfide bridges, and has a Y-shape. Each immunoglobulin molecule has 2 identical antigen-binding Fab fragments (Fragment antigen binding) and one Fc-fragment (Fragment cristalisable), with the help of which IGs complementarily bind to Fc-receptors of the cell membrane.
- There are two kinds of light chains: ƙ and ƛ; five types of heavy chains: α, γ, δ, ε and μ, which correspond to five isotypes (classes) of antibodies - IgA, IgG, IgD, IgE and IgM.
- Each L and H chain consists of a variable region (V region, VL and VH) and a constant region (C region, CL and CH). Each light chain has one V region and one C region.
- Each heavy chain has one V region and 3 or 4 homologous constant regions. IgG, IgD, IgA have three constant regions, Ig M, Ig E - 4 constant regions.
- The light chain of immunoglobulins is formed by 214 amino acid residues. The first 107 amino acid residues form the V region, the second 107 amino acid residues (108-214) form the C region of the light chain.
- Heavy chain IgG, IgD, IgA consists of 450 amino acid residues. The V region of these immunoglobulins is formed by 116 amino acid residues, the C region includes about 334 amino acid residues, its homologous regions CH1, CH2, CH3 consist of about 100-110 amino acid residues.
- H chains, regardless of the class of immunoglobulins, can be linked to either the kappa or lambda type of L chain. According to the type of H-chain (α, γ, δ, ε and μ), there are five classes of immunoglobulins: Ig G, Ig M, IgA, Ig D, Ig E. Each class of immunoglobulins has special properties and biological activity.
- The variety of immunoglobulins is possible due to genetic recombinations (discussed in the lecture "Regulation of gene expression").

https://www.ukessays.com/essays/sciences/introduction-immunoglobulins-structure-4000.php

https://www.123rf.com/photo_27277653_stock-vector-different-types-of-immunoglobulins-igg-iga-igd-ige-and-igm.html

Immunoglobulin M

- **Immunoglobulins M (IgM)** are the heaviest and most complex immunoglobulins. The free IgM molecule is a pentamer in which monomers are linked by disulfide bridges and a J-chain.
- When the antigen first enters the body, IgM immunoglobulins are formed first from all antibodies.
- Immunoglobulins M can interact with component C1 of the complement system and activate the classical pathway of the complement system, resulting in antigen opsonization and cytolysis.
- IgM do not cross the placenta (only immunoglobulins G pass through it). But, they are the first to appear in onto- and phylogeny.
- The presence of IgM in the blood plasma against certain pathogens indicates the early stages of infection, and in the blood of a newborn - an intrauterine infection.



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Immunoglobulin G

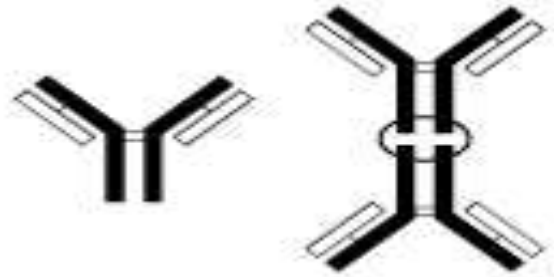
- **Immunoglobulins G (IgG) -** IgG make up about 75% of human plasma antibodies and are the most commonly found antibodies in the bloodstream.
- Antibodies constitute a major part of humoral immunity. IgG is secreted as monomers that easily penetrate tissues.
- IgG is the only type of antibody capable of crossing the placenta to protect the fetus. Along with IgA, which are part of breast milk, residues of IgG that have penetrated into the fetus through the placenta provide the infant with humoral immunity (for about 6 months) until his own immune system starts working.
- IgG is the main type of antibodies in blood and intercellular fluid, therefore it takes part in the control of infection throughout the body, binding with a variety of pathogens: viruses, bacteria, fungi. Binding of IgG to pathogens causes them to immobilize and bind to each other (agglutination). Coating the surface of the pathogen with IgG molecules (opsonization) allows phagocytes to recognize, absorb and destroy it.
- IgG activates the classic complement system pathway, which leads to the formation of proteins that destroy the pathogen.
- IgG is also capable of binding and neutralizing toxins. This type of antibody plays an important role in antibody-dependent cellular cytotoxicity and intracellular proteolysis. IgG is also associated with type II and III hypersensitivity reactions. IgGs are formed by switching antibody classes, so they are mainly involved in the secondary immune response.
- IgGs are involved in the development of allergic reactions and can prevent IgE-mediated anaphylactic reactions by interacting with antigens earlier than IgE associated with mast cells. Thus, IgG blocks systemic anaphylaxis caused by the penetration of a small amount of antigen into the body, at the same time participating in anaphylactic reactions provoked by a large amount of antigen

IgG

https://www.thermofisher.com/ua/en/home/life-science/antibodies/antibodies-learning-center/antibodies-resource-library/antibody-methods/immunoglobulin-structure-classes.html#:~:text=Antibodies- Structure%20of%20immunoglobulins identical

Immunoglobulin A

- **Immunoglobulins A (IgA)** - dominate in the secretions of the body (saliva, digestive juice, secretions of the nasal mucosa and mammary gland), their share in the blood plasma is 10-15% of the total amount of all immunoglobulins. It exists in two forms: monomeric and dimeric form. IgA monomers are most abundant in blood plasma, and dimers are found in secretions, also called secretory immunoglobulins (sIgA).
- In the secretory IgA molecule, in addition to heavy and light chains, there is a J-chain and a secretory component. The J chain is required for the molecule to polymerize. The J-chain is a small protein not homologous to immunoglobulins. The secretory component is several polypeptides with similar antigenic properties, which are expressed on the surface of epithelial cells and are capable of specific interaction with IgA dimers. The complex of the IgA dimer and the secretory component undergoes endocytosis and moves through the cytoplasm to the apical part of the cell. There it is exposed to proteolytic enzymes, due to which it acquires the ability to be released into the secretions of the subepithelial space.
- The main function of IgA is the first line of defense on the mucous membranes of the body, preventing the penetration of viruses. IgA does not interact with the complement system and does not possess bactericidal properties, but is involved in neutralizing bacterial toxins. IgA is contained in colostrum in an amount sufficient to ensure the specific immunity of newborns.
- In the blood, IgA interacts with the Fc receptor CD89, which is expressed by effector immune cells, thereby triggering inflammatory processes. The interaction of IgA-containing complexes with CD89 causes antibody-dependent cytotoxicity, degranulation of eosinophils and basophils, and also triggers the phagocytic activity of monocytes, macrophages and neutrophils.



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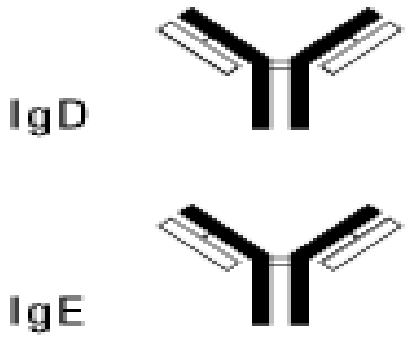
Immunoglobulins D и E

- **Immunoglobulins D (IgD) -** make up 1% of the membrane proteins of immature B-lymphocytes, and usually IgD is expressed with other membrane antibodies called immunoglobulins M (IgM). In blood plasma, IgD is present in a very small amount and accounts for 0.25% of all immunoglobulins in blood plasma.



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- **Immunoglobulins E (IgE)** are contained in blood plasma at very low concentrations. Their main role is in the development of allergic reactions, in addition, they are involved in the immune response to the ingress of parasites, such as helmints.

- IgE play a key role in the development of type I hypersensitivity reactions and, therefore, various manifestations of allergy (allergic asthma, allergic rhinitis, food allergy, etc.) Fc-regions of IgE molecules interact with special receptors on mast cells and basophils and activate the secretion of histamine , Leukotrienes and some interleukins, which leads to the development of allergic reactions. The action of IgE associated with basophils and mast cells also targets helminths.

Cytokines

- **Cytokines** are a group of biologically active substances that have a hormone-like effect and ensure the interaction of the immune, nervous and endocrine systems. They regulate intercellular and intersystemic interactions, determine cell survival, stimulation or suppression of their growth, differentiation, functional activity and apoptosis.
- Cytokine producers - lymphocytes, macrophages, granulocytes, reticular fibroblasts, endothelial cells.Основные свойства цитокинов:

✓ have a peptide nature, as a rule, the molecular weight does not exceed 30 kDa.

✓ have membrane receptors;

✓ have autocrine and paracrine effects;

✓ are synthesized in the course of the immune response and participate in its regulation;

✓ are active at very low concentrations;

✓ have a pleiotropic effect - one cytokine performs several fundamentally different functions;

✓ have a duplicate effect - different cytokines can have the same effect.

- **Types of cytokines:**
- Interleukins
- Interferons
- Tumor necrosis factors
- Colony-stimulating factors
- Chemokines
- Growth factors

Interleukins

- To date, about 20 interleukins have been described. According to their functional activity, they can be divided into **pro-inflammatory** (IL-1, IL-2, IL-6, IL-8) and **anti-inflammatory** (IL-4, IL-10, IL-13).
- ***Interleukin 1 (IL-1).***

✓ Produced by monocytes, macrophages, fibroblasts, endothelial cells.

✓ One of the main mediators of inflammation. It induces the production of IL-2 and the expression of receptors for it, and also induces the production of IL-3 IL-6 IL-8, colony-stimulating factors. Stimulates the synthesis of proteins of the acute phase by hepatocytes. Acts on the central nervous system - causes fever, drowsiness, anorexia. Activates gene expression of phospholipase A2.

- ***Interleukin 2 (IL-2).***

✓ Produced by T-helper type 1.

✓ Induce proliferation of T cells, maturation of T-killers, proliferation and differentiation of B-lymphocytes, induces the synthesis of interferon γ.

- ***Interleukin 3 (IL-3).***

✓ Produced by activated T-lymphocytes, stimulates hematopoiesis.

- ***Interleukin 4 (IL-4).***

✓ It is produced by T-helpers 2 , blood basophils.

✓ Induces the proliferation of B-lymphocytes and Th2, activates mast cells. Enhances the expression of Fc-receptors to the Fc-fragment of IgE. Activates IgE production. IFN-γ antagonist.

- ***Interleukin 5 (IL-5).***

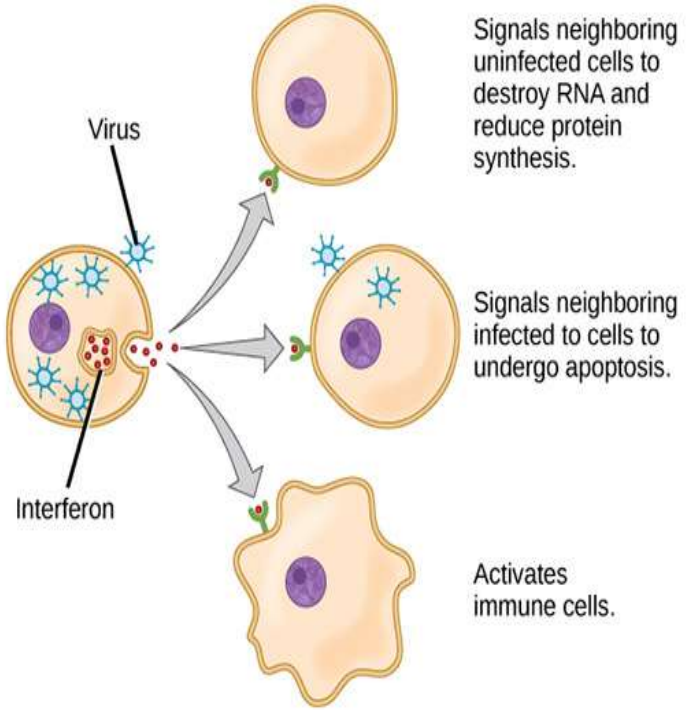
✓ Produced by type 2 T-helpers, monocytes, endothelial cells

✓ Activates eosinophils. Increases IgA secretion.

- ***Interleukin 6 (IL-6).*** It is produced by type 2 T-helpers, blood monocytes, macrophages. Stimulates the synthesis of proteins of the acute phase by hepatocytes, enhances the differentiation of B-lymphocytes, one of the main participants in the induction of the acute phase of inflammation.
- ***Interleukin 10 (IL-10).*** It is produced by type 2 T-helpers, blood monocytes. It has a suppressive effect on the production of pro-inflammatory cytokines (especially IFN-γ and IL-2).
- ***Interleukin 13 (IL-13).*** Th2 is synthesized. Stimulates the growth and differentiation of B-lymphocytes, inhibits the function of monocytes / macrophages, in particular the secretion of pro-inflammatory cytokines.

Interferons

- **Interferons (IFN).** They are secreted by the cells of the body in response to the invasion of the virus, to some bacterial substances and to low-molecular-weight chemical compounds.
- They have immunoregulatory, antitumor, antiviral, radioprotective activity.
- By structure - glycopeptides or glycoproteins.
- There are three main groups of interferons: IFN α, β, γ.



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Interferons

- **Interferon α (IFNα, IFN-α).** Includes a family of 20 peptides produced by leukocytes.

✓ Has antiviral and antiproliferative effects on cancer cells.

✓ They stimulate the synthesis of leukotrienes and prostaglandins, reduce the synthesis of m-RNA and virus proteins:

✓ The cell begins to synthesize the enzyme 2'-5'-oligoadenylate synthetase, which activates the synthesis of 2'-5'-oligoadenylates, which, in turn, activate an endonuclease that destroys the viral mRNA molecule.

✓ Activate protein kinase, which phosphorylates translation factor - eIF-2, which suppresses protein synthesis.

✓ Inhibits methylation or glycosylation of viral RNA.

✓ Activates the Expression of the MHC I and II classes. Activation of MHC I synthesis provides effective presentation of viral peptides to cytotoxic T-lymphocytes and natural killer cells, and the immunoproteasome processes viral peptides prior to presentation. A high level of MHC II ensures the presentation of viral antigens to helper T cells. Helper T cells, in turn, release cytokines that coordinate the activity of other cells in the immune system. The antitumor effect is similar to the above, plus they inhibit the metastatic activity of cells, activate the restoration of the cytoskeleton, activate the synthesis of collagen, fibronectin by fibroblasts.

- **Interferon β (IFN β, IFN-β).**

✓ It is synthesized by fibroblasts when exposed to double-stranded RNA.

✓ The protein portion of human β-interferon consists of 166 amino acid residues and contains a glycosylation site (Asn-Glu-Thr) Approximately 30% homologous to alpha interferons.

✓ It acts through analogous receptors with IFNα and has a similar effect.

- **Interferon γ (IFN-γ, IFN-γ).**

✓ It is synthesized by T-lymphocytes when exposed to mitogens (staphylococcal enterotoxin, some lectins, etc.). The protein part of γ-interferon consists of 143 amino acid residues and has two potential glycosylation sites. Natural γ-interferon is represented by three proteins.

✓ Activates the Expression of the MHC I and II classes.

✓ In general, it takes part in all stages of the immune response and inflammation. It has a very strong inducing effect on cytotoxicity. Activates the differentiation of Th1, B-cells, T-killers, macrophages, neutrophils.

✓ γ-Interferon acts on other cellular receptors than α - and β-interferons and differs from the latter in less pronounced antiviral and more pronounced immunoregulatory and antitumor activities.

Tumor necrosis factors

- **Tumor necrosis factors (TNF)** are extracellular proteins that are practically absent in the blood of a healthy person and are actively produced during inflammation, autoimmunization, and tumors. A family of cytokines that induce cell apoptosis. The first members of the family to be discovered were tumor necrosis factor-α and β proper. The family currently includes 18 proteins.TNF α (кахексин).

✓ Produced by monocytes, macrophages.

✓ Influences lipid metabolism, coagulation, insulin resistance, stimulates the production of IL-1, IL-6, IL-8, interferon-gamma

✓ Synergist with epidermal growth factor m and fibroblast growth factor.

✓ Stimulates the proliferation of endothelial cells, fibroblasts, lymphocytes.

✓ Activates apoptosis of tumor cells.

✓ Has a cytotoxic effect on neutrophils infected with viruses and parasites.

✓ Activates the nuclear transcription factor NF-κB.

- **TNF β.** It is synthesized by lymphocytes. Has a cytotoxic effect.
- Excessive production of TNF causes hemodynamic disorders (reduces myocardial contractility, minute blood volume, diffusely increases capillary permeability), a cytotoxic effect on body cells. Dysregulation of TNF in humans is associated with various diseases such as Alzheimer's disease, cancer, clinical depression, psoriasis, and inflammatory bowel disease (Crohn's disease, ulcerative colitis).

Colony-stimulating factors. Chemokines

- **Colony-stimulating factors (CSF)** are cytokines that regulate the division and differentiation of bone marrow stem cells and hematopoietic cells. In addition, they can stimulate the differentiation and functional activity of certain cells outside the bone marrow.
- **Granulocyte CSF (G-CSF)** is produced mainly by macrophages as well as fibroblasts. Stimulates the division and differentiation of stem cells, to some extent enhances the activity of neutrophils and eosinophils.
- ***Macrophage (M-CSF)*** is produced by monocytes, macrophages, endothelial cells, and fibroblasts. Activates the proliferation of macrophage precursors in the bone marrow. is a leukopoietic factor for monocytes.
- ***Granulocyte-macrophage (GM-CSF)*** is produced by macrophages, T-lymphocytes, monocytes, fibroblasts and endothelial cells. It stimulates the division and differentiation of granulocyte and macrophage precursors, activates their function, and affects the proliferation of T cells.

- **Chemokines** are synthesized by epithelial cells, fibroblasts, neutrophils, monocytes. About 50 different chemokines have been described. There are two classes of chemokines:

✓ **α-chemokines** (for example, IL-8) - mediate predominantly neutrophil chemotaxis;

✓ **β-chemokines** (for example, RANTES) - affect the chemotaxis of monocytes and lymphocytes.

- Chemokines play an important role in coordinating the movement of T- and B-lymphocytes, dendritic and other cells during their differentiation, participation in the immune response. They initiate local inflammation as a result of the involvement of cells in the process of chemotaxis, and then in the process of activating their function.

Growth factors

- The family of **transforming growth factors (TGF)** includes more than 30 members. polypeptides with a molecular weight of 5-50 kDa, combined into a group of trophic regulatory substances. Like hormones, these factors have a wide spectrum of biological effects on many cells - they stimulate or inhibit mitogenesis, chemotaxis, and differentiation. Unlike hormones, growth factors are usually produced by non-specialized cells found in all tissues and have endocrine, paracrine, and autocrine effects.

- The family includes **fibroblast, platelet and endothelial growth factors, insulin-like growth factor, epidermal growth factor,** etc.

- **Transforming growth factor-β (TGF-β)** is the most investigateded multifunctional growth factor. TGF-β is produced by lymphocytes, monocytes, macrophages. It affects the cells of the immune system as a key inhibitory factor, suppresses the proliferation of T and B cells and the functioning of monocytes and granulocytes.

- ***Fibroblast Growth Factor (FGF)*** Includes 19 different proteins. They are mitogens for various cells of neuroectodermal and mesenchymal origin, potential mitogens and stimulators of angiogenesis, support and stimulate cell differentiation. Thus, an increase in the level of this factor correlates with the degree of aggressiveness of the process in many solid tumors, leukemias, lymphomas in children and adults and can serve as a prognostic factor for the aggressiveness of the tumor process.

- ***Epidermal Growth Factor (EGF)*** - acts as a potent mitogen on various cells of endodermal, ectodermal and mesodermal origin. EGF is found in blood, cerebrospinal fluid, milk, saliva, gastric and pancreatic juices. The main site of EGF synthesis is the salivary glands. EGF controls and stimulates the proliferation of epidermal and epithelial cells, including fibroblasts, renal epithelium, glial cells, ovarian granulosa cells, and thyroid cells in vitro.

✓ EGF also stimulates the proliferation of embryonic cells and increases the release of calcium from bone tissue.

✓ It promotes bone resorption and is a potent chemoattractant for fibroblasts and epithelial cells.

✓ EGF alone and in combination with other cytokines is an essential factor mediating wound healing and angiogenesis.

✓ It also acts as an inhibitor of gastric acid secretion.

- Also, representatives of the TGF family are the **BMP (bone morphogenetic protein)** cytokines, which play a key role in cell proliferation, differentiation, apoptosis and migration.

Complement system

- **The complement system** is a system that consists of actually complement proteins (9 main), membrane receptors for complement, as well as regulators of complement activity. The principle of operation of complement is a cascade reaction, in which the product of one reaction is an enzyme for the next.
- **Complement system effects:**

✓ Cytolysis.

✓ The formation of anaphylotoxins (C3a, C4a, C5a), which stimulate the release of histamine and other substances from mast cells and basophils, which cause vasodilation, bronchospasm, etc.

✓ Formation of chemoattractants (Ba, C5a) for leukocytes.

✓ Activation of adhesion, phagocytosis, opsonization (C4b, C3b).

✓ Activation of the kallikrein-kinin system and the coagulation system (C2b).

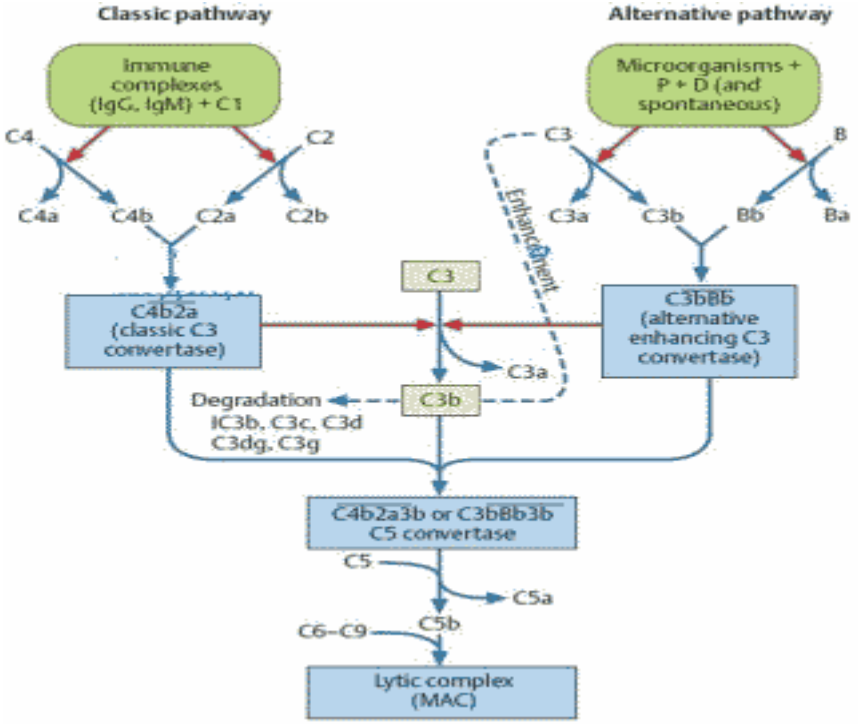
- **Complement activation.**
- There are 3 ways to activate complement:

✓ ***Classical***

✓ ***Alternative***

✓ ***Lectin***

- All complement activation pathways work in parallel, reinforcing each other.
- These three paths ultimately converge into one, where C3-convertase cleaves C3 into C3a and C3b. Cleavage of C3 can lead to the formation of a membrane attack complex (MAC), a cytotoxic component of the complement system. MAC is the cause of the lysis of foreign cells.



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Complement system

- **The classical pathway** is activated by antigen-antibody complexes. Antibodies belong to the IgG or IgM class. Or the pathway is activated by C-reactive protein.
- First, the C1 fraction is activated: it is collected from three subfractions (C1q, C1r, C1s) and is converted into the **C1-esterase enzyme** (C1qrs).
- C1-esterase cleaves the C4 fraction.
- The active C4b fraction binds covalently to the surface of microbial cells and combines with the C2 protein.
- C2 in a complex with the C4b fraction is cleaved by C1-esterase to form the active C2a fraction.
- Active C4b and C2a in one complex - **C4bC2a** - with enzymatic activity. This is the so-called **classical path C3-convertase.**
- C3-convertase breaks down the C3 fraction, producing large amounts of the active C3b fraction.
- The active C3b fraction joins the C4bC2b complex and converts it to the **C5-convertase (C4bC2aC3b).**
- C5-convertase cleaves the C5 fraction to form C5b, which binds further to the C6-9 proteins, forming a **membrane-attacking complex**, which is incorporated into the phospholipid bilayer of the microbial cell membrane.
- This polymer forms a non-falling pore with a diameter of about 10 nm in the membrane of a microbial cell, Na +, Cl-, water, Ca2 + ions enter the cell through the pores, which leads to lysis of the microbe (since many such pores are formed on its surface - the "activity" of one unit C3-convertase leads to the appearance of about 1000 pores.

- In contrast to the classical pathway, the **alternative pathway** of the complement system does not require the participation of antibodies; therefore, it is referred to the humoral mechanisms of innate immunity (and the classical one - to the humoral mechanisms of adaptive immunity). In addition, C1, C4 and C2 proteins are not required. But the participation of proteins of the properdin system, represented by properdin (P), and factors D and B, is required. Using an alternative pathway, the activation of the complement system occurs quickly.
- **An alternative pathway** of complement activation begins with the covalent binding of the active C3b fraction (which is always present in blood serum as a result of the spontaneous cleavage of the C3 fraction constantly occurring here) with the surface molecules of not all, but some microorganisms. C3b binds **factor B** (which is structurally and functionally homologous to factor C2), forming the C3bB complex.
- When bound to C3b, factor B acts as a substrate for **factor D** (serum serine protease), which cleaves it to form the active complex C3bBb.
- This complex has enzymatic activity, is homologous to the C3-convertase of the classical pathway (C4bC2b) and is called the C3-convertase of the alternative pathway.
- C3-convertase of the alternative pathway is unstable, therefore it is stabilized by **factor P (properdin).**
- The resulting complex is a C5-convertase.
- Further events of the formation of the membrane attack complex are the same as in the classical route.

Biochemical mechanisms of immunodeficiency: primary (hereditary) and secondary immunodeficiencies.

- **Immunodeficiencies** are disorders of immunological reactivity caused by damage to certain links of cellular or humoral immunity.
- Immunodeficiencies are divided into primary and secondary.
- Primary immunodeficiencies are congenital (genetic or embryopathic) defects in the immune system. Depending on the level of violations and localization of the defect, they are:

✓ humoral or antibody - with a predominant lesion of the B-lymphocyte system

- X-linked agammaglobulinemia (Bruton's disease)
- deletion of genes of heavy chains of immunoglobulins
- k-chain deficiency
- selective deficiency of IgG subclasses with or without IgA deficiency
- deficiency of antibodies with normal levels of immunoglobulins
- IgA deficiency

✓ cellular

- Di Giorgi syndrome
- primary CD4 cell deficiency
- multiple cytokine deficiency

✓ combined:

- Wiskott-Aldrich syndrome
- ataxia-telangiectasia (Louis-Bar syndrome)
- severe combined immune deficiency
- adenosine deaminase deficiency

- **Primary immunodeficiencies have a number of common manifestations:**

✓ Recurrent and chronic bacterial or fungal infections of the upper respiratory tract, sinuses, skin, mucous membranes, gastrointestinal tract.

✓ Leukocytopenia, thrombocytopenia, anemia

✓ Autoimmune disorders: arthritis, systemic scleroderma, chronic active hepatitis, thyroiditis

✓ Allergic reactions of type 1 in the form of eczema, Quincke's edema, allergic reactions to the administration of drugs, immunoglobulin, blood.

✓ Tumors and lymphoproliferative diseases.

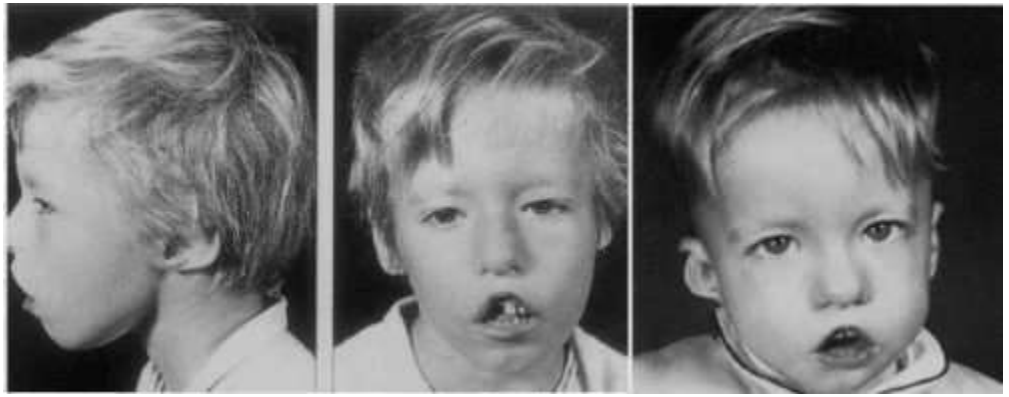
✓ Diarrheal syndrome and malabsorption syndrome**.**

✓ Deficiencies, for example, hypoplasia of cellular elements of cartilage and hair, cardiovascular defects.

- **Secondary immunodeficiency** disorders of the immune system that develop in the late postnatal period in children or adults, which are not the result of genetic defects.
- Secondary immunodeficiency can be caused by both environmental factors and internal factors of the body, for example, exposure to radiation, xenobiotics, chronic stress, viral (for example, acquired immunodeficiency syndrome caused by HIV) and bacterial infections, etc. Secondary immunodeficiencies are a common complication of many diseases and conditions.

Primary (hereditary) immunodeficiencies.

- One example of these pathologies is **Di George's syndrome**, which is characterized by the **congenital absence of the thymus gland (thymus),** which contributes to the normal production of T-lymphocytes.
- **Di George's syndrome** is characterized by: the development of heart defects (Fallot's tetralogy, defect of the interventricular septum), cleft palate, progression of the lower jaw and an open upper lip. Children have a typical appearance, characterized by a small mouth, a small nose, an enlarged bridge of the nose, deformed or underdeveloped cartilage of the auricles. Against the background of hypoplasia of the parathyroid glands, it leads to hypocalcemia, resulting in convulsions and involuntary painful muscle contractions. The disease is also characterized by a pronounced primary immunodeficiency, which is formed with underdevelopment or aplasia of the thymus. Patients often suffer from bacterial, viral and fungal infections. In some cases, the clinical picture is complemented by mental retardation and neurological seizures.



Nezelof's syndrome is a primary immunodeficiency caused by **hypo- or dysplasia of the thymus**. In this case, as a result of its functional insufficiency, there is a violation of the differentiation of T-lymphocytes.

https://osindromah.ru/geneticheskie/sindrom-di-dzhordzhi.html

Primary (hereditary) immunodeficiencies.

- **Синдром Бру́тона** или **агаммаглобулинемия бру́тоновского типа** — недостаточность иммуноглобулинов всех классов. В первые годы жизни развиваются инфекционные осложнения, преимущественно бактериальные. Часто развивается вялотекущий *артрит, похожий на ревматоидный*, со стерильным выпотом в полость одного из крупных суставов.
- В том случае, если заместительная терапия (введение препаратов иммуноглобулинов) начата прежде, чем повторные инфекции вызовут серьёзные морфологические изменения (например, бронхоэктазы, хроническую пневмонию и дыхательную недостаточность), ближайший прогноз очень хороший.
- В подростковом и юношеском возрасте нередко развивается постепенно прогрессирующее неврологическое заболевание, напоминающее медленную вирусную инфекцию и проявляющееся дерматомиозитоподобным синдромом с выраженными отёками и периваскулярными лимфогистиоплазмоцитарными инфильтратами.
- Высокая чувствительность к энтеровирусам. Дети с синдромом Брутона чаще болеют полиомиелитом, и он протекает у них тяжелее.
- **Атаксия-телеангиэктазия Луи-Бар** — наследственное заболевание, при котором, наблюдается низкий уровень или отсутствие IgA — встречается примерно у 70 % больных.
- Помимо иммунодефицита развиваются следующие синдромы:
- Церебеллярная гипоплазия (недоразвитие ткани мозжечка) проявляется нарушением координации движений (*атаксией*); нарушение походки развивается, как правило, с 4-летнего возраста и постепенно прогрессирует.
- Недостаточность ферментов репарации *ДНК* в клетках различных органов, вследствие чего повышается частота соматических мутаций (*нестабильность генома*) и нередко возникают злокачественные опухоли.
- Телеангиэктазии — множественные очаги расширенных мелких сосудов конъюнктивы и кожи (обнаруживаются к концу первого года жизни).
- Недоразвитие половых органов вследствие гипогонадизма (дефицита половых гормонов).
- Раннее поседение волос.

Primary (hereditary) immunodeficiencies.

- **Wiskott-Aldrich syndrome** is a primary immunodeficiency disorder that includes combined disorders of humoral and cellular immunity.

✓ It is a hereditary disease linked to the X chromosome. The cause of the development of Wiskott-Aldrich syndrome is a mutation in the gene that encodes the Wiskott-Aldrich syndrome protein (WASP), a cytoplasmic protein necessary for the normal exchange of signals between T and B lymphocytes.

✓ Due to the dysfunction of T and B lymphocytes, patients develop infections caused by pyogenic bacteria and opportunistic organisms, especially viruses and Pneumocystis jirovecii. Varicella-zoster virus and herpes simplex virus infections are common.

✓ It is characterized by a decrease in the number of T cells and function, an increase in the level of IgE and IgA, a decrease in IgM and IgG, a decrease in the cytotoxicity of natural killer cells, a violation of neutrophil chemotaxis.

- **Adenosine deaminase deficiency**

- The enzyme adenosine deaminase (ADA) in mammals is found in all tissues, but its highest concentration is found in the thymus (10-15 times more than in other tissues). Therefore, a deficiency or defect of this enzyme is accompanied primarily by disorders in the functioning of the thymus.

- **Miller's lazy leukocyte syndrome** is a combination of hereditary defects in the function of neutrophilic granulocytes:

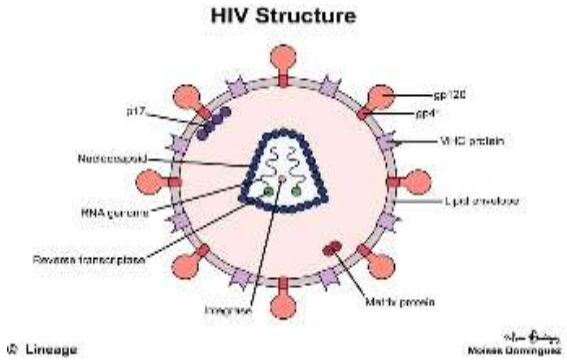
✓ Lack of migration activity (delayed chemotaxis)

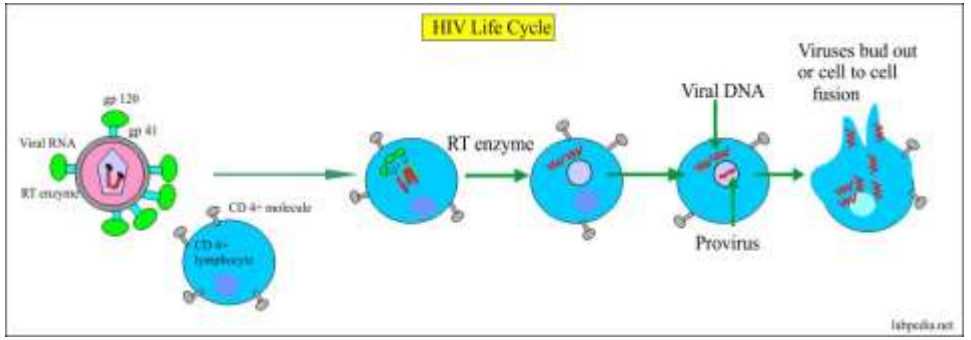
✓ Decrease in the intensity of phagocytosis (delayed chemotaxis and sluggish phagocytosis are the result of dysfunction of the cytoskeleton, which provides cell locomotion and phagocytosis)

✓ Lack of bactericidal function, primarily due to a defect in the oxygen mechanism.

Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)

- **The human immunodeficiency virus (HIV)** is known as the causative agent of a disease called *acquired immunodeficiency syndrome (AIDS)*. Structurally, HIV is similar to the influenza virus (A).
- The group of RNA-containing viruses, to which HIV belongs, is called retroviruses, since their life cycle begins with the synthesis of DNA on an RNA template, that is, with the process of reverse normal transcription, when DNA serves as a template.
- HIV directly infects T-helper cells by binding to CD4.
- HIV has a very high production rate (5000 viruses in 5 minutes). High degree of variability (10-100 times higher than the variability of the influenza virus).
- The HIV genome consists of two single-stranded RNA molecules [ssRNA], each molecule contains 9,200 nt). The virus has a bilayer capsid and is surrounded by a protein-containing membrane. HIV mainly infects T-helper cells, which ultimately causes the development of secondary immunodeficiency.
- During infection, the membrane of the virus fuses with the plasma membrane of the target cell and the nucleocapsid nucleus enters the cytoplasm. There, viral RNA first forms an RNA / DNA hybrid and then is transcribed to form DNA. Both reactions are catalyzed by the reverse transcriptase of the virus. DNA integrates into the genome of the cell, where it can remain in an inactive state.
- When it is activated, a DNA fragment corresponding to the viral genome is first transcribed with the help of host cell enzymes. In this case, there is a replication of both viral RNA and mRNA (mRNA) encoding the precursors of viral proteins. Then proteins are incorporated into the plasma membrane of the cell and there they undergo proteolytic modification. The cycle ends with budding of the newly formed viral particles.





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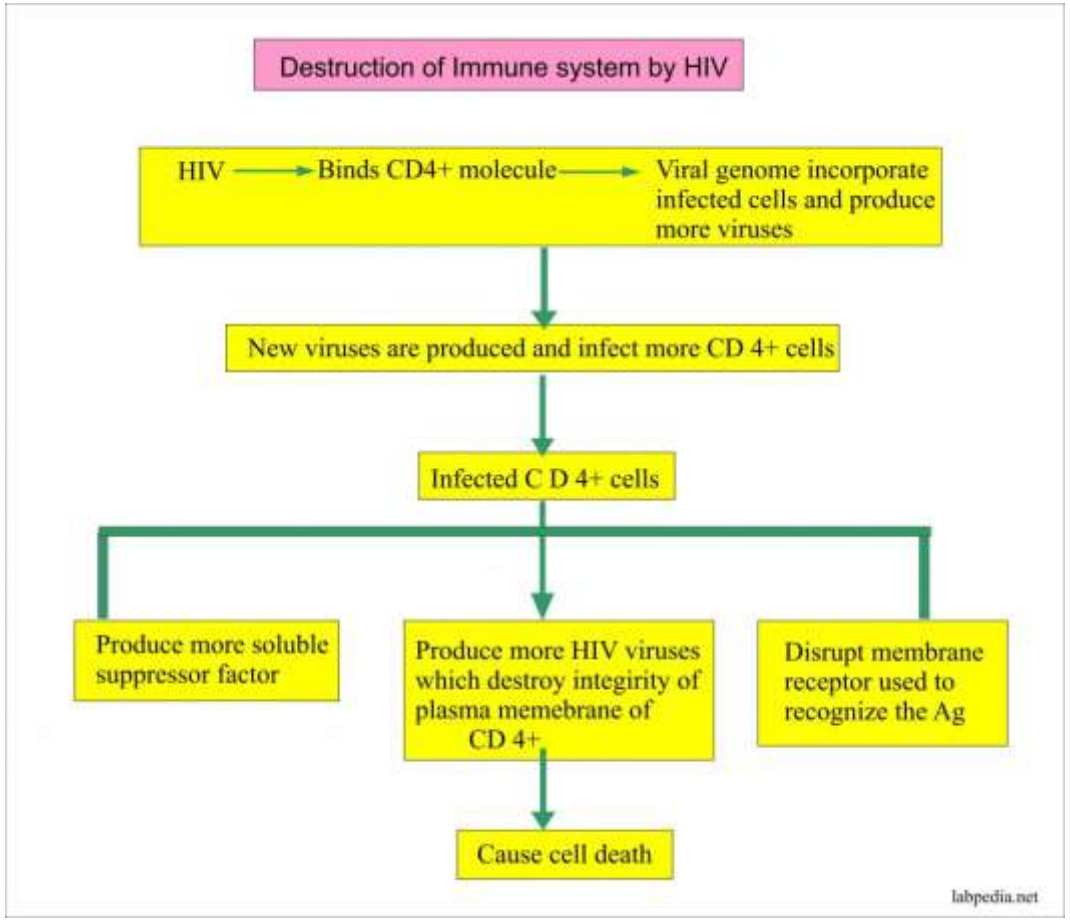
Human Immunodeficiency Virus (HIV) and Acquired Immunodeficiency Syndrome (AIDS)

- Human Immunodeficiency Virus damages T-helper cells, which weakens cellular immunity, increasing the risk of opportunistic infections and cancers.
- The initial infection can cause nonspecific febrile illness. The risk of subsequent manifestations - associated with immune deficiency - is proportional to the decrease in the level of CD4 + lymphocytes.
- HIV can directly damage the brain, gonads, kidneys, and heart, causing cognitive impairment, hypogonadism, renal failure, and cardiomyopathy.
- HIV infection can be diagnosed by tests for antibodies, nucleic acids (HIV RNA) or antigen, characterized by a decrease in CD4 count <200 / μL. Screening should be done regularly for all adults and adolescents.
- Treatment is aimed at suppressing HIV replication with a combination of ≥ 3 drugs that inhibit HIV enzymes; treatment can restore immune function in most patients if suppression of replication persists.



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