LESSON 6

Introduction to immunology. Immunity, its types and forms. Innate immunity and its features. Transplantation immunity. Oral immunity.

Immunity

- From Greek. "immunitas" - liberation from something, inviolability.
- Immunity is a way of protecting the body from genetically alien substances - antigens of exogenous and endogenous origin, aimed at maintaining and maintaining homeostasis, structural and functional integrity of the body.

Types of immunity

- Congenital or species immunity is the inherited immunity of a given species and its individuals to any antigen.
- Acquired immunity is immunity acquired in the process of ontogenesis as a result of a natural encounter with this antigen of the body. It is not transmitted from generation to generation.

Forms of manifestation of immunity

- Antibacterial
- Antiviral
- Antitoxic
- Antifungal
- Antiparasitic
- Transplacental
- Antitumor
- Sterile and non-sterile immunity

- Nonspecific and specific immunity

Sterile and non-sterile immunity

- Sterile immunity - provides complete elimination of the pathogen from the body.
- Non-sterile immunity - does not ensure the complete removal of the pathogen from the body, it is accompanied by the presence of the pathogen, for example, with tuberculosis, syphilis and other diseases. It is also called infectious immunity.

Factors of nonspecific immunity

- Nonspecific protective factors can be divided into: humoral and cellular, specialized and non-specialized.
- Specialized protective factors first of all express the function of protection, while non-specialized factors or non-specific resistance, perform another function, while the protective function plays a secondary role.
- Humoral factors - represented by soluble substances.
- Cellular factors - are represented by various cells.

Non-specialized protective factors, or non-specific resistance

- The skin and mucous membranes are the outer protective barriers of the body.
- A prerequisite for the implementation of protection from antigens coming from outside is the integrity of the skin and mucous membranes.
- In case of violation of the integrity of the skin and mucous membranes, the penetration of microorganisms into the body is facilitated.

Non-specific humoral protective factors

- Nonspecific protective factors are found in all tissues of the body and in the blood in large quantities.
- Usually they have an antimicrobial effect, or they are involved in the activation of other immune factors.
- Nonspecific humoral protection factors include secretory immunoglobulins, complement system proteins, lysozyme, C-reactive protein, transferrin, interferon (IFN), etc.

Lysozyme

- Lysozyme is a substance with enzymatic activity, has a molecular weight of about 14 kDa.
- Destroys glycosidic bonds between N-acetylmuramic acid and N-acetylglucosamine of the bacterial cell wall.
- As a result, the synthesis of the bacterial cell wall is disrupted, and spheroplasts and protoplasts are formed.

Lysozyme

- Lysozyme is produced mainly by monocytes, macrophages, and neutrophils.
- Relatively high concentrations are found in egg white, in lacrimal fluid, in saliva, sputum, in the secretion of the nasal mucosa, and in blood serum.
- High concentrations of lysozyme are found in tissues - cartilage tissue, stomach, at a lower concentration - in the intestines, kidneys, liver, tonsils and brain.
- Lysozyme is not found in the cerebrospinal fluid, its content in tears is 100-160 times higher than in blood serum.

Complement

- Approximately 130 years ago, V. Isaev and R. Pfeiffer discovered a substance with a bacteriolytic effect in fresh animal blood serum.
- Subsequently, this serum antimicrobial factor was called alexin or complement (from Latin Complementum - replenishment).
- According to modern concepts, the complement system is represented by more than 20 thermolabile and thermostable components (C1, C2, C3, etc.) and make up to 10% of the globulin fraction of blood.

Complement

Complement activation occurs as a result of mutual biological transformations of proteases in a certain sequence.

The complement system has a fairly wide biological activity, but the main function is cell lysis.

Activation of the complement system

Three ways of activation of the complement system are known:

classic way

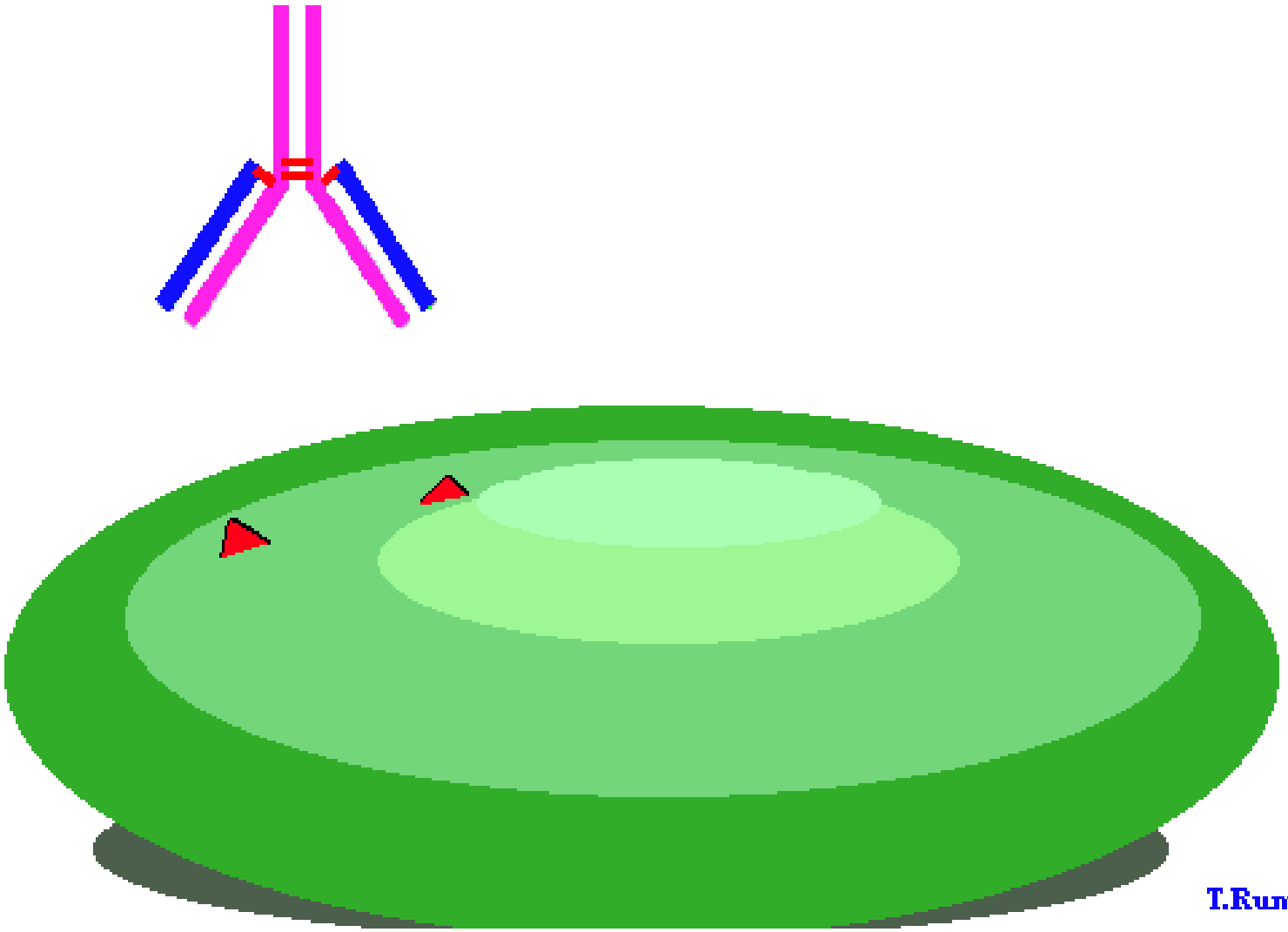
Alternative path

lectin pathway

Activation of the complement system

- In the classical way, the first component (C1) of the complement system is activated by the antigen-antibody complex.
- As a result, the C1 component acquires enzymatic properties and cleaves the following components of the C2 and C4 system.
- The subcomponents formed from C2 and C4 (C2a and C4b) form a protease complex and cleave the C3 component to form C3 convertase of the classical pathway
- As a result, a membrane attack complex is formed.

Activation of the complement system



T.Rummens

Activation of the complement system

- An alternative pathway for complement activation occurs without the participation of antibodies. This pathway is characteristic of protection against gram-negative microbes.
- The cascade reaction in the alternative pathway begins with the interaction of the antigen (polysaccharide) with proteins B, D and properdin P, followed by activation of the C3 component. Further, the reaction proceeds as in the classical way - a membrane attack complex is formed.

Activation of the complement system

- The lectin pathway of complement activation also occurs without the participation of antibodies.
- It is initiated by a special serum mannose-binding protein, which, after interacting with mannose residues on the surface of microbial cells, catalyzes C4. The further cascade of reactions is similar to the classical one.
- Mannose-binding protein is a normal serum protein. Strongly binding to mannose on the surface of microbial cells, it is able to opsonize them.

C-reactive protein

- During an acute inflammatory process in the blood serum, there is a sharp increase in the amount of acute phase proteins, for example, C-reactive protein
- The C-reactive protein was named because of its ability to interact with the C polysaccharide of the pneumococcal cell wall.
- Together with properdin, C-reactive protein initiates complement activation via an alternative pathway.
- The amount of C-reactive protein in the blood increases with various infectious diseases.

Prostaglandins

- Prostaglandins are synthesized during phagocytosis, under the influence of thymus hormones, complement components (C3b), antibodies, etc.

- They contribute to the migration of neutrophils to the focus of inflammation and their degranulation, have pyrogenic activity.

Kinins

- Kinins are alkaline proteins. Formed in plasma or tissues from high-molecular proteins (kininogens) under the action of special enzymes - kallikreins during activation of blood coagulation processes and proteolysis

- They change vascular tone, lower blood pressure, and promote the production of soluble factors by leukocytes.

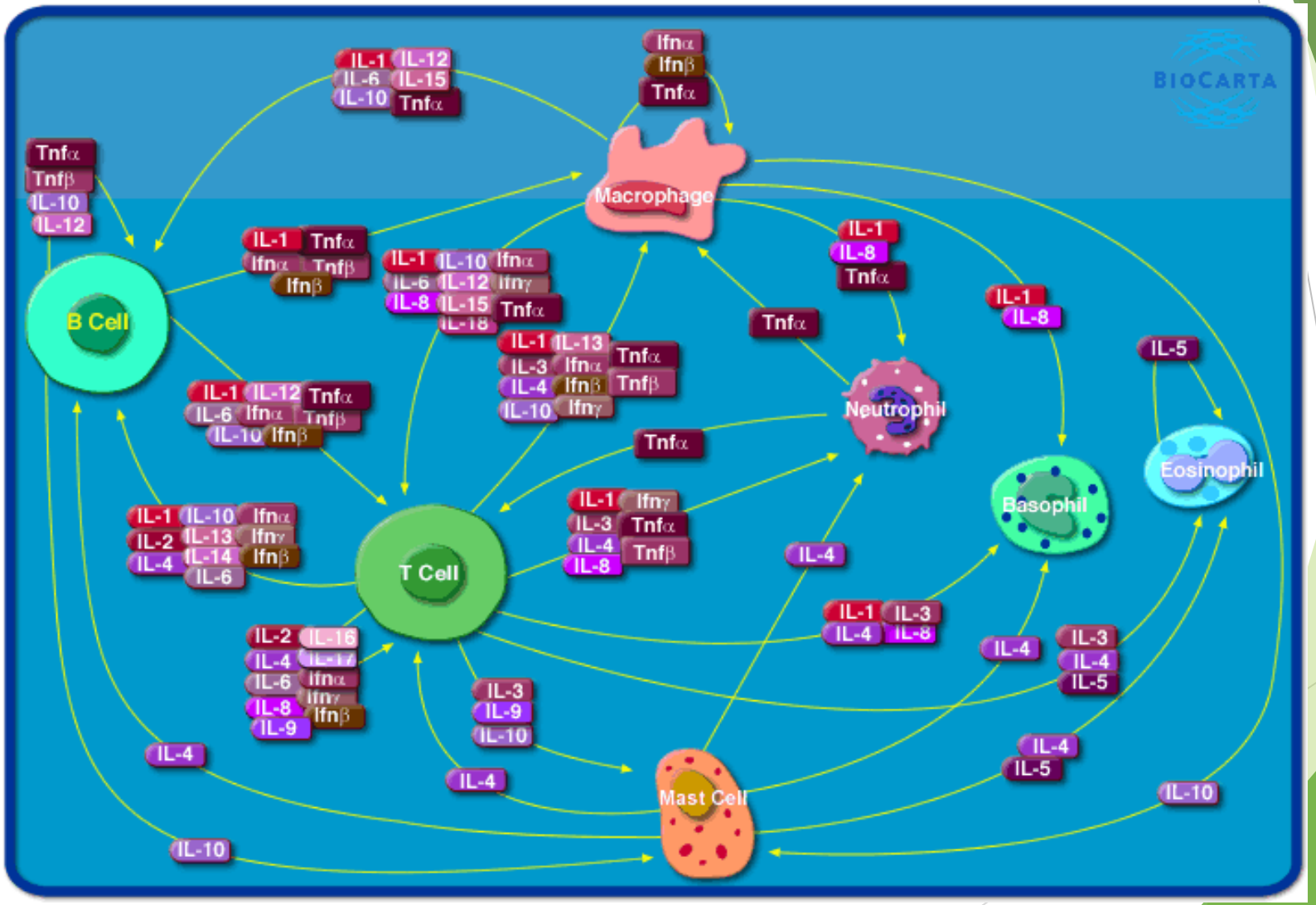
Cytokines

- Cytokines are low molecular weight immunomediators of a protein nature, synthesized by cells of the immune system and providing intercellular cooperation.
- In the absence of antigenic stimulation, cytokines are not synthesized.
- As a result of antigenic stimulation of the corresponding cells, they induce genes that trigger the synthesis of cytokines.

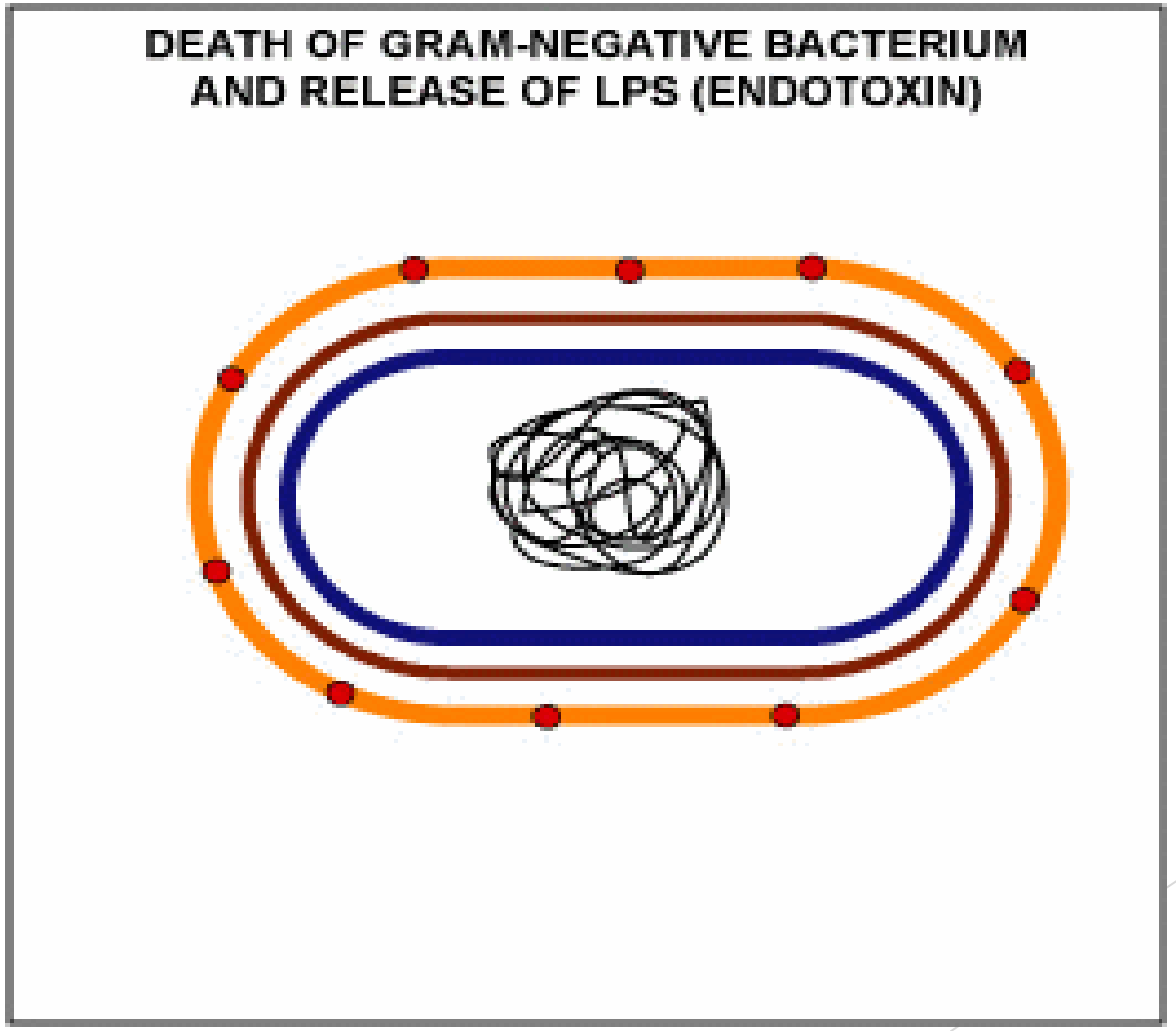
Cytokines

- Cytokines are low molecular weight immunomediators of a protein nature, synthesized by cells of the immune system and providing intercellular cooperation.
- In the absence of antigenic stimulation, cytokines are not synthesized.
- As a result of antigenic stimulation of the corresponding cells, they induce genes that trigger the synthesis of cytokines.

Cytokines


BIOCARTA
Macrophage
B Cell
T Cell
Neutrophil
Basophil
Eosinophil
Mast Cell
IL-1 IL-12 IL-6 IL-15 IL-10 Tnfα
Ifnα Ifnβ Tnfα
Tnfα Tnfβ IL-10 IL-12
IL-1 Tnfα Ifnα Tnfβ Ifnβ
IL-1 IL-10 Ifnα IL-6 IL-12 Ifnγ IL-8 IL-15 Tnfα IL-18
IL-1 IL-13 Tnfα IL-3 Ifnα IL-4 Ifnβ Tnfβ IL-10 Ifnγ
IL-1 IL-12 Tnfα IL-6 Ifnα Tnfβ IL-10 Ifnβ
IL-1 IL-10 Ifnα IL-2 IL-13 Ifnγ IL-4 IL-14 Ifnβ IL-6
IL-2 IL-16 IL-4 IL-6 Ifnα Ifnγ IL-8 Ifnβ IL-9
IL-3 IL-9 IL-10
IL-4
IL-4
IL-10
Tnfα
Tnfα
Tnfα
IL-1 Ifnγ IL-3 Tnfα IL-4 Tnfβ IL-8
IL-4
IL-1 IL-8 Tnfα
IL-1 IL-8
IL-5
IL-1 IL-3 IL-4 IL-8
IL-4
IL-3 IL-4 IL-5
IL-4 IL-5
IL-10

Induction of cytokine synthesis



Classification of cytokines

According to the biological action and structure, there are:

interleukins (IL),

interferons (IFN),

tumor necrosis factor (TNF),

colony stimulating factor

chemokines and other cytokines.

Classification of cytokines

Depending on the producer cell, there are:

monokines synthesized by monocytes and macrophages

synthesized by lymphocytes - lymphokines, etc.

Lymphokines

- The main producer of lymphokines is T-helpers.
- Stimulation of T-helper (Th) by antigen leads to activation and synthesis of IL-2, differentiation into Th1 and Th2 lymphocytes.
- Th1 lymphocytes synthesize interferon, IL-2, TNF.
- Th2 lymphocytes synthesize IL-4,5,6,9,10,13.

Cytokines are classified according to their function.

- Pro-inflammatory immune mediators (IL-1, -6, -12, TNF-¤, etc.);
- Inflammatory immune mediators (IL-5, -9, -10, ¤-IFN, etc.);
- Regulators of proliferation and differentiation of lymphocytes (IL-2, -4, -13, etc.);
- Cell development factors and colony-stimulating factors (IL-3, -7, GM-CSF, etc.);
- Chemokines, or cellular chemoattractants (IL-8, etc.);

Interleukins (IL-1)

To date, more than 20 species are known. They are denoted by Arabic numerals.

One of the first to be discovered was IL-1, the main producers of which are monocytes and macrophages.

At the first stages of immune response reactions, they play the role of non-specific carriers of information about antigenic stimulation from macrophages to T-helpers.

Interleukins (IL-2)

- IL-2 was also studied one of the first. The main producers are T-helpers, the main objects of action are activated T- and B-lymphocytes and natural killers.
- It promotes the proliferation of T-lymphocytes, stimulates the differentiation of T-killers, enhances the cytotoxic activity of natural killers.
- IL-2 is considered one of the growth factors of activated B-lymphocytes. Under its action, the synthesis of immunoglobulins is enhanced.

Tumor necrosis factors

- *Tumor necrosis factors (TNF) are named for their ability to induce tumor cell lysis.*
- *▫-TNF and ▫-TNF, ▫-lymphotoxins are glycoproteins of this group.*
- *▫-TNF is also called ▫-lymphotoxin. The main producers of ▫- and ▫-lymphotoxins are T-killers.*
- *These cytokines have corresponding receptors on target cells. Through receptors, they transmit a signal into the cells, resulting in apoptosis of the target cell.*

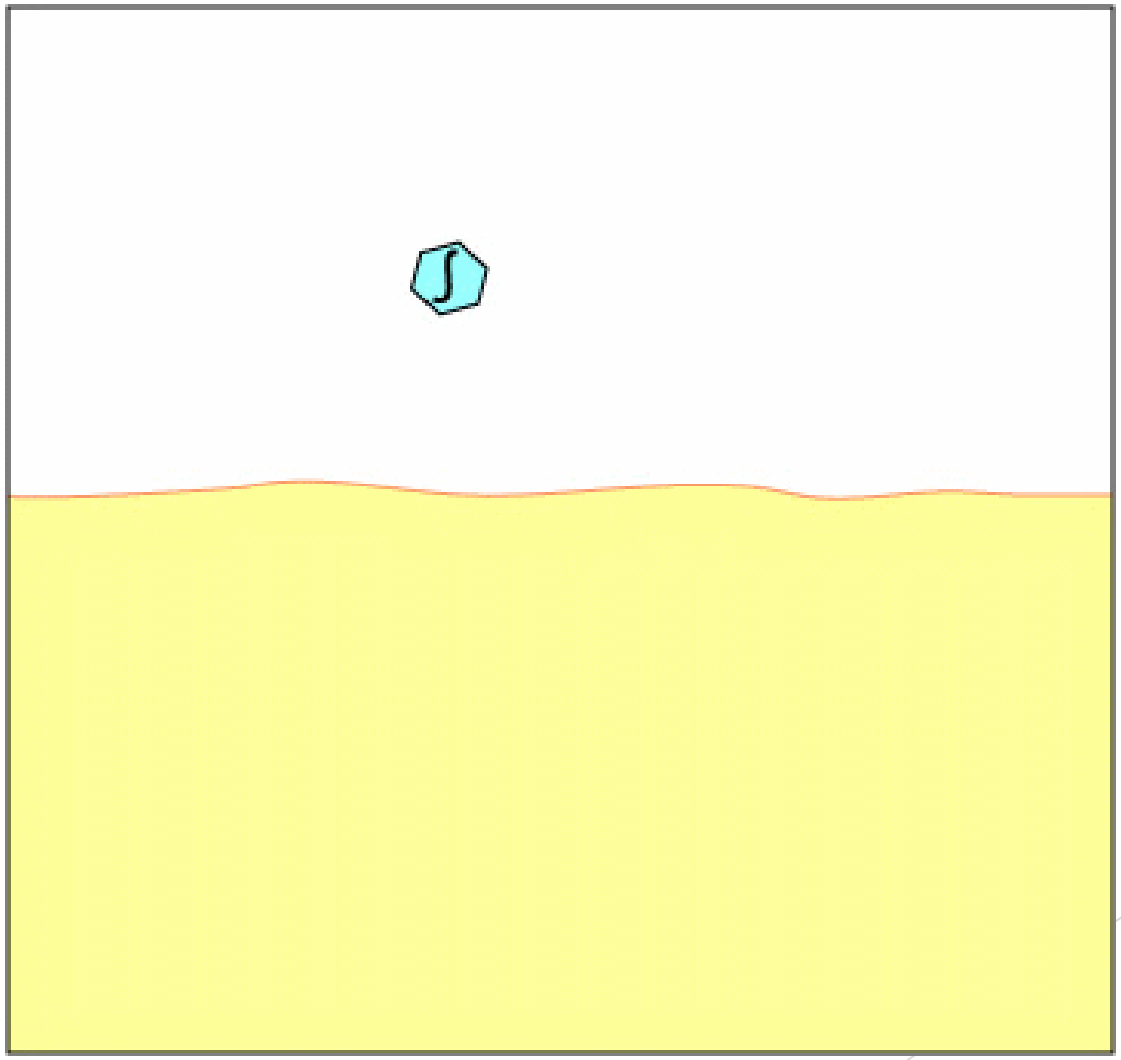
Interferon

- Interferon (IFN) is synthesized not only in immunocompetent cells, but also in somatic cells.
- It has species specificity - interferon formed by human cells is functionally active only in the human body
- IFN synthesis is primarily caused by viruses. Bacteria, fungi, mycoplasmas and other microorganisms, their antigens and nonspecific stimulants such as phytohemagglutinin can also be its inducers.
- Interferon slows down the replication of viruses within the host cell by affecting tRNA and protein synthesis.

Interferon

- *Interferon (IFN) is synthesized not only in immunocompetent cells, but also in somatic cells.*
- *It has species specificity - interferon formed by human cells is functionally active only in the human body*
- *IFN synthesis is primarily caused by viruses. Bacteria, fungi, mycoplasmas and other microorganisms, their antigens and nonspecific stimulants such as phytohemagglutinin can also be its inducers.*
- *Interferon slows down the replication of viruses within the host cell by affecting tRNA and protein synthesis.*

Synthesis of interferon



Types of interferons

- Depending on which cells synthesize interferon, there are:
- Leukocyte (alpha),
- fibroblastic (beta),
- Immune (gamma).

Alpha-IFN (¤-IFN)

- α-IFN is produced by leukocytes.
- α-IFN, influencing the functional activity of immunocompetent cells, plays the role of a mediator of the immune system.
- Under its action, macrophages, lymphocytes, natural killers are activated.

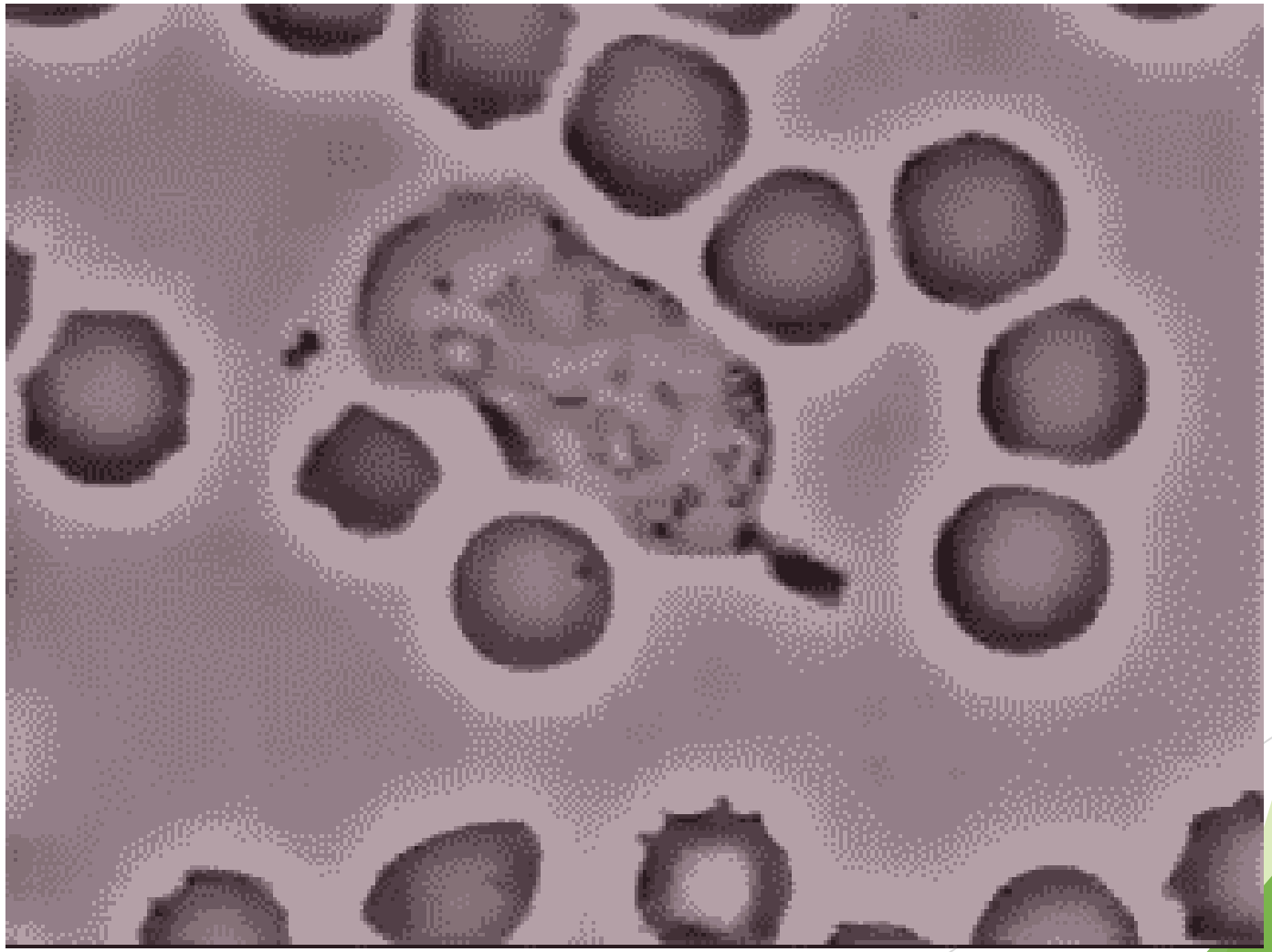
Beta-IFN (β-IFN)

Produced by somatic cells (fibroblasts) of the body in response to a viral infection.

Gamma-IFN (¤-IFN)

- It is synthesized as a result of activation by mitogens or restimulation by antigens of T- and B-lymphocytes.
- ¤-IFN weakens the proliferation of leukocytes and other cells, reduces the biosynthesis of antibodies in vitro.

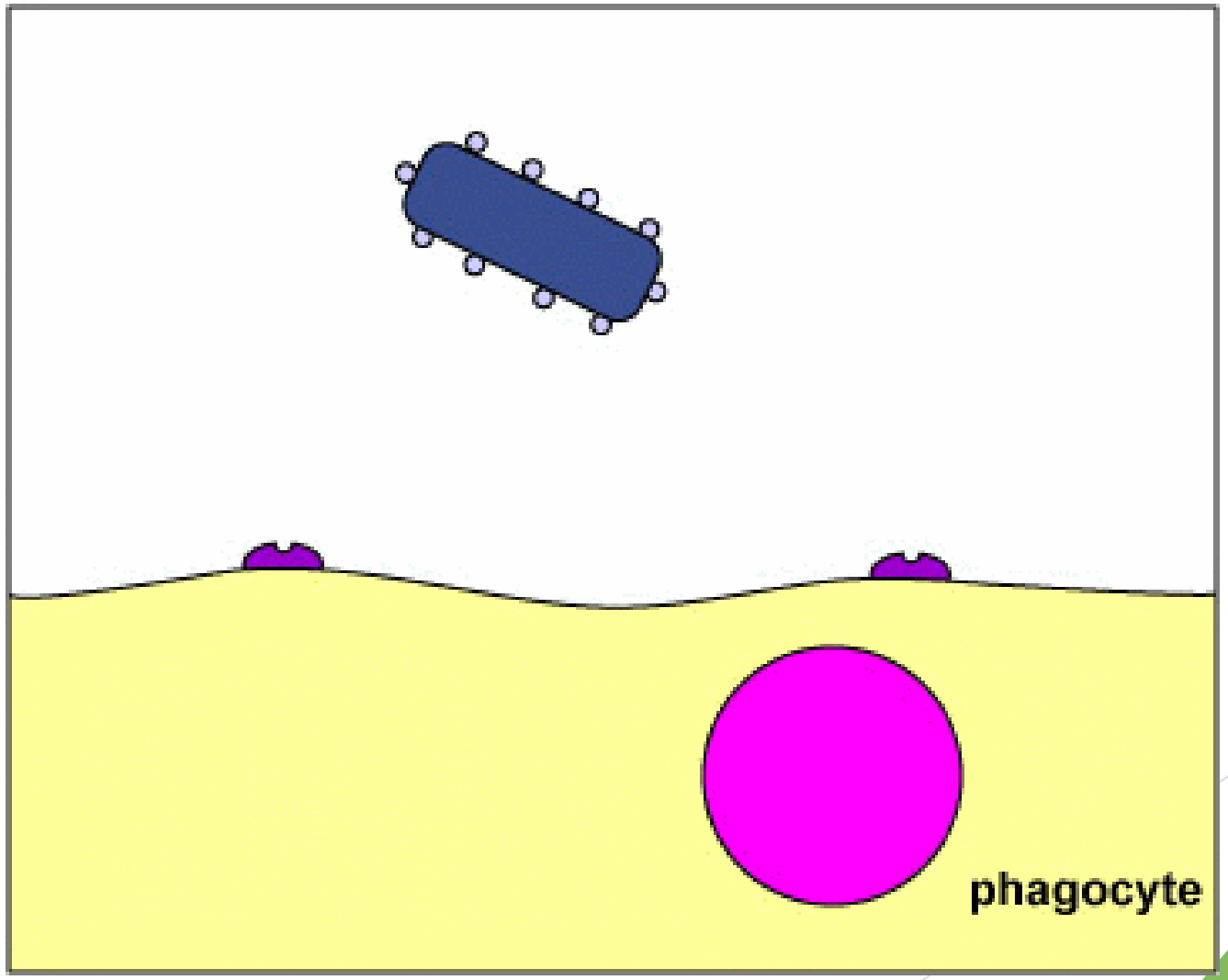
Phagocytosis



Stages of phagocytosis

- The process of phagocytosis consists of three stages - migration, absorption, death (killing).
- The process begins with the approach-migration of the phagocyte to the object of absorption.
- Chemoattractants - products of the activity of microorganisms, substances formed as a result of tissue damage and cell destruction. Under their influence, chemotaxis occurs (from the Greek chymeia - the art of fusion of metals, takhis - arrangement, construction).

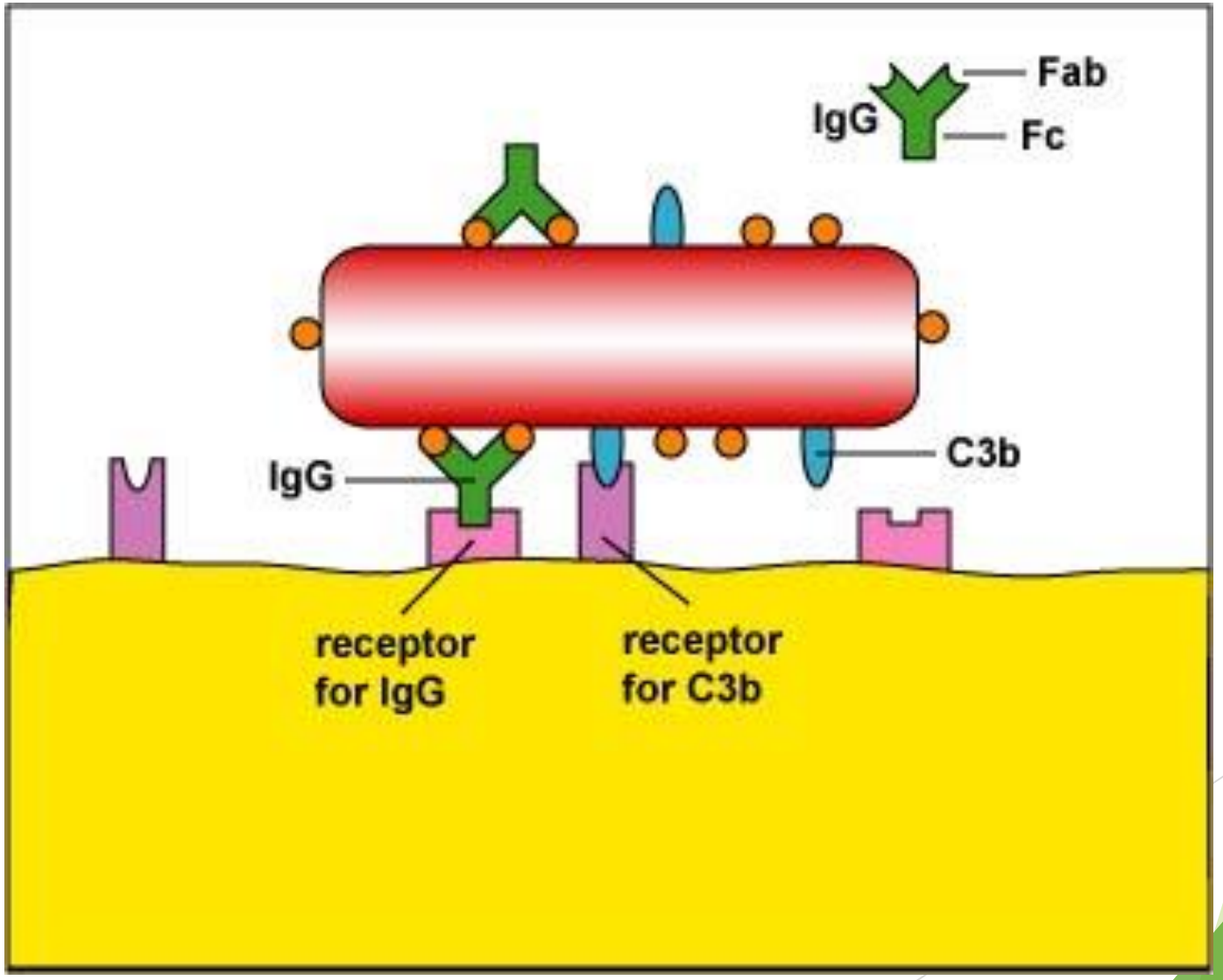
The process of phagocytosis



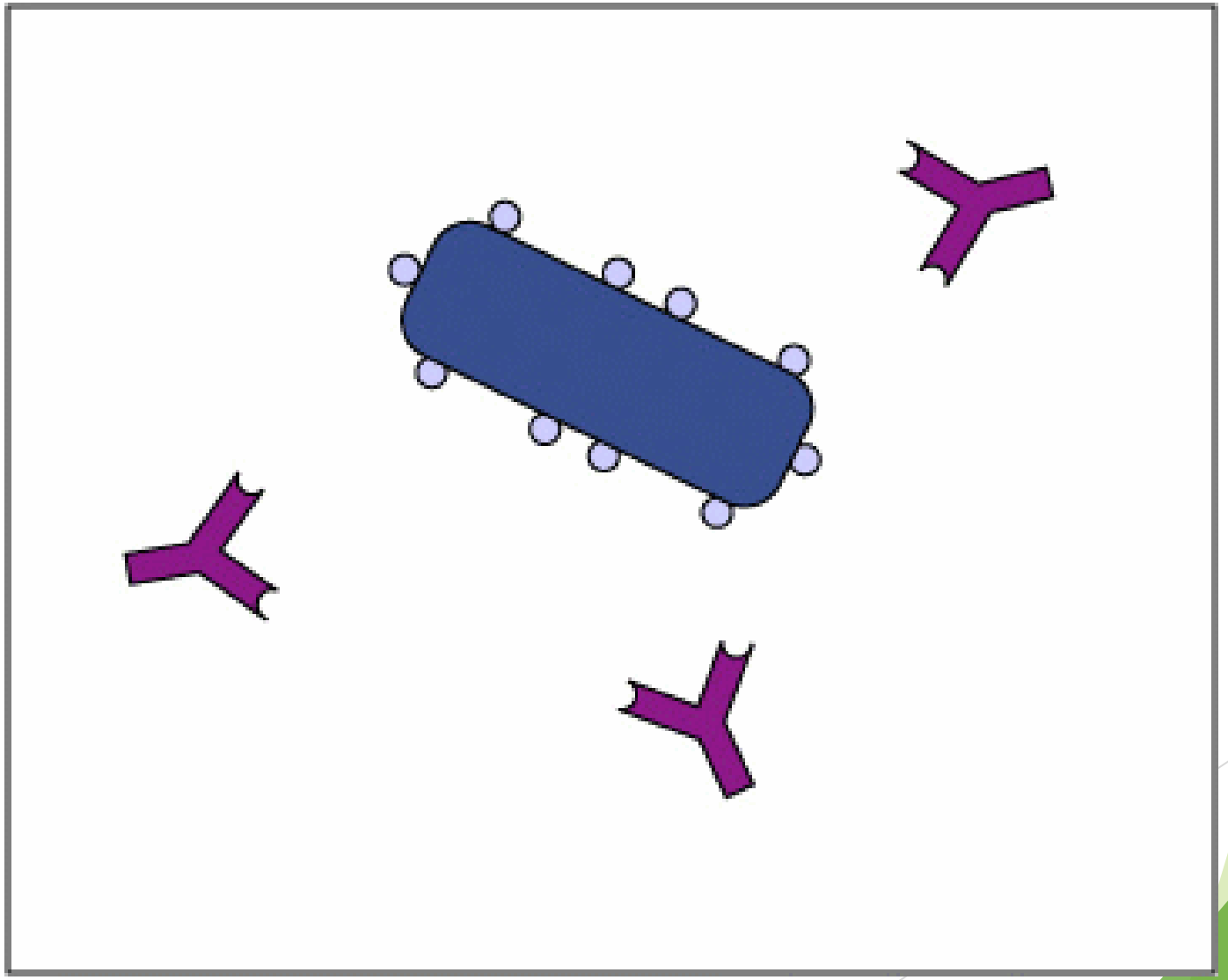
Opsonization

- Opsonization of an object subjected to phagocytosis, i.e. its combination with immunoglobulins and complement is of great importance in the process of phagocytosis.
- The object undergoing opsonization is easily adhered or adsorbed on the surface of the phagocyte, since phagocyte membranes have opsonin receptors.
- The process of phagocytosis can also proceed without opsonization of the object, in which case its efficiency is low.

Opsonization



Opsonization



The mechanism of phagocytosis

- Objects adhered to the phagocyte membrane are surrounded by pseudopodia and swallowed. And as a result, phagosomes (vacuoles) are formed in their protoplasm of the phagocyte.
- In the next stage, inside the phagocyte, the phagosome merges with lysosomes - a phagolysosome is formed, in which the object is processed with enzymes, disintegration and digestion.
- Complete digestion of microorganisms absorbed by phagocytes is called complete phagocytosis.

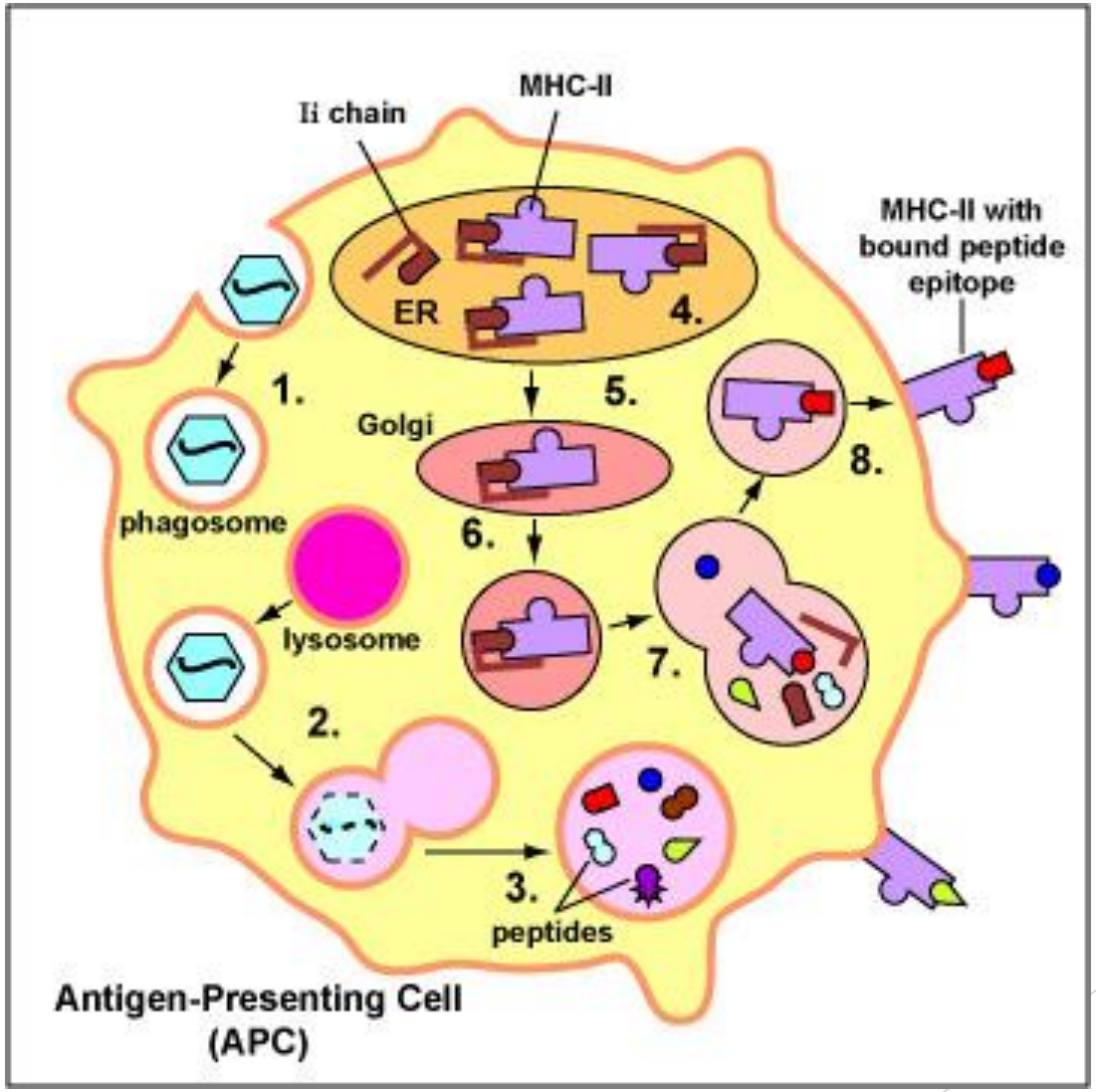
The mechanism of phagocytosis

- Processing, processing, of some microorganisms inside the phagocyte can occur without the process of opsonization.
- In some cases, objects are not processed in activated phagocytes. This phenomenon is observed in granulomatous infections (eg, tuberculosis, brucellosis) and is called incomplete phagocytosis.

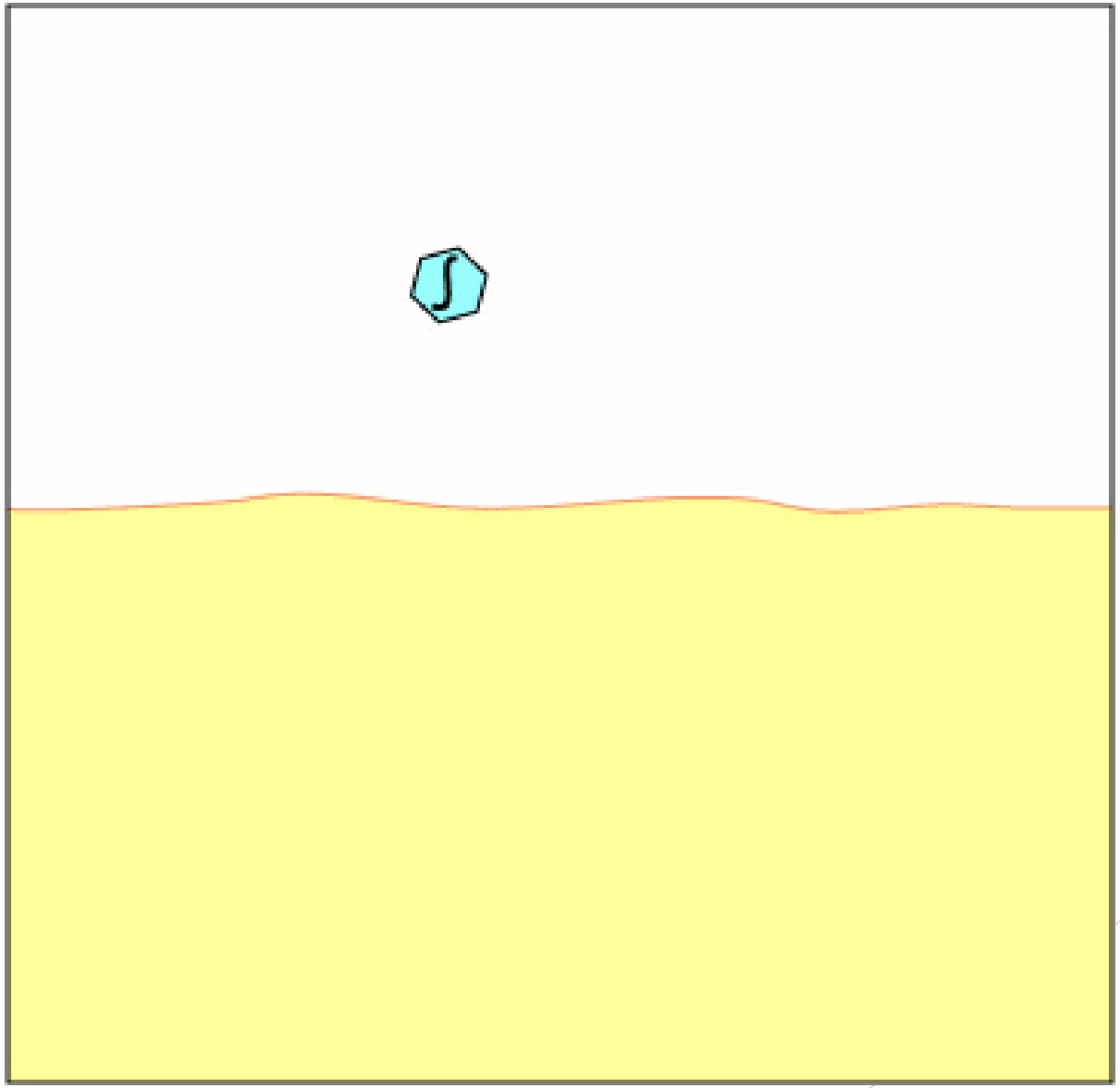
Killing microorganisms in phagocytes

- Killing of microorganisms in phagocytes proceeds by several mechanisms. They can be divided into two types - oxygen-dependent and oxygen-independent.
- The oxygen-dependent mechanism begins immediately after the formation of the phagosome, the death of microbes occurs due to oxygen radicals.
- The absorption of objects by phagocytes is accompanied by a "respiratory explosion" - the production of free oxygen radicals (superoxide radical and hydrogen peroxide).

"digestion" - processing of microorganisms inside phagocytes



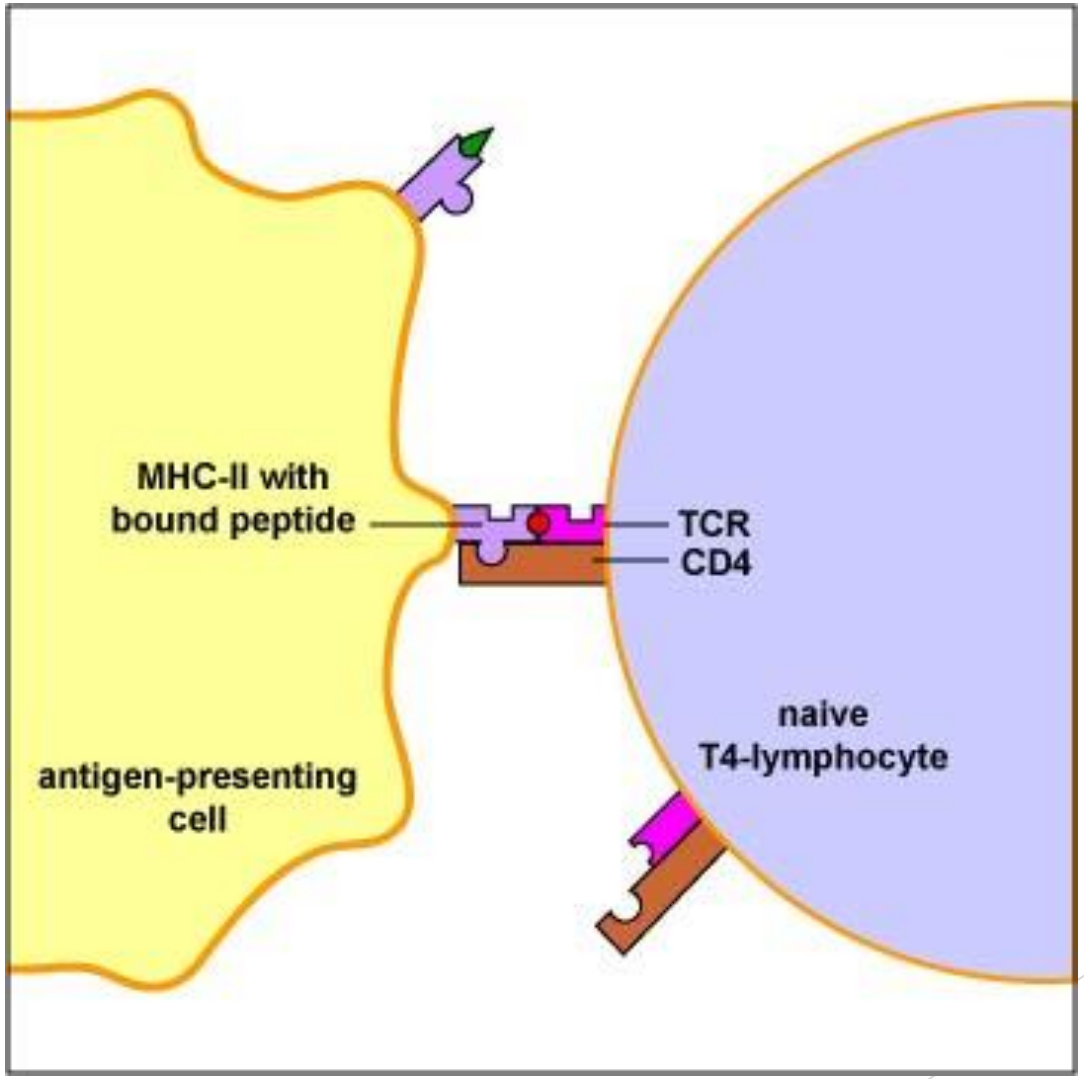
Processing



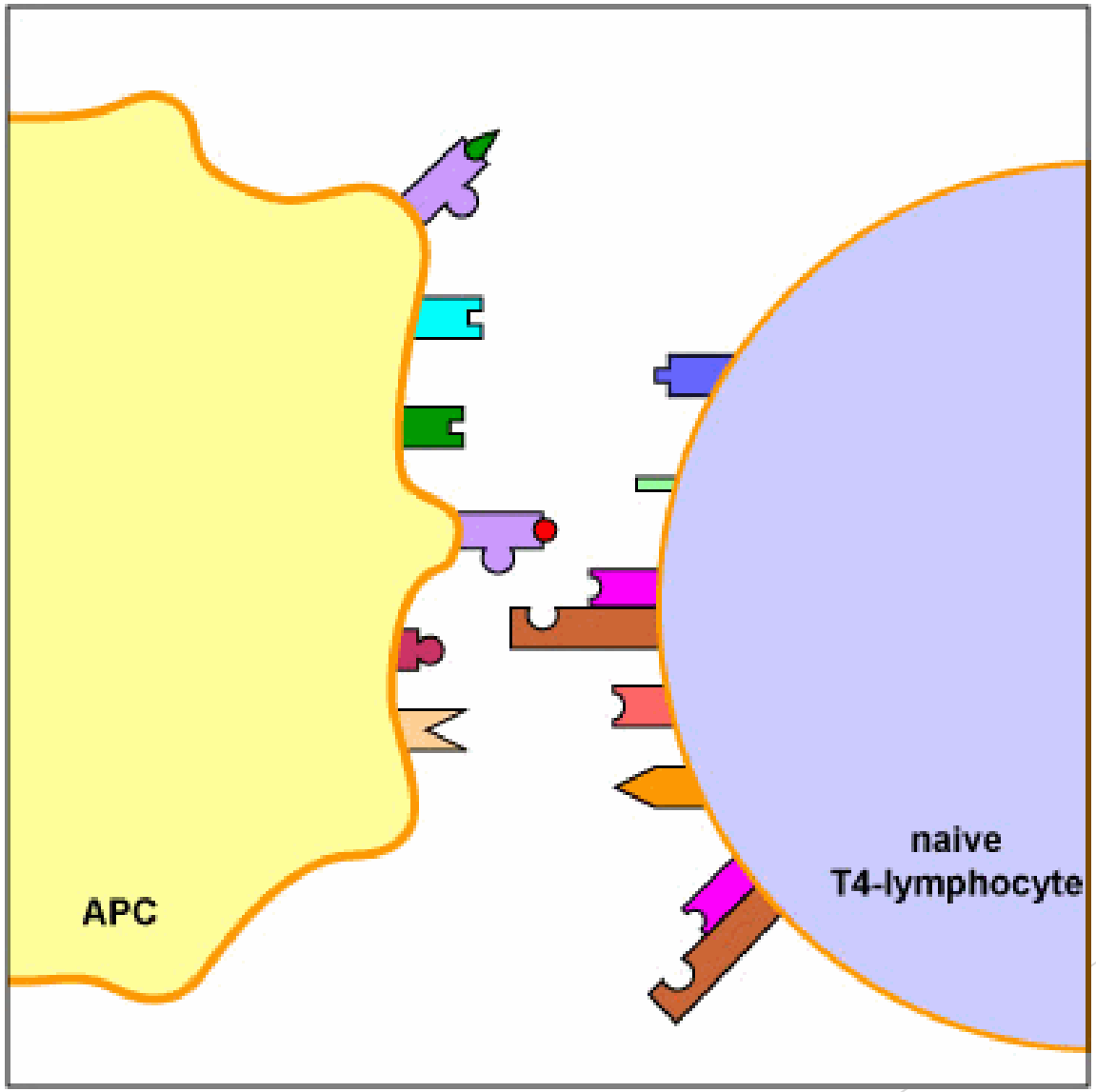
Antigen presenting cells (APCs)

- Macrophages and monocytes perform not only the phagocytic function. According to their functional activity, they are divided into 2 large subpopulations:
- The former are involved only in the process of phagocytosis, the latter are involved in phagocytosis and antigen presentation to lymphoid cells.
- These cells are called antigen presenters. They process the antigen, process it and present it to the cells of the immune response - T- and B-lymphocytes, thus participating in the formation of specific immunity.

Presentation

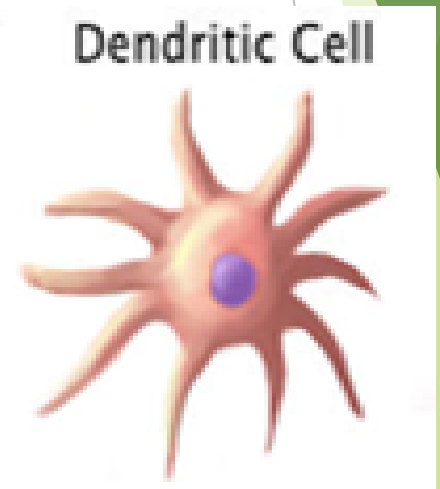


Presentation



Dendritic cells

- Dendritic cells - process cells (hence the name), are localized in the lymphoid organs and barrier tissues - mainly in the epidermis of the skin (Langerhans cells), in the lymph nodes (intergital cells) and thymus dendritic cells.
- MHC class II is expressed on the surface of these cells. They are the most active antigen-presenting cells. They are able to absorb by endocytosis, process (process) and present (present) the antigen to T-helpers in combination with MHC class II.



Eosinophils

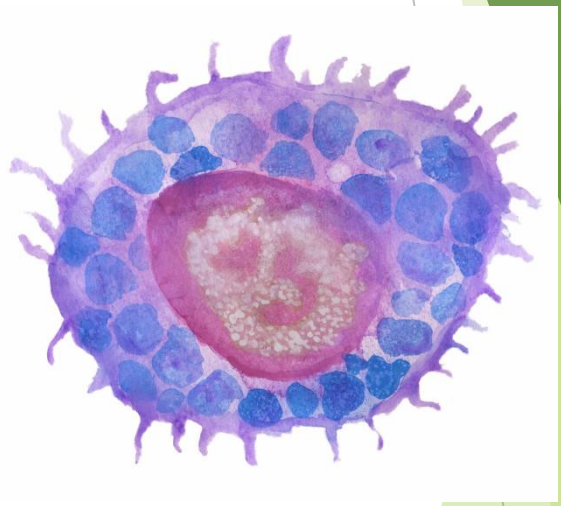
- Eosinophils are granular white blood cells found in connective tissue. They are effector cells involved in the immune response.
- They accumulate in large quantities in the foci of local inflammation caused by helminths and perform the function of killers (antibody-dependent cell-mediated cytotoxicity).
- On membranes, eosinophils carry receptors for IgA and IgE, "recognizing" parasites marked with such antibodies.
- An activated cell releases a number of toxic substances that have a detrimental effect on helminths.

Basophils

- The cells involved in nonspecific protection include basophils - granular leukocytes circulating in the blood.
- There are basophils of mucous and connective tissues.
- Their greatest amount is found in the skin, where, together with the immune system, they participate in the reactions of the immune response, performing an effector function.

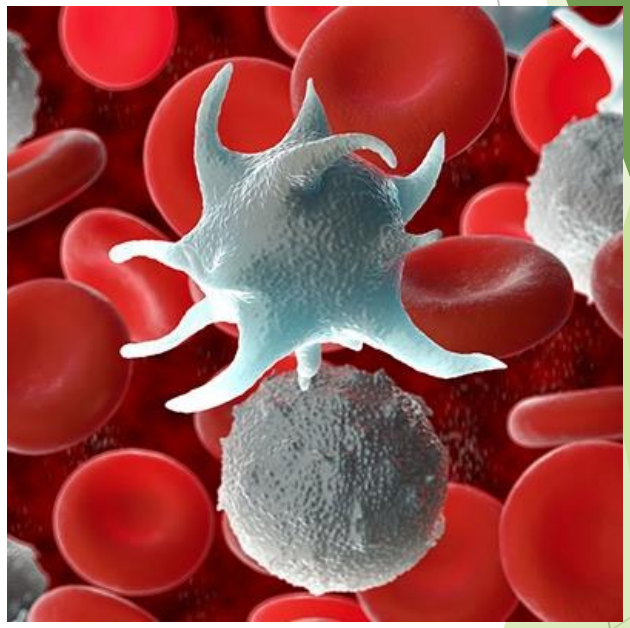
mast cells

- Myeloid cells located along the barrier tissues - mucous membranes and subcutaneous connective tissue.
- According to the set of synthesized biologically active compounds and localization, two types of mast cells are distinguished - cells of the mucous membranes and cells of the connective tissue.



Erythrocytes and platelets

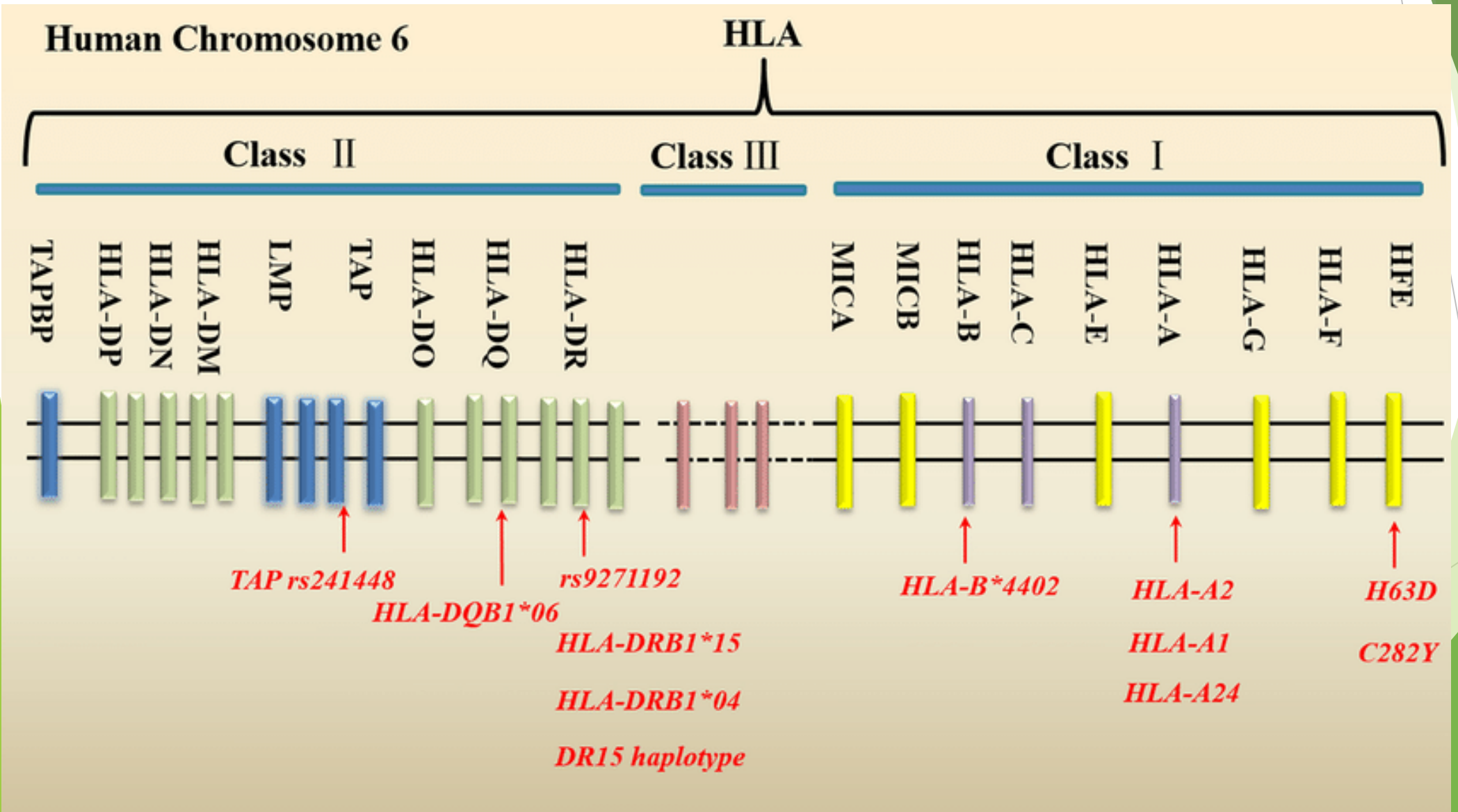
- Erythrocytes, producing erythropoietin, are involved in immune defense. By stimulating hematopoiesis, they contribute to the formation of not only erythrocytes, but also other blood cells, including immunocompetent cells.
- Platelets also belong to the category of protective cells, due to the production of large amounts of serotonin and participation in antitumor defense.



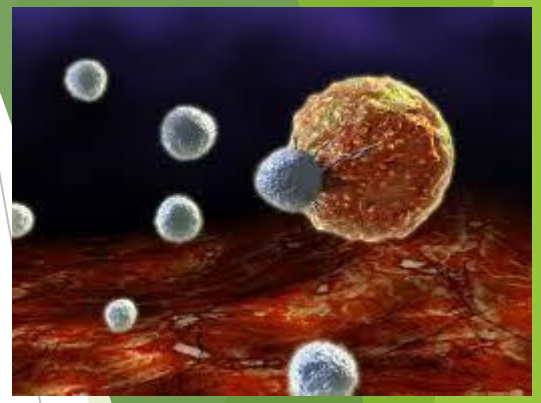
transplant immunity

- After transplantation of non-immunocompetent organs or tissues (kidneys, heart, liver), the immune response of the host organism to the transplant develops, up to its rejection (graft rejection reaction - "host against transplant").
- In the case of transplantation of immunocompetent tissues (bone marrow, peripheral blood stem cells), both the host-versus-graft and graft-versus-host reactions develop (donor lymphocytes attack recipient tissues).
- The rejection reaction can be avoided or reduced by selecting a transplant to the recipient's tissues according to histocompatibility antigens - HLA, therefore they are called transplantation antigens.

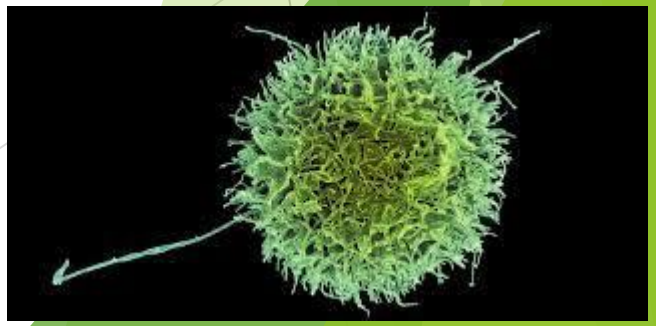
Major histocompatibility complex genes



transplant immunity



- Hyperacute rejection develops on days 1–5 after organ transplantation (for example, liver). It is due to the presence of previous antibodies resulting from a blood transfusion or pregnancy (AB0 or HLA sensitization). Acute graft rejection develops within 5 to 30 days, while chronic graft rejection develops after 6 months or more.
- Acute and chronic graft rejection occurs as a result of activation of cellular immunity: CD8+ cytotoxic T-lymphocytes, recognizing graft antigens that are unusual for them, attack it.
- NK cells are also involved in rejection.
- Activated TH2 is involved in development
- humoral immunity, stimulating B-lymphocytes to
- antibody production

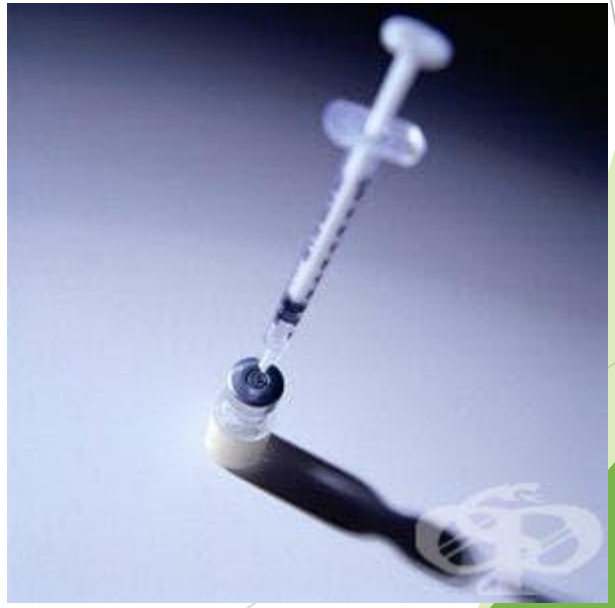


transplant immunity

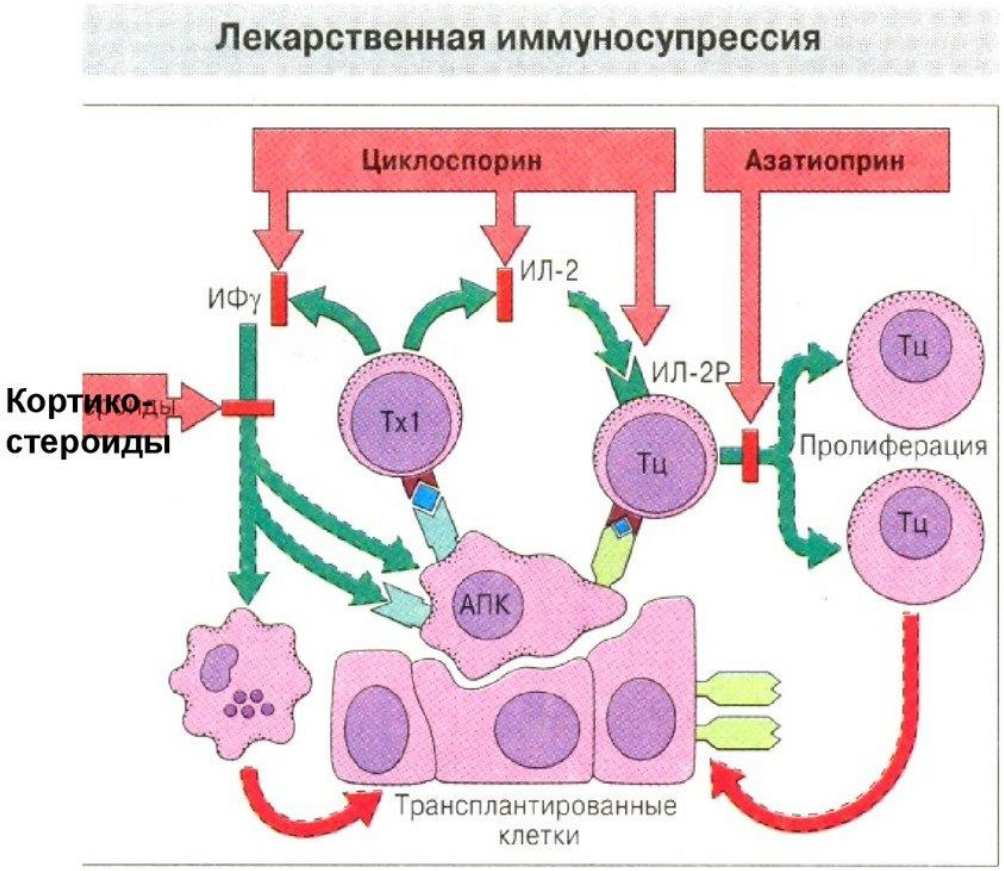
- Passenger leukocytes remaining in the transplanted organ with the dendritic cell phenotype can stimulate CD4+ T-helpers and CD8+ cytotoxic T-lymphocytes of the recipient as antigen-presenting cells.
- Thus, the T-lymphocytes of the recipient recognize the graft antigens presented by the donor APC.
- In addition to this so-called direct recognition of graft antigens, there is also indirect recognition.
- Indirect recognition of the graft antigens is carried out by the antigen-presenting cells of the recipient, presenting the graft antigens to T-lymphocytes in combination with their own MHC molecules.

MHC typing

- Typing of the donor and recipient by MHC is carried out using a microcytotoxic test with B-lymphocytes, monospecific sera and complement, as well as DNA typing based on PCR.
- Humanized monoclonal antibodies are used to block the activation of T-lymphocytes
- (daclizumab and basiliximab) to IL-2 receptor (CD25)



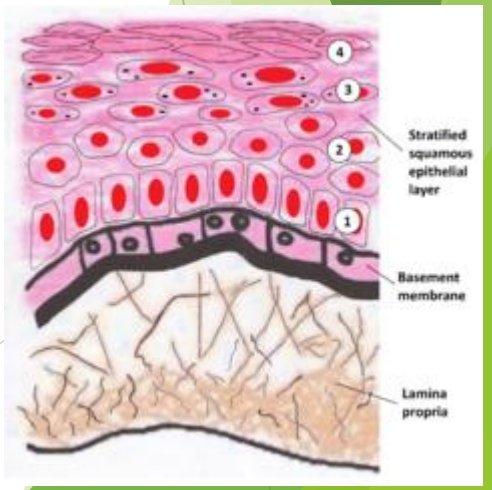
prevention and treatment of the rejection crisis



To prevent and treat the crisis of rejection, the following are used: azathioprine, an antimetabolite of protein synthesis that suppresses CTL induction; corticosteroids (prednisolone, etc.), inhibitory macrophages, T-lymphocytes, cytokine and complement synthesis; cyclosporine A, which inhibits the synthesis of IL-2 by T-helpers.

Features of oral immunity (non-specific factors)

- The immune defense system of the oral cavity combines a variety of specific and non-specific factors that provide effective protection against pathogenic microbes.
- Mucosal cells act as a mechanical barrier
- The antimicrobial activity of saliva is of particular importance.
- It is not only a physico-chemical, but also a biological barrier
- Saliva contains up to 200,000 phagocytic cells
- In the connective tissue stroma of the oral cavity, tissue macrophages,
- fibroblasts, granulocytes and mast cells are found.



Features of oral immunity (specific factors)

- Specific immune protection is represented by powerful tonsils of the pharyngeal ring, a well-developed system of lymphoid drainage in the submandibular, sublingual, parotid and cervical lymph nodes.
- Lymphocytes and a wide range of immunoglobulins are found in saliva (sIgA dominates)
- A decrease in the content of immunoglobulins in saliva is fraught with purulent-inflammatory or allergic diseases of the oral mucosa.