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This training manual sets out theoretical material covering the main parts of the immunology course for medical schools and provides the necessary reference materials.

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CONTENS:

Lecture 1
The organs of the immune system.

Immunity (from lat. Immunitas - “deliverance”, “liberation from anything”) is the body’s immunity to various infectious agents, as well as their vital products, substances and tissues that possess foreign antigenic properties and carry foreign genetic information.

The immune system consists of the central and peripheral departments.

The central department contains organs (primary, or central, lymphoid organs) in which differentiation and maturation of lymphocytes occur: red bone marrow and thymus (thymus gland), as well as peripheral organs and systems in which lymphocytes realize their functions (lymph nodes, spleen, liver, and also diffusely located lymphoid tissue - individual lymphoid follicles and their accumulations in different organs, especially distinguish lymphoid tissue associated with mucous membranes (Mucosa-Associated Lymphoid Tussue - MALT).

Encapsulated organs (thymus, spleen, lymph nodes, liver) and unencapsulated lymphoid tissue (lymphoid tissue of the mucous membranes - MALT - Mucosal-Associated Lymphoid Tissue).

Peripheral blood is a transport and communication component of the immune system.

Primary lymphoid organs include bone marrow and thymus. Bone marrow is the main organ of lymph and hematopoiesis. Hematopoietic stem cells (HCC) are concentrated in the bone marrow. Its main function is the production of blood cells and lymphocytes, ensuring the development of T-lymphocytes, the differentiation of monocytes and lymphocytes from CCM to a mature cell. The barrier function of the bone marrow normally ensures that only mature elements enter the peripheral blood.

In the bone marrow, the stages of erythropoiesis (the formation of red blood cells), myelopoiesis (the formation of neutrophils, monocytes, eosinophils, basophils), megakaryocytopoiesis (the formation of

platelets), as well as the differentiation of dendritic cells, NK cells and B lymphocytes, pass.

Having completed development in the bone marrow, myeloid cells enter the bloodstream and circulate in the bloodstream. Before the birth of the fetus, the development of B-lymphocytes occurs in the fetal liver. After birth, this function is transmitted to the bone marrow.

The thymus, or thymus gland, is located behind the hilt of the sternum. The thymus consists of two main parts - the cortex and medulla. In the cortex, the outer, subcapsular layer, deep cortex and corticomedullary zone (or corticomedullary joint) are distinguished. The thymus is covered with a connective tissue capsule, from which interlobular septa departing into the cortex, dividing the cortex into lobules. The brain of the thymus is not divided into lobules. The most important functionally, post-capillary venules through the wall of which the progenitor cells penetrate into the thymus and mature T-lymphocytes exit. Thymus lymphocytes, called thymocytes, as well as macrophages, dendritic and mast cells come from progenitor cells that migrate to this organ from the bone marrow. Epithelial cells form a three-dimensional framework - the epithelial reticulum, inside which the main events associated with the development of T-lymphocytes occur. Macrophages are contained in the epithelial skeleton of the corticomedullary zone, and dendritic cells are also contained in the medulla.

The specific function of the thymus is to ensure the development (maturation, selection, differentiation) of T-lymphocytes. This involves mainly epithelial cells.

An important feature of the thymus is its age-related involution. About 3% is lost annually in youth, and 1% of active thymus tissue in older age. Involution primarily affects the cortical layer and begins at the age of 15.

Secondary (peripheral) lymphoid organs. Mature lymphocytes enter the peripheral part of the immune system, where they perform their functions, participating in the development of the immune response. However, only lymphocyte clones that recognize a specific antigen are

involved in the immune response. The peripheral part of the immune system includes specialized lymphoid organs. These include lymph nodes that control certain areas of the body, from which lymph enters them; spleen, under the control of which there are hematogenous pathways of distribution of foreign agents; lymphoid structures of barrier tissues - mucous membranes and skin, through which the bulk of pathogens penetrate the body. The ways of communication in the peripheral part of the immune system are blood and lymph.

Lymph nodes - bean-shaped formations of 0.2-1.0 cm in size, forming groups or chains. They drain lymph from various regions of the body. Lymph node tissue consists of cortex and medulla. In the outer part of the cortex there are rounded formations - lymphoid follicles, which serve as the site of concentration of B-lymphocytes. In resting lymph nodes, they have a uniform structure, and they are designated as primary follicles. With an immune response, in addition to B-lymphocytes, T-cells migrate to the follicle, and multiplication centers — germinal centers — are formed in it. Such a follicle is called secondary.

The spleen serves as an immune barrier to the hematogenous pathways of pathogens and other foreign agents. In addition to the functions of an organ of the immune system, it participates in the removal of old lymphocytes, regulates the volume of circulating blood, and in some animals it serves as an organ of hematopoiesis. The spleen is divided into red and white pulp. The basis of the spleen is a red pulp, which provides homeostasis of red blood cells. NK cells migrate into the red pulp, which are practically absent in the white pulp (as in the lymph nodes). From T and B lymphocytes, effector cells and memory cells predominate in the red pulp. Since some plasma cells migrate into the red pulp, it takes part in the effector phase of the humoral immune response. In this organ, the predominance of B-lymphocytes over T-cells is noteworthy.

There are 2 types of organized lymphoid structures of the mucous membranes - Peyer's plaques and single follicles. Peyer's plaques are

real lymphoid organs that can be considered as structural and functional analogues of the lymph nodes. They are contained only in the mucous membrane of the small intestine, which is subjected to the greatest antigenic load. Peyer's plaques include lymphoid follicles, thymus-dependent zones and areas of joint localization of T and B cells. The main function of Peyer's plaques is to maintain the immunogenesis of B-lymphocytes and their differentiation into plasma cells producing antibodies - mainly secretory IgA. The most developed structures of this type are unencapsulated clusters of follicles surrounded by lymphoid tissue, tonsils located in the nasopharynx and larynx. They form a Waldeyer ring, including 6 tonsils - lingual, palatine, trumpet and pharyngeal (palatine and trumpet tonsils - paired). Single follicles are also found in the mucous membrane of the small and large intestines. Lymphoid tissue of this type is very developed in the appendix.

Lecture 2
Types of immunity. Nonspecific and specific immunity.

Immunity - the protection of organisms from genetically foreign substances (antigens) of endogenous or exogenous origin in order to maintain and maintain homeostasis.

Types of immunity:

1. Congenital - natural, hereditary, non-specific immunity or non-specific resistance. It acts on antigens nonspecifically, it is the primary inflammatory protective reaction to the antigen. It is formed in ontogenesis.

2. Acquired - adaptive, specific. It is formed during a specific interaction of cells of the immune system with an antigen, as a result of which antibodies appear that directionally recognize this antigen. Formed throughout life.

It is natural and artificial, active and passive.

Natural active immunity appears as a result of contact with the pathogen (after a previous illness or after hidden contact without the onset of symptoms of the disease - post-infectious). Saved for life.

Natural passive immunity arises as a result of transmission from the mother to the fetus through the placenta (transplacental) or breast milk Ig G - the antibodies of the mother and the ready-made protective factors - lymphocytes, antibodies, cytokines. It lasts about 6 months.

Artificial active immunity is induced after the introduction of vaccines and toxoids (post-vaccination) into the body, which contain microorganisms or their substances - antigens. Saved for life.

Artificial passive immunity is created after the introduction of ready-made antibodies or immune cells into the body. In particular, such antibodies are contained in the blood serum of immunized donors or animals. It is saved as the introduced antibodies are recycled.

Natural immunity is primarily due to mechanical barriers and factors that prevent infection from entering the body. It is due to various mechanisms of natural resistance. Such factors include intact skin, secrets (tears, urine, sputum, saliva and other body fluids), as well as

various epithelial cells and villi of the respiratory tract, preventing direct contact between the internal environment and a foreign agent.

Natural Resistance Mechanisms:

- the protective role of the skin and mucous membranes;
- normal microflora of a macroorganism;
- inflammation;
- fever;
- the barrier role of lymph nodes;
- function of the excretory system;
- humoral factors;
- phagocytosis.

General properties of non-specific resistance factors:

a) are formed in the body before the introduction of foreign agents and can turn on almost immediately after the appearance of a foreign microorganism;

b) under conditions of biological aggression, they are activated in the process of developing an inflammatory reaction;

c) the source of activation is the pathogens themselves and damaged body cells;

d) a chemotactic signal coming from the site of inflammation contributes to the entry of circulating leukocytes into the site of injury and the development of local protective reactions;

e) activated leukocytes produce bactericidal substances;

e) the destruction of foreign agents is implemented in the form of extracellular, intracellular and contact cytolysis;

g) contact cytolysis mediated by apoptosis.

The protective role of the skin and mucous membranes. Clean and intact skin has bactericidal properties due to oleic and other unsaturated fatty acids secreted with the secrets of the sebaceous and sweat glands. Free saturated aliphatic acids, which are part of the secretion of the sebaceous glands, exhibit a fungistatic effect.

Mucous membranes are capable of removing or destroying microorganisms that have fallen using various devices: cilia and

antimicrobial enzymes (lysozyme), which break down the bacterial cell wall and facilitate their further lysis.

The acidic environment of the secretion of the gastric mucosa has a powerful antimicrobial effect, so most microorganisms are destroyed in the stomach.

Normal microflora of the body. The characteristic communities of microorganisms that inhabit the skin and mucous membranes of hollow organs support symbiotic relationships and supply the macroorganism with vitamins, amino acids, and secrete substances that are harmful to pathogenic microflora. A change in the ratio of normal microflora - dysbiosis promotes the propagation of pathogenic microorganisms resistant to antibiotics and develops as a result of serious illnesses or after the use of broad-spectrum antibiotics.

Inflammation is a protective reaction of the body to excessive irritation and tissue damage by physical, chemical and biological agents. The mechanism of inflammation is due to: a) the production of inflammatory mediators; b) increased vascular permeability under the action of biologically active substances (histamine, serotonin, etc.; c) fixation and accumulation of microorganisms; d) the destruction of microorganisms with the help of humoral factors and phagocytic cells - macrophages and microphages (neutrophils), therefore phagocytosis is an essential component of the inflammatory reaction.

Fever suppresses intracellular reproduction of viruses and promotes the activation of macrophages, which function better at 38-40 ° C. A further increase in temperature has a depressing effect on phagocytosis and causes mutations in phagocytes, resulting in strains that are ineffective and resistant to high temperatures.

The barrier role of lymph nodes is manifested in the ability to filter lymph, retain and eliminate pathogenic microorganisms with the help of lymphocytes and macrophages in numerous lymph nodes (more than 1000).

The functions of the excretory system (gastrointestinal tract, urinary tract, sweat glands, respiratory system, etc.) provide the

neutralization and elimination of microorganisms or their metabolic products.

Humoral factors of non-specific resistance (Interferon system, complement, cytokines, acute phase proteins, pentraxins, eicosanoids, lipid mediators, biogenic amines).

Lecture 3
Interferon.

Interferons (IFN or IFN) - glycated proteins produced by the penetration of the virus into the cell. Depending on the type of producing cells, three types of interferon are distinguished:

- IFN-α (alpha - macrophage or leukocyte),
- IFN-β (beta - fibroblast)
- IFN-γ (gamma - lymphocytic or immune).

Alpha interferon and beta interferon are powerful factors in antiviral as well as antitumor immunity. They block the replication of viruses in cells. These proteins are produced by cells infected with the virus, as well as after stimulation of the cells with interferonogen drugs or vaccines. Interferons are species-specific: human ones do not affect animal infections and vice versa. When leukocytes are stimulated with viral and other antigens, they are released in significant quantities. Interferons-drugs are used to treat hepatitis, tumors and other diseases.

Interferons do not block the penetration of the virus into the cell and their antiviral effect is mediated through a change in cellular metabolism. They bind to specific receptors on the membranes of infected cells and trigger the synthesis of antiviral proteins and enzymes.

Gamma - interferon - is significantly different from the previous two. In general, it exhibits the properties of a typical interleukin. This cytokine is produced mainly by type 1 T-helpers, activates various cell populations, especially macrophages, natural killers, stimulates the conversion of Tx0 into Tx1, thereby enhancing the inflammatory component of the immune response.

Interferon gamma enhances the synthesis of HLA antigens by cells, which accelerates the recognition and processing of antigens, the adhesion of leukocytes and monocytes, phagocytosis, enhances the expression of Fc receptors on monocytes / macrophages and hence their binding to antibodies.

The interaction of cells with the virus stimulates the production of interferon, which acts on neighboring cells and enhances the additional

synthesis of interferon, preventing the multiplication of the virus, the formation of viral particles and its further spread.

Interferons have a pronounced antiviral and antitumor effect, but are active mainly in the tissues on which they are obtained. According to the type of biological action, interferons belong to the mediators of the immune system cytokines.

The immunomodulating effect of interferons is manifested in the regulation of the interaction of cells involved in the immune response. Interferons perform this function by increasing the sensitivity of cells to cytokines and the expression on the cell membranes of molecules of the main histocompatibility complex of type I (MHC I). Enhanced expression of MHC I on virus-infected cells significantly increases the likelihood that they will be recognized by immunocompetent cells and eliminated from the body. The most pronounced immunomodulatory properties have IFN-γ produced by ThI. Like pro-inflammatory cytokines, IFN-γ activates macrophages, cytotoxic T-lymphocytes, NK-cells, inhibits the activity of B-lymphocytes, activates the prostaglandin and corticosteroid systems. All these factors enhance phagocytic and cytotoxic reactions in the area of the inflammatory focus and contribute to the effective elimination of the infectious agent.

Phagocytosis

Phagocytosis is a factor of nonspecific resistance, plays an important role in inflammation, wound healing. The phenomenon of phagocytosis was first discovered by I. Mechnikov in 1882 and is an active capture and absorption of microscopic particles and foreign living objects (bacteria, cell fragments) by specialized cells - phagocytes. Phagocytosis - (from the Greek. Phagos - eater), means eating, absorption. Phagocytes are divided into microphages (neutrophilic granulocytes) and macrophages that form the monocytic-phagocytic system (MFS), line the spleen sinusoids and medullary sines of the lymph nodes. With the development of inflammation, in the first place (after minutes and hours) granulocytes are mobilized, which have a moderate ability to absorb microbes. Macrophages with high phagocytic

potential are activated later (in hours and days). Phagocytosis is often preceded by the process of opsonization (from other Greek. Opsoniazo - to provide food, nourish) of an object (a cell that carries foreign information). During opsonization, an antigen-antibody complex is formed on the surface of an object due to a small number of antibody molecules (“normal antibodies”) in the body. Antibodies on the surface of a foreign cell initiate the attachment of complement system proteins to them. The resulting complex "Ag-AT-C" starts the subsequent stages of phagocytosis.

Stage of phagocytosis.

Phagocytosis reaction is carried out in 8 stages:

1) chemotaxis (directed movement of the phagocyte to the object);

2) adhesion (attachment to an object);

3) activation of a portion of the membrane of the phagocyte (actin-myosin system of the phagocyte);

4) the onset of phagocytosis proper, associated with the formation of pseudopodia around the absorbed particle;

5) the formation of the phagosome;

6) the fusion of the phagosome with lysosomes;

7) destruction and digestion;

8) the release of degradation products.

Numerous cells absorb foreign material, but the ability to enhance this activity in response to opsonization with antibodies and / or complement, as well as acquiring specificity for the antigen, is limited to myeloid cells, namely polymorphic nuclear leukocytes, monocytes and macrophages, and they are called professional phagocytes.

Lecture 4
Complement system.

Complement - a system of serum proteins (up to 10%) and several proteins of cell membranes. Unlike antibodies, the complement content in normal fresh serum during immunization does not increase and is not associated with a specific immune response. The complement system forms a cascade system in which the product of one reaction serves as a catalyst for the subsequent one.

The bactericidal properties of blood are determined not only by antibodies, but also by additional serum proteins, which differ in composition from antibodies and were discovered in 1888. The name complement (from lat. Complementum - supplement) was obtained in connection with the ability to activate the opsonization of bacteria: to lyse and phagocytize microorganisms.

A number of complement components are indicated by the letter C and a number (C1; C2; C3; C4; C5 - C9, etc.), which corresponds to a greater extent to the chronology of the discovery, rather than to the serial number of participation in the reaction sequence. The first five proteins of the complement system are capable of being split in a certain sequence into active products, in the designation of which they add a small Latin letter, for example, C1q, C5a and C2b. As a rule, the letter “a” is assigned to the smaller fragment, and the letter “b” to the larger one.

The functions of the cleavage products are numerous and varied. Some of them have protease activity, while others bind to the membranes of cells and microorganisms, antigen-antibody complexes, activate mast cells, and participate in vascular reactions in inflammation. An important property of these substances is the ability to perforate the membranes of bacterial cells.

Activation of the complement system. The spontaneous activity of the complement system is low, but in pathological conditions (trauma, penetration of infectious agents, etc.) it is capable of quick activation in several ways: classic, alternative and lectin. The classical complement

activation pathway (KPAK) is evolutionarily new, but first discovered, initiated by a complex formed by antigen (Ag) and antibody (AT - immunoglobulin IgG1,2,3 or IgM). Ig can “replace” C-reactive protein. It is conditionally possible to distinguish two phases of the implementation of KPAK.

The first phase of recognition (initiation). The active C1qrs complex is formed - trypsin-like protease / esterase (C1-esterase) as a result of sequential additions to the Ag-AT complex (IgM) and activation, first, C1q, then C1r, C1s subfractions:

Ag-IgM + C1q → Ag-IgM C1q (serine protease-esterase activity)

Ag-IgM C1q + C1r → Ag-IgM C1qr

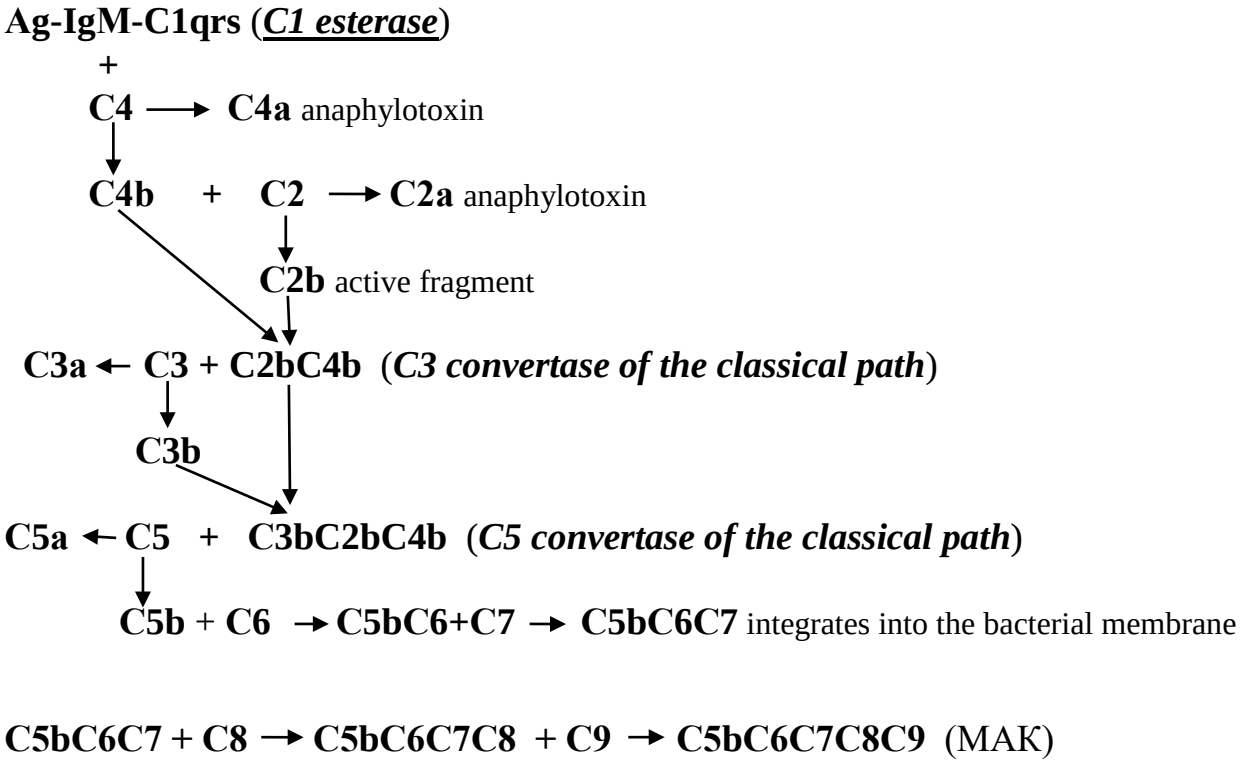
Ag-IgM C1qr + C1s → Ag-IgM C1qrs

The second phase of amplification (amplification). C1-esterase first cleaves C4 into C4a (anaphylotoxin) and C4b (active fraction): C4 → C4a + C4b. The active fraction of C4b covalently binds to the surface of microbial cells (but not with its own eukaryotic cells of the macroorganism) and attaches to it a fraction of C2. The C2 fraction in complex with the C4b fraction (C2C4b) is cleaved with C1 esterase to form the active C2b fraction and anaphylotoxin C2a.

The active fractions C4b and C2b are combined into one complex - C4bC2b - with enzymatic activity. This is the so-called C3 convertase of the classic path. C3 convertase cleaves the C3 fraction, producing large amounts of the active C3b fraction. The active fraction C3b joins the complex C4bC2b and turns it into a C5 convertase (C4bC2bC3b). C5 convertase cleaves the C5 fraction. The resulting active fraction C5b joins the fraction C6. The C5bC6 complex joins the C7 fraction.

The C5bC6C7 complex is integrated into the phospholipid bilayer membrane of the microbial cell. Protein C8 is attached to this complex. Together with the entire complex in the phospholipid bilayer of the membrane of the microbial cell, protein C8 catalyzes the polymerization of 10-16 molecules of protein C9. The resulting complex forms a non-decaying pore in the membrane of the microbial cell with a diameter of about 10 nm, which leads to lysis of the microbe (since many such pores

are formed on its surface - the “activity” of one unit of C3 convertase leads to the appearance of about 1000 pores). The C5bC6C7C8C9 complex, which is formed as a result of complement activation, is called the membrane-attacking complex (MAC).



The complement system activation scheme along the classic path:

C2b; C3b; C4b; C5b — active fragments. C2a; C3a; C4a; C5a – anaphylotoxins

The lectin (mannose) pathway of activation of the complement system is homologous to the classical pathway, but without the participation of antibodies. It is triggered by a protein - lectin, similar to the C1q of the classical path. Mannose-binding lectin (mannose-binding lectin, MBL, or mannan-binding lectin, mannose polymer, MBP) - a whey protein belonging to the group of collectin proteins, is synthesized mainly in the liver and can activate the cascade of the complement system, directly binding to the surface of pathogens trapped in the blood.

MBL binds the residues of mannose and some other carbohydrates that make up the bacterial cell wall and opsonizes pathogens. In serum, MBL forms a complex with MASP-I and MASP-II (Mannan-binding

lectin Associated Serine Protease, MBL-binding serine proteases). MASP-I and MASP-II are very similar to C1r and C1s of the classical activation pathway and, possibly, have a common evolutionary predecessor. When several active MBL centers bind in a certain way to oriented mannose residues on the phospholipid bilayer of bacteria, MASP-I and MASP-II are activated and cleave C4 protein into C4a and C4b, and C2 protein into C2a and C2b. Then C4b and C2a combine on the surface of the microorganism to form a C3 convertase, and C4a and C2b act as chemoattractants for the cells of the immune system.

The activation of the complement lectin pathway is initiated by many gram-positive and gram-negative bacteria, as well as biopolymers with numerous mannose residues.

Gene polymorphisms and serum concentrations of MBL in different people can vary thousands of times and cause pathophysiological conditions. MBL deficiency is associated with low survival of newborns under the age of one year, because during this period they are most sensitive to infectious diseases. C1q of the classical activation path can directly, i.e. without the participation of antibodies, binds to mannose residues and other sugars, which allows recognition of mycoplasmas, a number of retroviruses, but not HIV.

An alternative way to activate the complement system is triggered by spontaneous hydrolysis of C3 directly on the surface of the pathogen. In an alternative way, factors B and D (enzymes of the complement system), P (properdin), H, I.

Factor B is a single-chain b-globulin serine proteinase that is cleaved by factor D to form two fragments: Ba and Bb. Factor D is a single chain glycoprotein. Its low concentration limits the assembly of C3 convertase. Carries out the proteolysis of factor Bb in case of its binding to C3b.

Factor P (properdine, means to destroy). It consists of two fractions: native (nP) and activated (P). It can bind to complement (C3-C5), reduces the conversion rate of convertase, enhances the activation of the alternative pathway, and accelerates the assembly of C3bBb.

Factor H is a single chain peptide that inhibits C3 cleavage. Serves as a cofactor of factor I, when C3b is inactivated.

Factor I - glycoprotein, consists of two polypeptide chains. Turns C3b into C3bi, introducing gaps into the a3 chain of C3.

Using these factors, the formation of the enzyme C3bBb occurs, the stabilization and long-term functioning of which is ensured by the P protein (properdine). PC3bBb (C3 convertase of the alternative pathway) activates C3, resulting in the formation of a C5 convertase (C3bBb3b) and the formation of MAA is triggered. Further activation of the terminal components of complement occurs in the same way as in the classical way of complement activation. In the liquid phase in the complex, C3bBb B is replaced by the H-factor and, under the influence of a deactivating compound (H), turns into C3bi.

Microorganisms that enter the body accumulate the C3bBb complex on the membrane. It combines with C5, which splits into C5a and C5b, C5b remains on the membrane, then combines with C6, C7, C8 and C9. After combining C9 with C8, C9 polymerizes (up to 18 molecules crosslink with each other) and a pore forms that penetrates the bacterial membrane through which water enters the bacterium and the bacterium bursts.

In contrast to the classical pathway, the alternative does not require the formation of immune complexes and the participation of the first components of the complement system - C1, C2, C4. An alternative pathway is distinguished by the fact that it works immediately after the appearance of antigens - bacterial polysaccharides and lipopolysaccharides (mitogens), bacterial endotoxins, viruses, and tumor cells can be its activators.

Regulation of the complement system. The complement system is regulated by special proteins, the concentration of which in the blood plasma exceeds the content of the components of the complement system. The same proteins are present on the membranes of the body’s own cells, protecting them from attack from the proteins of the complement system.

Violation of the regulation of the complement system can cause damage to body tissues, so most components remain active for a short time and only as part of complexes. In case of violation of the cascade of sequential activation reactions or a decrease in the concentration of components below the threshold (critical), the physiological functions of the complement system are not realized.

Regulatory mechanisms mainly operate at three points: C1, C3a-convertase, C9.

The role of complement system components in neutralizing viruses.

1. C3b promotes the formation of virion aggregates, reducing the number of free viral particles.

2. The complement covers the viral particles with a dense layer (with or without antibodies), preventing their fusion with and penetration into the cell.

3. MAK lyses enveloped viruses.

4. Complement enhances phagocytosis of virions.

The role of the complement system in the clearance of immune complexes. The main role in this process belongs to C3b, which attaches on the one hand to the immune complex, and on the other to the CR1 receptor on red blood cells. Red blood cells are able to adsorb and "transport" immune complexes to the liver and spleen, where they are absorbed by macrophages. In this case, red blood cells are not damaged.

Deficiency of components of the complement system. Deficiency of some components of complement causes the development of systemic lupus erythematosus (SLE).

The most severe consequences develop with C3 deficiency, to a lesser extent with C9 deficiency (since the complete assembly of MAC is not always necessary for complement-dependent lysis).

Lecture 5
Immune system mediators - cytokines.

Cytokines - a group of humoral factors of the immune system, equally important for the implementation of innate and adaptive immunity. Cytokines are involved in many processes; they cannot be called factors related exclusively to the immune system, since they play an important role in hematopoiesis, tissue homeostasis, and intersystem signal transmission.

Cytokines can be defined as protein or polypeptide factors lacking specificity with respect to antigens, produced mainly by activated cells of the hematopoietic and immune systems and mediating intercellular interactions during hematopoiesis, inflammation, immune processes and intersystem communications.

Cytokines are produced in response to an activating stimulus not only by immunocompetent, but also by many cells of the body. Not all synthesized material is secreted. A certain amount of cytokines is expressed on the cell surface or contained in cytoplasmic granules. The release of granules can cause the same activating signals as the production of cytokines. This provides a quick (within 20 min) the flow of cytokines into the lesion.

Cytokines are secreted in extremely small, picogram amounts and in serum cytokine concentrations, as a rule, do not exceed 100 pg / ml.

Different types of cells can produce the same cytokines and express receptors for them. The action of cytokines is excessive. On the one hand, different cytokines can cause externally the same cell reactions, on the other hand, each cytokine induces different biological effects in different cells. In the vast majority of cases, cytokines are short-range mediators that determine local cell interactions in the foci of the development of processes in tissues.

In healthy people, blood usually manages to detect many different cytokines, including interferons, but at concentrations not exceeding a few picograms per 1 ml. A systemic effect was detected mainly for four cytokines: TNF-α, IL-1, IL-6 and M-CSF.

Most cytokines are not deposited in cells, but are synthesized in pulses — “on demand”. This process begins with the transcription of matrix RNA from the corresponding cytokine gene. However, small amounts of TNF - α or other cytokines can be deposited in granules of neutrophils, platelets, and mast cells. Matrix cytokine RNA is very short-lived, which explains the transitory nature of their production by the cell: they are produced for a short time after receiving a “request” for their formation.

The action of cytokines is characterized by cascade, expressed in the fact that under the influence of one cytokine, a cell can begin to produce other cytokines (or the same one). This leads to increased biological effects. The cascade of cytokines self-regulates: a cell that begins to produce activation cytokines switches after several hours or days to the synthesis of suppressor cytokines and / or expresses inhibitory receptors or receptors for apoptosis signals.

According to the functional purpose, 5 main groups of cytokines are distinguished:

1. Hematopoietic cytokines regulate the proliferation and differentiation of all cells of the hematopoietic system. These include colony-stimulating factors - CSF: GM-CSF, M-CSF, G-CSF, erythropoietin, thrombopoietin, IL-3, IL-5, IL-7, stem cell factor - SCF. IL-1α is also referred to as hematopoietins, the second name is hematopoietin-1, since it supports the growth of the earliest hemopoietic precursor cells. Negative regulators of hematopoiesis are TNF-α and transforming growth factor β, (TGF-β,).

2. Primary pro-inflammatory cytokines (cytokines of innate immunity) - IL-1α, IL-1β, TNF-α and IL-6. They are extremely pleiotropic and act on cells of nearby tissues. They are mainly produced by macrophages and DC of integumentary structures at the site of pathogen introduction.

3. Immunoregulatory cytokines regulate the proliferation and differentiation of T and B lymphocytes and NK cells in peripheral lymphoid organs and tissues. First of all, they are produced by activated

professional APCs (macrophages and DCs) and the lymphocytes themselves. This group includes IL-2, IL-4, IL-12, IL-15, IFN-γ.

4. Cytokines - inflammatory mediators are products of activated T-lymphocytes and cause activation of leukocytes of "general inflammatory purpose": IFN-γ, IL-5, lymphotoxins, TNF-β.

5. Anti-inflammatory (immunosuppressive) cytokines. These include IL-10 and TGF-β. In addition, IL-4 and IL-13 are cytokines that inhibit macrophages, and also act as anti-inflammatory in some processes.

Features of the cytokine network:

1. Redundancy - the same cytokines can be produced by different cells of the body;

2. Pleiotropicity - manifested in the ability of cytokines to act on different target cells;

3. Synergism - many functions of cytokines are due to the action of not one, but several cytokines, showing consistency in actions;

4. Antagonism - some cytokines are negative regulators of the production of other mediators;

5. Cascade - due to the sequential increase or decrease in the production of other cytokines, positive or negative mechanisms for controlling production during inflammation;

6. Action through specific receptors on cell membranes - the biological effects of cytokines appear after binding to the corresponding high affinity receptors.

Biological and physico-chemical properties of cytokines:

1. Cytokines differ in amino acid sequence, the presence of carbohydrate residues, the degree of polymerization of the polypeptide chain, etc. Four classes of cytokines are distinguished depending on the spatial structure of the polypeptide chain.

2. Most cytokines exist in soluble form, but some may be associated with the cell membrane in complex with the receptor. There are also transmembrane forms of cytokines.

3. Cytokines are synthesized in the form of inactive precursors with a signal peptide that is involved in the transport of the molecule through the plasma membrane. After cleavage of the signal peptide, the cytokine becomes active.

4. The biological activity of cytokines is manifested in a wide range of pH and heating for 10-60 minutes at a temperature of 560^0C. Many cytokines remain active for several months at + 40^0C. Repeated freezing and thawing is undesirable, as it reduces the activity of cytokines.

5. Under the influence of proteolytic enzymes (trypsin, chemotrypsin protease Staphylococcus aureus), the activity of almost all cytokines is lost.

Classification of cytokines by the mechanism of action:

Cytokine regulation depending on the target cell is carried out according to the autocrine, paracrine or endocrine mechanism. Some cytokines may have three mechanisms of action.

- autocrine effects (act on the cell itself, secreting a cytokine);
- paracrine effects (act on other adjacent cells) of cytokines;
- endocrine (distant, or systemic) effects occur when the cytokine reaches the target cell, circulating with the blood.

Cytokines do not act in isolation from each other and form a cytokine network, in which the mediator-receptor component of the cells of the immune system is important.

More than 100 cytokines are known that differ in structure and biological activity, as a result of which they are distributed into groups:

• interleukins (IL or IL) - secretory regulatory proteins; interferons (IFN or IFN) - antiviral agents with a pronounced immunoregulatory effect;

• tumor necrosis factors (TNF or TNF) - cytokines with cytotoxic and regulatory properties;

• colony stimulating factors (CSF or CSF);

• chemokines (HC).

Depending on the role in the development of inflammatory reactions of the body, cytokines are divided into pro-inflammatory (IL-1, TNF, IL-6) and anti-inflammatory (IL-4, IL-10).

Functionally cytokines are divided into groups:

• pre-immune cytokines, the production of which is stimulated directly by infectious agents and occurs in monocytes and macrophages, skin keratinocytes and in other barrier tissues. Pre-immune cytokines include IFN-α, IFN-β, pro-inflammatory cytokines TNF, IL-1α, IL-1β, and chemokines.

• lymphocytic cytokines, produced mainly by T-lymphocytes and which regulate the activation, proliferation and differentiation of lymphocytes. The signal for their production is the binding of the receptor to a specific antigen. This group includes interleukins IL-2, IL-4, TNF-β.

• cytokines - regulators of immune inflammation - lymphotoxin (LT), IL-10, IL-12, IL-5, IFN-γ. They activate cells of general inflammatory purpose: neutrophils, eosinophils, macrophages, NK and they are produced by immune lymphocytes.

The main producers of cytokines are activated lymphocytes, but not only them. A number of cells synthesize a wide range of mediators.

Cytokine receptors:

Cytokine receptors are expressed on the membranes of activated cells and are found in significant quantities in biological fluids. Almost all cytokines have two types of receptors, differing in affinity for cytokines. Capable of the most strong binding to cytokine receptors are called high affinity. The appointment of low-affinity receptors is still unknown, but it is possible that they are traps for excess numbers of mediators.

Lecture 6
Specific immunity. Antigens.

Unlike nonspecific, specific immunity is finally formed only in the process of an organism's response to genetically foreign agents and is an evolutionarily later protective device. Specific reactions of the body are called immune. All immune reactions are based on mechanisms specific for specific antigens that are recognized by protein structures - antibodies that are complementary to antigens (i.e. spatially corresponding to them as an imprint of the original).

Antigens are microorganisms or structures that are genetically alien in nature and secrete substances that differ in structure from macroorganism molecules and are capable of eliciting an immune response. These molecules are recognized by the immune system as foreign, therefore they are called antigens (from the Greek. Anti - against, genos - genus) - substances that are different in structure and origin, causing immune reactions.

There are 4 groups of antigens: natural, modified, synthetic (immunogens) and incomplete antigens - haptens:

1. Natural (native), as a rule, high molecular weight compounds: proteins and nucleic acids.

2. Modified (immunogens) contain a carrier (for example, protein) covalently linked to a low molecular weight compound (aniline, etc.).

3. Synthetic are obtained in the process of synthesis from low molecular weight (poly-α-amino acids).

4. Haptens - low molecular weight substances (for example, aniline) that can only cause immune reactions in combination with a high molecular weight compound. Do not possess immunogenicity.

Exogenous and endogenous antigens are distinguished by origin. Exogenous: antigens of viruses, bacteria, parasites, as part of dust, food, drugs, etc. Endogenous antigens can be infectious (protein and non-protein components of the saprophytes of the gastrointestinal tract, respiratory tract, tonsils) and non-infectious genesis (autoantigens, damage products own proteins, abnormal proteins, etc.).

According to the effect on individual cell populations, antigens are divided into thymus-dependent (protein, cellular and viral) and thymus-independent (polymers, lipopolysaccharides) antigens. The latter activate b-lymphocytes.

The antigen molecule consists of two parts: the active part is the epitope or antigenic determinant that binds to the active center of the antibody; the inactive part - the determinant carrier, promotes the penetration of antigen into the internal environment of the body.

Antigenic determinants (epitopes) are isolated areas on the surface of a protein molecule containing 6-7 amino acid residues.

Antigen molecules have specific regions called antigenic determinants. It is to them that specific antibodies are produced. The number of such determinants is due to the chemical structure of the antigen. Regardless of origin, several levels of specificity are distinguished in antigens: species, group and heterospecificity.

Properties of antigens:

- antigenicity - the ability to specifically interact with cells of the immune response;

- immunogenicity - the ability to elicit an immune response;

- specificity - the ability to selectively react with specific antibodies or sensitized lymphocytes that appear after immunization.

The manifestation of these properties depends on the molecular weight, size, chemical nature, foreignness, dose, method of administration of antigen, action of adjuvants, immunoreactivity of the body.

The molecular weight of the antigen. For the manifestation of immunogenic properties, a substance must have a certain molecular weight. There is no strict border, but substances with Mr <1kDa (with a few exceptions) are not immunogenic, with Mr <10kDa immunogenicity is rather weak and most pronounced if Mr> 1000kDa. With a decrease in molecular weight, the level of immune response decreases. Monosaccharides, amino acids, lipids are not immunogenic. Proteins

exhibit immunogenicity depending on the composition, with a minimum size of 7-10 amino acid residues.

The chemical composition of the antigen. Chemical heterogeneity is a prerequisite for immunogenicity. Copolymers of monoamino acids do not possess such properties, despite the large molecular weight. The introduction of aromatic amino acids increases immunogenicity. The most powerful immunogens are high molecular weight proteins, but under certain conditions polysaccharides and synthetic polymers may possess such properties. Nucleic acids, despite their high molecular weight and structure, are not immunogenic per se, but after immunization with nucleoproteins or conjugates of nucleoprotein carriers, antibodies capable of reacting with nucleic acids are produced.

Alienness. The immune response develops to foreign substances, therefore, the more phylogenetically distinct the donor and recipient, the stronger the immune response develops.

Dose of antigen. Determines the intensity of the immune response, but varies for different substances. Low doses cause the production of a small amount of antigen, but with high affinity. High doses only to a certain state increase the concentration of antibodies, after which a state of reactivity or immunological tolerance occurs.

Methods of administration of antigen. Depending on the nature of the antigen, oral and parenteral administration options are possible: intradermal, subcutaneous, intramuscular. With intravenous administration, the spleen and liver take part in the development of the immune response. With subcutaneous and intramuscular administration, it accumulates in the lymph nodes. When introduced through the mucous membranes it accumulates in MALT - mucoso-associated lymphoid tissue.

Immunoreactivity or genetic control of the immune response. The ability to respond to an antigen is genetically determined. Different types of mammals differ in their ability to respond to antigen. The immune response is controlled by the Immune response located in the MHC.

The action of adjuvants. Adjuvants (adjuvant) - substances of heterogeneous composition (aluminum hydroxide, aluminum and calcium phosphates, calcium chloride, alum, dextrans, methyl cellulose, tapioca, agar, glycerol, protamines and other substances.), Enhancing the immunogenicity of antigens.

The main property of most adjuvants is the ability to deposit antigen, that is, adsorb it on its surface and keep it in the body for a long time, increasing the duration of its effect on the immune system.

The most powerful adjuvants contain microorganisms of attenuated strains or any substances extracted from them. These components are stimulants of innate immunity cells, such as macrophages and other antigen-presenting cells.

The use of adjuvants: in medicine in the manufacture of vaccines; in laboratory practice to enhance the production of antibodies during immunization of animals in the process of obtaining hybridomas.

Lecture 7
Specific immunity. Antibodies.

In response to a foreign antigen invading during vaccination or infection, the body produces protective substances (antibodies - Ig immunoglobulins) that can specifically bind antigen, forming an antigen-antibody complex.

Antibody functions: 1) recognition and specific binding of the corresponding antigens; 2) effector - the induction of physiological processes aimed at the destruction of antigen; 3) complement fixation.

By their chemical nature, all antibodies, including post-vaccination ones, are plasma proteins and belong to globulins, which is why they are called immunoglobulins (Ig).

Immunoglobulins are characterized by specificity, valency, affinity, avidity.

Specificity - the ability to react only with a specific antigen. The specificity phenomenon is based on the presence of antideterminants (paratopes) on an immunoglobulin molecule that combine with antigenic determinants (epitopes) on an antigen molecule.

Valency - the number of antideterminants in an antibody molecule; as a rule, they are bivalent, although there are 5 and 10 valent.

Affinity is the degree of compliance (accuracy), which determines the strength of the interaction of one antigen-binding region of an antibody - a paratope with a single antigen epitope. An indicator of the strength of the bond between the epitope and the paratope.

Avidity ("greed") - the total bond strength of an entire antibody molecule, determined by the number of antigen-binding sites - paratopes and their ability to interact with all epitopes of antigens. Avidity depends on valency, affinity, and the number of active sites on the antibody molecule. The more epitopes an antibody binds to, the higher its avidity. The greater the valency, the greater the avidity.

The structure of immunoglobulins Ig

Molecules of immunoglobulins have a complex structure, consist of four polypeptide chains. The polypeptide chains of immunoglobulins

are represented by 2 heavy (H - heavy) and 2 light (L - light) chains, forming a Y-shaped or other forms. The chains are interconnected and held together by disulfide bonds.

Light chains are represented by two types: κ (kappa) and λ (lambda), and heavy chains by five types of α- (alpha), γ- (gamma), δ- (delta), μ- (mu), ε- (epsilon) . Heavy chains determine the class of immunoglobulins - IgA - α, IgG - γ, IgD - δ, IgM - μ, IgE - ε.

In each heavy and light chain there are very important similarities: variable (V), constant (C) regions and the hinge part are distinguished in them. The variable region consists of light and heavy chains, is different for different immunoglobulins, and is responsible for the specificity of Ig in relation to a specific antigen. The variable domains of both chains have a highly varying amino acid composition, which allows them to bind different antigens. Within the variable domains of each chain, hypervariable regions are distinguished - regions of the immunoglobulin molecule that determine its specificity and complementarity (compliance) with the antigen; these are zones of increased amino acid variability, which provide a variety of antibody specificity spectrum and play a key role in antigen recognition and binding.

In the variable and constant region of the light chains contains one domain (site). Each of the heavy chains of IgG, IgD and IgA molecules consists of 4 domains: one variable and three constant. The heavy chains of IgM and IgE molecules contain an additional constant domain. The constant domains make up approximately 80% of the polypeptide chain and determine the functions of immunoglobulins that are not associated with antigen recognition: for interaction with cell receptors, activation of complement and the implementation of other functions of antibodies. The large number of possible combinations of L and H chains creates a variety of antibodies for each individual. Antibody molecules are diverse due to variable domains and hypervariable sites.

The variable domains of heavy (VH) and light (VL) chains form slit-like depressions - antigen-binding sites or active centers of antibodies that directly enter into ionic, hydrogen, van der Waals and

hydrophobic bonds with antigens. All hypervariable regions of variable domains take part in the formation of the active center. Variability is a prerequisite for the manifestation of specificity of antibodies.

Ig molecules consist of two fragments: Fab - fragment (antigen-binding, specific): one for the light and heavy chains, and the Fc-fragment (crystallizing) is a non-specific site in the constant region of only the heavy chain. Provides the ability to bind to complement and leukocyte receptors.

The hinge region is the portion of the Ig molecule in which Fab and Fc fragments are joined. Due to the hinge region of the subunit, Ig molecules (chains) are capable of rotation with respect to each other, which makes the Ig molecules flexible.

Molecules of immunoglobulins of the same specificity are present in the body in three forms: soluble, transmembrane and bound. Soluble form - secreted by the Ig cell is found in blood and other body fluids. Transmembrane - on the membrane of a B-lymphocyte as part of an antigen-recognizing receptor - BCR (B-Cell Receptor). The bound form of Ig is formed with the participation of Fc fragments that bind to cell receptors (macrophages, neutrophils, eosinophils and mast). All antibodies, except IgE, can be fixed by FcR receptors of cells only in combination with antigen.

Subtypes and subclasses of immunoglobulins

According to the type of heavy chains, immunoglobulins are divided into 5 classes: A, D, G, M and E.

IgA - produced by lymphoid tissue of the upper and lower respiratory tract, urogenital and digestive tracts. IgA is a factor of antimicrobial immune defense of mucous membranes, skin, milk and colostrum. The half-life of 5-6 days. Ig A exists in two forms - serum and secretory. Serum Ig A is able to neutralize microbes and toxins circulating in the blood, but its effect is weaker than secretory Ig A. It can activate the complement system in an alternative way. Secretory Ig A neutralizes bacterial toxins and localizes viruses, stimulates phagocytosis and provides local resistance to infection.

There are 2 subclasses of Ig A.

IgE - reagins or skin - tropic antibodies, which play an important role in type I anaphylactic hypersensitivity (immediate allergic reactions). The half-life of 2-3 days. It does not bind complement, quickly and firmly binds to tissue basophils, which causes their degranulation with the release of biologically active substances. It is produced by plasma cells (B-lymphocytes) of the spleen, tonsils, adenoids, mucous membranes of the respiratory, digestive and urogenital tracts.

IgM - forms a pool of natural antibodies, is present in the cytoplasm and on the surface of b-cells in the early stages of their maturation. It is the first class of antibodies produced by B-lymphocytes in the primary immune response. The half-life of 4-5 days. By 4-6 days after immunization, IgM synthesis switches to IgG synthesis. It has high avidity, activates the complement system along the classical pathway, activates phagocytosis, and is an effective opsonin and agglutinin. Present in the blood and tissues. In small quantities, it is produced locally and is classified as secretory.

IgG is an antiviral and antibacterial factor, the main participant in the secondary immune response, a toxin neutralizer. The half-life is 21 days. Passes through the placenta, providing passive immunity of newborns from 3 to 6 months. IgG activates the complement system, phagocytosis and is an opsonin. The maximum synthesis is observed after repeated administration of the antigen. Lichens are produced with the mandatory participation of T-lymphocytes (it is thymus-dependent).

IgD - is found on the surface of immature B cells and in serum. It is believed that he is involved in the antigen-dependent differentiation of B-lymphocytes. It can play the role of an antigen-recognizing receptor for B-lymphocytes and play an important role in the process of their differentiation under the influence of antigenic stimulation. The half-life is 3 days. Biological function is not fully understood.

Serum immunoglobulins: IgG (80%), IgA (15%), IgM (10%), IgD (less than 0.1%), IgE (less than 0.01%). Immunoglobulins are produced

by functionally active B-lymphocytes (plasmocytes) and are responsible for humoral immune responses. Post-vaccination immunological reactivity and the immune response is the reaction of the body, which consists in the recognition, inactivation, destruction and elimination of exogenous and endogenous antigens.

Lecture 8
Effectors of specific immunity.

Depending on the origin and functional differences, the cells of the immune system differ in effector, auxiliary and stromal. Effector cells (lymphocytes) recognize foreign antigens and participate in reactions to eliminate them. Auxiliary process antigen and present (present) them to lymphocytes, and stromal create conditions for the normal functioning of cells and microenvironment for their migration.

Cells of the immune system: white blood cells (lymphocytes, monocytes, macrophages, neutrophils, eosinophils, basophils, mast cells, dendritic cells, Langerhans cells, platelets) The white blood cells are the direct agents of immune reactions. Their purpose is to recognize foreign substances and microorganisms, to combat them, and to record information about them.

The following types of leukocytes are distinguished:

1) lymphocytes (T-killers, T-helpers, T-suppressors, B-lymphocytes);

2) neutrophils (stab and segmented);

3) eosinophils;

4) basophils.

Lymphocytes are the main figures in immunological surveillance. In the bone marrow, the precursors of lymphocytes are divided into two large branches. One of them (in mammals) ends its development in the bone marrow, and in birds - in a specialized lymphoid organ - the bursa (bag). These are b-lymphocytes. After B-lymphocytes leave the bone marrow, they circulate for a short time in the bloodstream, and then they are introduced into the peripheral organs. They are in a hurry to fulfill their mission, since the lifespan of these lymphocytes is small - only 7-10 days. A variety of B-lymphocytes is formed already during intrauterine development, and each of them is directed against a specific antigen. Another part of the lymphocytes from the bone marrow moves to the thymus, the central organ of the immune system. This branch is T-lymphocytes. After completion of development in the thymus, part of

mature T-lymphocytes continues to be in the brain layer, and part leaves it. A significant part of T-lymphocytes becomes T-killers, a smaller part performs a regulatory function: T-helpers enhance immunological reactivity, and T-suppressors, on the contrary, weaken it. Helpers are able to recognize the antigen and activate the corresponding B-lymphocyte (directly by contact or at a distance with the help of special substances - lymphokines). The most famous lymphokine is interferon, which is used in medicine in the treatment of viral diseases (for example, influenza), but it is effective only at the initial stage of the onset of the disease.

T-suppressors have the ability to turn off the immune response, which is very important: if the immune system is not suppressed after antigen neutralization, the components of the immune system will destroy the body's own healthy cells, which will lead to the development of autoimmune diseases. T-killers are the main link in cellular immunity, as they recognize antigens and effectively defeat them. They oppose cells that are affected by viral infections, as well as tumor, mutated, aging body cells.

Neutrophils, basophils and eosinophils are varieties of white blood cells. They got their names for their ability to perceive coloring substances in different ways. Eosinophils react mainly to acidic dyes (Congo red, eosin) and are pink-orange in blood smears; basophils are alkaline (hematoxylin, methyl blue); therefore, they appear blue-violet in smears; neutrophils are perceived by both of them, therefore they are stained with a gray-violet color. The nuclei of mature neutrophils are segmented, that is, they have constricts (therefore they are called segmented nuclei), the nuclei of immature cells are called stab nuclei. One of the names of neutrophils (microphagocytes) indicates their ability to phagocytize microorganisms, but in smaller quantities than macrophages do. Neutrophils protect against bacteria, fungi and protozoa from entering the body. These cells eliminate dead tissue cells, remove old red blood cells and clean the wound surface. When evaluating a detailed blood test, a sign of the inflammatory process is a

shift of the leukocyte formula to the left with an increase in the number of neutrophils.

Eosinophils take part in the destruction of parasites (secrete special enzymes that have a damaging effect on them), in allergic reactions.

Macrophages (aka phagocytes) are “eaters” of foreign bodies and the most ancient cells of the immune system. Macrophages come from monocytes (a type of white blood cell). The first stages of development they pass in the bone marrow, and then leave it in the form of monocytes (round cells) and circulate in the blood for a certain time. From the bloodstream they enter all tissues and organs, where they change their rounded shape to another, with processes. It is in this form that they acquire mobility and are able to adhere to any potentially alien bodies. They recognize some foreign substances and signal them to T-lymphocytes, and they, in turn, to B-lymphocytes. Then B-lymphocytes begin to produce antibodies - immunoglobulins against the agent that the "phagocyte cell and T-lymphocyte" reported. Sedentary macrophages can be found in almost all human tissues and organs, which provides an equivalent response of the immune system to any antigen that enters the body anywhere. Macrophages eliminate not only microorganisms and foreign chemical poisons that enter the body from the outside, but also dead cells or toxins produced by the body (endotoxins). Millions of macrophages surround them, absorb and dissolve to remove from the body. Reducing the phagocytic activity of blood cells contributes to the development of a chronic inflammatory process and the occurrence of aggression against the body's own tissues (the appearance of autoimmune processes). With inhibition of phagocytosis, dysfunction of destruction and elimination of immune complexes from the body is also observed.

T-lymphocytes form three main subpopulations:

1) T-killers carry out immunological genetic surveillance, destroying mutated cells of their own body, including tumor cells and genetically foreign transplant cells. T-killers make up 10% of peripheral blood T-lymphocytes. It is T-killers that cause rejection of transplanted

tissues by their action, but this is also the first line of defense of the body from tumor cells;

2) T-helpers organize an immune response by acting on B-lymphocytes and giving a signal for the synthesis of antibodies against the antigen that appears in the body. T-helpers secrete interleukin-2, acting on b-lymphocytes, and alpha-interferon. There are up to 60–70% of the total number of T-lymphocytes in peripheral blood;

3) T-suppressors limit the strength of the immune response, control the activity of T-killers, block the activity of T-helpers and B-lymphocytes, suppressing excessive synthesis of antibodies that can cause an autoimmune reaction, i.e., turn against the body's own cells.

T-suppressors make up 18–20% of peripheral blood T-lymphocytes. Excessive activity of T-suppressors can lead to inhibition of the immune response up to its complete suppression. This happens with chronic infections and tumor processes. At the same time, the insufficient activity of T-suppressors leads to the development of autoimmune diseases due to the increased activity of T-killers and T-helpers, not controlled by T-suppressors. To regulate the immune process, T-suppressors secrete up to 20 different mediators that accelerate or slow down the activity of T- and B-lymphocytes. In addition to the three main types, there are other types of T-lymphocytes, including T-lymphocytes of immunological memory, which store and transmit information about the antigen. Upon repeated encounter with this antigen, they ensure its recognition and the type of immunological response. T cells, performing the function of cellular immunity, also synthesize and secrete mediators (lymphokines) that activate or slow down the activity of phagocytes, as well as mediators with cytotoxicological and interferon-like actions, facilitating and directing the action of a non-specific system.

Another type of lymphocyte (B-lymphocyte) differentiates in the bone marrow and group lymphatic follicles and performs the function of humoral immunity. When interacting with antigens, B-lymphocytes change into plasmocytes that synthesize antibodies (immunoglobulins).

On the surface of a B-lymphocyte may contain from 50 to 150 thousand molecules of immunoglobulins. As they mature, B-lymphocytes change the class of immunoglobulins they synthesize.

The main functions of lymphocytes are reduced to the active movement, reproduction and synthesis of protein molecules “for export”. With the participation of auxiliary cells (macrophages, APCs), lymphocytes realize effector and regulatory immune processes: protect the body from genetically foreign substances, have the unique property of recognizing antigens.

Recycling of lymphocytes in the lymphoid organs occurs continuously for 6 hours according to the scheme: tissue → blood → lymph → blood. Lymphocytes penetrate almost all organs, with the exception of the vitreous body of the eye, brain, and testicles. Naive cells, as a rule, are retained in the lymphoid organs, and memory cells can migrate to epithelial tissues and to foci of inflammation.

To systematize immune cells, a classification of CDs (differentiation clusters) has been proposed. Specific immunity is realized by two links: humoral and cellular. Humoral is realized by B-lymphocytes and the production of immunoglobulins by plasma cells. Cellular immunity is represented by a population of T-lymphocytes (T-helpers, T-suppressors, T-killers or cytotoxic T-lymphocytes).

Non-lymphoid cells (macrophages, neutrophils, dendritic cells, Langerhans cells, etc.) also take part in immune reactions, which perform a number of important functions: capture, processing, processing and presentation of antigen to T-lymphocytes, activation of the immune system.

Lecture 9
The main histocompatibility complex (MHC).

The main histocompatibility complex (HCH) is a group of genes encoding the proteins responsible for the presentation (presentation) of antigens to T-lymphocytes, which play a crucial role in recognizing a foreign agent and developing an immune response. Initially, the products of these genes were identified as antigens that determine tissue compatibility, which determined the name of the complex (from the English major histocompatibility complex). In humans, MHC antigens (and the complex itself) are called HLA (from the English. Human leukocyte antigens), since they were originally found on white blood cells. These antigens are found in almost all cells with a nucleus. HLA antigens are glycoproteins located on the surface of cells and encoded by a group of closely linked genes of the 6th chromosome. HLA antigens play a crucial role in regulating the immune response to foreign antigens and are themselves strong antigens.

The high polymorphism of MHC molecules, as well as the ability of each antigen-presenting cell (APC) to express several different MHC molecules, makes it possible for T-cells to present many different antigenic peptides.

It should be noted that although MHC molecules are usually called antigens, they show antigenicity only when they are recognized by the immune system not of their own, but of a genetically different organism, for example, during organ allotransplantation.

Genes MHC-I - are membrane glycoproteins, have high polymorphism, these are classical (basic) genes. Contained on the surface of cells of all types having a nucleus.

MHC-I functions: synthesis of transplantation antigens, production of antibodies, recognition of transformed cells by cytotoxic white blood cells (T-killers).

Genes MHC-II - are membrane glycoproteins, represented by genes of immune resistance. Located on the surface of the agro-industrial complex.

MHC-II functions: provide interaction between T-lymphocytes and APC in the process of the immune response, T-helpers recognize a foreign antigen only after it is processed by macrophages and combined with MHC-II class and subsequent expression of this complex on the surface of the macrophage.

MHC-III genes - located between the MHC-I and MHC-II genes, components of the complement system, encode molecules of innate immunity.

MHC-III functions: encode molecules of innate immunity - synthesis of components of the complement system C2, C4, factor B; tumor necrosis factor-α; enzymes involved in the biosynthesis of steroid hormones.

Transplantation antigens encoded by MHC are individual genes (the law of transplantology - nature is not designed to mix the organs of already born individuals). Initially, MHC molecules were identified by their ability to cause transplant rejection, but they perform other biologically important functions in the body:

The natural functions of MHCs are to introduce peptide antigens to T lymphocytes that destroy infected cells or stimulate other cells (B cells and macrophages) to coordinate the cells of the immune system in suppressing the infection process.

Immunological reactions MHC:

- Intensity of rejection of tissue transplants;
- Stimulation of antibody formation;
- Stimulation of the reaction in a mixed culture of lymphocytes;
- The reaction "graft versus host";
- Cellular lympholysis reaction;
- Strength of the immune response;
- Restriction of the immune response

The main functions of human MHC:

• Material carrier of biological personality;
• predisposition or resistance to disease;
• Participation in reproduction;

• Stability and evolution of species;

One of the most important physiological functions of the HLA system is associated with reproduction, which provides the genetic diversity of the animal world - evolutionary material and disease resistance. Homozygous individuals have an increased risk of developing infectious, autoimmune and oncological diseases, as it is high polymorphism (genetic diversity) that is a necessary condition for the full activity of the human immune system. The biological significance of embryo rejection is associated with the need to achieve the individual's genetic diversity (heterozygosity) in order to actively adapt the species as a whole.

The commonality of genes (gene compatibility) of the HLA system in spouses and the homozygosity of parents (couples) and offspring (embryos) significantly increase the risk of degeneration (termination) of the genus in subsequent generations. In HLA-compatible couples, repeated miscarriages, toxicosis in the second half of pregnancy are more often observed, immunological mechanisms involved in physiological delivery are not realized.

In humans, inbreeding increases sharply in "closed" populations - small ethnic groups living in hard-to-reach areas or isolated, for various reasons. Due to the accumulation of genes and their appearance in a homozygous state among representatives of various royal houses, an increase in the number of hereditary diseases and deformities was often noted.

Polymorphism is the existence of a large number of different specificities of HLA genes (alleles) within each locus, which differ in the nucleotide sequences of DNA. The genes MHC-I and MHC-II possess the greatest polymorphism.

MHC antigens associated with diseases.

A number of human diseases are associated with histocompatibility genes that determine the fate of an allograft.

- MHC molecules form the body's resistance and predisposition to the development of various diseases.

- Hereditary predisposition to diseases, due to the MHC genes, genes of cytokines and their receptors.

Genes of human personality, encoded by the MHC, determine resistance or predisposition to a particular pathology.

HLA gene-protective and gene-associated diseases:

- Insulin-dependent diabetes mellitus
- Systemic lupus erythematosus
- Rheumatic fever
- Juvenile rheumatoid arthritis
- Polypous rhinosinusitis
- Acute pyelonephritis
- Acute glomerulonephritis
- Acute pneumonia in children
- Chronic tonsillitis

In multifactorial diseases (cancer, diabetes mellitus, multiple sclerosis, etc.), trigger mechanisms are not known, but it has been shown that streptococcal infection is involved in the development of rheumatism, and urogenital and intestinal infections are involved in Reiter's disease. HLA can also be affected by various environmental factors: physical, chemical, and biological.

It has been experimentally proved that at the individual level there is no general immunological reactivity, since the immune response to any antigenic effect is strictly specific and does not depend on the intensity of the immune response to another antigen. This means that at the same time an unlimited number of immune responses can occur in one organism, each of which will be strictly specific and be characterized by different intensities of immune antibody formation or cytolytic activity of cell-type effector reactions.

Lecture 10
Intercellular cooperation. Regulation of immunity.

Types of contact interactions of cells of the immune system can be combined into three groups:

a) interactions associated with the presentation of antigen, the participation of auxiliary cells (dendritic, macrophages, B-lymphocytes) and T-helpers;

b) cooperation of lymphocytes: T-helpers with B-lymphocytes and T-killer precursors;

c) the interaction of T-killers with target cells.

Adhesion is a vital process that ensures intercellular contacts, tissue integrity, promotes leukocyte migration, and takes part in immune and hemostatic reactions. On the surface of the recirculating lymphocytes, there are special adhesive molecules - homing receptors.

Antigen-presenting cells.

Cells specialized for the presentation of antigen are called antigen-presenting (APC), different in morphological and functional features, but nevertheless having a common (myeloid-cell) origin of the cell: macrophages, dendritic cells, B-lymphocytes. The purpose of these cells is to absorb (phagocytosis) and present (present) the antigen to T-helper cells.

Macrophages are predominantly phagocytic, but to a certain extent can process and present the antigen to lymphocytes. The most specialized antigen-presenting cells of the immune system are dendritic cells. They play an extremely important role in the immune system and possess higher than macrophages the ability to process and present antigen.

General principles of the functional interaction of cells of the immune system.

Cooperative cell interaction in immune responses has common features:

a) regardless of the variant of the immune response (synthesis of antibodies, the formation of killer cells, etc.), the core element of the

reaction is the process of converting an inactive precursor into an active effector cell;

b) maturation consists in acquiring a powerful apparatus for the synthesis of a particular protein, the production of which this cell is programmed;

c) the differentiation of precursors into mature cells is accompanied by the necessary regulatory mechanisms.

The interaction of T and B lymphocytes. Macrophages, T- and B-lymphocytes participate in intercellular interactions during antibody formation. Despite the fact that B-lymphocytes without APC can independently bind the native antigen, nevertheless, additional signals, the source of which are T-helpers, are necessary to stimulate their differentiation. The interaction of B- and T-lymphocytes is based on the formation of an antigenic bridge. B and T lymphocytes specifically recognize by their receptors different parts of the antigen - its different epitopes. According to modern concepts, the antigenic bridge connects the specific T-helper receptor to the MHC-II molecule of the B cell, and its specific receptor binds the free antigen through its other epitope. The recognition interaction leads to the differentiation of a T-lymphocyte into Th2, and a B-lymphocyte into a plasma cell. For effective and lasting interaction, cells express adhesion molecules.

Macrophages and T-helpers take part in the reactions of T-killer formation. Of great importance for the activation of T-helpers are macrophages that produce IL-1. In turn, the activity of macrophages themselves is enhanced by the same IL-1.

The key role of macrophages or varieties of APC is also manifested in such intercellular interactions as activation of suppressor reactions, development of local immune reactions in the skin and activation of individual leukocyte populations, as well as in the induction of delayed hypersensitivity.

Immunological memory. Individual recognition of the antigen allows, upon repeated contact with it, to develop a more effective secondary immune response, which is carried out using memory cells.

Fundamental to memory cells are two properties: the ability to recirculate and long life. T and B lymphocytes, which are morphologically defined as small lymphocytes, are referred to memory cells.

Immunodeficiency states (IDS).

The term immunodeficiencies refers to violations of normal immunological status that are caused by a defect in one or more parts of the immune response to different antigens.

Distinguish between primary (congenital) and secondary (acquired in the process of life, as well as due to violations of immunoregulation associated with infections, injuries, therapeutic effects and other causes) immunodeficiency states (IDS).

Primary IDS are often caused by a genetic block and are associated with impaired immune mechanisms (production of antibodies and / or T-lf). Depending on the level of disorders and localization of the defect of the immune system, distinguish between isolated (with a predominant lesion of one link of the immune system) and combined IDS (with the defeat of two or more links of the immune system).

Clinically, immunodeficiency states are manifested by syndromes: infectious, allergic, autoimmune, and lymphoproliferative.

Immune status. The immunogram.

The main methods for assessing the functioning of the immune system are tests of I and II levels, which are carried out using special immunological methods in immunological laboratories.

Level I - determination of the total number of leukocytes and lymphocytes, phagocytosis indicators, percentage and absolute number of T- and B-lymphocytes, concentration of serum immunoglobulins IgA, IgG, IgM (according to Mancini). Tests of level I allow you to evaluate the functioning of the main parts of the immune system (phagocytic, cellular and humoral).

Level II - determination of the percentage and absolute number of regulatory T-lymphocyte subpopulations: T-killers, T-helpers, T-

suppressors. Tests of the II level are aimed at an in-depth study of the immune status at the cellular, molecular and molecular genetic levels.

The state of nonspecific resistance of the body is assessed by the phagocytic activity of blood neutrophils.

The totality of the obtained indicators of cellular, humoral immunity, the functional activity of neutrophils are reflected in the immunogram.

Evaluation of the results of an immunogram is carried out by a qualified immunologist and requires a professional approach to subsequent immunotherapy.

The value of the immunogram. Evaluation of the immune system is necessary for a number of clinically relevant tasks: determining the state of health, diagnosing immunological pathology and monitoring immunotropic therapy.

Immunological studies (immunograms) are indicated for frequently and long-term ill individuals with various allergic manifestations (respiratory allergies, allergic dermatitis, including psoriasis); autoimmune diseases (polyarthritis, rheumatism, glomerulonephritis, hemorrhagic syndromes, etc.), with oncopathology.

Depending on the manifestation of certain clinical syndromes, certain changes are observed in the immunogram associated with the functioning of cellular, humoral and phagocytic units.

The clinical approach to immunodeficiency states of various genesis, persistent or chronic in nature, includes immunorehabilitation and immunocorrection.

Diagnostic methods for immunodeficiency.

The first stage of the diagnosis of IDS is clinical. The doctor collects and evaluates the immunological history: heredity, duration of a particular pathology, the presence of injuries, burns, operations; the presence of psychoemotional stress; vaccination history (in children); the frequency of infectious diseases, the nature of their course; the severity of the temperature reaction; the manifestation of allergic

diseases (food allergies, respiratory allergoses, etc.), autoimmune and oncological diseases. The effect of the drug treatment is noted.

Next, the results of a clinical blood test (the content of granulocytes, lymphocytes, platelets, ESR), biochemical parameters are studied. The presence of pathogenic microflora in the nasopharynx, urogenital pathology are investigated; the state of the microbiocenosis of the gastrointestinal tract, the presence of foci of chronic infection, helminth carriage. Instrumental examination methods are used (ultrasound, etc.).

With the help of molecular biological (DNA diagnostics - PCR) bacteriological, virological and serological (ELISA) studies, bacteriological or virus carriers are detected.

Based on the medical history, objective examination, and clinical data, the leading clinical syndrome is determined, which makes it possible to judge the defeat of a particular link in the immune system.

Immunogram requirements:

1) a study of the immune status is carried out 2-3 weeks after an acute illness;

2) 2-3 weeks after receiving courses of immunosuppressive therapy (using hormones, antibiotics, etc.).

Indications for the examination of the immune status of patients with:

1. Fungal, viral lesions of the skin and mucous membranes (candidiasis, stomatitis, herpes, etc.); with a chronic bacterial infection of the skin (boils, pyoderma, streptoderma, abscesses); with allergic dermatitis, psoriasis.

2. Diseases of the respiratory system (persistent viral and / or bacterial infections of the respiratory tract; groups of often and long-term sick - BCH); respiratory allergies (bronchial asthma, hay fever, vasomotor rhinitis, etc.); pneumonia, pleurisy.

3. Damage to the gastrointestinal tract (enterocolitis, cholecystitis, intestinal dysbiosis, etc.) and other organs and systems

4. Autoimmune lesions (acute rheumatic fever, polyarthritis, hemorrhagic vasculitis, glomerulonephritis, diabetes mellitus).

5. Post-vaccination complications.

6. Oncopathology, lymphadenopathy syndrome and subfebrile condition of unknown etiology.

7. AIDS, sexually transmitted diseases.

Contingents of persons subject to immunological examination:

1. Children of all age groups, with indications for examination;

2. Persons subject to vaccination;

3. Examination before and after surgical interventions;

4. Patients receiving chemotherapy and radiotherapy;

5. Able-bodied population in contact with harmful production factors;

6. A healthy contingent of individuals to determine regional parameters of the immune status.

At the second stage, immunological laboratories conduct studies of venous blood using special immunological methods. The main methods for identifying IDS are tests of I and II levels.

Lecture 11
Apoptosis

Apoptosis (other Greek-falling leaves or leaf fall) is a regulated process of programmed cell death, as a result of which the cell breaks up into individual apoptotic bodies bounded by a plasma membrane. Fragments of a dead cell are usually very quickly (in an average of 90 minutes) phagocytosed by macrophages or neighboring cells, bypassing the development of an inflammatory reaction. The morphologically recorded process of apoptosis lasts 1-3 hours. One of the main functions of apoptosis is the destruction of defective (damaged, mutant, infected) cells.

In multicellular organisms, apoptosis is involved in the processes of differentiation and morphogenesis, maintenance of cellular homeostasis, and the development and functioning of the immune system. Apoptosis is characteristic of all eukaryotes: from unicellular protozoa to higher organisms.

Violation of the processes of programmed cell death can lead to the appearance of pathological conditions and diseases that are accompanied by both degenerative and proliferative processes. Increased activation of apoptosis is a link in the pathogenesis of neurodegenerative myelodysplastic changes, ischemic injuries, and AIDS. Inhibition of programmed cell death causes tumor lesions of various nature, autoimmune and viral diseases.

The mechanisms of apoptosis. The main mechanisms for the implementation of apoptosis in eukaryotic cells have been established, scientific interest is due to the possibility of applying knowledge about programmed cell death in medicine in the treatment of oncological, autoimmune and neurodegenerative diseases.

Cell death is not considered only in the context of the catastrophic destruction of cellular integrity, but is the endpoint of a cascade of certain metabolic events. Molecular processes that occur under the influence of a damaging effect are not a mandatory cause of the death of a particular cell, but a signal for such changes that will lead to death.

The apoptosis signal is perceived by specialized receptors called apoptosis receptors.

With apoptosis, biopolymers are broken down in the cell, primarily DNA and certain enzymes, and viruses are destroyed. Apoptosis also rejects cells that are dangerous to the life or normal functioning of a multicellular organism, thus avoiding the production of antibodies to their own proteins.

Aging and death are special biological functions of the body that contribute to the progressive evolution of a species that reproduces sexually. And, like any important function of an organism, it is caused by the action of several molecular mechanisms working in parallel.

Apoptosis in immune processes. Apoptosis is involved in the vital functions of the immune system, ensuring the survival of antigen-specific clones and culling of autoreactive lymphocytes during positive and negative selection of T and B lymphocytes. Unselected cells die as a result of apoptosis in the thymus and red bone marrow.

The effector functions of cytotoxic T cells and NK cells are realized by the apoptosis mechanism involving serine proteases (granzymes) and by activating death receptors on the surface of target cells.

Cells that perform a barrier function initiate receptor-dependent apoptosis of effector T lymphocytes migrating through the “barrier” tissues, isolating the “immunologically privileged” zones (the internal environment of the eye, testes, and other organs).

Differentiation apoptosis - the death of part of the cells of an organ by apoptosis during their maturation is most pronounced in the thymus and in the tissue of the genital glands. At the stage of antigen-independent differentiation, 90 - 99% of T-lymphocytes entering the thymus die by apoptosis. Rigid selection of T cells in the thymus tissue is due to the need of the immune system for lymphocytes with a certain phenotype.

Cells expressing other antigens are eliminated, but if the process of differentiation apoptosis is disturbed, a more intense death of

thymocytes or getting into the systemic circulation of T-lymphocytes with auto-aggressive properties is possible. This contributes to the development of immunodeficiency states with insufficient cellular immunity or autoimmune diseases. The main role in the rejection of T cells is played by the so-called "nanny cells."

Mature lymphocytes form in the lymph nodes, tonsils, Peyer's patches, vermiform appendix, spleen, thymus (thymus) and bone marrow.

Proliferation and differentiation of lymphocytes. There are antigen-independent, antigen-dependent differentiation and specialization of B- and T-lymphocytes. Antigen-independent differentiation of T and B lymphocytes occurs in the thymus and bone marrow. Antigen-dependent differentiation of T- and B-lymphocytes - in the peripheral organs of the immune system.

Antigen-independent proliferation and differentiation are genetically programmed to form cells capable of giving a specific type of immune response to a particular antigen. Antigen-independent proliferation is carried out in the central organs of the immune system (thymus, bone marrow) under the influence of specific factors produced by the cells forming the microenvironment - the reticular stroma or reticuloepithelial cells in the thymus gland.

Antigen-dependent proliferation and differentiation of T- and B-lymphocytes occurs when they meet with antigens in peripheral lymphoid organs, and effector cells and memory cells are formed (which store information about the acting antigen).

The role of apoptosis in aging. Hepatocytes, cardiomyocytes, macrophages, megakaryocytes, neurons, oocytes, splenocytes, T-lymphocytes, chondrocytes, endotheliocytes of an aging organism increase their sensitivity to the development of apoptosis. However, for fibroblasts, there is an inverse tendency to decrease sensitivity to apoptosis. The sensitivity to apoptosis does not change mainly in keratinocytes.

Apoptotic death of cardiomyocytes, neurons, and certain types of leukocytes is associated with aging of the heart muscle, age-related neurodegenerative processes, and aging of the immune system. On the other hand, aging is associated with cell resistance to apoptosis. As an example, we consider the resistance of aging fibroblasts to apoptosis, resulting in premature aging of normal fibroblasts and in impaired connective tissue functions.

Pathology in violation of apoptosis. With apoptosis deficiency, autoimmune processes and malignant neoplasms progress. With increased apoptosis, aplasia and degenerative processes occur, as well as some malformations with tissue defects.

Normally, virus-infected cells die as a result of activation of receptor-dependent apoptosis to prevent the spread of the virus. However, some viruses can disrupt the normal regulation of the programmed cell death mechanism, or even actively prevent apoptosis.

Increased apoptosis manifests itself in the pathology of the blood system. The death of bone marrow progenitor cells through apoptosis is associated with a deficiency of iron, folate, vitamin B12 and the development of aplastic anemia; thalassemia; thrombocytopenia; lymphopenia neutropenia; pancytopenia. Some infectious diseases may be associated with increased apoptosis under the influence of bacterial endo- and exotoxins. Mass apoptosis develops with sepsis. Elimination of CD4 + lymphocytes by apoptosis positively correlates with AIDS progression.

With atrophy of certain areas of the nervous tissue as a result of apoptosis, amyotrophic lateral sclerosis, Alzheimer's disease, spinal muscular atrophy develops, etc.

In the early stages of myocardial infarction, cardiomyocytes die by apoptosis due to hypoxia, ischemia, calcium overload, inflammation, and toxins. Toxic hepatitis (including alcoholic) is accompanied by apoptosis.

Apoptosis progresses under the influence of ionizing radiation. In this case, lymphoid cells die mainly, and immune deficiency develops.

A similar effect is given by many anticancer chemotherapeutic drugs and hormones used in the treatment of various diseases.

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