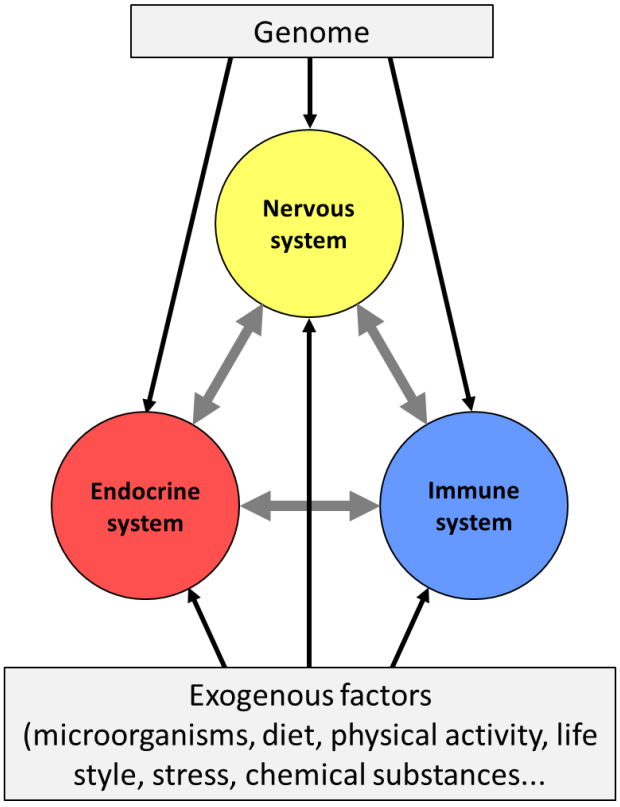
Pathophysiology of the immunity

Immunity is the ability to respond to alien substances and pathogens as well as to own altered cells and resist their action on the organism, the ability to distinguish one's own from another's. Its role in the initiation of various pathological conditions and in the development of diseases is crucial. Individuals with both reduced and disproportionately increased immune responses are in life threatening situation.

Immune response

- Recognition of alien antigen and its exposure on the cell surface
- Communication, cooperation, coordination
- Destruction of the pathogen

The immune system is one of the three basic control systems of the human body. Together with the nervous and endocrine systems, it forms a whole system, interconnected by regulatory mechanisms, responding to external signals in order to maintain a stable internal environment (homeostasis).



everything in balance = self-maintenance (homeostasis)

Psycho-neuro-immune relationships

Mutual interactions of the nervous, endocrine and immune systems.

Many mediators (information molecules) act and are produced in more than one of these systems.

An example of the interconnection of all 3 systems is the axis hypothalamus - pituitary - adrenal glands:

Stress activates the secretion of corticoliberin (CRF) in the hypothalamus

→ Stimulation of ACTH secretion in the adenohypophysis (anterior pituitary)

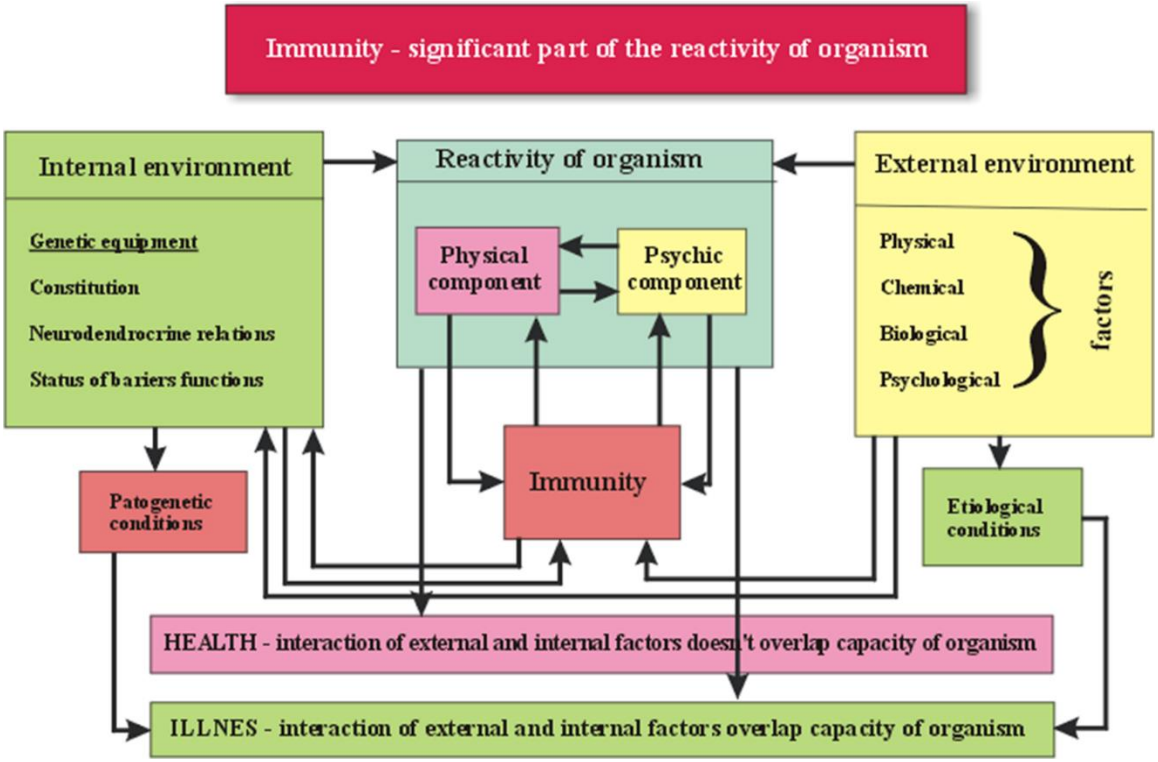
→ Stimulation of glucocorticoids secretion in the adrenal cortex

→ Anti-inflammatory and immunosuppressive effect of glucocorticoids

There is a constant exchange of information among the central nervous system, the endocrine system and the immune system. Any damage to one of the components of this system leads to imbalance and disease. For example, brain injury leads to significant damage of the immune system and reduced resistance, infectious and inflammatory diseases, and sometimes to general sepsis.

Immunity and pathogenesis

Immune processes are involved in the initiation of various pathological conditions. The reaction of the immune system can also mediate tissue damage, such as the destruction of virus-infected cells, which is one of the mechanisms of organism damage in viral diseases.



A. INFORMATION AND EFFECTOR MOLECULES OF THE IMMUNE SYSTEM

Cytokines

Cytokines are tissue hormones producing by cells of the immune system, glia and neurons. They mediate and control immune responses. It is a diverse group of proteins, mostly glycoproteins, whose binding to effector cell receptors induces gene expression and the final effect (e.g. pro-inflammatory or anti-inflammatory action). One cytokine has multiple effects, different cytokines may have a similar effect. Selected cytokines and their possible effects:

- IL-1, IL-6 (interleukin 1 and 6 - pro-inflammatory cytokines having positive effect on wound healing or stimulation of hematopoiesis)
- IL-4, IL-8, IL-10 (anti-inflammatory cytokines, immunosuppressive action)
- IL-2, IL-12 (NK-cells stimulating cytokines)
- INF- α (interferon alpha, a key component of the natural resistance against viral infection, i.e. antiviral activity, cytostatic effect)
- INF-γ (interferon gamma, enhances macrophage activity)
- TNF-α (tumor necrosis factor alpha, pro-inflammatory cytokine, enhances T and B-cell activation, endogenous pyrogen and apoptosis activator)

- MIP-1 (microphage inflammatory protein)
- TGF-ß (transforming growth factor beta, supporting the growth of immune cells)
- GM-CSF (granulocyte and macrophage colony stimulating factor, hematopoietic factor promoting cell differentiation)

Gaseous neurotransmitters

They are low molecular weight chemicals acting in the immune, nervous and vascular systems. They modulate inflammatory reactions in the immune system; they also participate regulation of stress response in brain and nerve plasticity, and in nociception, too.

- NO - Nitric oxide
- CO - Carbon monoxide
- H_2S - Hydrogen sulfide

Adhesive proteins

They provide cell contacts and targeted movement of immune cells in the body. These include adhesins that allow leukocytes passing through the vessel wall into the tissues; also mucins that allow leukocytes coming into contact with the endothelium during inflammation, selectins and integrins. They occur, for example, on the surface of antigen-presenting cells and mediate contact with T-cells (ICAM-1, ICAM-3 adhesins).

Antigens and MHC system

Antigens are protein molecules situated on the surface of all cells (except sperm) that are able (but not necessarily) to elicit an immune response. The antigens themselves do not activate the immune response and are bound as part of the major histocompatibility complex (MHC I).

Most MHC glycoproteins are on leukocytes, so in humans the MHC complex is also called the HLA complex (human leukocyte antigen). The MHC (HLA) system is characteristic of each individual.

MHC class I are transmembrane glycoprotein molecules that are expressed by majority of all nuclear cells. MHC I presents peptides (MHC I / self-antigen complex) produced by self-cells to the cytotoxic T-cells. After viral infection attack, the cells themselves begin to form protein products of the virus, and the infected cells form a MHC I / viral antigen complex, activating cytotoxic T-cells; next step is the apoptosis activation and removing virus-infected

cells. The same mechanism during recognizing one's own tumor and damaged cells is used.

MHC class II are transmembrane glycoproteins on the surface of immune cells, namely antigen presenting cells (macrophages, dendritic cells) and B-lymphocytes, which phagocytose alien substances; their antigens then present on their surface by forming stable MHC II / alien antigen complexes. MHC II presents alien antigens to helper T-cells, thereby activating inflammatory and antibody immune responses.

If the particles are not antigenic substance (e.g. low-molecular weight poisons), immunity will not affect them and an immune response will not occur.

Antibodies

Antibodies are glycoproteins whose production is induced in B-lymphocytes as a response to antigen. Their function is to neutralize and remove this antigen. We recognize different classes of antibodies (immunoglobulins) - A, D, E, G and M (IgA, IgD, IgE, IgG and IgM). Individual antibodies differ in amino acid sequence at the antigen binding site and, due to this hypervariable region, can bind specifically to a particular antigen. They are either bound in B-cell membrane and serve as a receptor for a specific antigen, or bound to Fc-receptors of epithelial and placental cells and mediate the active transport of IgA (epithelium) or IgG (placenta); they occur freely in plasma and mucosal secrets, too.

Complement

Complement is a functionally linked system of plasma proteins. Its role in the immune system is the activation of classical and alternative pathways which initiate the immune response. The classical pathway begins with the activation of the C1 component by binding to an immunoglobulin in complex with an antigen. An alternative pathway begins with the activation of component C3 via bacterial wall lipopolysaccharides (or fungal wall polysaccharides) or via endotoxins.

Complement acts as a pro-inflammatory system (components C3a, C4a, C5a called anaphylatoxins). Anaphylatoxins cause mast cell degranulation and histamine release which increases microvascular permeability.

The complement components C3b, C4b bind to antibody molecules or the cell surface, they are opsonized and bind to corresponding receptors on phagocytic cells and erythrocytes (having a transport role).

The terminal membrane complex of complement C5b-9 has cytolytic activity for defense against G-bacteria. During dysregulation of complement activation, the cytolytic activity of this terminal complex causes hemolysis.

Defects of individual components of complement and its regulatory molecules are manifested in the whole spectrum of diseases. Decreased resistance to infection occurs in the absence of the C3 component and recurrent infectious diseases are severe. In the absence of components C6, C7, C8, a disseminated infection with Neisseria (Neisseria gonorrhoeae, Neisseria meningitis) develops.

B. CELLS OF THE IMMUNE SYSTEM

Macrophages and monocytes

Tissue macrophages are present in various tissues and are capable of phagocytosis. The osteoclasts in bone, microglia in the CNS or Kupffer cells in liver are typical examples.

They are produced from blood monocytes, which mature after entering the tissue, increase their volume and the number of lysosomes (vacuoles with enzymes). They are involved in both non-specific and specific immune responses. They phagocytose alien substances and participate in the initiation of inflammation, utilize alien antigens and display them on their surface, where can be recognized by immunocompetent T-lymphocytes (specific T-cell receptors against this antigen). They are called as antigen presenting cells (APC), too.

Macrophages have MHC II molecules in the membrane, which allows them to react with T-lymphocytes. Macrophage activity is enhanced by the cytokine IFN-γ (interferon gamma), produced by activated T cells.

Macrophages release proteolytic enzymes and some cytotoxic substances into their environment. They are important by cytokines production which causes an inflammatory response (IL-1, TNF-α). The local immune response to pathogen intrusion also involves the production of TNF-α at this site, which has the effect of increasing the permeability of the surrounding capillaries and increasing blood clotting. Dysregulation of macrophages produced by TNF-α is involved in the pathogenesis of many diseases. If the infection spreads throughout the circulation (sepsis), a massive increase in TNF-α levels can lead to septic shock and organs failure.

Neutrophil granulocytes (microphages)

Mature neutrophilic granulocytes circulate in the blood and penetrate the vessel wall by diapedesis at the site of inflammation and travel through the tissue in the direction of inflammation (i.e., at a site marked on the endothelium by adhesive molecules). Neutrophils recognize the antigen non- specifically, e.g. by lipopolysaccharides (LPS) in the bacterial wall, and they phagocytose immediately. They perish within 4 - 6 days. When a large number of neutrophils break down, pus (pyogenic infection) develops.

Antigen presenting cells (APC)

They are regulatory cells of the immune system capable of phagocytosis. During infection, microbial surfaces serve as a stimulus for their activation. For example, lipopolysaccharide microbial structures are recognized, and after entering into the cytosol of antigen-presenting cells, these antigens are metabolized and degraded into protein fragments. The antigens are presented on the APC surface in complex with MHC and APC mediate the immune response in this manner. They also modulate inflammation by regulatory factors.

These include dendritic cells, macrophages, monocytes and others.

Dendritic cells

They are the most important antigen-presenting cells distributed in almost all tissues except the brain, testes and cornea. Unlike other cells of the immune system, they express both MHC I and MHC II molecules. They can induce both immunological tolerance (immature dendritic cells) and an immune response (mature dendritic cells). They represent a link between the rapid non-specific and the slowly developing antigen-specific part of the immune system. Their interaction with other cells of the immune system is important, which allows the significant modulation of human body's immune response.

Long membrane protrusions jut from their bodies, similar to dendrites of neurons, allowing contact with many cells. They absorb dead cells of own tissues and, in the case of infection, the antigens which they present on their surface to T-cells. They produce cytokines (IL-1, IL-6, TNF - α, IL-12). They stimulate both native T-cells and B-cells, allowing the development of an effective immune response.

The examples are skin Langerhans cells, dendritic cells in the mucosa of the respiratory and digestive tract, lymph nodes, cells in the spleen, thymus, blood and others.

T-lymphocytes

T-lymphocytes, otherwise also T-cells, have the specific receptors on their surface (TCR, T - cell receptor) using for recognition of complex of antigen with MHC proteins on the surface of antigen-presenting cells. In addition, they have ligands on their surface that allow contact with the surfaces of costimulatory cells via adhesive molecules (e.g. ICAM-1, ICAM-3). This mechanism allows the stimulation of their proliferation, cytokines production and the binding of specific T cells to the antigen.

Cytotoxic T cells and helper T cells, through their receptors, recognize antigen fragments complexed with MHC I and MHC II proteins on APC cells. When the antigen is exposed on the MHC I protein, cytotoxic T cells are activated, which these, such as virus-infected cells, recognize and destroy. When the antigen is presented on the MHC II protein, it interacts with helper T cells and the immunomodulatory effects appear. They produce interferon gamma (INF- γ).

Specific T cells can also recognize the antigen in complex with MHC I proteins on immature dendritic cells and are not activated by this contact, or they form regulatory T cells. Regulatory T cells actively suppress immune responses against a given antigen. Thus, immature dendritic cells play a significant role in tolerance maintaining to their own tissues.

B-lymphocytes

We also call them B-cells. Naive and memory B-cells are activated by antigen-presenting cells either directly (by IL-12) or indirectly (by T-cell regulation) in secondary lymphoid organs, and they are differentiated into IgM antibody-producing B-cells. These immunoglobulins are bound in B-cell membranes and form specific immunoreceptors which bind the specific antigens. B-cells then differentiate into plasma cells producing specific antibodies, according to the immunoglobulins of specifically responding B-cells.

NK cells

NK cells (Natural Killer) are cytotoxic cells of non-specific immunity. It belongs to the granular lymphocytes. They recognize pathogens, cells containing abnormally low levels of HLA I (mainly tumor and virus-infected cells). They have a cytotoxic effect and produce cytokines, such as IFN-γ, which enhance the activity of macrophages.

They are able to interact with dendritic cells and modulate the immune response at the site of inflammation and in the lymph nodes. Their number

decreases under stress and excessive overload (acute or chronic), which negatively affects the body's antiviral immunity.

Mast cells

Mast cells are mastocytes (heparinocytes) in the connective tissue or along blood capillaries. The cytoplasm of heparinocytes contains granules with heparin and histamine. There are Ig E receptors on the cell surface, so they are involved in allergic reactions and inflammatory processes. They are the main cells of a type I hypersensitivity reaction.

Stem cells

Stem cells are important cells of the immune system. These include mesenchymal stem cells (MSCs) and hematopoietic stem cells. It suppresses excessive immune responses and restores damaged tissues. They also have anti-inflammatory effects. Stem cell damage leads to an insufficient hematopoiesis and lymphopoiesis. In addition, leukemic cell reversal may occur by this mechanism.

C. ORGANS OF THE IMMUNE SYSTEM

The immune tissues can be divided into two basic types which are connected by the blood and lymph vessels.

- PRIMARY LYMFOID ORGANS

Thymus

The thymus is formed by lymphatic tissue and is involved in regulation of the formation, differentiation and maturation of T-lymphocytes. There is a positive as well as a negative selection of T-cell clones. Both defective and autoreactive T-cell clones are eliminated. Thymus is a key organ for induction of tolerance to the body's own antigens. It produces thymic hormones through which it affects other organs of the immune system and the neuroendocrine system, too.

Peyer's plates

It is important immunoactive lymphatic tissue, the main component of mucosal immunity in the gastrointestinal tract mediating the transport of antigens to the basal surface, where these antigens can contact the dendritic cells and macrophages; then a mucosal IgA is produced.

Crohn's disease and ulcerative colitis are two types of inflammatory bowel disease. Crohn's disease usually involves inflammation of the ileum, while ulcerative colitis preferentially affects the large intestine. In patients with these diseases, lesions in the area of Peyer's patches are detected, which indicates their role in the pathogenesis of these conditions.

- PERIPHERAL LYMFOID ORGANS

Lymph nodes are organs inserted in the course of lymphatic vessels that serve as a biological lymph filter. Most cells are formed by B and T lymphocytes.

Spleen

The spleen is functionally divided, similar to lymph nodes, into both B and T-cell areas. Its function is the filtration and processing of antigens from the blood, there is also the place of erythrocytes destruction. Pathological processes in the spleen (or splenectomy) result in immunosuppression; the lymphoid component of the organ predominates over the blood cells.

Lymphoid tissue of mucous membranes, glands (mammary, genital)**, liver, bone marrow**

Pathophysiology – lymphadenomegaly**,** lymphomas

D. NONSPECIFIC IMMUNITY

It includes various types of phagocytes, complement and NK-cells; it recognizes the main, characteristic signs of antigens. The main effector mechanisms are phagocytosis and inflammation.

Phagocytosis – consists of a few subsequent phases:

- Migration
- Adhesion (after opsonization; opsonins = components of complement or antibodies that are recognized as alien)
- Absorption (phagosome)
- Destruction (phagosome connects with lysosome in phagolysosome)

Inflammation

Inflammation is one of the most important inborn defense mechanisms of the body. It is a nonspecific reaction of vascularized tissue; (see the separate educational material).

E. SPECIFIC IMMUNITY

This part of the immune system is based on the cooperation of B- and T-cells (lymphocytes), where each of the huge number of clones of these cells is equipped with specific receptors which recognize the detailed specific structures of the antigen. The subsequent reaction is focuses only against this antigen.

There is also a connection with the mechanisms of nonspecific immunity. Disorders of coordination of individual components of the immune system lead to a failure of the individual's defenses and to more frequent occurrence of inflammatory complications.

F. INSUFFICIENT ACTIVITY OF THE IMMUNE SYSTEM - IMMUNODEFICIENCY

PRIMARY IMMUNODEFICIENCY (congenital, inborn)

They are generally manifested by recurrent infections in early childhood, some disorders are incompatible with life in normal environment.

- **B-cell disorders and antibody production disorders**

Hereditary IgG deficiency or excess, impaired immunoglobulin chain production, IgA antibody deficiency or defect, hypogammaglobulinemia with IgM excess and lack of immunoglobulins of all classes.

Deficiency of IgA antibodies, which are the main class of antibodies on mucosal surfaces, manifests as atopy, diseases of the respiratory, gastrointestinal and urogenital tracts. Plasma IgA levels are also reduced, and anti-IgA antibodies may be present. Blood transfusions with normal immunoglobulin concentrations in these defects can cause a severe anaphylactic reaction, so the lack of antibodies in these patients is not compensated.

An example of congenital B-cell disturbance and subsequent dramatic IgG deficiency is Bruton's agammaglobulinemia. The gene defect for the enzyme tyrosine kinase is bound to the X-chromosome and only affects men. Children (usually 1 year old already) suffer from frequent purulent infections such as conjunctivitis, otitis media, bronchitis and pneumonias as well as skin infections. Parasitic infections of the lungs (Pneumocystis carinii) and frequent intestinal infections (Giardia lamblia) may occur. Resistance against viral and fungal diseases is normal. Autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus may also be associated.

- **T-cell disorders, hypoplasia or lack of thymus**

Di Georg´s syndrome is an example of the immune defect that occurs during embryonic development already and is accompanied by other developmental defects, especially the parathyroid glands, heart defects and large blood vessels. During aging, the number of functional T cells increases and immunity improves.

- **Severe combined immunodeficiency**

Impairment of T-cell and B-cell development (may be secondary), resulting in susceptibility to all types of infections, bacterial and viral, parasitic and fungal; the disease has a fatal prognosis. Different etiologies are characteristic. It can be caused by a defect in interleukin receptors (IL-2, IL-4). Another cause is a disruption of the development of lymphocytes (T and B-cells) in the bone marrow. The disease is inherited both autosomal recessively and X-linked. In therapy, bone marrow transplantation is promising.

- **Defects of the complement system**

These disorders increase the susceptibility to infections or organ damage; the most serious disorders occur in the absence of component C3.

- **Defect of phagocytes**, which have only a limited ability to destroy phagocytosed material (chronic granulomatosis).
- **Disorders of leukocyte adhesion** (disorder of adhesive proteins on all types of leukocytes, i.e. lymphocytes, granulocytes, monocytes, NK-cells).
- **Lack of NK cells**
- **Disorder of granulocytes** (decrease in the ability to destroy phagocytosed microorganisms).

SECONDARY IMMUNODEFICIENCY (acquired)

The etiology of secondary immune disorders is diverse, either obvious, or not fully understood. It develops as a result of damage to immune cells and disruption of the immune response. The imbalance between the immune system and the nervous and endocrine systems is developed.

- **May be iatrogenic** (therapy with cytostatics, immunosuppressants or hormones)
- **As a complication of diseases or injuries** (severe brain injuries, burns)
- **As a consequence of chronic or acute stress**
- **As a result of a viral infection.** A specific case is HIV infection, which causes AIDS - acquired immunodeficiency syndrome.

AIDS-acquired immunodeficiency syndrome

The pathology of HIV disease is characterized by $CD4^+$ T-cell infection and its subsequent deficiency. Attack of $CD4^+$ T-lymphocytes leads to dysregulation of immune responses and it also increases the susceptibility to new infections. Inadequate immune system responses can result in generalized lymphadenopathy. The actual immune response to HIV infection is relatively small because the cells (necessary for its regulation) are infected themselves.

We distinguish three stages of the disease:
• Initial HIV infection
• Clinically latent stage
• Clinically manifest stage – AIDS

During the course of the disease, other cells of the immune system (monocytes, macrophages, dendritic cells) are attacked, and they become a so-called reservoir of infection. By the spread of HIV infection, the immune reaction responds in a vicious circle because the activation of infected T-cells not only activates immune processes, but also increases the transcription of the HIV gene. Due to the high immunological load, also due to associated infections, immunological disruption and death occur. People with immunodeficiency suffer from, for example, bacterial tuberculosis, viral hepatitis, candidiasis, lymphomas, etc. The nervous system is also affected,

and spinal cord, brain and peripheral nerve disorders occur. The basis is an infection of macrophages of the nervous system.

G. EXCESSIVE ACTIVITY OF THE IMMUNE SYSTEM - HYPERREACTIVITY, ALLERGY

Inadequately increased response to an external antigen that does not elicit a response in another individual.

Type 1 allergic reaction

The antigen (so called allergen in this type) causes an immediate increase in the production of immunoglobulins E (Ig E), which bind to mast cell Ig E receptors. The effect occurs in a few minutes. During repeated contact with the allergen, it binds to Ig E and mast cells are degranulated. The allergic reaction is a cascade of cytokine-controlled events (IL-4, IL-5, IL-6, IL-13), including heparin and histamine release, complement activation, activation of the inflammatory response (prostaglandins, bradykinin), platelet activation and degranulation, and other release histamine and heparin and vasoactive peptides. Type 1 reactions (early, atopic, anaphylactic type) develop in patients with an inherited change in the HLA II system. It manifests itself as atopic rhinitis, asthma, atopic eczema, or as an anaphylactic reaction leading to anaphylactic shock.

An anaphylactic reaction is a life-threatening condition in which rapid vasodilation, increased capillary permeability, tissue swelling, bronchoconstriction, cardiovascular system disorders, and gastrointestinal function problems occur. Allergens are various foods, food additives, toxins (insect stings), drugs (antibiotics, contrast agents).

Type 2 allergic reaction

This is cytotoxic type of allergic reaction in which IgM and IgG antibodies react rapidly against self-antigens on the cell surface (within a few minutes or hours). Alien substances connected to cell membranes are detected by the immune system, antibodies bind to antigens and cytotoxic mechanisms are activated. Antigen cells are destroyed by cytotoxic T cells, damaging various tissues and organs. Examples are incompatibility in the AB0 system and hemolytic disease of the newborn. Allergens can also be so-called haptens, small molecules that are not immunogenic in themselves, but when they bound to protein structures, they elicit an immune response. Haptens can be drugs or herbicides, insecticides, cosmetic components, etc. By this mechanism, the binding of some drugs can cause, for example, hemolytic anemia.

Type 3 allergic reaction
The formation of immunocomplexes is typical of this type of allergic reaction; they are composed of an antigen (viral, bacterial, parasitic, or endogenous) and an IgG or IgM antibody to which complement binds, freely passing through the endothelium, and causing inflammation. Increased amounts of complexes stimulate neutrophils and macrophages, which damages the tissues. Examples are systemic lupus erythematosus or rheumatoid arthritis.

Type 4 allergic reaction
This type of allergic reaction is called the cell type. It is mediated directly by immune cells. Antigen-presenting cells activate helper T cells, producing cytokines that activate cytotoxic T cells, monocytes, and macrophages that directly damage the tissue. TNF-α, INF-γ and NK cells stimulating the cytokine IL-2 are involved in the reaction. Granulomas in tissues and on the skin, eczema, contact dermatitis are typical manifestations. This allergic reaction is the basis of both autoimmune and some infectious diseases (tuberculosis, leprosy, toxoplasmosis).

Type 5 allergic reaction
It is mediated by anti-receptor IgG antibodies, the response develops most slowly, weeks to months. An example is Graves-Basedow's disease, in which the binding of antibodies to thyrotropic hormone (TSH) receptors increases the production of thyroid hormones. Another example is myasthenia gravis, in which acetylcholine-positive ectopic muscle cells in the thymus produce antibodies that bind to postsynaptic acetylcholine receptors; they are destroyed and various levels of neuromuscular transmission disorders are provoked. In the case of myasthenic crisis, respiratory failure may occur due to atony of the respiratory muscles.

Specific allergen immunotherapy (AIT)
One of the treatment options for allergies is to increase the production of immunosuppressive cytokines by contact with allergens. Dendritic cells and regulatory T cells are activated, and they produce, for example, IL-10. The production of this interleukin suppresses the allergen-specific immune response.

H. THE ACTIVITY OF IMMUNE SYSTEM ACTING AGAINST THE INTRINSIC ANTIGENS - AUTOIMMUNITY

Immunological tolerance is the elimination of T-cell clones directed against self-antigens (negative selection) during their development in the thymus. Specific T cells recognize the antigen in complex with MHC I proteins on immature dendritic cells and are not activated by this contact, or they form regulatory T cells that actively suppress responses to the antigen. Thus, immature dendritic cells play a significant role in maintaining tolerance to their own tissues.

Dendritic cells transport antigen (own or alien) from the periphery to the thymus where positive selection of regulatory T-cells from naive precursors takes place under their influence. These tolerogenic dendritic cells also allow the induction of regulatory T cells in peripheral lymphoid tissues.

Antigen-presenting cells have the ability to regulate T-cell supply of two important amino acids, cysteine and tryptophan. T-cells cannot produce cysteine and are dependent on its delivery from the surroundings. Macrophages and dendritic cells produce cysteine and affect T-cell activation. This mechanism is used in the treatment of some autoimmune diseases. By administering drugs that block cysteine production in antigen-presenting cells, the activation of autoreactive T cells it indirectly blocks. Under certain conditions, for example during pregnancy, decrease of tryptophan availability (it is enzymatically degraded) leads to the suppression of T-cell activity, thus immunological tolerance of the fetus in the mother's body is allowed.

Antigen sequestration - autoantigens are separated from autoreactive T-lymphocytes by functional-anatomical barriers (blood-brain barrier, male gonadal microenvironment, antigens in the lens of the eye, thyroid gland) and no immunological tolerance has been induced. Antigens are in so-called immunologically privileged sites. In case of injury, this antigen will be revealed and the immunity is manifested because the T-cell clone persists against them (sympathetic ophthalmia - when the eye is injured, immune response can damage the second eye).

Some viral or bacterial infections cause a reaction not only against foreign antigens, but also against oneself. An example is the antigen-M of the bacterium Streptococcus pyogenes, which can trigger a reaction against own proteins (myosin, tropomyosin, laminin, keratine) and rheumatic fever develops (inflammatory diseases of the heart, kidneys and joints).

The formation of autoantibodies against β-cells of the pancreatic Langerhans´s islets is also conditioned by autoimmunity. Their destruction leads to the insulin deficiency (partial or complete) and type 1 diabetes mellitus occurs. Because the pancreas has a large secretory reserve, the manifestation of diabetes occurs only after the destruction of about 90% of all β-cells. Hyperglycemia and a tendency to ketoacidosis are typical. The onset in childhood is characteristic, but the so-called LADA variant of type 1 DM (latent autoimmune diabetes of adults) manifests at any age and usually progresses slowly. Patients are fully dependent on insulin substitution. Genetic predisposition at the level of the HLA system (endogenous factors) is always necessary for the development of this disease. The triggering mechanism is probably exogenous factors, such as viral infections. Manifestation can be facilitated by greater physical or mental stress or trauma.

I. IMMUNITY OF TRANSPLANTATION

Transplant immunology deals with interactions between the recipient and the transplanted organ, tissue, or cells of the donor.

The outcome of transplantation, rejection, or tolerance depends on the maturity of the antigen presenting cells. Prevention of graft rejection in transplantology can be achieved by suppressing the recipient's immune system (immunosuppression), reducing graft immunogenicity, or a combination of both approaches. To induce rejection and initiate a cytotoxic response, APCs must present an exogenous antigen in complex with MHC I molecules (cross-presentation). A cell that has an MHC I antigen-glycoprotein complex on its surface is taken up by an APC cell that cross-activates cytotoxic T cells. In this way, they can cross-present both foreign cell antigens and self-antigens.

The immune system generally tolerates its own MHC I in complex with peptides, while an immune response develops against foreign MHC I. For transplantation, donors are searched according to high concordance of alleles in the MHC gene. The high MHC I polymorphism is the cause of the difficult search for a donor even among relatives.

At present, a treatment of graft rejection in transplantology focuses on the cell manipulation and the development of graft tolerance. For example, an insertion of the required IL-10 gene using adenoviral vectors to induce inhibition of T-cell proliferation is used.