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Regeneration's Role in the Development of Desensitization and Immunological Tolerance

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Abstract

Blood group antigens and tissue-specific antigens, as well as peptide copies of tissue-specific antigens associated with dimeric class I MHC peptides, form a unique antigenic code of each individual, on the basis of which the immune system distinguishes its antigens from others. Due to the commonality of their phylogenetic development, micro-organisms express antigens similar to antigens of blood groups (AB0 and others), as well as to tissue-specific autoantigens. The immune response to cross-microbial antigens is one of the causes of autoimmune diseases. T-helpers (Th) can switch the cellular immune response to humoral, and vice versa: switch the humoral immune response to cellular. Participation of Th in regeneration can be used for desensitization – to switch activation of cytotoxic T-cells and B-cells to the formation of tissue-specific receptors in stem cells involved in tissue regeneration, to the antigens of which the immune system has developed hypersensitivity. The formation of chimerism through transfusion of allogeneic pluripotent stem cells in the mononuclear fraction of peripheral blood from young donors aged 18-23 years, having the same blood group and sex as recipients (RF patent number 2350340), leads to the development of recipients' immunological tolerance to tissue-specific antigens histo-compatibility of donors. Desensitization and the formation of immunological tolerance are an alternative to using immunosuppressive therapy in rheumatology and in transplantology.

Keywords: blood groups, tissue-specific histocompatibility antigens, innate and acquired immunity, pluripotent stem cells, regeneration, desensitization, immunological tolerance.

Introduction

Blood group antigens and tissue-specific antigens, as well as peptide copies of tissue-specific antigens associated with dimeric class I MHC peptides, form a unique antigenic code of each individual, on the basis of which the immune system

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distinguishes its antigens from foreign antigens that have entered the internal environment of the body and have come into contact with its skin or mucous membranes. Blood group antigens and tissue-specific antigens can bind to antibodies, and peptide copies of autoantigens associated with class I MHC dimers, and peptide copies of foreign antigens, modified own antigens, antigens of dead old and damaged cells associated with class II MHC dimers, can interact only with complementary receptors, with α- and β-chains of integrins and selectins. Antigens that are no different from autoantigens are recognized as "one's own," while those that are different from one's own antigens are considered to be "strangers." Normally, foreign antigens initiate an immune response aimed at their elimination. In contrast, native cells carrying blood group antigens, tissue-specific antigens, and peptide copies of tissue-specific autoantigens associated with class I MHC dimers are normally protected from immune reactions aimed at their elimination.

Autoantigens' Role in the Development of Innate and Acquired Immunity

The immune system recognizes its own antigens from foreign ones by analyzing non-covalent (electrostatic, hydrogen, hydrophobic, van der Waals) bonds that have arisen between antigens and amino acid residues of complementary receptors, α- and β-chains of integrins and selectins or heavy (H) and light chains (L) of V-domains of antibodies [1, 2, 3]. Autoantigens processed in proteosomes of eukaryotic cells are used as samples for comparing the analyzed antigens. Processing begins in proteosomes with enzyme cleavage of autoantigens. The resulting fragments of autoantigens (their separate parts) are bound by non-covalent bonds with proteins of proteosomes under the control of Ir-genes common to MHC. Three-dimensional protein molecules of proteosomes, which form non-covalent bonds with autoantigens, become their direct mirror copies ("casts of autoantigens"). Areas of proteins of proteosomes, making a non-covalent connection with the autoantigens, are excised by endopeptidase, and then combined in peptide subunits of the proteosomes with 5-15 amino acid residues. These subunits, which became a mirror copy of the sites of autoantigens that formed non-covalent bonds, are transferred to the rough endoplasmic reticulum as a matrix for the synthesis of peptide copies of autoantigens and dimers of MHC class I. On the basis of direct copies of autoantigens that can communicate only with autoantigens, the following are formed: inhibitory cell receptors, α-chains of integrins and selectin of macrophages, neutrophils, eosinophils, and NK cells, as well as α-chain dimers of MHC class I and II, α-chain dimers of receptors of T- and B-cells (TCR, BCR). On the basis of direct copies of autoantigens, the following are also formed: γ-chain dimers of γδT-cells (which bind to α-chains of dimers of foreign MHC class I), light (L) chains of V domains of Ig M and Ig D, molecules that destroy complement components, and light (L) chains of V domains of Ig G, Ig A, Ig E. They all serve at determining "their own." The connection of autoantigens with these chains of cell receptors, integrins, selectins or immunoglobulins, leads to blockage of the immune response aimed at the elimination of antigens.

From the first – direct copies of autoantigens on the rough endoplasmic reticulum, the second – reverse copies of autoantigens (similar to the photo-negatives of the first copies) are created. Sites of three-dimensional protein molecules of the second (reverse) copies have opposite charges analogous to sites of the first copies – "casts of autoantigens." Accordingly, the second (reverse) copies, being analogues of autoantigens, are not attracted, but rather repelled by autoantigens. The second – reverse copies of autoantigens (unlike the first – direct copies) because of the same charges cannot bind to auto-antigens, they can only bind to foreign antigens. On the basis of analogues of the second – reverse copies of autoantigens, the following are formed: activating cell receptors, β-chains of integrins and selectins of macrophages, neutrophils, eosinophils, NK-cells, MHC I class dimmers, δ-chains of γδT-cells dimers, heavy (H) chains of V-domains Ig M and Ig D, components of the alternative pathway of the complement system (defining "foreign"). For example, dimers of γδT-cells without involvement of Th are able to bind to β-chains of MHC class I dimers foreign cells. On the basis of analogues of the second – reverse copies of autoantigens, the following are

also formed peptide copies of autoantigens associated with two α-chains of MHC class I dimers.

All these factors of innate immunity are formed on the basis of autoantigens, as their direct or reverse copies. This is the biological value of autoantigens, forming each person's individual antigenic code. In human eukaryotic cells, dimers of MHC class I are formed from two domains of the α-chain (α_1 and α_2) [2, 3], which are complementary to peptide copies of autoantigens formed during processing. Located under the dimer of two domains of α-chain the β-chain of MHC of class I is formed from the second – reverse copy of autoantigens, being the "negative" α-chain. Accordingly, the β-chain capable of forming non-covalent connection only to peptide copies of foreign antigens, which are unable to form the two domains of α-chain, capable of forming non-covalent connection only to peptide copies of autoantigens. The specificity of innate immunity is determined by the distinction between "own" and "foreign" antigens, and not by the distinction of certain antigens, carried out by acquired immunity. Innate immunity is characterized by broad specificity (covering all foreign antigens) and low affinity of the established connections. This innate immunity differs from acquired immunity, whose relations are narrow specificity (to specific antigens) and a high affinity.

Each individual has common tissue-specific histocompatibility antigens, inherent in all tissues, as well as specific antigens of individual tissues, which appeared in the process of differentiation of their cells. Of the peptides presented with MHC class I, 90% are copies of antigens common to most tissues of the body, and 9% differ, determining the antigenic specificity of individual tissues and cells. Foreign antigens account for only 1% [2, 4]. The distinction of foreign antigens by innate immunity is based on the identification of their differences with autoantigens common to all tissues. This distinction is made by means of interaction of foreign antigens with α-, β-chains of integrins and selectins of macrophages, neutrophils, eosinophils and NK-cells, as well as components of the alternative pathway of the complement system, Ig M (including agglutinins), made on the basis of processing autoantigens, or by interaction of α- and β-chains of dimers of foreign MHC class I, with γ- and δ-chains of dimers of γδT-cells, also made on the basis of processing autoantigens. The response of innate immunity develops to all foreign antigens due to the formation of antigen-recognizing molecules during double copying of autoantigens during processing. This response does not require the formation of peptide copies of certain antigens associated with dimers of MHC class II, and the subsequent participation of Th. The response of innate immunity has a broad specificity (to all foreign antigens) and develops faster compared to the response of highly specific (to certain antigens) acquired immunity.

The formation of reactions of the acquired immunity begins with the processing of the analyzed foreign antigens, modified by their antigens or with antigens of their own dead old or damaged cells in the proteosomes of antigen-presenting cells. After enzymatic cleavage of the analyzed antigens in proteosomes, the fragments of antigens (their separate parts) bind in non-covalent bonds with proteins of proteosomes managed by Ir-genes the same as those in MHC. Three-dimensional protein molecules of proteosomes of antigen-presenting cells, which formed non-covalent bonds with foreign antigens, modified by their antigens or with antigens of their own dead old or damaged cells, become their direct – mirror copies ("casts" of the analyzed antigens). Areas of proteins of proteosomes that have established non-covalent bonds with the analyzed antigens, are excised by endopeptidases, and then combined into peptide subunits of the proteosomes with 5-15 amino acid residues. These subunits, which have become a mirror image of antigen sites that have formed non-covalent bonds, are transferred to the rough endoplasmic reticulum as a matrix for the synthesis of peptide copies of antigens and dimers of MHC class II molecules. On the basis of direct copies of the analyzed antigens that can bind only to these antigens, β-chains of MHC class II dimers, β-chains of T- and B-cell receptors (TCR, BCR), and heavy (H) chains of V-domains Ig G, Ig A, Ig E (determining "foreign") are formed. Connection with such formed cell receptor β-chains of integrins and selectins or immunoglobulins complementary to antigens determines the highly specific (to certain antigens) response by acquired immunity. From the first – direct copies of the analyzed antigens on the rough endoplasmic reticulum, the second – reverse copies of these antigens (similar to photonegatives)

are created. Sites of three-dimensional protein molecules of the second (reverse) copies are able to form non-covalent bonds similar to the bonds of the analyzed antigens. Accordingly, the second (reverse) copies become analogs of the analyzed antigens, capable of establishing the same non-covalent connections with them. On their basis, peptide copies of the analyzed antigens are formed, which are connected to the dimers of MHC class II molecules, replacing neutral proteins-chaperones (li peptide, calnexin). Thus, antigen-presenting cells along with all other eukaryotic cells carry out processing of autoantigens with expression of their peptide copies together with MHC class I dimers. Processing of foreign antigens, modified own antigens, antigens of dead old and damaged own cells is carried out only by antigen-presenting cells, expressing their peptide copies together with class II MHC dimers.

Recognition and differentiation of antigens appeared in the early stages of evolution [3] as a way of communication between the simplest beings, allowing them to unite with other beings similar to themselves in common colonies. Antigens became factors of species and clonal identification of protozoa. The preservation of the individual colonies of their identity by countering the carriers of foreign antigens, allowing the simplest to survive, fighting for existence with other protozoa colonies in the process of natural selection. In the conditions of collective struggle for survival, the appearance of specific identification antigens in some protozoa colonies required the appearance of antigens-antagonists in other protozoa colonies, competing with them, for their distinctive identification, and also required the appearance of biologically active substances (peptides) capable of binding foreign antigens to protect against their carriers.

Antigens of competitors initiated the appearance of antigens-antagonists (mirror copies of foreign antigens) in opposing individuals and their species seeking to preserve their identity for collective protection from external aggression. So different representatives of wildlife appeared antagonistic to each other antigens that formed pairs. In response to contact with foreign antigens, representatives of the two opposing sides developed three-dimensional peptide molecules capable of binding antigens to each other to protect against their carriers. As a result, paired antigens and their non-complementary peptides appeared, being the precursors of antibodies that divided beings of the living world into opposing sides. For example, the appearance of the conditional antigen A was accompanied by the formation of its mirror copy – antigen B together with the formation of the conditional peptide α to antigen A in the opposing individuals and their species. In response to the formation of antigen B among the carriers of antigen A, the peptide β to antigen B was formed. The peptides formed by protozoa for their protection, capable of binding to foreign antigens with non-covalent bonds, became mirror copies of foreign antigens, which had opposite charges to their sites, establishing non-covalent bonds. Being mirror three-dimensional copies of foreign antigens and performing a protective function, such peptides became precursors of antibodies (in particular agglutinins, complementary antigens-antagonists – agglutinogens-antagonists of group antigens of blood), as well as precursors of receptors of effector cells. Subsequently, the formation of antibodies was fixed genetically.

In the process of natural selection with the formation of dominant clones leaving numerous offspring which acquired individual characteristics, besides the antigens that were common for the whole clone, antigens also appeared which were specific to each level of organization of life, which determined the antigenic specificity of individuals, species, families, orders, classes, types (departments), kingdoms, super kingdoms, and empires of plants and animals. The order of appearance in the process of phylogenesis of antigens can be judged by the order of their appearance in the offspring during its development. Simultaneously with the isolation of representatives of individual communities with the acquisition of antigenic specificity, the reverse process also occurred, which was also due to the desire of living organisms to survive under the competition of natural selection. Living organisms acquired additional useful characteristics that are necessary for survival as a result of capturing the genetic information of one another (in addition to the adoption of new useful features appearing as a result of mutations). After capture, the foreign genetic material was delivered by means of protein carriers

to specialized cassettes. Then, those parts which encoded useful attributes were built into its own genome and were used. The exchange of genetic information has become a condition for the survival of living organisms. In the process of evolution, the exchange of genetic information between individuals was genetically fixed, turning into meiosis and fertilization during sexual reproduction. In humans, along with the exchange of genetic information in sexual reproduction (meiosis and fertilization), the direct exchange of genetic information between cells was preserved, implemented through CRISPR systems (Clustered Regularly Interspaced Short Palindromic Repeats).

After the appearance of sexual reproduction, alleles of carriers of each pair of antigens and antibodies in the inheritance of maternal and paternal attributes formed groups: AAββ, BBαα, A0ββ, B0αα, AB00 and 00αβαβ. Part of the groups (00αβαβ) in populations did not receive antigens. Contact of such individuals with antigens of external antigen carriers led to the formation of peptide precursors of antibodies to both paired antigens. Subsequently, the formation of non-complementary precursors of antibodies to paired antigens was fixed genetically. To prevent conflict with the mother's antigens, such antibodies began to appear after birth.

Colonies of protozoa, regulating autocrine and paracrine division of their representatives by biologically active factors (precursors of cellular growth factors and colony stimulating factors), became precursors of multicellular organisms and their constantly updated tissues. After the appearance of multicellular organisms with a life expectancy exceeding the life expectancy of individual cells, universal cells capable of differentiating into cells of all tissues of the body appeared for constant renewal of their tissues. Thus, pluripotent stem cells appeared in the process of evolution as a separate direction of differentiation of embryo cells implementing the development program [5]. To ensure directed migration of stem cells for the renewal of certain tissues, the former recognition of "their own" antigens from "strangers" became insufficient. The direction of migration of stem cells could be provided only by giving different tissues antigenic specificity and through the formation of receptors to their tissue-specific antigens in pluripotent stem cells. The appearance of tissue-specific histocompatibility antigens led to their separation from blood group antigens. Since the appearance of tissue-specific antigens was associated with the complication of differentiation of own tissues, and not with a mirror response to foreign tissue-specific antigens, unlike phylogenetically older antigens of blood groups, tissue-specific histocompatibility antigens did not become paired. After the division of the previously unified system of antigenic identification into two components – tissue-specific antigens and antigens of blood groups – the appearance of acquired immunity, forming a specific response to certain antigens, became possible. This division of autoantigens made it possible to bring the organization of tissue renewal and elimination of foreign antigens with their carriers to a qualitatively new higher level. To exclude independent recognition of tissue-specific antigens of histocompatibility and the response to them by phylogenetically older innate immunity (without narrow specificity), tissue-specific antigens of intact cells were hidden to its recognizing factors. Only peptide copies of tissue-specific antigens and dimers of MHC class I and II became available for recognition. These tissue-specific antigens and dimers of MHC class I and II were capable of binding only with specific receptors of T- and B-cells of the acquired immune system.

Peptides that are formed by processing, which connect to the dimers of MHC class I and II, are copies of antigens, and not the antigens themselves. Through the formation of peptide copies of antigens associated with dimers of MHC classes I and II, and through the formation of α and β peptide chains of MHC dimers of classes I and II, cells encode the properties of antigens of different nature (protein, carbohydrate or other). Peptides and dimers of MHC class I and II, without being an antigen, can show the properties of the encoded antigens only when in contact with α- and β-, ε- and γ-, ε- and δ-chains of dimers of receptors of T-cells (TCR), with α- and β-chains of dimers of receptors of B-cells (BCR), with γ- and δ-chains of dimers of γδT-cells, with α- and β-chains of dimers of integrins and selectins of macrophages, neutrophils, eosinophils and NK-cells. On the basis of antigenic information encoded by peptide copies and dimers of MHC class I and II, reactions of acquired immunity to antigens are

determined through Ir-gene control. In accordance with the composition and sequence of amino acid residues (more than 12) of peptide copies of antigens of MHC II class Th 2, there are 10-12 amino acid residues of heavy and light chains of V domain highly specific to these antigens of antibodies that are formed: Ig G, Ig A, Ig E (including Ig G – B-cell receptors). Tissue-specific receptors of the superfamily of immunoglobulins in cytotoxic T-cells and stem cells, as well as α- and β-chains of dimers of integrins and selectins of macrophages are formed in accordance with the composition and sequence of amino acid residues of peptides of MHS II class Th 1. The resulting antibodies and tissue-specific cellular receptors are direct (mirrored) copies of the sections of antigens that form when processing non-covalent connections with proteins of the proteosomes of antigen-presenting cells. Such antibodies are able to bind with high specificity to complementary sites of certain antigens, and cell receptors of cytotoxic T-cells and committed stem cells, capable of binding to complementary amino acid residues (8-10) of certain peptides of molecules of MHC class I. The duration of antigen processing by antigen-presenting cells and the duration of tissue-specific receptor formation determine the timing of cellular and humoral response of acquired immunity. The advantage of peptide coding is the ability of cells in contact with each other to transfer antigenic information about any antigens, regardless of their protein, carbohydrate or other nature. For this reason, peptides binding to molecules of MHC classes I and II, during antigen processing, become not part of antigens (most of which have a carbohydrate structure rather than a protein structure), but peptide copies of parts of antigens capable of establishing non-covalent bonds similar to antigens.

The transition to the coding of tissue-specific antigenic information through peptides and dimers of MHC classes I and II made it possible to establish control of Th of acquired immunity over the choice of a specific response to certain antigens. Representatives of innate immunity – macrophages that became antigen-presenting cells, as well as neutrophils, eosinophils, NK-cells, and components of the alternative pathway of the complement system lost the ability to recognize and respond to tissue-specific autoantigens. After the appearance of acquired immunity in macrophages (in relation to tissue-specific antigens), it was only possible to process tissue-specific autoantigens of dead old and damaged own cells for the subsequent presentation of their peptide copies together with MHC class II dimmers to Th. Th became the primary managers of acquired immunity, exercising their functions under Ir-gene control.

Th became regulators of the formation of tissue-specific receptors in pluripotent stem cells to ensure their directed migration to the places of death of old and damaged cells with their replacement by attracting antigen-presenting cells (carrying out processing of antigens) and the use of encoding of antigenic information by peptide copies and dimers of MHC class I and II. Regeneration control has become the main function of acquired immunity [6, 7, 8], whose Th analyze 99% of peptide copies of autoantigens of dead old and damaged cells and only 1% of peptide copies of foreign antigens [2]. Processing of foreign antigens by antigen-presenting cells and peptide coding of antigens made it possible for Th to also regulate the formation of specific Ig G, Ig A, Ig E by B-cells and the direction of migration of cytotoxic T-cells (through the formation of tissue-specific receptors – TCR).

Cells of innate immunity (macrophages, neutrophils, eosinophils, NK-cells, B-cells, forming without the participation of Th 2 Ig M) differentiate, under genetic control, their own antigens from others on the basis of double analysis: of their compliance to “their own” (their non-covalent bonds with the α-chains of integrins and selectins, characteristic of autoantigens) and their compliance to the “foreign” (their non-covalent bonds with β-chains of integrins and selectins, which autoantigens are unable to form). A similar double recognition of peptide copies of the analyzed antigens for compliance with “their own” and for compliance with the “foreign” is carried out by Th under Ir-gene control. For this reason, the presence of only one hapten (the antigenic determinant) that is determined to comply with the “alien,” is insufficient to initiate a response by either innate or acquired immunity. The initiation of an immune response to foreign haptens becomes possible only when a protein carrier is added to them, determined for compliance to “their own.”

Information on the compliance of the analyzed antigens to “their own” and “foreign” Th is obtained

by interacting with peptide copies of the analyzed antigens, as well as with α- and β-chains of MHC II class dimers of antigen-presenting cells formed during the processing of the analyzed antigens. Given the weakness and short-term nature of the formation of non-covalent bonds, Th use both sources of information for the accuracy and completeness of the information obtained. Non-covalent bonds that peptide copies of the analyzed antigens establish with α-chains of their T-cell receptors (TCR) dimers and bonds of the α-chain of dimers of MHC II class of antigen-presenting cells with δ- and ε-chains of their TCR, characteristic only for autoantigens, are analyzed for compliance to "their own" by Th through Ir-gene control. Non-covalent bonds, which peptide copies of the analyzed antigens establish with β-chains of their TCR dimers and bonds of β-chains of the MHC II class dimers of antigen-presenting cells with γ- and ε-chains of their TCR, characteristic only for foreign antigens, are analyzed for compliance to "foreign" by Th through Ir-gene control.

The formation of cytokines by Th 1 or Th 2 is insufficient for the formation of highly specific T-cell receptors (TCR) in cytotoxic T-cells and pluripotent stem cells, and forming highly specific Ig G, Ig A, Ig E by B-cells. This requires the transfer of information about foreign antigens, modified own antigens, antigens of dead old and damaged own cells (their peptide copies, associated α- and β-chains of MHC II dimers) from antigen-presenting cells to Th, and then from Th 1 or Th 2 through the mediation of activated antigen-presenting cells to cytotoxic T-cells, pluripotent stem cells or B-cells. This means that the command to form a certain type of immune response from Th 1 through antigen-presenting cells is delivered to cytotoxic T-cells and stem cells through the T-cell receptor (TCR), and the command from Th 2 through antigen-presenting cells is delivered to B-cells through the B-cell receptor (BCR). In this case, peptide copies of antigens associated with MHC class II dimers of activated antigen-presenting cells interact with α- and β-chains of TCR and BCR dimers. BCR has universality: the ability to interact with antigens and peptide copies of antigens. This is evidenced by the leading role of dendritic cells as antigen-presenting cells in determining the direction of differentiation of Th into Th 1 or Th 2. The participation in this process of B-cells, performing the dual function of antigen-presenting cells and effector cells, forming antibodies, is significantly smaller.

To activate antigen-presenting cells by Th 1 or 2 the interaction of peptide copies of antigens of MHC class II dimers of Th 1 or 2 with α- and β-chains of integrins and selectins of antigen-presenting cells is sufficient. Similarly, for the subsequent formation of highly specific cell receptors (TCR) in cytotoxic T-cells, pluripotent stem cells or highly specific Ig G, Ig A, Ig E by B-cells, it is sufficient to present them with peptide copies of antigens bonded with MHC class II dimers by antigen-presenting cells activated by Th 1 or 2. Accordingly, only α- and β-chains of dimers of cell receptors of cytotoxic T-cells (TCR) and B-cells (BCR) participate in the interaction with the peptide copies of the antigens associated with the MHC class II dimer of the antigen-presenting cells. Dimers with γ- and ε-, δ- and ε-chains of TCR cytotoxic T-cells do not participate in this interaction. Their presence in TCR cytotoxic T-cells is due to the universality of TCR (common for cytotoxic T-cells and Th 1 or 2). Naturally, B-cell receptors (BCR) have no dimers with γ- and ε-, δ- and ε-chains. BCR has only dimers with α- and β-chains to interact with the peptide copies of the antigens associated with the MHC class II dimer of the antigen-presenting cells. An additional condition for the activation of cytotoxic T-cells, pluripotent stem cells and B-cells is the formation of appropriate cytokines by Th 1 or 2.

Because of the short-term nature of education and the fragility of non-covalent linkages, relative rather than absolute indicators are taken into account. Peptide copies of the analyzed antigens are recognized by acquired immunity as "their own" in the case of a significant predominance of identicalness over differences when comparing their non-covalent connections with the links of peptide copies of autoantigens. With respect to these antigens, the immune response aimed at the elimination of antigens is blocked. On the contrary, peptide copies of the analyzed antigens are recognized as "foreign" by acquired immunity in the case of a significant predominance of differences over identicalness when comparing their non-covalent connections with the links of peptide copies of autoantigens. In this case, the acquired immunity initiates one of its responses

aimed at the elimination of antigens recognized as alien, together with their carriers.

Since the effector cells of innate immunity (macro-phages performing phagocytosis and forming components of the complement system, as well as B-cells, forming independently of Th Ig M) are also antigen-presenting cells, performing processing of extracellular antigens, the Ir-genes provide control over the recognition of “their own” and “foreign” antigens not only by cells of acquired immunity, but also by cells of innate immunity (determining their immunological specificity).

Particularities of Innate and Acquired Immunity

The response of innate immunity, as the first line of immune defense, is caused by the contact of the macro-organism with foreign antigens. The innate immunity response involves the participation of macrophages, neutrophils, eosinophils, basophils, mast cells, NK-cells, components of the alternative and lectin pathway of the compliment system, inflammatory cytokines, acute phase proteins, the kinin system (bradykinin and callidin, vasoactive peptides causing an increase in the lumen of the veins and vascular permeability), the coagulation system and fibrinolysis system [2]. The factors of innate immunity can also include antigens of blood groups (agglutinogens, acting as chemoattractant for microbial cells) and non-complementary antibodies (agglutinins, representing Ig M), B-cells, forming without the participation of Th 2 Ig M to foreign antigens, and γδT-cells, capable without the participation of Th to invade cells carrying foreign dimers of MHC class I.

The low affinity of Ig M binding to foreign antigens is compensated for by the combination of free Ig M at five molecules each into pentamers, as well as additional participation in the recognition of foreign antigens in the composition of B-cell receptors (BCR) components of the complement and lectin system. Along with Ig M monomers, the composition of the BCR also includes receptors of the complement – CR2, binding components of the alternative pathway of the complement system – C3, and lectin, binding mannose residues that aren't covered by sialic acid.

Acquired immunity, which has specificity to the individual foreign antigens, is not capable of responding to antigens of all agents which the microorganism comes in contact with. Protection against most viruses, bacteria and parasites, which are constantly in contact with the skin, mucous membranes of the lungs, gastrointestinal tract, pharynx, cervix and other organs of the macro-organism, is provided by innate immunity factors. Under insufficient effectiveness of innate immunity, its response is potentiated by acquired immunity that is narrowly specific to certain antigens. The formation of the response of acquired immunity begins with the processing of the analyzed antigens in antigen-presenting cells (in dendritic cells, in macrophages and in B-cells), which ends with the creation of peptide copies of analyzed antigens associated with molecules of MHC class I or II.

Molecules of MHC class II of antigen-presenting cells and Th bind to peptide copies of mainly autoantigens, and only with 1% of foreign antigens [4]. The presentation of 99% of peptide copies of autoantigens of dead old and damaged cells by molecules of MHC class II testifies to the subsequent formation of the same proportion of complementary receptors (to autoantigens) in pluripotent stem cells [6, 8]. Tissue-specific receptors of stem cells, similar to T-cell receptors (TCR) of cytotoxic T-cells, complementary to peptide copies of tissue-specific antigens of MHC class I dimers of dead or damaged cells, determine the direction of migration of stem cells to tissues of dead cells. Without the formation of tissue-specific receptors, directed migration of pluripotent stem cells is impossible. Accordingly, the regenerative function, rather than the protective function, is the main function of acquired immunity [6, 8]. Given the involvement of Th 1 in the formation of tissue-specific receptors in pluripotent stem cells [6, 8], Th differentiate into Th 1a, forming tissue-specific receptors in cytotoxic T-cells, Th 1b, forming tissue-specific receptors in pluripotent stem cells, and Th 2 that activate B-cells that form high-affinity immunoglobulins. Antigen-presenting cells are intermediaries for the interaction of Th 1a with cytotoxic T-cells, Th 1b with stem cells and Th 2 with B cells, since recirculating lymphocytes contact in

lymphoid organs with antigen-presenting cells more often than with each other.

After receiving peptide copies of antigens from MHC molecules of class II antigen-presenting cells and interaction with cytokines of Th 1a, Th 1b or Th 2, cytotoxic T-cells, activated macrophages and pluripotent stem cells form tissue-specific receptors (TCR), while B-cells (which became plasma cells) begin production of highly specific Ig G, Ig A or Ig E. Differentiation of T-cells into cytotoxic T-cells, B-cells into plasma cells, as well as activation of macrophages under the influence of Th 1a, 1b, 2 is accompanied by gene ranking – removal of part of the genetic material by rupture of activated cells by endonucleases of two strands of their DNA. After the formation of loops with DNA fragments removed from functioning, DNA integrity is restored [2, 3]. This mechanism determines the irreversibility of cell differentiation and in particular differentiation of cytotoxic T-cells, macrophages, stem cells and B-cells. With the development of compensatory reactions to various pathological conditions (impaired tissue renewal, decreased production of sex hormones, ischemia, and other pathologies) irreversible genetic changes occur in cells during differentiation, establishing the dominance of these compensatory reactions. Being aimed at stimulating mitogenic activity, the development of insulin resistance, hyper-cholesterolemia, spasm of arterioles and other changes, these compensatory reactions lead to malignant tissue transformation, type 2 diabetes, atherosclerosis, malignant hypertension, and other diseases. Accordingly, in the clone of activated B-cells, the production of low-affine broad-specific Ig M and Ig D changes to the production of high-affine narrow-specific Ig G, Ig A or Ig E, complementary to antigens, the peptide copies of which were presented to them. Similarly, after interaction with the antigen in the process of differentiation, the properties of antigen-presenting cells change. Thus, after the presentation of Th of antigen's peptide copies of MHC class II dimers, antigen-presenting cells, including macrophages, lose their ability to bind and process new antigens [2]. They form a pool that preserves the antigens obtained, and thus turn into a copy of immunological memory cells.

The general pattern is the formation by most cells of the immune system of forward and backward bonds, which have an activating and blocking function. Thus, contacting cells have not only receptors for the cell ligands with which they interact, but also ligands for the receptors of the contacted cells. Th have receptors (TCR) for peptide copies of antigens and MHC class II dimers of antigen-presenting cells, as well as ligands to α- and β-chains of their integrins and selectins [2].

NK-cells, affecting the old, virus-infected and rapidly proliferating malignant cells (end residues of mannose that have lost the cover of sialic acid) also have two antagonistic regulators (one: activating, two: inhibiting). Binding of C-lectin receptors of NK-cells with free end residues of mannose membranes of target cells leads to the fulfillment of cytotoxic action of NK-cells only upon receipt of confirmation from activating receptors (KAR) and in the absence of a blocking signal from inhibiting receptors (KIR) [2]. These receptors, analyzing the established non-covalent bonds with the antigens of target cells under gene control, determine the specificity of the action of the NK-cells (preventing invasion by these cells into unchanged own tissues) [3].

When processing tissue-specific autoantigens, their first-direct (mirror) copies become the basis for the formation of α-chains of classical MHC class I dimers (A, B, C), β-chains of non-classical MHC class I dimers (G, F, E) and their peptide copies for bonding with the latter, and the second-reverse copies become the basis for the formation of β-chains of classical MHC class I dimers (A, B, C), their peptide copies associated with dimers of classic MHC class I, and α-dimer chains of non-classical MHC class I (G, F, E). Accordingly, the peptide dimers and copies of classical MHC class I (A, B, C) encode the non-covalent connection of "their own" histocompatibility antigens, while peptide copies and dimers of non-classical MHC class I (G, F, E) encode the non-covalent bonds of "foreign" histocompatibility antigens, the establishment of which with autoantigens is impossible. Non-classical MHC class I (G, F, E), simulating the "foreign," bind to cell receptors TCR and BCR of cytotoxic T-cells and B-cells, forming immunoglobulins, and then block their action through Ir-gene control. Also, non-classical MHC class I (G, F, E) block the expression of classical molecules of

MHC class I. Due to the expression of non-classical MHC class I (G) molecules, trophoblast and stem cells are protected from the action of acquired immunity factors.

Double regulation, forming a set of checks and balances, is present in the blood system. Autoantibodies are present in antigens of blood groups in the norm in a small amount (in a ratio of 1:32 with agglutinins). These autoantibodies are called “incomplete,” because they, communicating with antigens of blood groups, do not implement, but rather block the immune response [1, 2]. Their binding to autoantigens blocks the binding of other antibodies to them, thereby protecting the unaltered own tissues from damage. Destruction of such incomplete antibodies by enzymes of microbes leads to autoimmune invasion of erythrocytes and tissues containing agglutinogens, deprived of their protection. This mechanism determines the development of the Thomsen phenomenon [1]. Incomplete antibodies protecting unmodified native tissues may be Ig D. In this case, the cytotoxic effect of antibodies of the first line of immune protection – Ig M will be realized only in the absence of target cells links with Ig D, as antagonists of Ig M. Unaltered own tissues, autoantigens of which are associated with Ig D, will not be affected by Ig M. This inhibitory effect of Ig D can be realized through competitive binding to autoantigens. The need for a mechanism of blocking the cytotoxic action of Ig M is due to their broad antigenic specificity to all foreign antigens. It's noteworthy that in Ig G, Ig A and Ig E, highly specific to certain antigens, there is no such additional control mechanism.

All classes of immunoglobulins (Ig M, Ig D, Ig G, Ig A, Ig E) have antigens capable of initiating antibody production. Antigens of heavy chains of immunoglobulins are designated Gm, and antigens of light chains Inv. To Gm and Inv antigens, incomplete antibodies are normally formed, which, by binding to Gm and Inv of immunoglobulins, do not inactivate them; but, on the contrary, block the connection of other antibodies with them. These incomplete antibodies to antigens protect immunoglobulins from inactivation. Destruction of incomplete antibodies leads to inactivation of immunoglobulins by complete (immune) antibodies formed to antigens Gm and Inv of immunoglobulins [1].

Activation of the complement system also depends on two components of the complement system – on the components of the complement system that bind via the classical, lectin or alternative pathways to foreign antigens, and on the molecules that destroy these components that have found themselves on unchanged native cells [2, 3].

In the process of phylogenetic development in various species of plants, protozoa, parasites and animals, not only identification antigens were formed similar to the antigens of human blood groups (detected by the precipitation reaction), but also by peptides that are non-complementary to these antigens – precursors of antibodies (antibodies in animals), capable of causing hemolysis of red blood cells, carrying antigens complementary to them [1]. Accordingly, the system of blood groups, ensuring the maintenance of the unity of the antigenic composition of the body, received two components: antigens of blood groups (agglutinogens), as antigens of identification of individuals, binding foreign antibodies and similar molecules, as well as non-complementary antigens of blood groups of antibodies (agglutinins, presented by Ig M) for binding foreign antigens of other blood groups and similar molecules.

Red blood cells with foreign antigens and microbial carriers, bonded with agglutinins and adsorbed on their surface (agglutinogens for micro-organisms are chemo attractants), and with extraneous agents, bonded by agglutinogens, are phagocytized by macrophages of the spleen [2]. This prevents the blocking of the acquired immunity by the receipt of an excessive number of foreign antigens, most of which are eliminated by factors of innate immunity. Accordingly, according to G. P. Kotelnikov et al. the number of immune complexes fixed on erythrocytes is three orders of magnitude higher than the similar number of immune complexes fixed on leukocytes [9].

Erythrocytes without nuclei and expression of class I MHC molecules, adsorbing foreign antigens and their carriers, carrying antigens of blood groups for binding foreign antibodies exposed to phagocytosis by spleen macrophages, have become part of the innate immunity as the first stage of the body's response to foreign antigens. The absence of a nucleus in erythrocytes and, as a consequence, the

absence of expression of MHC class I molecules with peptide copies of antigens on their surface made it possible to exclude the interaction of erythrocytes with regulatory and effector cells of acquired immunity. Foreign antigens adsorbed on the surface of red blood cells are normally exposed only to innate immunity factors (which include agglutinins represented by Ig M). Also, the absence of a nucleus in erythrocytes eliminates the transmission of foreign genetic information to their own cells from adsorbed bacteria and viruses by CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats). After phagocytosis of erythrocytes by macrophages of the spleen, which are simultaneously antigen-presenting cells, to foreign antigens carrying by erythrocytes the response of acquired immunity is formed if necessary.

Table 1. Table of Victor I. Pechersky for the optimal selection of food in accordance with blood groups AB0 [12] (The table is compiled on the basis of the identified similarities of antigens H, A, and B with food antigens based on the precipitation reaction of agglutinins α and β with different food antigens in agar as per the method of O. Ouchterlony in the modification of V. I. Pechersky)

Blood type AB0	The degree of antigenic similarity of AB0 with food antigens	
	High	Low
0 (I) αβ	With antigens of the solanaceous family and with other antigens of: - corn, oats, wheat, barley; - red beets, potatoes, peppers, tomatoes, parsley, dill, watermelons, zucchini, cucumbers, pumpkins, onions, garlic, mushrooms, blueberries, raspberries, blackberries, gooseberries, grapes, cherries, pears, apples, plums; - corn oil, sunflower oil, cotton oil; - cow's milk, mare's milk, and products thereof; - beef, chicken, freshwater fish; - tea, barley coffee; - wheat vodka, beer.	Antigens of products preferred for people with A (II) β, B (III) α blood groups
A (II) β	With antigens of foods for people of 0 (I) αβ of the blood group, as well as the cruciferous family and with other antigens of: - peas, buckwheat, rye; - rutabagas, cabbage, radish, turnips, cranberries, black currants, poppy seeds; - mustard, linseed, poppy seed oil; - pork; - tea, Russian kvass, barley coffee.	Antigens of foods that are preferable for people with B (III) α blood group
B (III) α	With antigens of foods for people with 0 (I) αβ blood group, and also with antigens of: - millet, rice, soy; - carrots, bananas, artichoke, melons, figs, strawberries, dates, citrus; - peanut oil, sesame oil, and soy oil; - goat's milk, sheep's milk and products thereof; - lamb, rabbit, duck, goose, seafood; - coffee.	Antigens of foods that are preferable for people with A (II) β blood group
AB (IV) 00	With antigens of foods for people 0 (I) αβ, A (II) β and B (III) α blood groups.	-

The existence at the early stages of phylogenesis of a single system of autoantigens, providing antigenic identity of individuals and their colonies, predetermined the impossibility of complete separation of cells and tissues on carriers of tissue-specific antigens of histocompatibility and antigens of blood groups. For this reason, in humans, in addition to red blood cells, there is a small presence of blood group antigens in other tissues, on leukocytes and platelets, as well as in a significant amount together with agglutinins in various secretions: in saliva and in the secretion of glands of the gastrointestinal tract (for binding foreign food antigens similar to agglutinogens), secretion of the prostate (for binding foreign antigens in relation to the sperm of the female genital tracts), and in amniotic fluid (for binding of complementary antigens) [1]. On the introduction of foreign agglutinogens into the bloodstream of the

victim, followed by the development of disseminated intravascular coagulation, the mechanism of action of the poisons of many snakes, the poisonous glands of which in the process of phylogenesis occurred from the salivary glands.

Due to the general phylogenetic past, antigens similar to human blood group antigens are detected in plants, microbes, parasites and animals [1, 10, 11, 12, 13, 14].

The constant exchange of genetic information led to the emergence of paired autoantigens of blood groups and their analogues in different representatives of the same species. In species that have become the first owners of certain antigens, such antigens are determined more often. For this reason, there is a significant difference in the distribution of antigen analogues of blood groups in different types of microbes, plants and animals. For example, analogues of antigen A of the second group of human blood are more common in rice, in gram-positive coccal microflora, rabbits and other carriers, while analogues of antigen B of the third group of blood are more common in cabbage, gram-negative intestinal microflora, pigs and other carriers (Table 1) [10, 11, 12, 13, 14].

Desensitization and the Methodology of Its Implementation

Due to the commonality of their phylogenetic development, microorganisms express antigens similar to autoantigens of blood groups (AB0 and others), as well as to tissue-specific autoantigens. Common antigens between microbes and humans cause cross-immunological reactions [1, 2, 3, 10, 11, 12, 13, 14] of innate immunity (with the activation of the components of the alternative pathway of the complement system, agglutinins, macrophages and others) and secondary-acquired immunity (with the formation of highly specific antibodies and cytotoxic T cells). For example, antigens of gram-positive micro-organisms (*Streptococcus*, *Staphylococcus* and others) are similar to the group-specific factor A of human erythrocytes, and gram-negative micro-organisms (*Escherichia coli* and others) are similar to the group-specific factor B of human erythrocytes (Table 2) [10, 11, 13, 14]. Examples of the similarity of the antigens of microorganisms with tissue-specific antigens of humans are the similarity of polysaccharide antigens of *Streptococcus* with polysaccharide autoantigens of connective and epithelial tissues (for example, antigens of the heart valves, causing their autoimmune loss), the similarity of the antigens of the *Klebsiella* with tissue-specific antigen, a peptide which is an HLA-B27 (which becomes the cause of development of ankylosing spondylitis). In addition, a number of ligands of microbial antigens are complementary to individual receptors. So the bacterial heat shock proteins have an affinity to DR4 molecules (leading to the development of rheumatoid arthritis), and antigens of *Yersinia enterocolytica* have an affinity to the receptors of thyroid-stimulating hormone (initiating the development of thyroiditis) [1, 2, 3, 9].

The degree of similarity of microbial antigens with autoantigens of blood groups (AB0, phenotypes Rh, Kell and others), as well as with tissue-specific autoantigens largely determines the type of immune response. Hyporeactivity (areactivity) is observed with a significant similarity of microbial antigens with antigens of blood groups AB0 and tissue-specific antigens of patients, and hyperreactivity is observed with their significant difference. Hyperreactivity to antigens of gram-positive microflora (*Streptococcus, Staphylococcus* and others) is shown by owners of agglutinins α with the first and third blood groups, while hyperreactivity to antigens of gram-negative intestinal organisms (*Escherichia coli* and others) is shown by owners of β agglutinins with the first and the second groups of blood. Hyporeactivity to antigens of gram-positive microflora (*Streptococcus, Staphylococcus* and others) is shown by carriers of agglutinogen A with the second and fourth blood groups, while hyporeactivity to antigens of gram-negative organisms (*Escherichia coli* and others) is shown by carriers of B agglutinogens with the third and fourth blood groups (Table 2) [10, 11, 13, 14]. Interaction with antigens similar to blood group antigens is accompanied by increased levels of agglutinins [1]. Accordingly, to assess these reactions of innate immunity, it is necessary to determine the levels of agglutinins α and β, comparing them with their normal values, taking into account the daily fluctuations in the levels of agglutinins α and β (Figure 1) [15]. To reflect the dynamics of the

development of inflammatory diseases and the degree of intoxication, as well as to identify "in vitro" sensitization to various antigens, the vesicular reaction (lysis reaction) implemented by V.S. Kislyakov in the modification of V.I. Pechersky [16] can be used. To identify in vitro sensitization to various antigens, the precipitation reaction in agar implemented by Orjan Ouchterlony in the modification of V.I. Pechersky [15] can also be used. To assess the immunological reactivity of the macro-organism in its interaction with the microflora in various pathological conditions, we can use the assessment of the composition and number of microflora of the skin and mucous of patients [11, 14, 17], carried out by the culture express method on two media for gram-positive and gram-negative microflora using culture dishes implemented by V.I. Pechersky [18]. These studies can improve the diagnosis of systemic inflammatory response syndrome (SIRS) in addition to the applied determination of procalcitonin levels, lactate and other indicators. Procalcitonin, in addition to hormonal action, suppresses the activity of macrophages [19]. Since the hyperreactive response of the immune system to the antigens of pathogens and their toxins threatens the macro-organism, the development of systemic inflammatory response syndrome (SIRS), compensatorily increases the production of procalcitonin, suppressing excessive immune response. The increase of lactate during the development of systemic inflammatory response is conditioned by the beginning of replacement of aerobic glycolysis by anaerobic glycolysis in response to ischemia of tissues under the development of DIC with the formation of many microthrombi that block microcirculation.

Antigen-presenting cells represent cross antigens to Th, which, when activated, differentiate into Th 1 or into Th 2. The part of cross antigens peculiar only to microbes leads to activation of Th, breaking their tolerance, and the part of cross antigens peculiar to autoantigens prevents phagocytosis by macrophages of activated Th 1 and Th 2. Cytotoxic T-cells or macrophages activated by Th 1, or B-cells forming antibodies activated by Th 2 affect the body's own tissues. After the elimination of foreign antigens, the damage to own tissues continues, as Th 1 and Th 2, forming a separate pool in the process of differentiation and showing the properties of immunological memory cells, continue to stimulate the proliferation of cytotoxic T-cells and producing B-cells antibodies, and activation of macrophages. Multiple sclerosis and other type IV hypersensitivity diseases are caused by the action of activated cytotoxic T-cells and macrophages regulated by Th 1. Bronchial asthma and other type II hypersensitivity diseases are caused by the immune response regulated by Th 2. The formation of antibodies by B-cells to antigens of their own tissues often develops after bacterial or viral infections. Autoimmune damage of erythrocytes, which can lead to iron deficiency anemia, can also be caused by reactions of innate or acquired immunity to cross-infectious antigens [1, 2, 3].

Table 2. Table of Victor I. Pechersky to determine the type of immunological response of people to gram-positive microflora (*Streptococcus, Staphylococcus,* etc.) and gram-negative microflora (*E. coli*, etc.) depending on the blood groups of the AB0 system [10, 11, 13, 14]

(The table is compiled on the basis of the identified similarities of the antigens H, A, and B with antigens of gram-positive and gram-negative microflora on the basis of the precipitation reaction of agglutinins α and β with microbial antigens in agar as per the method of O. Ouchterlony in the modification of V. I. Pechersky)

Blood type AB0	Percentage of blood group carriers in the European part of the USSR	Types of immunological response of people to microflora			
		Hyper-reactivity		Hypo-reactivity	
		Gram + microflora	Gram – microflora	Gram + microflora	Gram – microflora
0 (I) αβ	34	Yes	Yes	No	No
A (II) β	36	No	Yes	Yes	No
B (III) α	22	Yes	No	No	Yes
AB (IV) 00	8	No	No	Yes	Yes

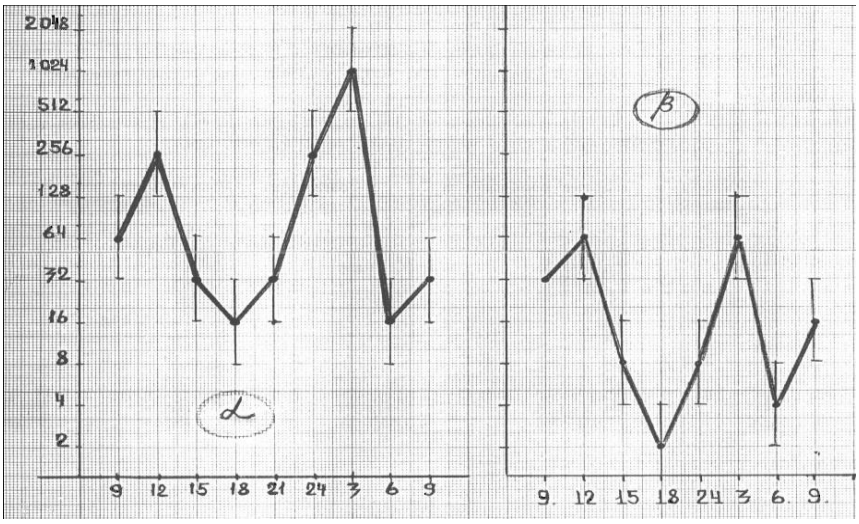

Figure 1. Daily fluctuations in the titer of agglutinins α and β in healthy men (20 people aged 20 to 40 years old, blood sampling was performed every 3 hours during the day). This diagram was made by immunologist V.I. Pechersky on the basis of his own research conducted in June, 1980 (the author's original drawing is shown) [15].

The response of acquired immunity to the presented antigens is fulfilled separately, directed by Th along the cellular or humoral pathway. After contact with antigen-presenting cells, Th differentiate into Th 1, regulating cellular immunity reactions, or into Th 2, regulating humoral immunity reactions with B-cell differentiation into antibody-forming plasma cells. Cytokines, allocated by Th 1 (INFγ, IL-2, TNFα, TNFß), inhibit the activity of Th 2 – their formation of IL-4, IL-5, IL-6, IL-9, IL-10, and IL-13, and vice versa. After repeated contact with the antigen, activated B-lymphocytes need to receive a confirmation signal from Th 2 to implement their immune response. Cytokines of Th 2 initiate the proliferation of activated B-cells and the formation of plasma cells derived from them of high-affine antibodies IgG, IgA, and IgE. T-suppressors forming transforming growth factor-β and other cytokines are capable of suppressing or switching the immune response regulated by Th 1 and Th 2 [2, 3].

In addition to T- and B-cells of immunological memory, the Th 1 and Th 2, formed in the process of differentiation, and activating cytotoxic T-cells and B-cells (having formed receptors to certain antigens) can be attributed in a broad sense to the cells of immunological memory, because they implement formed their immune response in contact with complementary antigens. Immunological memory cells include antigen-presenting cells, capable of keeping antigens in their proteosomes for a long time, and presenting their peptide copies together with molecules of MHC class II, after initiating contact with Th immune response. Reverse differentiation of clones of these cells is impossible, as their ability to bind to other antigens is impossible (due to the formation of one antigenic specificity). The life expectancy of these cells can range from a few days to 40 years. To proliferate and maintain their pool size, they need periodic interactions with complementary antigens. Antigen removal leads to the death of immunological memory cells [2, 3]. This effect can be obtained by plasmapheresis, or antiviral, antibacterial, or anthelmintic therapy, or correction of one's diet.

Th can switch the cellular immune response to humoral (differentiating into Th 2, suppressing the activity of Th 1), or, vice versa – switch the humoral immune response to cellular (differentiating into Th 1, suppressing the activity of Th 2). The participation of Th 1 in regeneration [6, 8] indicates that in the process of differentiation, from them there is formed either a subpopulation of Th 1a, forming tissue-specific receptors in cytotoxic T-cells, or a subpopulation of Th 1b that form similar tissue-specific receptors in pluripotent stem cells. Accordingly, in autoimmune diseases, Th can switch the immune response with the formation of Th 1a tissue-specific receptors in cytotoxic T-cells, damaging the cells with peptide copies complementary to them of autoantigens of dimers of

MHC class I on the production of Th 1b receptors in tissue-specific pluripotent stem cells involved in tissue regeneration, carrying these load-bearing peptide data copies of autoantigens. In this case, the Th 1b formed from Th in the process of differentiation will suppress the activity of Th 1a. Similarly, the pathological humoral immune response to autoantigens can switch to stimulation of regeneration with the formation of tissue-specific receptors in pluripotent stem cells (through differentiation of Th into Th 1b, inhibiting the activity of Th 2). This effect is possible both in immune reactions of hypersensitivity type I, due to the formation of B-lymphocytes Ig E in response to allergens, and in immune reactions of hypersensitivity type II, due to the formation of B-cells Ig G in response to the presentation of peptide copies of tissue-specific autoantigens associated with molecules of MHC class I, or autoantigens of blood groups of red blood cells.

Since microbial cells carry several antigens, separate clones of Th 1a or Th 2 are formed for them. Accordingly, a cellular and a humoral immune response can be formed simultaneously to one pathogen, but to its different antigens. Both of these responses, caused by different cross-microbial antigens, will be suppressed when switched to regeneration stimulation.

Desensitization with reconfiguration of the response of the acquired immunity should be preceded by the elimination of the antigens that caused the pathological immune response or the cessation of their further entry into the patient's body. Otherwise, antigens will stimulate the proliferation of T- and B-cells of immunological memory, as well as activated cells (Th 1a, Th 2, cytotoxic T-cells, B-cells, macrophages), or will cause re-sensitization. The fulfillment of this condition is also necessary for the termination of pathological immune reactions of innate immunity caused by the activation of the complement along the alternative and lectin pathway and other factors.

The type of the immune response, implemented by Th, depends on the amount of the presented antigen [2, 3]. In response to the presentation of antigen-presenting cells of a small amount of tissue-specific auto-, allo- or xenogenic antigen pathologically unchanged cells, Th begin to differentiate into Th 1b, forming tissue-specific receptors in pluripotent stem cells involved in the regeneration of the corresponding tissues. Large amounts of antigen (including autoantigen) cause differentiation of Th into Th 1a, initiating cellular immune response with activation of cytotoxic T-cells and macrophages, or in Th 2, initiating humoral immune response with the formation of B-cells of plasma cells, producing antibodies. The formation of an extra-large amount of antigen with high immunogenicity (for example, microbial antigens in septicemia, autoantigens in crash syndrome) initiates a generalized immune response, which can lead to the development of a systemic inflammatory reaction syndrome and to shock.

Switching of pathological humoral and cellular immune response caused by cross-viral, -microbial and -parasitic antigens to stimulation of regeneration occurs with the introduction of small doses of autogenous, allogenic or xenogenic antigens similar to antigens of the affected tissues. With a subsequent increase in the dose of antigens, the immune system does not switch from stimulation of regeneration. Desensitization to the administered antigens develops. This explains the desensitization used in the method of A.M. Bezredka. When prescribing preparations containing small doses of xenogeneic tissue-specific antigens, these tissue specific antigens are captured by antigen presenting cells, engaged in their processing and presented on their surface in the form of copies of the peptide bonded with molecules of MHC class II. Antigen-presenting cells represent tissue-specific xenogenic antigens to Th, which, when activated, differentiate into Th 1b, forming tissue-specific receptors in pluripotent stem cells. The similarity of xenogeneic antigens and autoantigens, as well as the small dose of xenogeneic antigens does not make it possible to break the tolerance of Th, preventing their differentiation into Th 1a and Th 2, as well as prevent phagocytosis of Th 1b macrophages. This is the basis of the regenerative effect of drugs used in clinical practice containing xenogenic antigens of various tissues (prostate, liver and other animal tissues) [6, 8]. These drugs, containing xenogenic tissue-specific antigens similar to autoantigens and having no highly immunogenic microbial antigens, in small doses are able to switch the differentiation of Th into Th 1a and Th 2 to differentiation into Th 1b with stimulation

of regeneration of the corresponding tissues. Accordingly, xenogenic drugs in small doses can be used for desensitization in autoimmune diseases initiated by cross-viral, -microbial and -parasitic antigens. Since the peptides associated with the dimers of MHC I and MHC II classes are encoded copies of antigens, and not the antigens themselves, and since for the manifestation of their action they need to be represented by living antigen-presenting cells, having dimers of MHC class II, to Th, these peptides cannot be used as pharmacological drugs (they will not be able to independently connect with molecules of MHC class II and will not have the desired effect). To make switches caused by cross-viral, -microbial and -parasitic antigens autoimmune reactions to regeneration, it is necessary to use tissue-specific antigens of the affected tissues themselves, and not their peptide copies associated with MHC class I molecules. As pharmacological preparations can be used antigens are xenogenic tissues, the same tissues, the targeted pathological autoimmune response. In this case, the antigens are xenogenic tissue captured antigen presenting cells, will be presented to Th, mimicking the loss of old or damaged cells own tissues. In response, Th will differentiate into Th 1b, which form tissue-specific receptors in pluripotent stem cells, which will be directed to the regeneration of previously affected autoimmune tissues. This pathological immune response will be replaced by the initiation of regeneration of the affected tissues.

Since cross-viral, -microbial and -parasitic antigens may have similarities not only with tissue-specific antigens, but also with antigens of human blood groups [1], different from antigens of blood groups of patients, xenogenic preparations used for desensitization should be produced separately for patients with different blood groups (AB0, phenotypes Rh, Kell) – from animal tissues, having the least antigenic differences with antigens of patients' blood groups. To simplify the technology of production and use, such drugs can be produced for all patients from animal tissues with minimal antigenic differences with antigen H, which do not interact with agglutinins α and β in people of 0 (I) blood group, as universal donors. The list of carriers of xenogenic antigens similar to the antigens of human blood groups AB0 is presented in the table by V.I. Pechersky (Table 1) [12]. The use of drugs made from animal tissues, taking into account the blood groups of patients (AB0, phenotypes Rh, Kell), prevents the risk of initiating a response of innate immunity (activation of the components of the alternative pathway of the complement system, agglutinins, macrophages and others), as well as the secondary addition of reactions of acquired immunity.

Desensitization can also be carried out through the use of autoantigens affected by pathological immune response of tissues formed in microtrauma of these tissues (for example, in Shockwave therapy). This methodology, along with the use of cosmetic peeling, the use of chemoattractants (propolis extracts and others), can be used to stimulate tissue regeneration [6, 8].

The formation of tissue-specific receptors in pluripotent stem cells is regulated by Th 1, which determine the cellular immune response (Th 1b subpopulation). Dendritic cells of interstitial space, mucous membranes or skin can be used as antigen-presenting cells by analogy with antigen-presenting cells initiating cell immune response in hyper-sensitivity type IV for desensitization or for stimulation of regeneration as antigen-presenting cells. Accordingly, xenogenic tissue-specific antigens can be applied to the skin, taken orally or inhaled as an aerosol to stimulate regeneration or to desensitize with a switch of the pathological immune response to stimulation of regeneration. Given the presentation of antigens by dendritic cells to Th in the regional lymph nodes in autoimmune lesions of specific tissues or organs for desensitization, one must select the region for administration of drugs tissue-specific antigens so that they are transported by migratory dendritic cells into regional lymph nodes for the organs or tissues. When applying tissue-specific antigens to the skin, the incoming tissue-specific antigens will be captured by the epidermal Langerhans dendritic cells, which as antigen-presenting cells will process and present antigens together with their class II MHC molecules. Langerhans cells will migrate from the epidermis through lymphatic vessels to the paracortical T-dependent region of regional lymph nodes to present tissue-specific antigens to Th, which will perceive their arrival as evidence of the death of old or damaged cells of the corresponding tissues. In response, Th will differentiate into Th 1b, which in

turn will form tissue-specific receptors in pluripotent stem cells (stimulating through them the regeneration of certain tissues or switching the pathological immune response to stimulation of regeneration). Other antigen-presenting cells of other tissues will carry out a similar way of presenting antigens. The time of development of desensitization will be determined by the period of development of activation of Th and their differentiation into Th 1b, which depends on the duration of antigen processing by antigen-presenting cells and the duration of tissue-specific receptors formation. The average duration of one course of treatment can be 1 month.

During the desensitization with the introduction of tissue-specific antigens through the skin, patients should be advised to avoid direct exposure to sunlight, because under the action of the B-spectrum of ultraviolet radiation, inactivation of dendritic Langerhans cells occurs. When administering preparations of tissue-specific antigens with their application to the skin, it should be taken into account that the reaction of the immune system depends on the number of tissue-specific antigens applied per unit area, and not on the total dose of the drug or the total area on which the antigen is applied [3]. The dose of xenogenic tissue-specific antigens of prescribed drugs should be sufficient for activation of Th and the beginning of their differentiation into Th 1b, forming tissue-specific receptors in pluripotent stem cells, but it (the dose xenogenic antigens of prescribed drugs) must not exceed thresholds above which Th begin to differentiate into Th 1a, forming tissue-specific receptors cytotoxic T-cells or Th 2 activates B cells that form antibodies.

Chemoattractants attracting antigen-presenting cells can have a desensitizing effect under the pathological immune response. Chemoattractants can be applied to the skin or mucous membranes, having common regional lymph nodes with the tissues affected by the autoimmune process, or are injected into the affected tissues themselves. Chemoattractants can be wood oil (for example, propolis extract of), autoblood (in the application of medical cans, creating a hematoma in the skin of certain regions), or autothrombocyte suspension (introduced into certain tissues) [6, 8]. Propolis consists of wood resins collected and fermented by bees. Wood resins and mineral oils are widely used in medicine in order to achieve an anti-inflammatory and regenerative effect. For example, tar and ichthyol are part of ointments used in dermatology as a "permissive" for various inflammatory processes. Tar is a major component of the famous Vishnevsky ointment. Unlike tar and ichthyol ointments, oil or spirit extract of propolis, having a comparable effect, has a pleasant aroma and is allowed for intracavitary application. Accordingly, preference may be given to a propolis preparation for stimulation of local regeneration [6, 8].

The complement system, which distinguishes "one's own" from "foreign", is capable not only of lysing membrane complexes to affect cells carrying foreign or modified own antigens, but can attract other cells and factors of innate and acquired immunity. Thus, degranulation of mast cells occurs not only when binding to Ig E, but also when they interact with components of complement C3a, C5a. Since the acquired immunity is not able to respond to the antigens of all viruses, bacteria and parasites with which the macro-organism contacts (especially its mucous membranes of the lungs and intestines, skin), the protection against penetration and generalization of microflora is provided mainly by factors of innate immunity. The components of the complement system are formed by macrophages in many tissues, including the liver (which receives a large number of antigens absorbed from the intestine). The largest number of mast cells of mucous membranes is found in the lungs and intestines [3], constantly in contact with the microflora. Mast cells are located in all tissues near blood vessels, being ready to act on them with their mediators after activation. Basophils similar in function to mast cells circulate in the blood. With the development of the inflammatory process, the number of mast cells in the tissues increases. When immunodominant antigen passes through antigen presenting cells, there is activation of Th that activate B-cells that form Ig E, binding to the appropriate receptor (F_{CE}) of mast cells. Granules of mast cells in addition to histamine, serotonin and other biologically active substances contain tryptase and chymase that cleave vasoactive intestinal peptide – a mediator of relaxation of bronchial smooth muscle (causing them to spasm). Also, tryptase itself can cause bronchial spasm. In addition to the cellular growth factors that activate fibroblasts formed during inflammation, tryptase also contributes to the development of

fibrosis during the activation of mast cells. Chymase stimulates the formation of bronchial mucus [3].

Immunological hypersensitivity reactions that develop in response to the antigens that caused them determine the pathogenesis of a number of diseases. Hypersensitivity type I determines the development of bronchial asthma, chronic obstructive pulmonary disease and other diseases. Hypersensitivity type IV determines the development of Crohn's disease, sarcoidosis, multiple sclerosis and other diseases [2, 3]. The development of chronic inflammation in response to autoimmune reactions, accompanied by cell death and increased formation of cellular growth factors, increases the risk of malignant degeneration of the affected tissues [6, 7, 8]. Intensive formation of cytokines that accompanies the autoimmune response, increases the risk of malignant diseases of blood. Desensitization can be an effective method of treatment of diseases accompanied by immunological hypersensitivity. Desensitization compares favorably with immunosuppressive therapy that suppresses bone marrow and tissue renewal, since it increases the risk of developing cancer [6, 7, 8, 20], as well as from the use of glucocorticoid drugs that increase the risk of obesity, type 2 diabetes and cardiovascular diseases [19, 21]. In comparison with genetic engineering therapy aimed at blockade of certain factors of development of pathological immune response (through the use of antibodies to tumor necrosis factor), desensitization is able to reformat the pathological immune response itself.

Desensitization should be preceded by the elimination or cessation of antigens in the body (including pathogens of sexually transmitted diseases – *Chlamydia trachomatis* and others, as well as helminths) that cause a pathological immune response. Accordingly, according to the indications, patients should be prescribed antiviral, antibacterial, antifungal, antiparasitic therapy, plasmapheresis, ultraviolet irradiation of blood that destroys antibodies. It is also necessary to normalize the intestinal microflora and exclude the antigens that caused sensitization from the diet (Table 1) [12]. Since different representatives of plant species, protozoa, parasites and animals like humans have both components of paired analogs of blood antigens [1], the distribution of these antigens in different species is of medical importance. The use of products of plant and animal origin from the species with the lowest frequency of detection of antigens complementary to agglutinins of patients can reduce the antigenic load on the body of patients. To completely exclude from one's diet foods, the antigens of which are complementary to the agglutinins of patients, is possible only by means of the rapid reactions of precipitation with antigens of prepared foods and agglutinins of secretions (saliva and others) or blood serum [11, 13, 14, 21]. Preparation of a diet taking into account the blood groups of patients (AB0, Rh, Kell) prevents the risk of initiation of the innate immune response (activation of the components of the alternative pathway of the complement system, agglutinins of blood groups, macrophages and others), as well as secondary attachment of the reactions of acquired immunity. In order for there to be binding of exogenous food antigens by agglutinins (Ig M), which are contained in a high titre in saliva, it’s important to chew carefully.

In Crohn's disease, caused by hypersensitivity type IV, there is a predominant lesion of the wall of the ileum and large intestine with the development of granules, fibrosis, and an increase in the number of mast cells. An increase in the level of Ig E is not characteristic of Crohn's disease. Since mast cells other than Ig E are activated by complement C3a, and C5a of the alternative pathway, the participation of innate immunity can be considered as a leading pathogenetic mechanism of Crohn's disease. The activators of the complement C3a of the alternative pathway are cross-microbial or food antigens that have similarities with the antigens of blood groups. The similarity of cross antigens with antigens of other blood groups other than blood groups of patients (AB0, phenotypes Rh, Kell), and their high immunogenicity lead to the activation of the components of the alternative pathway of the complement system, as well as their interaction with agglutinins of blood groups and macrophages of patients. With agglutinins of blood groups of patients represented by Ig M, foreign antigens with the participation of complement form immune complexes. The resulting immune complexes cause aggregation of red blood cells and subsequent microthrombosis of small vessels with microinfarcts. Developing tissue ischemia leads to pain, ulceration and cracks of the intestinal mucosa, to its fibrosis. In

the place of microinfarcts, fibrosis develops due to the activation of fibroblasts. Fibrosis of the intestinal walls, developing in Crohn's disease, causes narrowing of the intestinal lumen. The innate immunity response is complemented by the acquired immunity response. Cross antigens are captured by antigen-presenting dendritic cells performing antigen processing and migrating to regional lymph nodes. Further antigen-presenting cells interact with Th, which, differentiating into Th 1, activate cytotoxic T-cells and macrophages, affecting the wall of the ileum and colon and forming granulomas. Similar pathogenetic processes occur in multiple sclerosis. In pathological autoimmune reactions of innate immunity (associated with the activation of complement, macrophages and the action of agglutinins), in particular in Crohn's disease and multiple sclerosis, it is necessary to stop the contact of cross antigens with the intestinal mucosa through the restoration of normal intestinal symbiocinosis and exclusion from the diet of foods containing antigens similar to antigens of other blood groups on the basis of table V.I. Pechersky (Table 1) [12]. Given the significant content of blood group antigens on erythrocytes, foods containing animal blood should be excluded from one's diet. It is also necessary to exclude in patients the disease of helminthiasis and sexually transmitted diseases caused by *Chlamydia trachomatis* and other pathogens. When attaching pathological autoimmune reactions of acquired immunity in Crohn's disease, it can be recommended to prescribe preparations to be consumed of tissue-specific xenoantigens of the walls of the small and large intestine, vessels, and in multiple sclerosis – xenogenic preparations of the brain and vessels harvested from animals, whose antigens are compatible with agglutinins of patients (Table 1) [12]. To prevent digestion in the stomach and to accelerate entry into the intestine, these drugs are recommended to be taken on an empty stomach 30 minutes before meals and washed down with cool water.

In bronchial asthma and obstructive pulmonary disease, for desensitization, preparations of tissue-specific xenoantigens of the lungs and vessels (represented by antigens of stromal cells) can be recommended to be administered by inhalation in the form of an aerosol or taken orally. The use of tissue-specific xenoantigen entered by inhalation in aerosol form, can be supplemented by the use in a similar way of chemoattractants (for example, extracts of propolis). In addition to desensitization action, chemoattractant, attracting macrophages with the proteolytic enzymes, will contribute to the resorption of lung fibrosis. It is also necessary to exclude from the diet foods containing antigens similar to antigens of other blood groups (Table 1) [12]. In the initial examination of patients, it is necessary to exclude helminthosis and sexually transmitted diseases.

In the case of sarcoidosis, it is necessary to exclude contact of sensitizing antigens with the skin and mucous membranes of patients. It is necessary to exclude helminthosis and sexually transmitted diseases, as well as exclude foods from the diet containing antigens similar to antigens of other blood groups (Table 1) [12]. For desensitization, xenogeneic preparations of the skin can be recommended to be applied to the skin, while preparations of lung tissue-specific xenoantigen should be inhaled in aerosol form, and the drugs of tissue-specific xenoantigen vessels (carriers of antigens of stromal cells) and tissue-specific xenoantigen preparations of nervous tissue should be ingested. The use of tissue-specific xenoantigens applied to the skin and introduced through inhalation can be supplemented by the use in a similar way of chemoattractants (for example, extracts of propolis).

In chronic thyroiditis (Hashimoto), the auto-immune pathological process develops along with hypothyroidism. Due to the stimulation of antibodies to the receptors of thyroid-stimulating hormone (TSH) thyroid-stimulating receptors (like thyroid-stimulating hormone), hypothyroidism turns into moderate thyrotoxicosis, which is replaced by hypothyroidism as thyroid hormones are depleted. With the development of hypothyroidism, patients are prescribed thyroid hormone replacement therapy [19]. Hormone replacement therapy is of great importance. The immune system and endocrine system are interconnected. Through the formation of hormone-like antibodies to thyroid-stimulating receptors, the immune system compensates for the insufficiency of the endocrine system – hypothyroidism (in addition to the compensatory increase in thyroid-stimulating hormone). In this case, desensitization (with the appointment of drugs with xenogenic peptides of the thyroid gland and blood vessels) should be

supplemented with thyroxine replacement therapy, since hormonal thyroid insufficiency (hypothyroidism) is the reason for the involvement of the immune system in the compensatory formation of antibodies to thyroid-stimulating receptors.

The validity of these recommendations is confirmed by clinical examples. A 55-year-old patient with rheumatoid arthritis, interstitial nephritis and parenchymal nephrogenic hypertension before treatment noted pain and swelling of large joints, and increased upper and lower blood pressure. During the examination, the amount of protein in the urine, the proportion of urine, the number of red blood cells and leukocytes in the urine was normal, the level of creatinine in the blood was increased (111.07 μmol/l), the glomerular filtration rate was at the lower limit of the norm (64.46 ml/min), the level of renin in the blood was increased (153.2 μIU/ml), according to multispiral computed tomography with contrasting data for renal artery stenosis and their branches was not obtained. Helminth eggs in feces were not detected. Sexually transmitted diseases have also not been identified. The patient in accordance with his blood group was given an individual diet on the basis of the table by V.I. Pechersky (Table 1) [12], for the recovery of the intestinal microflora was appointed symbiotic (with probiotic microorganisms and prebiotic), was appointed preparations containing antigens are xenogenic tissues of the tissues of the kidneys and blood vessels. On the skin above the affected joints, chemoattractant (propolis spirit extract) was locally applied. Within six months after three courses of treatment lasting 1 month, each joint pain stopped, blood pressure returned to normal, the level of renin in the blood decreased nine times to normal levels (16.9 μIU/ml), the level of creatinine in the blood decreased to normal levels (102.09 μmol/l), and glomerular filtration increased (71.38 ml/min).

The next clinical case was a 60 year-old patient with interstitial cystitis. Prior to treatment, she noted constant intense pain over her lap in the projection of the bladder, marked by more frequent urination. According to the ultrasound, the maximum volume of the bladder was 78 ml, the bladder wall was fibrosed and thickened. Urine test was normal, urine culture of microflora growth was not revealed. Sexually transmitted diseases have not been identified. Helminth eggs in feces were not detected. The patient was examined by a gynecologist, inflammatory diseases (able to initiate the development of cystitis and damage to its wall by autoimmune factors) were not revealed. Also, the patient's attention was drawn to the need for sexual hygiene – the inadmissibility of ingress of oral microflora into the vagina, which can cause inflammation in the area adjacent to the bladder [23]. The patient did not have anorgasmia accompanied by insufficiency of secretion of bartoline glands into the vagina during sexual intercourse and microtrauma of the vaginal mucosa leading to inflammation [23]. The patient in accordance with her blood group was given an individual diet on the basis of the table by V.I. Pechersky (Table 1) [12], and a symbiotic was prescribed to restore intestinal microflora, while preparations containing antigens of xenogenic tissues of the bladder and vessels were prescribed. Candles with propolis were prescribed vaginally. Within eight months, four courses of treatment were carried out, one month each. After treatment, the pain syndrome significantly decreased and became irregular, the frequency of urination decreased, the maximum volume of the bladder doubled to 144 ml, the thickness of the bladder wall decreased to the normal value (3 mm), and the severity of the fibrous component in the bladder wall decreased.

Interstitial cystitis has an autoimmune nature, representing hypersensitivity of type IV [23], like Crohn's disease. The clinical picture (pain syndrome, fibrosis of the bladder wall, ulceration of the bladder mucosa) and histological changes in the bladder wall (macrophagalnolymphocytic infiltration with an increase in the number of mast cells) in interstitial cystitis are similar to the clinical picture and morphological changes in the intestinal wall in Crohn's disease. Pain syndrome in interstitial cystitis is caused by tissue ischemia and increased muscle tone.

Patient 54 years old with chronic pelvic pain syndrome and myofascial pain syndrome. Prior to treatment, he noted aching pain in the perineum, which was not accompanied by increased urination, as well as aching pain in the muscles of the lower extremities. The level of total PSA and microscopy data of the prostate gland secretion were normal, sowing of the prostate gland secretion of microflora growth was not revealed, sexually transmitted

diseases were not detected. Helminth eggs in feces were not detected. Ultrasound examination revealed fibrous changes in the prostate gland and prostatic hyperplasia. The patient in accordance with his blood group was given an individual diet on the basis of the table by V.I. Pechersky (Table 1) [12], for the recovery of the intestinal microflora was appointed symbiotic, was appointed preparations containing antigens are xenogenic prostate tissue, blood vessels and muscles. Candles with propolis were prescribed rectally. On the skin of the lower extremities it was recommended to apply the extract of propolis twice a day. Within four months, two courses of treatment were carried out, one month each. After treatment, pain in the perineum and muscles of the lower extremities stopped.

Chronic pelvic pain syndrome, as well as myofascial pain syndrome, are caused by reactions of innate and acquired immunity directed against own tissues. These reactions develop in response to the cross antigens of the microflora, which caused inflammatory diseases of the pelvic organs and other localizations. Reactions of innate and acquired immunity lead to the aggregation of red blood cells followed by microthrombosis of small vessels and tissue fibrosis. Pain syndrome in chronic pelvic pain and myofascial pain syndrome are caused by tissue ischemia and increased muscle tone. Reactions of acquired immunity in patients with chronic pelvic pain, as a particular manifestation of myofascial pain syndrome, directed against their own tissues, remain after the elimination of the pathogen due to the formation of cells of immunological memory. The conduct of desensitization for these patients is pathogenetic therapy.

Immunological Tolerance and Methodology of Its Formation

Due to the variability of species acquiring new features in the process of phylogenesis, including new antigens, mechanisms of adaptation of innate and acquired immunity were developed evolutionarily, allowing the macro-organism to perceive new auto-antigens as "its". The basis of variability, including the emergence of new antigens, is a change in the genome, which is fixed in the perception of new antigens as "one's own." The genome changes due to mutations, as well as through intercellular transmission of genetic information. The meaning of the CRISPR (Clustered Regularly Interspaced Short Palindromic Repeats) system is wider than the previously explained collection by cells of genetic information about viruses for the subsequent counteraction against them. In CRISPR systems, Cas1 and Cas2 proteins capture foreign genetic information and embed it in a CRISPR cassette. Then the CRISPR system inserts foreign genetic information in DNA or RNA, thereby changing the genome or affecting the way information is read from it. This mechanism provides a constant exchange of genetic information between cells, which along with mutations is the basis of variability, allowing species to survive in harsh conditions of natural selection. In some cases, the cells lose control over the genetic information received and the foreign site embedded in DNA or RNA begins to function independently, reproducing itself uncontrollably. Thus, the exchange of genetic information between cells, necessary for the evolution of the system, gives rise to viruses that have become a mortal threat to cells and macro-organisms consisting of them. Normally, new genetic information, going through multiple stages of testing, for a long time remains in a recessive status. Only after multiple confirmation of the usefulness of the acquired signs do they receive a dominant status. In viral infections, lost control over the new genetic information is integrated in CRISPR cassettes. In the future, one of the promising areas of treatment of viral diseases may be the management of the use of genetic information by CRISPR-cassettes to prevent the embedding of dangerous parts in the DNA of cells and prevent its subsequent replication (virus replication). Similar to the emergence of viruses as a result of the failure of the physiological process of updating the genome of cells, in which part of the genetic information begins to function independently of the rest of the genome, malignant tumors develop that, upon the loss of control on the part of the macro-organism, begin to develop independently. Compensatory reactions of the macro-organism, aimed at stimulating mitogenic activity in age-related disorders of tissue renewal and developing hormonal imbalance, result in malignant degeneration of cells. Stimulation of mitogenic activity leads to the loss of control over the division

and differentiation of individual cells, which are malignant [6, 7, 8]. These compensatory reactions are fixed genetically, their elimination with the use of CRISPR/Cas9 technology of genome editing is meaningless, because it is not able to eliminate tissue renewal disorders and endocrine hormone deficiency in aging people, which will only lead to increased alternative ways to stimulate mitogenic activity. At the same time, understanding the mechanisms of genome renewal makes it possible to use them to form chimerism and the associated tolerance to foreign antigens.

Colonization of the thymus with stem cells is necessary not only for the subsequent formation of T-cells, but also for the renewal of dead old cells of the cortical and cerebral substance of the thymus in ontogenesis, including epithelial-reticular cells. Epithelial-reticular cells of the thymus are training cells which transfer of Th information about the antigens of its own tissues and create their type of response to the presented antigens [2, 3]. Constant updating of thymus cells by migrating stem cells with subsequent transfer of information from the thymus epithelial-reticular cells formed from them to Th, and the subsequent positive and negative selection of the latter allow to constantly update data on new autoantigens in Th that appeared in the process of variability [6, 7, 8]. In contrast to the formation of antibodies to foreign antigens, the emergence of new self-antigens with the perception of their Th as “their own” is impossible without the transmission of genetic information to Th by epithelial-reticular cells of the thymus (resulting in the process of differentiation of migrated genetically upgraded stem cells). This is due to the fact that the recognition of “own” and “foreign” antigens by the cells of innate and acquired immunity is based on the comparison of the analyzed antigens with autoantigens. Changes in the recognition of autoantigens are impossible without changing the genome on the basis of which autoantigens are formed. The transfer of genetic information occurs through the CRISPR of systems. Thanks to this mechanism, during ontogenesis, the immune system is consistent with genetic and antigenic changes. After transfusion of the mononuclear fraction of peripheral blood the pluripotent stem cells form their pool in the bone marrow, which together with the recipient's own pluripotent stem cells takes part in the renewal of all tissues of the body, including the renewal of the dead old epithelial-reticular cells of the thymus. Accordingly, the recipient's Th begin to be trained in the epithelial-reticular thymus cells of two genotypes (formed from the recipient's and donor's stem cells). In the process of learning from the epithelial-reticular cells of the thymus, formed from the migrated allogeneic donor stem cells, the Th of the recipient get genetic information about the donor antigens through the CRISPR system, and under training of the epithelial-reticular cells of the thymus, formed from its own stem cells, the Th of the recipient get genetic information about new own antigens resulting from mutations through the CRISPR system. After that, the recipient's Th, in addition to their own modified antigens, begin to be perceived as “their” donor antigens. Transfusion of allogeneic pluripotent stem cells leads to the formation of Chimera. This individual has two types of pluripotent stem cells with two different genotypes involved in the renewal of all tissues of the body. Similarly, women who give birth become chimeric organisms, since in their bloodstream during childbirth they get a small amount of the child's blood, along with the pluripotent stem cells in it. The multigiving birth women live longer than not giving birth women as they receive natural cellular therapy from own children. Naturally, women who give birth many times have difficulties in determining their blood group [6, 7, 8]. Since during the life of each person there are mutations, each person during ontogenesis also becomes a chimeric organism.

The formation of chimerism leads to a change not only in the acquired immunity (through the training of Th by epithelial-reticular thymus cells of two genotypes), but also in the innate immunity. Antigen-presenting cells (dendritic cells, macrophages, B-cells) represent antigens to Th and serve as intermediaries for Th in the formation of tissue-specific receptors in cytotoxic T-cells, activated macrophages, pluripotent stem cells and in the producing highly specific antibodies by B-cells that turn into plasma cells. Under contact with Th antigen-presenting cells (including macrophages) receive new genetic information through the CRISPR system about new antigens that have become “their own” in the formation of chimerism due to mutations or

transfusion of pluripotent stem cells. Accordingly, the macrophages formed from monocytes (α- and β-chains of their integrins and selectins), as well as the components of the alternative pathway of the complement system produced by macrophages, begin to perceive the antigens of transfused donor stem cells as "their own." For targeted migration for the regeneration of certain tissues, pluripotent stem cells (including donor pluripotent stem cells) need, through antigen-presenting cells, contacts with Th to form tissue-specific receptors. At the same time, through the CRISPR system donor pluripotent stem cells get genetic information from Th cells about the antigens of the recipient. Due to this, donor stem cells after differentiation into cells of various tissues of the body begin to express enzymes that protect them like the recipient's own cells from damage to the components of the recipient's complement system (destroying them). A similar process of training in antigen-presenting cells are NK-cells, on the surface of which killer inhibitory receptors (KIR) begin to be expressed, perceiving tissue-specific antigens and antigens of donor blood groups on cells formed during differentiation of donor stem cells as "their" [2].

Constant recirculation of Th, trained in thymus epithelial stromal cells, serve not only the exchange of antigenic, but also genetic information. Constantly going throughout the ontogenesis of the exchange of genetic material between cells through the CRISPR system, as well as the ongoing processing of autoantigens to form their peptide copies, α- and β-chains of MHC class I dimers allow all eukaryotic cells of the body to express constantly updated peptide copies of autoantigens. As a result, immune cells expressing class I and II MHC molecules, T- and B-cell receptors (TCR, BCR), α- and β-chains of their integrins and selectins use constantly updated autoantigens as a comparative basis for their formation. This allows eukaryotic cells of innate and acquired immunity to perceive tissues as "their own," constantly updating their antigenic code in the process of mutations and the formation of chimerism in the admission of allogeneic pluripotent stem cells (in women who give birth and recipients). Genetic and antigenic tissue renewal is accompanied by the renewal of innate and acquired immunity, which begins to perceive new tissue antigens, their peptide copies, and antigens of blood groups as "their own."

Pluripotent stem cells have suppressed expression of all tissue-specific antigens represented by MHC class I molecules, with the exception of HLA-G. Peptide copies of HLA-G antigens, as inhibitors of interaction with antigen-presenting cells (including macrophages), NK-cells and cytotoxic T-cells, protect stem cells from them (including those with mutations necessary for evolutionary development, as well as allogenic donor stem cells). Likewise, the repression of the expression of tissue-specific antigens presented by MHC molecules of class I, peptide expressed copies of the antigens HLA-G in trophoblast cells (the outer layer of the blastocyst mammals), carrying the genotype of the fetus and the contact after the formation of the placenta with the mother's blood to protect the fetus from the antigen presenting cells (including macrophages), NK-cells and cytotoxic T-cells of the mother [3].

Suppression of the expression of tissue-specific antigens presented by MHC class I molecules in pluripotent stem cells allows transfusing them without the risk of rejection. The few Th present in the mononuclear fraction of peripheral blood or bone marrow of donors (their number is significantly lower compared to the spleen and lymph nodes) are not sensitized to the recipient's tissue-specific antigens. To activate, they must migrate to the lymph nodes or spleen to interact with antigen-presenting cells. In the lymph nodes and in the spleen, donor Th are phagocytized by the recipient's macrophages because they carry foreign antigens. In the same place, donor cytotoxic T-cells and B-cells undergo phagocytosis, except for donor pluripotent stem cells, in which the expression of tissue-specific antigens of MHC class I molecules is suppressed, and they themselves are protected by HLA-G expression. The activity of donor T-helper cells are further suppressed by T-suppressor cells of the recipient. For this reason, donor T-helpers contained in the allogeneic mononuclear fraction of peripheral blood or in the allogeneic bone marrow cannot interact with the recipient antigens and cannot initiate a graft reaction against the host. Differentiated cells formed from transfused donor pluripotent stem cells are also not rejected due to the formation of chimerism in recipients with the perception of their immune system

peptide copies of donor antigens associated with MHC class I dimers as “their own.” The formation of chimerism with the development of immunological tolerance of the recipient to tissue-specific antigens of its differentiated cells formed from transfused donor pluripotent stem cells allows to refuse the selection of donors pluripotent stem cells for HLA. Bone marrow transplantation based on the selection of donors for HLA due to ignoring blood groups and gender of donors is accompanied by a high risk of complications. Complications of bone marrow transplantation, regarded as “graft-versus-host response” (as “non-engraftment of transplanted bone marrow”), are due to the incompatibility of recipient agglutinins with erythrocyte agglutinogens formed from transfused donor pluripotent stem cells. This incompatibility is due to the formation of red blood cells from transplanted pluripotent stem cells faster than the restructuring of innate immunity due to chimerism. Selection of donors should be carried out in accordance with the blood groups, sex and age of the recipients. Criteria for the selection of donors for bone marrow transplantation should be taken: age (donors should not be older than patients, and when correcting age-related changes, they should be significantly younger than patients, their age should be from 18 to 23 years), sex (donors and recipients should be of the same sex) and blood groups (antigens of blood groups with the highest immunogenicity: AB0, phenotypes Rh, Kell, should be the same in donors and recipients). Accordingly, the bone marrow transplantation Protocol should be reviewed. The formation of chimerism through transfusion of allogeneic pluripotent stem cells in the mononuclear fraction of peripheral blood from young donors aged 18-23 years, having the same blood group and sex with the subsequent development of immunological tolerance (RF patent No. 2350340) allows the recipient to transplant any cells, tissues or organs from the primary donor without the risk of rejection [6, 7, 8]. This is confirmed by the development of mother's tolerance to tissue-specific antigens of the child [1]. The formation of chimerism can be used in organ and tissue transplantation, as well as for the successful treatment of radiation sickness, hereditary and a number of infectious diseases (AIDS and others) [6, 7, 8].

The immune system's perception of tissue-specific donor antigens as “its own” makes it possible to use transfusion of allogeneic donor pluripotent stem cells in the composition of mononuclear fraction of peripheral blood to restore the normal number of pluripotent stem cell pool in persons older than 45-50 years, as well as to form immunological tolerance to tissues and organs of the donor of transfused pluripotent stem cells [6, 7, 8].

Transfusion of the mononuclear fraction of peripheral blood can be used in autoimmune diseases caused by the formation of antibodies not to cross-microbial antigens, but initially to autoantigens (for example, in systemic lupus erythematosus). This can occur as a result of mutations, in which autoantigens instead of samples for the formation of prohibitive reactions of innate and acquired immunity themselves become a target for reactions of innate and acquired immunity, aimed at their elimination. In these cases, the proposed method of desensitization in pathological immune response initiated by cross antigens will not be effective. Treatment of such autoimmune diseases should be carried out similarly to the treatment of patients with leukemia with the appointment of high-dose chemotherapy (for the destruction of immunological memory cells and Th) and with subsequent transfusion of the mononuclear fraction of peripheral blood. Considering the toxicity of high-dose chemotherapy, in these cases it may be enough to conduct a less toxic course of immunosuppressive therapy followed by transfusion of the mononuclear fraction of peripheral blood, with the expectation that cells of innate and acquired immunity formed from normal donor pluripotent stem cells will suppress the function of the reduced number of pathological cells.

In various hereditary diseases, transfusion of the mononuclear fraction of peripheral blood will lead to partial replacement of the changed cells with normal donor cells. Similarly, in AIDS and a number of other diseases, patients can be transfused pluripotent stem cells harvested from donors with mutations of receptors through which the pathogen affects the cells (from donors not susceptible to these diseases). This will not lead to the elimination of pathogens, but will avoid the development of the clinical stage of the disease without the use of etiotropic drugs with pronounced side effects. To suppress the own

pluripotent stem cells of patients, a course of immunosuppressive therapy can be carried out beforehand [6, 7, 8].

Every second there is a necrosis (or apoptosis) of several million old cells, leading to many local sites of inflammation [4]. To maintain a normal state in the body, the same number of new cells should be formed every second at the same time. In persons older than 35-40 years, necrotic old cells are not compensated by an adequate number of low-differentiated progenitor cells replenished with an insufficient number of stem cells, which makes it impossible to complete the regeneration process [6, 7, 8]. One of the reasons for this is the increase in the number of cross-linking DNA in people with age. Such connections complicate mitotic cell division [3], including pluripotent stem cells. As a result, after 35 years in humans, there is a 1% reduction per year in the number of the pluripotent stem cell pool (which is supported by their mitotic division). This process is determined by the development program, which starts after the beginning of meiosis and operates throughout the ontogenesis [4, 6, 7, 8]. Unlike mitosis, in meiosis in the process of crossing-over there is destruction of the DNA cross-links that appear with age, so that the program of development of a new individual is restarted again. Accordingly, regardless of the age of their parents, the child is able to start a new life.

After 35 years, a decrease in the pool of pluripotent stem cells is progressing, leading to insufficiency of replacement of dead old cells with progenitor cells. In response, in all tissues in proportion to age increases the formation of cellular growth factors that stimulate the division of the remaining progenitor cells. The increase in the formation of cellular growth factors is the cause of cancer, the frequency of which in humans increases exponentially after 40 years. The increase in the formation of cellular growth factors with age also causes intensive proliferation of fibroblasts, which begin to prevail over the progenitor cells. Accordingly, in people over 40 years in all tissues there is a growing development of fibrosis and atrophy. The restoration of the pool of pluripotent stem cells in individuals older than 40-50 years allows us to recover the replenishment of their progenitor cells, with subsequent adequate replacement of the necrotic old cells by cells-predecessors. Thus, the restoration of the pluripotent stem cell pool makes it possible to stop the growth of pathological processes developing with age, the prevention of oncological diseases and the normalization of reparative processes in traumatic injuries [6, 7, 8, 24].

Nerve tissue renewal has a number of features. During embryonic development, neuronal progenitor cells that do not form axons and dendrites migrate along radial glial cells. According to the sequence of migration, neurons of the cerebral cortex are arranged in layers. Renewal of the central nervous system throughout the ontogenesis is also due to the migration of cells (stem cells). Fragments of dead neurons (carrying tissue-specific peptide copies of autoantigens of MHC type I dimers) become chemoattractants that allow migrated stem cells that have begun differentiation to restore not only the dead old neurons, but also their previous connections with other cells. Unlike neurons, which cannot divide, most glial cells retain this ability [4]. Having entered the path of differentiation, glial cells, like any other cells, have a limited number of divisions and, accordingly, need to replenish their composition throughout the ontogenesis of migrating stem cells [6, 8]. Age-related reduction of pluripotent stem cells leads to disruption of nervous system cell renewal with activation of macrophages (microglia) and fibroblasts [6, 8]. Senile dementia is associated with progressive brain atrophy, which is accompanied by the activation of fibroblasts that produce amyloid. Amyloidosis is detected in 100% of cases of senile dementia [25]. Migration to the site of the dead old cells of a smaller number of simulated stem cells and a reciprocal increase in the production of cellular growth factors become the most important pathogenetic factors of Alzheimer's disease (due to a violation of neuronal renewal) and Parkinson's disease (due to a violation of glial cell renewal). Restoration of the pluripotent stem cell pool makes it possible to normalize the nervous tissue renewal.

Restoring a pool of pluripotent stem cells in males allows you to restore the number of Leydig cells of the testes and the formation of their testosterone in the physiological pulse mode, and in women in the premenopausal period to normalize the formation of the granulosa cells of the ovarian follicle with the formation they need to change the

follicular to the luteal phase of the menstrual cycle the number of estradiol [26, 27, 28]. The subsequent normalization of elevated levels of FSH and LH, which are pathogenetic factors in the development of ovarian cancer, contributes to the prevention of this disease. Normalization of estradiol formation, which determines the division and differentiation of estrogen-dependent cells of the uterus and mammary glands, is the prevention of tumor diseases of the latter. This also contributes to the normalization of the formation of progesterone and testosterone [6, 7, 8, 20, 21].

Rejection of transplanted allogeneic tissues or organs can be prevented without preliminary formation of chimerism in the recipient [6, 8, 29]. Connective tissue of the donor organ sets the direction of differentiation of migrating stem cells by means of cellular growth factors located on the glycoproteins of the intercellular matrix and on the basal membranes. The sequence and composition of cellular growth factors form a unique code of differentiation of stem cells into cells of certain tissues. A unique code from the sequence and composition of cellular growth factors of glycoproteins of the intercellular matrix and basal membranes is formed during the implementation of the development program initiated after the beginning of meiosis. After removal by proteolytic enzymes of parenchymal cells of the donor organ or tissue carrying peptide copies of tissue-specific antigens associated with class I MHC dimers, when transplanting the remaining stromal basis to the recipient, the tissue structure will be restored due to migration of the recipient's stem cells with their subsequent differentiation into the cells of this organ or tissue [6, 8]. Stromal basis of allogeneic and xenogeneic organs and tissues, composed of vessels, fibroblasts and extracellular matrix, has low immunogenicity [4], which is insufficient for differentiation of Th to Th 1a, forming tissue-specific receptors cytotoxic T-cells, but which is able to initiate the differentiation of Th to Th 1b, forming tissue-specific receptors at pluripotent stem cells [6, 8]. On the exposed collagen of the basal membrane, extracellular matrix and blood vessels there is platelet aggregation, producing vasoactive amines and chemoattractant [3]. Through the involvement of antigen-presenting cells and Th 1b with the subsequent migration of stem cells with tissue-specific receptors formed, there is stimulation of regeneration with the restoration of the stromal base in a full-fledged tissue or organ own stem cells of the recipient. When transplanting the stromal base of parenchymal organs, it is necessary to connect their vessels to the bloodstream to ensure a sufficient number of stem cells [6, 8]. When using xenogenic material for the preparation of stromal basics for transplantation, tissues and organs should be collected from animals with a minimum of antigenic differences with the factor H of people with 0 (I) blood groups as the universal donor, and which do not interact with the α and β agglutinins (Table 1) [12], to minimize the risk of development of innate immune reactions and secondary connection of adaptive immune responses.

Hemato-tissue barriers (hematotestericular, hematovarial, hematoplacental, hematoencephalic, and also formed by the peritoneum) prevent rejection by the immune system organs and tissues containing foreign antigens or autoantigens that are different from the autoantigens of humans (e.g., colon, testicular, ovarian and others). Hemato-tissue barriers are represented by the basal membrane of the vessels on endothelial cells and often part of the second basal membrane with the mesotheliocytes located on it (for the peritoneum), pneumatocytes (for alveoli), etc., as well as by macrophages in the extracellular matrix, located between the basal membrane. Macrophages phagocytose antigens, different from autoantigens of the microorganism (for peritoneal macrophages) and effector cells of the immune system, capable of entering through protected tissue (for macrophages of testes, ovaries, placenta and other organs) [3, 4, 30]. Vascular and epithelial basal membranes together with the cells located on them prevent the passage through them of foreign antigens and autoantigens other than autoantigens of other tissues of the body, as well as prevent the migration of effector cells of the immune system. This protects organs and tissues with other antigens (intestine, testicles, ovary and others) from the reactions of the immune system of the macro-organism, as well as the macro-organism itself from the antigens of these organs and tissues. At the same time, vascular and epithelial basal membranes and the cells on them pass through migrating stem cells in which tissue-specific antigens of MHC I class are suppressed [4, 5, 6, 8]. Given the described

properties of the peritoneum, its duplicate can be used to prevent rejection of transplanted cells and tissues. In the duplicate of the peritoneum it is necessary to transplant functional cells together with their microenvironment, represented by progenitor cells, fibroblasts, basal membrane and other components of the intercellular matrix, whose glycoproteins carry a unique code of composition and sequence of cell growth factors, providing the direction of differentiation of migrating stem cells. Transplantation of individual cells (for example, insulin cells of the islets of pancreatic Langerhans in patients with type 1 diabetes to restore the physiological increment of insulin or Leydig cells in patients with testicular aplasia to restore the physiological increment of testosterone) cannot provide their subsequent renewal. The period of functioning of such transplanted cells will be limited to the duration of their lives.

Conclusion

Desensitization and the formation of immunological tolerance is an alternative to the use of immunosuppressive therapy in rheumatology and transplantology, which does not eliminate pathological autoimmune reactions, disrupting tissue renewal and increasing the risk of carcinogenesis.

Ethical Compliance

The authors have stated all possible conflicts of interest and all sources of funding for this work. If this work involved human participants, informed consent was received from each individual and it was conducted in accordance with the 1964 Declaration of Helsinki. If this work involved experiments with humans or animals, it was conducted in accordance with the related institutions' ethics guidelines.

Dedication

This research is devoted to the memory of the Great scientist – immunologist Victor Ivanovich Pechersky, who made a great contribution to the theoretical justification of regeneration, carcinogenesis, desensitization, and immunological tolerance, founded the concept of nutrition by blood groups.

Immunologist Viktor I. Pechersky (1932-2017)

References

[1] Kosyakov PN. Human Isoantigens and isoantibodies in norm and pathology. *Medicine* (Moscow). 1974: 3-360.

[2] Yarilin AA. Fundamentals of Immunology. *Meditsina* (Moscow). 1999: 8-600.

[3] Roitt I, Brostoff J, Male D. *Immunology*. Mir (Moscow) 2000: 1-564.

[4] Alberts B, Bray D, Lewis J, Raff M, Roberts K, Watson JD. *Molecular Biology of the Cell.* Mir (Moscow). 1994;2:176-529,3:7-381.

[5] Pechersky AV. Revisiting Terminology and Characteristics of Stem Cells. *Journal of Stem Cells* 2016;11(2):63-67.

[6] Pechersky AV, Pechersky VI, Aseev MV, Droblenkov AV, Semiglazov VF. Several aspects of the regeneration process carried out by means of pluripotent stem cells. *Tsitologiya* 2008;50(6):511-520 (submitted July 06, 2007).

[7] Pechersky AV, Pechersky VI, Smolyaninov AB, Vilyaninov VN, Adylov ShF, Shmelev A Yu, Pecherskaya OV, Semiglazov VF. Regeneration and carcinogenesis. *Journal of Stem Cells* 2015;10(4):255-270.

[8] Pechersky AV, Pechersky VI, Aseev MV, Droblenkov AV, Semiglazov VF. Immune system and regeneration. *Journal of Stem Cells* 2016; 11 (2): 69-87.

[9] Gylmiyarova FN, Radomski WM, Gerkel NO, Gusyakova OA, Sidorova IF. *Blood group: Biological variability of cellular composition and metabolism in normal and pathological conditions*, edited by GP Kotelnikov. Meditsina (Moscow). 2007:7-387.

[10] Pechersky VI, Chepcheruk GS, Shalaev SA. *Particularities of the course of the wound process in the immunodeficiency state in surgical patients*. Paper presented at the annual meeting "Gunshot wound." SM Kirov Military Medical Academy (Leningrad). May 28-29, 1991: 37-38.

[11] Pechersky VI. Medical and social certification of the population. *Methodology "Individual nutritional needs"*. Paper presented at the annual meeting "Problems of assessment and forecasting of the health of military personnel under the conditions of modern military reform". SM Kirov Military Medical Academy (Leningrad). February 16-17, 1985: 139-142.

[12] Pechersky VI. Menu by blood type. *Gastronom* 1998;4 (8):2.

[13] Pechersky VI. Blood type on the sleeve. *Sankt-Peterburgskiye Vedomosti*, October 12, 1991:3.

[14] Pechersky VI. Medical and social certification of the population. *Life and Safety* 1998;4:13-15.

[15] Kolesnikov IS, Lytkin MI, Korosteleva TA, Shalaev SA, Belokhvostova AT, Pechersky VI, Katchenko NA, Kuznetsov SI. Immunological reaction of 3-oxandrolone acid in the diagnosis of lung cancer. *Herald of Surgery in the Name of II Grekov* 1981;4 (126):3-7.

[16] Lytkin MI, Ovrutsky GD, Gurtovoy BL, Zolotarev II, Ivanovskaya TE, Kaem RI, Sarkisov DS, Misharev OS, Palchun VT, Pokrovsky VI, Tabolin VA, Tsivilko VA. Sepsis. In: *Great Medical Encyclopedia*. Soviet Encyclopedia (Moscow). 1984;23:114-132.

[17] Klemparskaya NN, Shalnova GA. Autoflora as an indicator of radiation damage to the body. *Meditsina* (Moscow) 1966: 3-208.

[18] Pechersky VI. Culture dish (pocket laboratory of Dr. Pechersky). *Military-Medical Journal* 1983;4:81.

[19] Lavin N. Endocrinology. 2nd ed. *Practica* (Moscow). 1999:27-996.

[20] Pechersky AV. The influence of partial androgen deficiency in aging men (PADAM) on the development of benign prostatic hyperplasia and prostate cancer. *American Research Journal of Urology* 2019;3(1):1-16.

[21] Pechersky AV. Role of partial androgen deficiency of aging men in development of the metabolic syndrome. *American Research Journal of Urology* 2016;1:1-13.

[22] Petlenko VP, Pechersky VI. On the dialectic of nutrition. *Military Doctor* 1981; 30(839):3.

[23] Pechersky AV. Stimulation of regeneration in the treatment of interstitial cystitis. *Urologicheskie Vedomosti* 2018;8:88-89.

[24] Pechersky VI. Pelvic immobilizer "saddle" for immobilization of pelvic bones. *Military Medical Journal* 1960;2 86-87.

[25] Strukov AI, Serov VV. Pathological Anatomy. *Meditsina* (Moscow). 1993: 47-262, 453-458.

[26] Pechersky AV. Influence of violation of regeneration in people over 35-40 years old on decrease in production of sexual hormones. *Journal of Stem Cells* 2016; 11(2): 99-109.

[27] Pechersky AV, Semiglazov VF, Loran OB, Karpishenko AI, Pechersky VI, Mazurov VI. The influence of partial androgen deficiency (PADAM) on the impulse regime of incretion of several hormones and mitotic activity. *Tsitologiya* 2006; 48(10):862-866.

[28] Pechersky AV. Features of diagnostics and treatment of partial androgen deficiency of aging men. *Central European Journal of Urology* 2010;67(4):397-404.

[29] Pechersky VI. The effect of progesterone on the prevention of the rejection of skin grafts in an experiment. Paper presented at the annual meeting "Final conference." SM Kirov Military Medical Academy (Leningrad) 1965(2):44-45.

[30] Petlenko VP, Pechersky VI. Darwinism and the theory of phagocytosis. *Military Doctor* 1983; 2 (912):3.

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