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Features of the Immune Response to One's Own Antigens and Foreign Antigens

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Abstract

The inability of one's own innate, and then acquired, immunity to ensure the elimination of foreign antigens and their carriers leads to additional stimulation by Th17 responses of innate immunity. Excessive stimulation by Th17 can lead to the development of autoimmune diseases. Autoimmune diseases can also be caused by excessive formation of products of catabolism of nucleic acids (purine mononucleotides and their metabolites). Tumor cells which have lost peptide copies of tissue-specific MHC class I antigens (HLA analogues), on the contrary, turn out to be unavailable for elimination by acquired immunity.

Keywords: tissue-specific antigens, nuclear antigens, pluripotent stem cells, regeneration, desensitization, cancer, antitumor immunotherapy

Introduction

Normally, foreign antigens initiate an immune response aimed at eliminating these antigens and their carriers, while a person's own blood group antigens, tissue-specific antigens, peptide copies of tissue-specific autoantigens associated with class I MHC dimers (HLA analogues), and nuclear antigens, on the contrary, are protected from the immune response [1, 2]. If the response of innate, and then acquired immunity, does not lead to the elimination of foreign antigens and their carriers, then additional stimulation by Th17 of innate immunity reactions begins. Excessive stimulation can lead to autoimmune diseases. In malignant tumor diseases, on the contrary, there is failure of one's immune response (due to the loss, caused by tumor cells, of the expression of peptide copies of tissue-specific antigens associated with class I MHC dimers / HLA analogues) [1, 2].

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Characteristics of the Immune Response to Foreign Antigens

Antigens of viruses, fungi, bacteria and parasites (protozoa and helminths) cause a primary response of innate immunity in humans (macrophages, components of the complement system, agglutinins and other factors), and then a secondary response of acquired immunity (with the formation of highly specific antibodies or cytotoxic T-cells). The response of acquired immunity is determined by T-helper cells 0 (Th0) after receiving processed peptide copies of antigens from antigen-presenting cells [1, 2].

Depending on the selected immune response, Th0 are differentiated into Th1 or Th2 [1, 2], and if necessary, additional stimulation of innate immune responses - into Th17. As representatives of acquired immunity, Th17 not only stimulate the intensity of innate immune responses, but also regulate the interaction of innate immunity and acquired immunity. Th17 enhance the acquired immune response through stimulation of antigen-presenting cells, or suppress the acquired immune response through production of IL-10 and other methods. Th1a regulate cellular immunity, and determine the directed migration of cytotoxic T-cells [1, 2], while Th1b determine the migration of stem cells [3, 4, 5, 6]. Th2 regulate humoral immunity, and determine the differentiation of B-cells into plasma cells that form high-affinity IgG, IgA, and IgE antibodies [1, 2].

Due to the fact that the acquired immune system is not able to respond to the antigens of all viruses, fungi, bacteria and parasites that the macroorganism contacts with (through its skin, the mucous membranes of its lungs, gastrointestinal tract, and genitourinary organs), protection against their penetration and generalization is mainly provided by innate immunity [1, 7]. Additional stimulation by Th17 of responses of innate immunity (that can lead to the development of type IV hypersensitivity) develops upon failure of elimination of extracellular bacterial and fungal infections by innate immunity and secondarily, by acquired immunity with the participation of Th1 or Th2. Differentiation of Th0 into Th17 occurs, for example, when there is a significant increase in the antigenic load through the skin, mucous membranes of the lungs, intestines or genitourinary organs, the content of which alone is not sufficient to initiate an acquired immunity response. The participation of Th17 is also required to enhance the innate immune response to T-independent antigens recognized by specific receptors (lipopolysaccharide receptors and others) of innate immune cells (monocytes / macrophages, dendritic cells, B-cells), as well as endothelial and other cells involved in triggering the inflammatory response [1, 2]. An example of T-independent antigens is the endotoxin of gram-negative bacteria, represented by lipopolysaccharides, which, due to the lack of the protein part in their molecule, are not processed by antigen-presenting cells, do not form peptide copies presented by MHC class II molecules, and, accordingly, do not initiate the response of acquired immunity. Due to the lack of response by the acquired immune system to T-independent antigens for the elimination of T-independent antigens and their carriers, Th0 differentiate mainly into Th17, which stimulate innate immune responses. Thus, the lysis of some gram-negative bacteria, i.e. those with a lipid bilayer, is carried out by a complement that is formed by macrophages and cationic proteins formed by macrophages and granulocytes [2].

Under excessive or prolonged entry of antigens into the bloodstream, and with the inability of macrophages to phagocytize the immune complexes formed after their binding to antibodies, there is also a need for additional stimulation of macrophages by Th17. Without timely and adequate phagocytizing of immune complexes by macrophages with the participation of the complement, immune complexes can cause type III pathological immune hypersensitivity reactions [2]. By attaching to the endothelium of kidney vessels and other organs, immune complexes cause damage to their tissues (as happens with the new coronavirus infection – 2019-nCoV [7]). The inability of innate immunity and secondary-acquired immunity with the participation of Th2-cells to ensure the elimination of antigens and their carriers can lead to the production by activated B-cells of IgE (to the development of type I hypersensitivity).

Cross-antigens of viruses, fungi, bacteria, and parasites that resemble tissue-specific and nuclear antigens, as well as blood group antigens, can initiate an immune response directed not only against them (as carriers of foreign antigens), but also against human cells and tissues [1, 2]. Autonucleoproteins

and nucleoproteins of other eukaryotes are not recognized by the human immune system as foreign antigens, in contrast to the nucleoproteins of bacteria and viruses [8]. Therefore, the formation of antinuclear antibodies under autoimmune diseases is due to the response of the human immune system to cross-antigens of bacterial and viral nucleoproteins (similar to the response to cross-bacterial antigens that resemble tissue-specific antigens), and not to the nucleoproteins of their own cells.

Over-response of acquired immunity (include an over-stimulation by Th17 of the reactions of innate immune responses), as well as an immune response to cross-antigens, can lead to autoimmune diseases.

Similar to differentiation of Th0 into Th1 and Th2 [1, 2], differentiation of Th0 into Th17 begins after Th0-cells interact with antigen-presenting cells. Antigen-presenting cells (dendritic cells, macrophages, and B-cells) absorb antigens and process them, expressing peptide copies of antigens together with MHC class II molecules to represent Th0 [1, 2]. Differentiation of Th0-cells into Th17-cells is regulated by IL-1β, IL-6, transforming growth factor β (TGFβ), IL-21, and IL-23. The cytokines IL-1β, IL-6, and TGFβ initiate differentiation of Th0 into Th17. IL-21 stimulates differentiation of Th0 into Th17. The functional activity of differentiated Th17-cells is supported by IL-23, produced by dendritic cells and macrophages [9].

Th17-cells produce IL-17A, IL-17F, IL-22, and TNFα [9]. IL-17A and IL-17F, when binding to specific receptors of the IL-17R family of macrophages, fibroblasts, neutrophils, epithelial, endothelial and other cells, stimulate the production by them of pro-inflammatory cytokines (IL-1, IL-6, TNFα) and chemokines, as well as the formation of nitric oxide and other cytotoxic factors by macrophages/ monocytes. IL-17, stimulating the production of pro-inflammatory cytokines by macrophages and other cells, increases the production of Willebrand factor endothelial cells, which increases platelet adhesion and aggregation [2, 9, 10, 11, 12]. IL-17A also causes an increase of granulocyte and granulocyte-macrophage colony-stimulating factors [10] for additional formation of immunocompetent and stem cells.

IL-22 binds to IL-22R1 and IL-10R2 non-immune cells (keratinocytes, lung and intestinal epithelial cells, hepatocytes, fibroblasts, and other cells), initiating the innate immune response to extracellular bacterial and fungal infections. Being a member of the IL-10 superfamily, IL-22, unlike IL-10, does not inhibit the production of pro-inflammatory cytokines by macrophages / monocytes (since they do not have IL-22 receptors). IL-22 induces the synthesis of proteins of the acute phase of inflammation, proinflammatory cytokines, and chemokines, and causes cell hyperproliferation [9].

Th, which produce not only IL-17, but also interferon-γ (INF-γ), are called "double positive T-lymphocytes", or "Th17/Th1-lymphocytes" [9]. Besides Th17, IL-17 are also produced by γδT-cells, cytotoxic T-cells, NK-cells, as well as macrophages, mast cells, and neutrophils [13]. These examples indicate that in addition to the three known Th subpopulations (Th1, Th2, and Th17), there are other Th subpopulations that perform combined functions, as well as other cells other than Th that participate in the regulation of the immune response. Differentiation of Th0-cells and other cells involved in regulating the immune response is accompanied by ranking of their genes [1, 2], leaving parts of DNA (similar to exons of matrix RNA [14]) that ensure their combined and duplicate functions.

In psoriasis, Th17 migrating to the dermis and epidermis form excessive amounts of IL-17A and IL-22. IL-17A induces the formation of pro-inflammatory cytokines and chemokines by macrophages and other cells that attract additional macrophages, and IL-22 causes increased proliferation of keratinocytes. The production of cytokines by macrophages and dendritic cells that stimulate differentiation of Th0 to Th17 in people with psoriasis, psoriatic arthritis, and ankylosing spondylitis is initiated by streptococcal and other antigens that occur when the skin barrier function is impaired [1, 2, 9, 15], and in other ways. The resulting antibodies to N-acetylglucosamine of group A streptococci can interact with the epitope of cytokeratin of epithelial cells due to their antigenic similarity [2], since the cytoskeleton of all eukaryotic cells has homologues of the cytoskeleton proteins of their phylogenetic progenitors – prokaryotes. Antigens are absorbed (internalized) by antigen-presenting dendritic cells (represented in the skin by Langerhans cells) and monocytes/macrophages that process antigens and

form pro-inflammatory cytokines. Then antigen-presenting cells migrate to regional lymph nodes and interact with Th0, which in turn differentiate into Th1 and activate cytotoxic T-cells and macrophages that affect the skin and form granulomas. If the response of innate immunity and secondary – acquired immunity is insufficient to eliminate antigens and their carriers, Th0 are differentiated into Th17 for additional stimulation of innate immune responses. In psoriasis, macrophages, Th1, memory T-cells, cytotoxic T-cells, and then Th17 and additionally attracted macrophages migrate to the dermis and then to the epidermis, causing increased keratinocyte proliferation and angiogenesis. IL-17A produced by Th17, also stimulates osteoclast differentiation and formation by these osteoclasts of IL-6 and TNFα [16], which are involved in the development of joint inflammation and destruction. Accordingly, psoriasis in some patients is accompanied by psoriatic arthritis.

Hyperproliferation of keratinocytes leads to a reduction in the cell cycle of keratinocytes and to a violation of their differentiation. Increased proliferation of keratinocytes is accompanied by intensive angiogenesis, as well as massive infiltration of the skin by macrophages, Th1, Th17, and cytotoxic T-cells. Macrophages and cytotoxic T-cells, continuing to increment pro-inflammatory cytokines (TNFα, IL-1β, IL-6), and increase inflammation [17]. Chronic cytokine stimulation leads to the transformation of macrophages/monocytes into giant epithelial cells. The core of the granuloma, consisting of macrophages and epithelioid cells, is surrounded by lymphocytes. Necrosis and fibroblast proliferation-induced fibrosis are possible [2].

The reverse development of psoriatic plaques when a patient undergoes administration of monoclonal antibodies to IL-17A formed by Th17 [12], indicates the leading role of Th17 in the pathogenesis of psoriasis, while additionally stimulating innate immune responses. Unfortunately, anti-T-cell and anti-cytokine therapy, used for patients with psoriasis, can only achieve remission, rather than cure the disease, since it is aimed at reducing the severity, and not at stopping or reformatting the pathological immune response. Desensitization opens up new possibilities in the treatment of autoimmune diseases, in particular psoriasis, psoriatic arthritis, and ankylosing spondylitis. In comparison with genetic engineering therapy aimed at blocking the action of certain factors of the pathological immune response (through the use of monoclonal antibodies-inhibitors of TNFα, IL-17A and other cytokines), desensitization is able to reformat the pathological immune response itself.

To stop the pathological immune response of innate immunity (including to reduce the activity of macrophages), as well as for desensitization with reformatting the second-formed response of acquired immunity (in this case, to reduce the activity of Th17), it is necessary to eliminate the antigens that caused the pathological immune response, and to stop their further entry into the body / their contact with the body. Otherwise, the antigens that caused the abnormal immune response will continue to initiate innate and secondarily-acquired immune responses.

In patients with psoriasis, psoriatic arthritis, and ankylosing spondylitis, it is necessary to exclude the contact of antigens that caused a pathological immune response with the skin and mucous membranes of patients. In the presence of streptococcal diseases of the skin, tonsils and other tissues and organs, parasitic diseases caused by helminths and/or protozoa, intestinal dysbiosis, sexually transmitted diseases caused by *Chlamydia trachomatis* and other infections, as well as when receiving sensitizing antigens from food, patients should receive appropriate antibacterial, antifungal, and anti-parasitic therapy, plasmapheresis (to remove antigens that support the viability of immunological memory cells), ultraviolet irradiation of blood that destroys antibodies, as well as the normalization of the intestinal microflora and the exclusion of sensitizing antigens from the diet [6].

Food antigens with high immunogenicity that are similar to blood group antigens (AB0, Rh, Kell phenotypes), if they don't match the patients' antigens, activate components of the alternative pathway of the complement system, and also bind to AB0 agglutinins (IgM), activating components of the classical pathway of the complement system. As a result, the activity of macrophages is stimulated and the response of acquired immunity is formed a second time. The use of products of plant and animal origin that have the lowest frequency of occurrence of antigens that are complementary to patients' agglutinins, based on the table of Dr. V.I. Pechersky [6] reduces the antigenic load on the patient's body

and the risk of developing a pathological immune response. Products whose antigens are complementary to patients' agglutinins can be completely excluded from the diet by performing rapid precipitation reactions with product antigens and agglutinins in patients' saliva or blood serum. Given the high content of blood group antigens on red blood cells, it is necessary to exclude products containing animal blood from the diet. These measures will prevent the risk of initiating a response of innate immunity and secondarily acquired immunity with differentiation of Th0 into Th1/Th2 and/or Th17. To bind exogenous food antigens with agglutinins (IgM) contained in a high titer in saliva, the food should be thoroughly chewed [6].

Cytokines produced by Th1 (INF-γ, IL-2, TNFβ) suppress Th2 activity, and cytokines produced by Th2 (IL-4, IL-5, IL-6, IL-9, IL-13) suppress Th1 activity, thereby directing the response of the acquired immune system to the presented antigens along the cellular or humoral pathway. Th0 can change the direction of their differentiation by switching the cellular immune response to a humoral one (differentiating Th2, and suppressing the activity of Th1) and vice-versa: switching the humoral immune response to a cellular one (differentiating into Th1, suppressing the activity of Th2) [1, 2]. Th1 and Th2 are not only antagonists to each other, but also inhibit Th17 activity through the formation of INF-γ (by Th1) and IL-4 (by Th2). Th17, in their turn, form IL-22, and inhibit the production of IL-4 by Th2 [9]. Redirecting differentiation of Th0 into Th1b, which regulate regeneration, allows switching the pathological immune response to initiate regeneration with the formation of tissue-specific receptors in stem cells [3, 4, 5, 6]. In this way, the pathological humoral or cellular acquired immune response, the pathological enhancement by Th17 of the innate immune response, and the pathological innate immune response to autoantigens can be reformatted.

Suppression of the immune response regulated by Th1a, Th2, and Th17 is promoted by T-suppressors that form transforming growth factor-β (TGF-β) and other cytokines [1, 2]. TGF-β, which is a critical cytokine for differentiating Th0 to Th17, induces Th17 formation at low doses, but inhibits Th17 formation at high doses. In the presence of TGF-β, some Th17 populations express the anti-inflammatory cytokine IL-10, which limits the excess activity of Th17 [9, 18]. Switching off the TGF-β gene leads to the development of a fatal generalized autoimmune inflammatory process [1].

Drugs containing xenogenic tissue-specific antigens that are similar to autoantigens of tissues affected by autoimmune diseases can switch the differentiation of Th0 into Th1a and Th2, and Th17 caused by microbial antigens to differentiation into Th1b, which regulates the formation of tissue-specific antigens in stem cells that migrate to the corresponding tissues for their regeneration. Therefore, xenogenic drugs with tissue-specific antigens of the affected tissues can be used for desensitization in autoimmune diseases [3, 4, 5, 6]. In patients with psoriasis, xenogenic drugs with tissue-specific antigens of the skin and blood vessels (affected by this disease) can be recommended for oral administration. For patients with psoriatic arthritis and ankylosing spondylitis, xenogenic drugs with tissue-specific cartilages articulars and blood vessels antigens can be recommended for oral administration too. Local application of these drugs to the skin is impractical, since they can be perceived as chemoattractants and thereby increase the pathologically increased macrophage reaction. In patients with psoriasis the physiotherapy can be applied locally, such as heating with a gradual increase in temperature using baths with a decoction of chamomile flowers, which has a pronounced anti-inflammatory effect [7].

The Participation of Nucleotides and Their Metabolites in the Initiation of the Immune Response

The immune response can be initiated not only by antigens, but also by purine nucleotides and their metabolites, which together with purinergic receptors are among the oldest mediators and receptors that appeared at the early stages of evolution. Purinergic receptors, represented by several families, are the most numerous group of receptors among all living organisms [19, 20]. Under the influence of extracellular ATP, there is a release of calcium from intracellular depots, proliferation of bacteria and seaweed cells, as well as $CD34^+$ cells of peripheral blood and bone marrow [21]. The release of nucleo-

tides and nucleosides with regulatory functions to the external environment occurs normally (for example, ATP), and, under pathology - when damaged by physical, chemical, or biological factors that lead to cell death (necrosis or apoptosis - programmed cell death). Nucleoproteins found in the extracellular environment are broken down mainly by hydrolysis to mononucleotides and their derivatives [14]. Mononucleotides and their derivatives having purine nitrogenous bases – adenine and guanine (including ATP and adenosine – a product of extracellular hydrolysis of ATP), are able to bind to specific purinergic receptors involved in the regulation of proliferation, apoptosis, cytokine incretion, and other vital processes. The most significant of the purinergic receptors are: P2X (binding to ATP), P2Y (binding to ATP, ADP, UTP, UDP and their metabolites) and P1 (binding to adenosine, formed during ATP hydrolysis) [22].

The response of immune cells to nucleotides and their metabolites depends on their concentration. In high concentrations, extracellular ATP binds to P2X7 purinergic receptors of macrophages, dendritic, epithelial, and other cells and induces their production of proinflammatory cytokines (IL-1β, IL-6, TNFα), oxygen and nitrogen free radicals, and chemokines that additionally attract macrophages and dendritic cells. Thus, high concentrations of extracellular ATP induce differentiation of Th0 into Th1 [23]. The high concentrations of extracellular ATP stimulates not only the formation by Th1a of tissue-specific receptors in cytotoxic T-cells to destroy virus-affected, malignant, and other altered cells, but also the formation by Th1b tissue-specific receptors in stem cells to replace dead cells [3, 4, 5, 6].

In low concentrations ATP, binding to P2Y receptors, on the contrary, increases the production of anti-inflammatory cytokine IL-10 and reduces the production of macrophages, dendritic and other cells of pro-inflammatory cytokines (TNFα and others), and inhibits their ability to initiate the differentiation of Th0 into Th1. Adenosine in low concentrations, acting through P1 receptors, also inhibits the formation of pro-inflammatory cytokines and increases the formation of the anti-inflammatory cytokine IL-10 [24].

Activation of P1A1 adenosine receptors stimulates the differentiation and functioning of osteoclasts, while activation of P1A2 adenosine receptors suppresses the functioning of osteoclasts [25].

Purinergic receptors can bind not only to adenosine, but also to other degradation products of purine nucleosides such as inosine, hypoxanthine, and xanthine [26]. The development of autoimmune inflammatory reactions in response to an increase in the content of uric acid in human blood (hyperuricemia) in people with gout indirectly indicates the ability of uric acid to bind to purine receptors of macrophages/monocytes, dendritic, epithelial and other cells with the initiation of the formation of pro-inflammatory cytokines.

Stimulation of P2Y1-receptors by ADP increases the level of calcium ions coming from intracellular depots and causes platelet aggregation, while stimulation of P2Y12-receptors by ADP contributes to the formation of the correct thrombus structure [27].

Extracellular purines promote the proliferation of fibroblasts, binding to their purinergic receptors. Accordingly, an increase in the content of purines, including adenosine, during cell death and inflammation contributes to the development of fibrosis [28].

Increased cell death in people over 35 years old [3, 4, 5, 6, 29, 30] leads to hyperuricemia, which, by stimulating the formation of pro-inflammatory cytokines by macrophages, dendritic, epithelial and other cells, increases the risk of developing gout, lymphoma, leukemia and other diseases [31]. An increase in cell death with an increase in the extracellular space of nucleotides and their metabolites is also observed in inflammatory (including autoimmune) diseases. Elevated levels of ATP and adenosine are observed in the airways of patients with chronic obstructive pulmonary disease [32]. In patients with psoriasis, the extracellular DNA of decaying keratinocytes, which stimulates the purinergic receptors of macrophages and dendritic cells and their formation of pro-inflammatory cytokines, is an additional factor that supports inflammation [33].

Most microorganisms, plants, fish, and amphibians contain a complete set of uricolytic enzymes that allow for the metabolism of purines to urea. In humans and primates, there are no enzymes for splitting uric acid, which remains the main end product of the breakdown of purine bases [34] (only proteins catabolism is completed by the formation of

urea [14]). The content of uric acid in the blood plasma is determined by the rate of its intake and excretion. Uric acid is excreted mainly by the kidneys (two-thirds of the excretion) and through the gastrointestinal tract (one-third of the excretion). Purines from food make up only 30% of the uric acid excreted. Prescription of a purine-free diet reduces the content of uric acid in the blood plasma by only 15-20% [35]. The main reason for the increase in uric acid in blood plasma is that there is a constant increase in cell death with age. After age of 35, a person's pool of pluripotent stem cell decreases by 1% per year [3, 4, 5, 6, 29, 30, 36]. Because of the insufficient replenishment of stem cells, dead old cells are not replaced by an adequate number of low-grade progenitor cells, which makes it impossible to complete the regeneration process [3, 4, 5, 6]. In response, the formation of cellular growth factors that stimulate the division of the remaining progenitor cells increases in proportion to age in all tissues. In addition, an increase in the formation of cellular growth factors and endocrine activators of cell division (insulin, growth hormone, and other hormones) in people over 35 years of age occurs in response to a decrease in the production of sex hormones with age and the resulting violation of division and differentiation of cells carrying sex hormone receptors [3, 4, 5, 6, 29]. An increase in mitogenic activity causes the response of the immune system, whose cells, releasing cytotoxic factors (free radicals and others), cause multiple death of old and intensively proliferating cells to prevent malignant transformation of the latter. There is also an increase in cell death by apoptosis due to increased levels of glucocorticoid hormones, which is caused, among other things, by a decrease in the production of sex hormones with age [30]. Increased cell death in people over 35 years of age leads to an increase in the content of nucleotides and their metabolites in the extracellular space, including uric acid, and naturally – to an increased risk of gout. The increase in life expectancy today has led to an increase in the proportion of older people with elevated uric acid levels. To date, elevated uric acid levels are detected in one third of the world's population [37].

When treating gout in people older than 35-40 years old, in addition to limiting the intake of purines from food, it is necessary to eliminate the main cause of this disease - to reduce the supply of nucleotides and their metabolites into the extracellular space, reducing increased cell death. The restoration of the pool of pluripotent stem cells in individuals older than 35-40 years old makes it possible to re-establish the replenishment of their population of progenitor cells for subsequent adequate replacement of dead old cells, a concomitant decrease in compensatory increased cell growth factors, and reduce the immune system response (destroying the old and rapidly-dividing cells to prevent malignant transformation of the latter) [3, 4, 5, 6]. Thus, the restoration of the pluripotent stem cell pool makes it possible to stop the growth of age-related pathological processes that lead, among other things, to increased cell death and a concomitant increase in the supply of nucleotides and their metabolites (including uric acid) to the extracellular environment.

The formation of chimerism through transfusion of allogeneic pluripotent stem cells in the mono-nuclear fraction of peripheral blood prepared from young donors aged 18-23 years who have the same blood group (AB0, Rh phenotype, Kell) and gender with the subsequent development of immunological tolerance (RF patent No. 2350340) makes it possible to safely restore the pool of pluripotent stem cells in people older than 35-40 years old [3, 4, 5, 6]. Restoring the pool of pluripotent stem cells in men can also restore the number of testicular Leydig cells and their production of testosterone in a physiological pulse mode, and in women in the premenopausal period – to normalize the formation of estradiol by granulose cells of ovarian follicles, which is necessary for changing the follicular phase to the luteal phase of the menstrual cycle [38].

A reduction in the formation of mitogenic factors and a subsequent decrease in the severity of the immune system response to increased mitogenic activity, which leads to excessive cell death, can be achieved with adequate replacement therapy with sex hormones – testosterone in men, and tibolone in women [38, 39].

For autolysis of granulomas and deposits of uric acid salts in joints among people with gouty arthritis, chemoattractants (alcohol extract of propolis and others) that attract macrophages carrying proteolytic enzymes can be used locally [3, 5, 6, 40].

Restoration of Tissue Regeneration in Cancer Patients after Radiation Therapy and Chemotherapy

The participation of antigen-presenting cells (dendritic cells and macrophages) in the processing and the presentation of Th0 of tissue-specific antigens of dead cells for formation by Th1b tissue-specific receptors in stem cells (replenishing the composition of progenitor cells) can be used to improve tissue regeneration in cancer patients who have undergone radiation therapy and/or chemotherapy. This pattern can be used in the complex treatment of radiation fistulas, cystitis, proctitis, and other complications of radiation therapy. In the absence of a recurrence of cancer, chemoattractants (propolis oil extract/propolis candles, auto-platelet suspension injected into the surrounding fistula tissues, and others) can be used locally in order to attract antigen-presenting cells. Chemo-attractants should not be used in the presence of a tumor, since they can help direct the migration of stem cells to replenish the cell composition of the tumor with progressive growth of the latter [3, 5, 6, 40, 41].

Restoration of the pluripotent stem cell pool in cancer patients to normalize tissue regeneration, to reduce elevated (due to impaired regeneration) levels of cellular growth factors, and to reduce the risk of cancer recurrence can be obtained by transfusion of allogeneic donor pluripotent stem cells in the mononuclear fraction of peripheral blood that is collected from young donors 18-23 years of age and of the same sex and blood groups with recipients [3, 4, 5, 6]. Temporarily increasing the pool of pluripotent stem cells to restore regeneration in cancer patients in the treatment of radiation fistulas and other complications of radiation therapy and chemotherapy can be done through the appointment of drugs containing granulocyte colony-stimulating factors.

Prescription of hyaluronic acid can improve the conditions for migration of stem cells through extracellular matrix, and thereby the stimulation of regeneration [36, 40].

Formation of an Immune Response to One's Own Antigens Altered by Tumors and Viruses

The reverse development of tumors after their infection through a skin incision (probably by gram-positive skin microflora, including streptococci) was empirically detected in Ancient Egypt. In a similar empirical way, Dr. William Coley identified regression of tumors after their infection with group A streptococci. Initially, Dr. Coley used live bacteria, but then began using killed bacteria (considering them to be safer), called "Coley toxins." Later, Dr. Old suggested using the live BCG anti-tuberculosis vaccine for tumor immunotherapy, which is still used in the treatment of bladder cancer and other tumors. Doctor-immunologist V. I. Pechersky in the 1970's made antitumor vaccines from part of removed tumor tissues and successfully applied them, injecting vaccines to the same patients intradermally to interact with antigen-presenting monocytes / macrophages and dendritic cells in order to prevent relapse of the disease.

In cancer and viral diseases, a predominantly cellular immune response is formed with the activation by Th1 of cytotoxic T-cells that have tissue-specific receptors for their own cell antigens altered by tumors and viruses. To a lesser extent, in cancer and viral diseases, a humoral immune response is formed with activation by Th2 B-cells that form antibodies to tumor antigens and virus antigens [1, 2, 7].

In the course of evolution, after the appearance of acquired immunity, tissue-specific antigens of living intact cells were hidden for recognition by both phylogenetically older innate immunity (which does not have a narrow specificity) and newly acquired immunity. Peptide copies of tissue - specific antigens and class I MHC dimers (capable of binding to specific T- and B-cell receptors) became available for recognition only by acquired immunity in living intact cells [1, 2, 6]. The expression of peptide copies of tissue-specific MHC class I antigens (HLA analogues) was not found only in living stem cells and in similar living tumor cells [1, 2]. At the same time, in living tumor cells, like other living cells, the tissue-specific antigens themselves remain hidden from recognition by innate and acquired immunity. Due to

the termination of the expression of peptide copies of tissue-specific MHC class I antigens (HLA analogs) and the unavailability of recognition of tissue-specific antigens, the immune system's surveillance of living tumor cells is weakened. An example of tissue-specific epithelial cell antigens is their cell wall and cytokeratin antigens. In dead cells and cells infected with intracellular infections (viruses, Mycobacterium tuberculosis, and others), tissue-specific antigens, on the contrary, become available for recognition by innate and acquired immunity (initiating antitumor and antiviral immune responses).

Under intracellular localization of infectious pathogens (viruses, mycobacteria, and others) one forms acquired cellular immunity to one's own altered antigens of affected cells (in contrast to the extracellular localization of infectious agents – bacteria, initiating the formation of acquired humoral immunity to the antigens of the pathogens themselves) [1]. In order to enhance the immunogenicity of tumor cells with the formation of acquired cellular antitumor immunity, tumor cells are required to infect them through tropic viruses (e.g., adenoviruses used as vectors for live vaccines, which have an affinity for many tissues and do not block the transport of molecules of MHC class I to the surface of cells, or through viruses obtained through genetic engineering, with an affinity to specific antigens of certain types of tumor cells). To ensure infection of mainly tumor tissues, viruses that are tropic to many types of cells (for example, used as vectors for creating live vaccines) must be applied to the surface of tumors, injected in the tissue of tumors (together with a synthetic matrix that provides a long-term release of viruses) or endovascular injected into tumors.

When carrying out antitumor immunotherapy to improve immunogenicity of tumor cells and their subsequent recognition by the immune system after injection in the tissue of tumors of viruses, endovascular injected into tumors of viruses or absorption of viruses on the surface of tumor cells (after replication of a sufficient number of viruses, and their changing of antigens of cells) to enhance the antitumor response of acquired cellular immunity, one can cause death of the tumor cells. For this purpose, 1-2 ml of 10% calcium chloride solution depending on sizes can be injected inside the tumors (strictly within the tumors), or focal antitumor therapy can be performed using focused ultrasound, photodynamic therapy, or other methods. A solution of 10% calcium chloride is non-toxic at coming in blood, and when injected into tumor tissues, it causes focal necrosis. Focal necrosis of tumor tissues (previously infected with tropic viruses) must be carried out with the preservation of blood supply and lymph outflow of tissues and organs affected by tumors in order to enter them from the circulating blood of antigen-presenting cells and migrate from them to regional lymph nodes of the same antigen-presenting cells after they absorb tumor antigens. This methodology of immunotherapy can be used both for surgically removed tumors (with subsequent cultivation of tumor cells with tropic viruses and their destruction for the preparation of antitumor vaccines), and for non-removed tumors (with the introduction of tropic viruses into their tissues and subsequent necrosis of part of their tissues). When preparing antitumor vaccines from a part of removed tumor tissues, modified tissue-specific antigens must be left as part of the cell wall fragments and cytokeratin of dead tumor cells (to form the response of acquired cellular immunity), while modified nuclear antigens must be left as part of nucleoproteins (to preserve their immunogenicity with the formation of the response of acquired humoral immunity - to form antinuclear antibodies to altered tumor nuclear antigens). This can be achieved by destroying the tumor cells, for example, osmotically, by immersing them in a hypotonic solution, or by other methods.

Tissue-specific and nuclear antigens of dead tumor cells in anti-cancer vaccines, additionally modified by viruses, will be absorbed by the antigen-presenting cells and will be represented by them to Th0. In response to further virus-modified tissue-specific antigens of dead tumor cells, Th0 will differentiate into Th1a, forming the corresponding tissue-specific receptors in cytotoxic T-cells. In response to the tumor's nuclear antigens, Th0 will differentiate into Th2, forming specific receptors in B-cells that turn into antibody-forming plasma cells. This combined cellular and humoral acquired antitumor immune response to various tumor antigens will be directed toward the elimination of malignant cells. Since tumor cells carry many altered antigens, separate Th1a or Th2 clones will be formed for each of them. Accordingly, a complex antitumor immune

response (cellular mainly to tissue-specific antigens and humoral mainly to nuclear antigens) will be formed to one and the same tumor cells, but to their different antigens.

To form an antitumor immune response, antitumor vaccines containing altered tissue-specific antigens of cell membranes and cytokeratin, as well as altered nuclear antigens of dead tumor cells, should be administered intradermally, inside the mucous membranes or in interstitial spaces to absorb their antigens by antigen-presenting cells located there (monocytes/macrophages and dendritic cells). Unlike tissue-specific antigens of living tumor cells that are protected from recognition by the immune system, tissue-specific antigens of virus-infected and dead tumor cells are available for recognition by innate and acquired immunity. When administered intradermally (preferably because of its simplicity and greater safety), tissue-specific and nuclear antigens of dead tumor cells, additionally modified by viruses, will be absorbed by antigen-presenting cells of the dermis and epidermis (monocytes/macrophages and dendritic cells - Langerhans cells), which process and present peptide copies of these antigens associated with MHC class II molecules (HLA analogues). Migrating from the epidermis through the lymphatic vessels to the paracortical T-dependent region of regional lymph nodes, monocytes/macrophages, dendritic cells (including Langerhans cells) will present tumor antigens to Th0, which, differentiating into Th1a, will form receptors for altered tumor tissue-specific antigens in cytotoxic T-cells, or, differentiating in Th2, will form receptors for altered tumor nucleic antigens in B-cells. Even under the formation of a less desirable humoral immune response to tissue-specific antigens on the surface of tumor cells, effector cells carrying Fc and C3 receptors will be activated a second time with the involvement of complement, as occurs in type II hypersensitivity (when target cells are damaged by antibodies to cell surface antigens – IgM and/or IgG, with the participation of complement and various effector cells [2]). The time of formation of the acquired antitumor immune response will be determined by the duration of antigen processing by antigen-presenting cells, Th0 differentiation into Th1a/Th2, and the formation of tissue-specific receptors in cytotoxic T-cells/specific receptors in B-cells. According to I. Roitt and coauthors, in humans, the sensitization period lasts 10-14 days [2].

When using preparations of tissue-specific and nuclear tumor antigens as part of antitumor vaccines, it should be taken into account that the immune system response depends on the number of antigens applied per unit area, and not on the total dose of the drug or the total area to which the antigen is applied [1, 2]. The dose of tissue-specific and nuclear tumor antigens should be sufficient to initiate Th0 differentiation into Th1a (forming tissue-specific receptors in cytotoxic T-cells) or Th2 (forming specific receptors in B-cells).

This concept of antitumor therapy is confirmed by an experimental example. A 12 year-old female German shepherd dog O. was held under observation for a tumor of the right inguinal region. A biopsy revealed a fibrolipoma. The tumor grew rapidly, became dense, tuberous, and the size of the tumor reached 10 x 12 x 9 cm. The animal was given 1.5 ml of 10% calcium chloride once a month inside the tumor (strictly within the tumor). In total, three injections were performed. By the end of the third month, the size of the tumor had decreased by more than three times to 3 x 3 x 2 cm, and the consistency of the tumor became soft and elastic. A repeated histological examination also revealed fibrolipoma.

The introduction of tropic viruses in the tissue of tumors (together with a synthetic matrix that ensures their gradual release), endovascular injected into tumors of tropic viruses or absorption of tropic viruses on the surface of tumors, followed (after the start of virus replication) by the introduction of 10% calcium chloride inside the tumors (strictly within the tumors) or the use of focused ultrasound, photodynamic therapy and other methods of focal therapy can lead (through the formation of an acquired immune response to tissue-specific and nuclear antigens of dead tumor cells) to regression of not only benign, but also malignant tumors.

To increase the immunogenicity of tumor cells with the formation of an acquired cellular immunity response to them, additionally, cross-antigens of group A streptococci, similar to tissue-specific cytokeratin antigens of epithelial cells, can be introduced into the tumors (or absorbed on their surface together with a synthetic matrix). Cross-antigens of group A streptococci, introduced into tumor tissues or

absorbed on the surface of their cells, can attract antigen-presenting cells to tumor cells as chemo-attractants (providing an adjuvant effect), and as antigens similar to tissue-specific antigens of cancer cells and tissue-specific tumor antigens themselves, they can initiate differentiation of Th0 into Th1a (forming receptors in tissue-specific cytotoxic T-cells for altered cytokeratin antigens and other tumor tissue-specific antigens, including membrane antigens). A non-optimal choice of Th1 or Th2 cell activation results in an ineffective immune response. The use of cross-antigens of group A streptococci together with a synthetic matrix for intra-tumor administration or application to the tumor surface can minimize the flow of streptococcal antigens into the blood to prevent the formation of acquired humoral immunity to them, which suppresses the formation of acquired cellular immunity (necessary for the defeat of tumor cells), as well as to prevent the development of autoimmune diseases.

Focal antitumor immunotherapy compares favorably with blocking immune control checkpoints (immune checkpoint blockade therapy), since it forms an immune response only to the antigens of the existing tumor, without causing autoimmune damage to healthy tissues with the development of autoimmune complications. In contrast to live antitumor viral vaccines obtained by genetic engineering, which have a tropicity to the antigens of certain types of tumors, antitumor immunotherapy using autovaccines is able to form an immune response to all altered tissue-specific and nuclear antigens of patients' tumors. Local (interstitial) use of viruses to increase the immunogenicity of tumor cells is more effective than using a live BCG anti-tuberculosis vaccine for the same purpose, since mycobacteria of tuberculosis, getting inside cells (in this case, inside tumor cells), are inside cytoplasmic vesicles that reduce the immunogenicity of affected cells, preventing their interaction with antigen-presenting cells and the subsequent formation of acquired cellular immunity with the activation of cytotoxic T-cells (necessary for the destruction of tumor cells).

Creating a natural interaction of antigen-presenting cells (monocytes/macrophages and dendritic cells) with tumor antigens during intradermal administration of antitumor vaccines is significantly simpler than the applied cultivation of dendritic cells and monocytes/macrophages of patients with tumor antigens "*in vitro*," mistakenly called "T-cell activations". Th0 sensitization occurs "*in vivo*" in immune structures after their contact with peptide copies of antigens delivered by antigen-presenting cells that process antigens, and not in direct contact with Th0 antigens; only after this, the resulting Th1 cells form tissue-specific receptors in cytotoxic T-cells [1, 2].

Elimination of malignant cells, including through antitumor immunotherapy, is insufficient, since it does not eliminate the causes that initially led to malignant growth. Malignant transformation of cells in people older than 35-40 years is caused by compensatory reactions of the macroorganism aimed at increasing mitogenic stimulation in response to age-related disorders of tissue renewal and hormonal imbalance. Replacement of dead old cells with a smaller number of progenitor cells leads to compensatory autocrine and paracrine stimulation of cell division by cellular growth factors to complete tissue regeneration. A decrease in the pool of pluripotent stem cells in people over 35 years of age at an intensity of 1% per year and the constantly progressing violation of regeneration leads to an increase in compensatory mitogenic stimulation in all tissues with age, condemning people to the development of malignant tumor diseases [3, 4, 5, 6]. Similarly, a decrease in testosterone production in men over 35 years of age, occurring at an intensity of 1% per year (due to a violation of testicular tissue renewal/regeneration), accompanied by a violation of the physiological impulse mode of testosterone increment, disrupts the division and differentiation of testosterone-dependent cells, including prostate cells. In response to a decrease in testosterone production, and in addition to impaired regeneration, compensatory and adaptive responses are also developed to increase mitogenic stimulation: this increases the formation of cellular growth factors (bFGF and others) and endocrine factors (dihydrotestosterone, estradiol, insulin, STH and others) that stimulate cell division. These changes lead to the development of benign hyperplasia and prostate cancer [29, 30, 42]. Model of the changes happening at age decrease in production of testosterone at men is the androgenic blockade appointed to patients with a prostate cancer [29, 30, 42].

During differentiation, low-grade basal androgen-independent cells of the prostate epithelium become differentiated by the main androgen-dependent secretory cells. In patients with an androgen blockade, low-differentiated androgen-independent prostate cancer cells and normal low-differentiated androgen-independent prostate epithelial cells cannot continue to develop into differentiated androgen-dependent cells. Despite the atrophy of highly differentiated cells of the primary prostate cancer, the androgen blockade, which aggravates the effects of the age-related decrease in testosterone production, which increases mitogenic stimulation, leads to the progression of low-differentiated androgen-independent prostate cells (with tumor heterogeneity), as well as to the development of a new tumor from normal low-differentiated androgen-independent epithelial cells. Thus, hormone-resistant, androgen-independent prostate cancer is induced by an androgen blockade [29, 42]. Adequate hormone replacement therapy with individual selection of the dose of testosterone in accordance with its decrease with age (while maintaining the production of testosterone in a physiological pulse mode by Leydig cells) allows reducing compensatorily increased levels of cellular growth factors, dihydrotestosterone, estradiol, insulin, somatotropic hormone and other mitogenic factors [29, 30, 39, 43], stimulating proliferation, including of the prostate epithelium. Accordingly, the administration of age-appropriate testosterone reduction testosterone replacement therapy between courses of androgen blockade and active surveillance in patients with prostate cancer can significantly improve the results of treatment, reducing the risk of developing hormone-resistant prostate cancer and the risk of disease progression [29, 39, 42].

Cell therapy and testosterone replacement therapy can be used for the prevention of tumors, including prostate tumors in men over 35 years of age, and for rehabilitation after antitumor therapy. In women, the methodology of treatment and prevention of hormone-dependent tumors of the uterus and mammary glands is similar to those in men, differing from them in the mirror nature of the treatment methods used [38]. Thus, in order to reduce the risk of cancer progression, metastasis, and recurrence, the elimination of malignant cells must be supplemented by restoring the pool of pluripotent stem cells and regeneration, as well as correcting the hormonal imbalance that develops with age [3, 4, 5, 29, 30] (including adequate compensation for the lack of sex hormones in people over 35 years of age – by testosterone in men, and by tibolone in women [38, 39]).

Cell differentiation is accompanied by gene ranking – the removal of non-coding sections of DNA that form facultative heterochromatin (which, under certain conditions, can again become euchromatin with transcriptionally active DNA) [1]. In contrast to the differentiation process, which is accompanied by changes in the genome when ranking genes, the response of cells to individual extracellular signals (cytokines, hormones, and others) is accompanied by functional changes. Transcription factors (hormone receptors and others), after interacting with ligands via the DNA-binding domain, bind to their corresponding DNA regions, initiating or suppressing the expression of the corresponding genes [14]. Proteins of transcription factors, establishing non-covalent connections with their corresponding multiple (“mosaic”) sections of DNA (binding sites), which together form genes responsible for the manifestation of certain features or functions, form the tertiary structure of DNA (which changes with subsequent interactions with other transcription factors). Due to the constantly changing tertiary structure of DNA, transcription factors are able to bind to any distant “mosaic” sections of DNA that together represent a gene or genes. This is the biological meaning of the formation of the tertiary structure of DNA.

Under prolonged action of compensatory reactions (for example, with increased mitogenic stimulation in response to age-related disorders of tissue renewal / regeneration), functional changes due to the binding of transcription factors to the corresponding DNA regions are supplemented by difficult-to-reverse genetic changes similar to changes occurring during cell differentiation (when ranking genes). After that, the action of the formed compensatory reactions does not stop when the causes that caused them are eliminated [6]. For example, restoring the pool of pluripotent stem cells and regeneration is not capable of restoring the normal functioning of the cell growth factor receptors of malignant cells (which remain permanently activated regardless of their connection with ligands [6, 36]).

Due to difficult-to-reverse genetic changes, malignant cells must be destroyed. The causes of increased mitogenic stimulation must be eliminated to prevent malignant transformation of the remaining normal cells. Restoration of regeneration and correction of hormonal imbalance can normalize or reduce excessive mitogenic stimulation by cell growth factors and endocrine stimulators of cell division (insulin, growth hormone, and other hormones), leading to the formation of a primary tumor, its metastasis, and relapse [3, 4, 5, 29, 30].

Inactivation of antigen-presenting cells (macrophages/monocytes/osteoclasts, dendritic cells) is not an optimal way to prevent metastasis. Blocking their representation to Th0 tissue-specific antigens of dead old cells can prevent their (Th0) differentiation into Th1b, which form tissue-specific receptors in stem cells and tumor cells (which compensate for the decrease in the number of pluripotent stem cell pool) for their directed migration to the corresponding tissues. In contrast to stem cells that provide tissue regeneration after damage or the death of old cells, tumor cells, migrating to the tissues to whose antigens they have tissue-specific receptors formed by Th1b, form metastases [3, 4, 5]. Inactivation of antigen-presenting cells in addition to an age-related decrease in the pool of pluripotent stem cells leads to an even greater disruption of tissue renewal (regeneration), causing the response of compensatory autocrine and paracrine formation of cell growth factors (promoter factors of carcinogenesis that stimulate cell division), and, accordingly, the progression of tumor growth and an increased risk of their metastasis (due to increasing instability of cells in their tissues [36]). Moreover, blocking the pathway for presenting to Th0 of tumor antigens disrupts the formation of the antitumor immune response.

Compensating for the insufficiency of the pluripotent stem cell pool that develops with age, tumor cells acquire the properties of stem cells and repeat their migration path (similar to the path of lymphocyte recirculation [1]), compensating for incomplete tissue regeneration after the death of old cells. Like lymphocytes and stem cells, tumor cells from organs migrate to the lymphatic channel, then to the bloodstream, and from there back to the lymphatic channel or other organs, forming metastases [3, 4, 5, 6]. The intensity of such recirculation can be judged by the 1-2-fold repetition of this migration of "naive" lymphocytes per day from the organs to the lymphatic channel, to the bloodstream and back [1]. Given the potential micro-metastasis of malignant tumors in any of the existing lymph nodes, performing traumatic extended removal of lymph nodes together with radical surgical removal of tumors that do not have convincing data of tumor damage, is ineffective. To eliminate tumor cells that form micro-metastases in the lymph nodes, it's necessary to conduct anti-tumor immunotherapy and/or chemotherapy, and for hormone-sensitive tumors, to conduct a hormonal blockade (androgen blockade/ADT in prostate cancer).

Reducing the risk of metastasis of malignant tumors can help reduce increased mitogenic stimulation by restoring regeneration and correcting hormonal imbalances [3, 4, 5, 29, 30]. This will result in a decrease in the severity of immune system reactions that lead to multiple deaths of actively dividing and old cells (whose antigens, through antigen-presenting cells, direct the migration of not only stem cells, but also tumor cells to the sites of their death with the formation of metastases).

Changing the antigens of viral proteins (atigenic shift or drift) protects viruses from the resulting antibodies, and is one of the reasons for their persistence in the host (for example, human immunodeficiency virus), and also complicates the creation of vaccines against them. Humoral immunity to such viral infections persists only until a new serovariant of the virus appears [2]. To overcome the antigenic variability of viruses, it seems promising to create vaccines that initiate the formation not only humoral immunity, but also cellular immunity. Such vaccines can be prepared from fragments of the cell walls, cytoskeleton and nucleuses of one's own cells or foreign cells infected "*in vivo*" or cultured "*in vitro*" with these viruses, and then destroyed, for example, osmotically in a hypotonic solution or by other means, which have been decontaminated while preserving their antigenic properties. Intradermal administration of such vaccines will produce sensitized Th1/Th2, and then cytotoxic T-cells/B-cells that have tissues-specific/nucleic-specific receptors for altered auto-antigens of virus-affected cells (permanent as opposed to changing surface antigens of viruses). When

infected with the measles virus, cytotoxic T-cells are formed in the body that recognize and lyse virus-infected cells that express MHC class II molecules (Th, monocytes/macrophages, and dendritic cells with virus-modified peptide copies of MHC class I antigens) [2]. These cells were not exactly correctly called $CD4^+$ cytotoxic T-cells, since they are not Th ($CD4^+$), but rather cytotoxic T-cells ($CD8^+$), sensitized to modified measles virus peptide copies of Th class I MHC antigens and other cells expressing class II MHC molecules. Accordingly, cytotoxic T-cells can be formed that recognize and lyse Th, monocytes/macrophages, and dendritic cells infected with the human immunodeficiency virus and which express modified peptide copies of MHC class I antigens. A vaccine for creating acquired cellular and humoral immunity against the human immunodeficiency virus can be prepared from fragments of the cell walls, cytoskeleton and nucleuses of one's own cells or foreign cells of the mononuclear fraction of peripheral blood that have been obtained on a separator from HIV patients or cultured with the human immunodeficiency virus types 1 and 2 and decontaminated. The vaccine must be administered intradermally to absorb and process its antigens by antigen-presenting cells (monocytes/macrophages and dendritic cells) along with adjuvant (a bacterial: pyrogenal, prodigiosan, and others or antigens of foreign cells that have been cultured with the HIV). This vaccine can be used both for the prevention of infection with the human immunodeficiency virus, and for the treatment of patients infected with HIV during the latent period and with the development of acquired immunodeficiency syndrome (AIDS). In AIDS, it is advisable to use the vaccine against a background of minimal viral load, and, accordingly, with minimal infection of monocytes/macrophages and lymphocytes (after a course of antiretroviral therapy). The reason for the lack of formation of acquired cellular immunity in HIV patients with the death of human immunodeficiency virus-infected Th and monocytes/macrophages is probably the insufficient number of tissue-specific antigens modified by the virus per unit volume of blood (since sensitization depends on the concentration of the antigen per unit area/volume [2]), as well as the virus damage to monocytes/macrophages and lymphocytes.

Conclusion

The elimination of microbial antigens together with their carriers that caused an excessive macrophage reaction in patients with psoriasis, psoriatic arthritis and ankylosing spondylitis, as well as desensitization, open up new opportunities in the treatment of psoriasis, psoriatic arthritis, ankylosing spondylitis and pathogenetically similar autoimmune diseases. A reduction in the death of one's own cells, caused by the response of the immune system to increased mitogenic activity in people older than 35-40 years of age, reduces the intensity of nucleic acid catabolism and the resulting production of cytokines that cause gout. Providing recognition of tissue-specific and nuclear antigens of tumor cells by antigen-presenting cells can lead to the formation of an antitumor immune response. In the future preparation and use of antitumor autovaccines from the tissues of removed tumors, as well as the elimination of the causes (disorders of regeneration and hormonal imbalance) that led to the development of malignant tumors in people older than 35-40 years, should be made the gold standard for the treatment of malignant tumors, complementing the accepted protocols for their treatment.

Ethical Compliance

The authors have stated all possible conflicts of interest within this work. The authors have stated all sources of funding for this work. If this work involved human participants, informed consent was received from each individual. If this work involved human participants, 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' research ethics guidelines.

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