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ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

Медицинские новости Грузии

საქართველოს სამედიცინო სიახლენი

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გამოიცემა თბილისის სახელმწიფო სამედიცინო უნივერსიტეტთან
თანამშრომლობითა და მისი პატრონაჟით

ЕЖЕМЕСЯЧНЫЙ НАУЧНЫЙ ЖУРНАЛ

ТБИЛИСИ - НЬЮ-ЙОРК

GMN: Georgian Medical News is peer-reviewed, published monthly journal committed to promoting the science and art of medicine and the betterment of public health, published by the GMN Editorial Board and The International Academy of Sciences, Education, Industry and Arts (U.S.A.) since 1994. **GMN** carries original scientific articles on medicine, biology and pharmacy, which are of experimental, theoretical and practical character; publishes original research, reviews, commentaries, editorials, essays, medical news, and correspondence in English and Russian.

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GMN: Медицинские новости Грузии - ежемесячный рецензируемый научный журнал, издаётся Редакционной коллегией и Международной академией наук, образования, искусств и естествознания (IASEIA) США с 1994 года на русском и английском языках в целях поддержки медицинской науки и улучшения здравоохранения. В журнале публикуются оригинальные научные статьи в области медицины, биологии и фармации, статьи обзорного характера, научные сообщения, новости медицины и здравоохранения.

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GMN: Georgian Medical News – საქართველოს სამედიცინო სიახლენი – არის ყოველთვიური სამეცნიერო სამედიცინო რეცენზირებადი ჟურნალი, გამოიცემა 1994 წლიდან, წარმოადგენს სარედაქციო კოლეგიისა და აშშ-ის მეცნიერების, განათლების, ინდუსტრიის, ხელოვნებისა და ბუნებისმეტყველების საერთაშორისო აკადემიის ერთობლივ გამოცემას. GMN-ში რუსულ და ინგლისურ ენებზე ქვეყნდება ექსპერიმენტული, თეორიული და პრაქტიკული ხასიათის ორიგინალური სამეცნიერო სტატიები მედიცინის, ბიოლოგიისა და ფარმაციის სფეროში, მიმოხილვითი ხასიათის სტატიები.

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При представлении в печать научных экспериментальных работ авторы должны указывать вид и количество экспериментальных животных, применявшиеся методы обезболивания и усыпления (в ходе острых опытов).

4. К статье должны быть приложены краткое (на полстраницы) резюме на английском, русском и грузинском языках (включающее следующие разделы: цель исследования, материал и методы, результаты и заключение) и список ключевых слов (key words).

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2. Size of the article, including index and resume in English, Russian and Georgian languages must be at least 10 pages and not exceed the limit of 20 pages of typed or computer-printed text.

3. Submitted material must include a coverage of a topical subject, research methods, results, and review.

Authors of the scientific-research works must indicate the number of experimental biological species drawn in, list the employed methods of anesthetization and soporific means used during acute tests.

4. Articles must have a short (half page) abstract in English, Russian and Georgian (including the following sections: aim of study, material and methods, results and conclusions) and a list of key words.

5. Tables must be presented in an original typed or computer-printed form, instead of a photocopied version. **Numbers, totals, percentile data on the tables must coincide with those in the texts of the articles.** Tables and graphs must be headed.

6. Photographs are required to be contrasted and must be submitted with doubles. Please number each photograph with a pencil on its back, indicate author's name, title of the article (short version), and mark out its top and bottom parts. Drawings must be accurate, drafts and diagrams drawn in Indian ink (or black ink). Photocopies of the X-ray photographs must be presented in a positive image in **tiff format**.

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7. Please indicate last names, first and middle initials of the native authors, present names and initials of the foreign authors in the transcription of the original language, enclose in parenthesis corresponding number under which the author is listed in the reference materials.

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ავტორთა საყურადღებოდ!

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2. სტატიის მოცულობა არ უნდა შეადგენდეს 10 გვერდზე ნაკლებს და 20 გვერდზე მეტს ლიტერატურის სიის და რეზიუმეების (ინგლისურ, რუსულ და ქართულ ენებზე) ჩათვლით.

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6. ფოტოსურათები უნდა იყოს კონტრასტული; სურათები, ნახაზები, დიაგრამები - დასათაურებული, დანომრილი და სათანადო ადგილას ჩასმული. რენტგენოგრამების ფოტოასლები წარმოადგინეთ პოზიტიური გამოსახულებით **tiff** ფორმატში. მიკროფოტოსურათების წარწერებში საჭიროა მიუთითოთ ოკულარის ან ობიექტივის საშუალებით გადიდების ხარისხი, ანათალების შეღებვის ან იმპრეგნაციის მეთოდი და აღნიშნოთ სურათის ზედა და ქვედა ნაწილები.

7. სამამულო ავტორების გვარები სტატიაში აღინიშნება ინიციალების თანდართვით, უცხოურისა – უცხოური ტრანსკრიპციით.

8. სტატიას თან უნდა ახლდეს ავტორის მიერ გამოყენებული სამამულო და უცხოური შრომების ბიბლიოგრაფიული სია (ბოლო 5-8 წლის სიღრმით). ანბანური წყობით წარმოდგენილ ბიბლიოგრაფიულ სიაში მიუთითეთ ჯერ სამამულო, შემდეგ უცხოელი ავტორები (გვარი, ინიციალები, სტატიის სათაური, ჟურნალის დასახელება, გამოცემის ადგილი, წელი, ჟურნალის №, პირველი და ბოლო გვერდები). მონოგრაფიის შემთხვევაში მიუთითეთ გამოცემის წელი, ადგილი და გვერდების საერთო რაოდენობა. ტექსტში კვადრატულ ფჩხილებში უნდა მიუთითოთ ავტორის შესაბამისი N ლიტერატურის სიის მიხედვით. მიზანშეწონილია, რომ ციტირებული წყაროების უმეტესი ნაწილი იყოს 5-6 წლის სიღრმის.

9. სტატიას თან უნდა ახლდეს: ა) დაწესებულების ან სამეცნიერო ხელმძღვანელის წარდგინება, დამოწმებული ხელმოწერითა და ბეჭდით; ბ) დარგის სპეციალისტის დამოწმებული რეცენზია, რომელშიც მითითებული იქნება საკითხის აქტუალობა, მასალის საკმაობა, მეთოდის სანდოობა, შედეგების სამეცნიერო-პრაქტიკული მნიშვნელობა.

10. სტატიის ბოლოს საჭიროა ყველა ავტორის ხელმოწერა, რომელთა რაოდენობა არ უნდა აღემატებოდეს 5-ს.

11. რედაქცია იტოვებს უფლებას შეასწოროს სტატია. ტექსტზე მუშაობა და შეჯერება ხდება საავტორო ორიგინალის მიხედვით.

12. დაუშვებელია რედაქციაში ისეთი სტატიის წარდგენა, რომელიც დასაბეჭდად წარდგენილი იყო სხვა რედაქციაში ან გამოქვეყნებული იყო სხვა გამოცემებში.

აღნიშნული წესების დარღვევის შემთხვევაში სტატიები არ განიხილება.

Содержание:

ANALYSIS OF IMMUNE CHANGES AND THEIR ROLE IN THE DEVELOPMENT OF ORAL AND OROPHARYNGEAL CANCER

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Cancer of the oral cavity and oropharynx is an immunosuppressive disorder. In its etiopathogenesis there is a fundamental insufficiency of immune surveillance, that is, the ability to recognize tumor cells as abnormal and destroy them before they build an obvious malignant tumor [15]. Due to the suppression of the immune system, tumor cells avoid recognition and lysis of tumor antigen (TA) by cytotoxic T-lymphocytes (CTL) of adaptive immunity [17]. In such patients there is a decrease in the absolute number of lymphocytes, disturbance of natural killer cellular activity (NK) [13], spontaneous apoptosis of cytotoxic T-lymphocytes [13], unsatisfactory antigen-presenting function [14].

Tumor cells can initiate and develop various mechanisms to avoid the body's immune response. Typically, this is one of the following mechanisms [10, 23]:

1. A resistance formation to apoptosis with variable expression of Fas-ligand (FasL), which leads to the death of tumor-infiltrating lymphocytes (TILs).
2. Producing of immunosuppressive molecules such as the transforming growth factor TGF-β, prostaglandin (PG) E2 and adenosine.
3. Loss of expression of co-stimulating molecules or cytokines, such as IL-6 and IL-10 interleukin.
4. A defect in the expression of antigens on the surface of the tumor cell, because antigens remain unidentified.
5. A reduction or loss of the molecule expression of the main complex of histocompatibility (MHC) class I and selective loss of human leukocyte antigen (HLA) and histocompatibility molecules (MHC) required for the interaction between TA and TA-specific CTLs, especially if there is low IFN-α regulation [14].

The violation of processes or insufficient recognition and TA processing is performed in tumor cells and in dendritic cells. An important role in these processes is played by the protein of the STAT family (signal transducer and activator of transcription). Reducing the amount of activated STAT1 contributes to lowering the expression of human leukocyte antigen (HLA) and MHF [16]. HLA are the proteins of the molecules of histocompatibility (MHC), which appear with antigen and are recognized by T-lymphocytes. Antigen-presenting molecules (antigenic peptide transporters – TAP1, TAP2; proteins – calnexin, calreticulin, ERp57 and tapasin) play an important role in the ability of MHC Class I molecules to migrate to the cell surface and to represent peptides of CD8+ T-lymphocytes, that is, to carry out the presentation of antigen [6, 13]. Reducing the regulation or loss of the expression of HLA molecules I class or other components, representing an antigen is one of the mechanisms for avoiding the immune response of the tumor. Lowering the MHC level class I is due to ganglioside, which is produced by cancer cells. So that, the tumor uses various mechanisms to induce changes in the system and to avoid an immune response to its development [25].

The role of dendritic cells in the development of oral and oropharyngeal cancer.

Dendritic cells (DC) that are the guards of the immune system are specialized, the strongest antigen-presenting cells (ARCs) and tolerant mediators [18, 20]. It is known that dendritic cells are divided into myeloid (MDC) and plasmacytoid (PDC). The first ones are the Langerhans cells contained in the epidermis and the mucous membrane of the upper digestive organs and breathing and thermal/interstitial MDCs that are in the dermis. Plasmacytoid DC of lymphoid origin are found in the blood and lymphoid organs.

DC mature in the presence of microbial products and inflammatory mediators such as TNF-a, IL-1 and IL-12. Mature DCs increase the regulation of other co-stimulating molecules - CD86, CD80 and CD40, as well as cytokines such as TNF a, IL-1 and IL-12. Subsequently, they pass through the bloodstream towards the lymph nodes and represent antigens, which they captured in peripheral tissues, T-lymphocytes [20], stimulating their differentiation into cytotoxic CD8 + cells capable of killing tumor cells [13].

MDC force tumor cells in the oral cavity and oropharynx to secrete immunosuppressive cytokines such as IL-1 and IL-10 [10]. IL-10 and TGF-β transform immature DCs in mature ones and at the same time tolerant to the antigen, which induces antigen-specific T cells, by activating Tregs and differentiating naïve CD4+ T-cells in Tregs.

Langerhans cells bind antigens to the flat epithelium and migrate back to the regional lymph nodes and/or other secondary lymphoid organs where they stimulate naïve T-lymphocytes. They can also represent antigens of T-lymphocytes memory to stimulate a secondary immune response [13]. A significant role of dendritic cells, in particular, Langerhans cells in the immune response to the development of oral cancer and oropharyngeal cancer, is confirmed in studies.

Increased concentration them in blood correlates with a positive prognosis and a greater survival of patients with oral and oropharyngeal cancer, and a decrease in metastasis in the cervix of the lymph nodes [13].

Cancer cells of the oral cavity and oropharynx with the help of tumor-associated fibroblasts stimulate the development of hepatocyte growth factor (HGF) [15], which inhibits the maturation of dendritic cells [19] and, relatively, the reduction of immune responses. Violations of monocyte chemotaxis and the ability of DC to form a cell cluster also reduce the protective response of the organism [25].

The role of cytokines in the development of oral and oropharyngeal cancer.

Different cells of the immune system provide a complex defense system with effective cytokine bindings. Cytokines are interleukins, interferons, tumor necrosis factor, growth factors and chemokines regulate cellular growth, proliferation, migration, signaling, both in tumor cells and in immune cells. In addition, the inflammatory component of the micro-environment of the tumor in the oral cavity and oropharynx is important in the immune surveillance and a response as its main component is cytokines. The micro cavity of the tumor of the oral cavity and the oropharynx is characterized by an unbalanced cytokine profile, which is dominated by immunosuppressive cytokines. It is also important to consider that the tumor cells of the oral cavity and the oropharynx independently produce anti-inflam-

matory cytokines that correlate with the survival of such patients [2]. Cytokines particularly cause an increase in the transmission signal and the activator of transcription of phosphorylation and phosphorylated extracellular signal-regulated kinase in patients with oral and oropharyngeal cancer [13].

Due to the secretion of chemokines and colony-stimulating factor (CSF)-1, cancer cells accumulate tumor-associated macrophages (TAMs) in their microenvironment, which create a favorable environment for developing of the tumor and avoiding the immune response by secreting TGF-β1, interleukin-6 (IL-6) and prostaglandin-E2 among other immunosuppressive cytokines [25].

According to several studies, patients with oral and oropharyngeal cancer have an imbalance of Th1/Th2 types of cytokines and increased Tregs [8,18]. Among the Th1 types of cytokines, IFN-γ, IL-12, TNF-α, whose levels are reduced, and Th2 cytokines, IL-4, IL-10, are elevated, while in healthy people the opposite result is observed [6].

It is investigated that the level of synthesis of soluble IL-2 receptor activated by T-cell antagonism of IL-2 is higher in patients with oral and oropharyngeal cancer, which is associated with an increased probability of the metastasis development and low overall survival [25]. IL-4 levels have also been significantly elevated, however, they have not confirmed the association of their overexpression with the tumor stage [22].

Elevated levels of IL-10 in serum of patients with oral and oropharynx cancer are correlated with an unsatisfactory prognosis of the treatment and are independent indicators of low survival [8]. In addition, such inflammatory cytokines as IL-6, HGF and VEGF are also determined in high serum concentrations and correlate with the recurrence [1].

In diagnosed patients with oral and oropharyngeal cancer, an increase in the level of IL-18 was observed. This cytokine is mainly synthesized by macrophages. Its role for cancer-ill patients is to stimulate the production of IFN-γ by NK cells and T-cells, which provides the immune response of the body [25].

In the environment of cytokines there is a production violation of pro-proliferative, immunosuppressive cytokines with the help of macrophage-associated tumors (TAM), unbalanced Hepatocyte Growth Factor (HGF) by fibroblast-associated tumor (TAF) as well as unbalanced STAT1/STAT3 signaling within tumor cells. The deficiency of tumor STAT1 signaling results in low production of chemokines CCL5 and CXCL10, and those chemokines that involve effector T-cells in the microenvironment of the tumor [16]. Excessive signaling pSTAT3 increases the production of cytokines that negatively regulate proinflammatory signals of danger, mature dendritic cells and cytolysis with natural killers and CTLs, and more specifically IL-6, IL-10, TGF-β1 and VEGF [15,16]. Compared to the control group, in patients with oral and oropharyngeal cancer, a 5-fold increase in TNF-α cytokine in blood [3].

The Tumor microenvironment.

The favorable conditions for the cancer growth of the mouth and the oropharynx are the conditions of the tumor microenvironment, which contains immune and stromal cells.

Cytokines, chemokines, T-cells, macrophages, dendritic cells, and natural killer cells (NK) are intracellular regulators of the immune cells activation. All of them are important participants in the formation of the tumor microenvironment. Any of their functional changes or their inhibition, affects the immune system response. For example, when there is an imbalance in the signal exchange system through cytokines, then tumor cells develop mechanisms to avoid the inhibitors growth of cytokines presented in the microenvironment of the tumor [13].

An important key to the progression of cancer is the loss of cellular connections and cellular polarity, called epithelial-mesenchymal transition (EMT). There are the factors that influence the process of EMT. It is promoted by the hypoxic environment and changes in the expression of the miRNA, which leads to a decrease in the regulation of E-cadherins (membrane protein CDH) [11]. Endothelial cells that secrete Bcl-2, an apoptotic regulatory protein, increase EMT-related changes by secreting IL-6, an important mediator of the acute phase of response.

EMT process in a tumor acquires migratory and invasive properties. In general, these changes can increase the metastatic potential of oral cancer and oropharyngeal cancer [25].

A malignant tumor of the oral cavity or oropharynx directly suppresses the immune response by developing mediators such as vascular endothelial growth factor (VEGF), prostaglandin E2 (PGE2), TGFβ, IL-6, and IL-10 [13]. Tumor cells also release pro-inflammatory mediators, including such a receptor as the IL-15 alpha subunit (IL15RA). In combination with IL-15, it provides enhanced synthesis of pro-inflammatory cytokines – IL-6, TNF-α and IL-17, which affects the immune response and as a result a low survival prognosis [10].

The role of T-cells in the antitumor immune response.

Stem cells in the bone marrow are the source of immature T-lymphocytes, which mature then in the thymus and migrate to the secondary lymphoid organs (lymph nodes, a spleen) as a naïve T-cell. ARCs represent antigens, by activating T-lymphocytes, after signaling of co-stimulatory molecules and binding of MHF to ARCs and T-cell receptors (TSRs). They become effector cells (CD4+ helper T cells that promote the production of antibodies B-lymphocytes and phagocytosis, or CD8+ cytotoxic T cells that can lead to cell death) or memory cells [13]. Although an effective antitumor immune response involves a lot of components of the immune system, T-cells remain the most important cells that take part in the antitumour immunity [13]. Therefore, T-cell defects reduce the effectiveness of the antitumor immunity. These defects include: reducing of expression of CD3 – zeta chain (CD3z), key signaling molecule in TCR pathway [13], inability of T cells to destroy targets of tumor cells [14], a lack of IL-2 and / or IFN-γ [13], slowing down proliferative responses to mitogen or IL-2 [13], as well as the presence of pronounced apoptotic symptoms in a significant proportion of TIL (lymphocytes that infiltrate the tumor) [13].

A number of defects in TIL that are isolated from the tumor, have been identified in patients with oral cancer and oropharyngeal cancer. T-cell apoptosis was detected in a significant proportion of TIL [13], and was associated with Fas / FasL signaling [14]. The expression of FasL on the surface of tumor cells leads to an apoptotic signal in lymphocytes, causing a spontaneous loss of circulating Fas+ T-lymphocytes [8]. Other ways of TLI damage are associated with TNF-associated apoptotic-induced ligand (TRAIL), TNF-α antigen, FasL+, MHC Class I, and tumor derived membrane vesicles, all of which induce apoptosis in cells [8,13,25]

It is considered that the balance between subgroups of T-cells in cancer patients modulates antitumor immunity [9].

The effector cell of adaptive antitumor immunity is activated by CD8+ cytotoxic T-lymphocytes (CTLs). An activation of antigen-limited CD8+ cytotoxic T-lymphocyte initially requires binding of a T-cell receptor (TCR) to its corresponding TA in a complex with HLA-I. But this is not enough to activate cytotoxic T-lymphocytes and cytolysis of the tumor. The initial activation also depends on the balance of co-stimulating or co-inhibitory signals of dendritic cells and CD4+ T-helper

cells, as well as on avoiding CD4 suppression + regulatory T-cells (Treg). Cancer tumors induce anergy of T-cells in both peripheral and tumor-infiltrating lymphocytes (TILs). Functional defects in TIL affect the low productivity and response to IL-2 [5,13] and the susceptibility to spontaneous apoptosis mediated by the Fas / Fas-ligand by [8]. A low expression required for signaling TCR, co-stimulating molecules: CD3-ζ (part of the T-cell antigen receptor complex – TCR-CD3), OX40 (TNFRSF4 or CD134 – membrane protein, receptor from the superfamily receptor of the tumor necrosis factor of the ligand OX40L) and 4-1BB (CD137, TNFRSF9, a member of tumor necrosis factor superfamily 9) [18] and a high expression of co-inhibiting receptors – (CTLA-4) and a programmed protein cell death (PD-1) [4] cause changes in the regulation of immune responses. We should note that the PD-1, PD-L1 ligands are expressed in most tumor tissues of the oral cavity and oropharynx [9].

Cytotoxic T-lymphocytes are also inhibited by the disproportionate accumulation of Tregs (thymic regulatory T-lymphocytes) in the micro cavity of the oral cavity and oropharynx. Tregs promote signaling tolerance through an inhibitory CTLA-4 receptor [7]

CD4+ T-helper lymphocytes are the center of the antitumor response. CD4+ CD25+ T cells play a central role in initiating and maintaining antitumor immune response. Detecting of a large number of CD4 + CD25+ T- lymphocytes is associated with a good prognosis [17], although CD25+ is produced in small quantities by tumor cells. Also, the presence of CD4+ CD69+ T cells is associated with a good prognosis in patients with oral and oropharyngeal cancer [8].

The percentage of CD8+ T cells increased with the growth of the oral cavity and oropharynx, CD4+ T cells and Tregs in these patients are increased as well. The proportion of B-lymphocytes decreased in patients with local regional metastasis, while NK-cells decrease compared with the control group [6].

In patients with oral and oropharyngeal cancer, the following changes in the number of blood lymphocytes with markers of early and late activation were found: an increase in the percentage of CD25+ and the absolute number of CD 71+ lymphocytes, a slight increase in the number of CD16+ and a decrease in the relative number of cells ready for apoptosis-CD95+. Thus, the ratio of CD25 / CD95 and CD71 / CD95 cells is 2-2.5 times higher than in the control group, which indicates the predominance of positive lymphocyte activation processes in tumor development. It is also known that the percentage of CD3 is reduced, while CD8, CD22 increases without any changes in the absolute number of lymphocytes. This phenomenon is due to the migration and fixation of lymphocytes in the tumor [3].

Changes in the cellular composition of the immunity and effector line are observed in patients with cancer of the oral cavity and oropharynx. The number of activated T-cells with the CD45+ CD3+ HLA-DR phenotype is 2 times higher than in the control group, as well as the increased number of nonspecific effector cells with the CD45+ CD3+ CD5+, CD45+ CD8+ CD16+ phenotype.

Studying the immune status of patients with oral cancer and oropharyngeal cancer, a significant increase in the content of CD3+ T-cells with simultaneous expression of NK markers was found. The elevated blood levels of CD45+ CD3+ CD16+ CD56+ NK T-lymphocytes are determined 1.6 times, and CD45+ CD16+ NK cells are significantly elevated. Statistically significant increases in the overall level of CD45+ CD8+ lymphocytes with the expression of intracellular perforin (CD45+ CD8+ Perforin+) and NK cells with the CD45+ CD16+ Perforin+ phenotype, which is the evidence of increased activity of the effector immunity. Indicators of the latest increased due to the subpopulation of nonspecific effector cells with the phenotype CD45+ CD3- CD8+. And the number of CD45+ CD3+ CD4+ T-lymphocytes is reduced.

The study of CD45+ CD3- CD19+ B-lymphocytes in patients with oral cancer and oropharyngeal cancer are not revealed a statistical difference from the control group [3, 6].

In addition, tumor cells can avoid the recognition of T-lymphocytes by reducing the transporter associated with the heterodimer of antigen processing (TAP-1/2). This process is controlled by IFN-γ phosphorylated signals and transcription activators of the mediated signaling path (pSTAT1) [16].

Tregs and their role in the immune response in patients with oral and oropharyngeal cancer.

Tregs are tumorous regulatory T-lymphocytes, a subpopulation of suppressor T-cells that respond to the inflammation. They are involved in the construction of immune responses and according to research data that revealed an excessive expression of Tregs, they are inhibitors of antitumor immune responses [9], that is, they contribute to the evasion of tumor cells from the immune response and the progression of oral cancer and oropharyngeal cancer [8, 17]. Tregs also play a major role in maintaining the tolerance of T-cells to the antigens themselves [8]. The antitumor immune response is suppressed by Tregs subtype Tr1 in the microenvironment of the tumor.

Various factors can enhance the production of Tregs in the microenvironment of the tumor. An overexpression of cyclooxygenase 2 (COX-2) and PGE2 synthesis in patients with oral cancer and oropharyngeal cells induce the generation of Tregs type1 in the microenvironment of the tumor, which enhance its carcinogenicity and progression of the disease [6, 8]. Particularly important are Tregs type 1 cells with a phenotype other than CD4+ CD25 (high) FoxP3+ Tregs. Tr1 produces IL-10 and TGF-β1. They mediate IL-10-dependent immune oppression in cells by contact-independent method [8]. IL-10 itself induces Tregs [21].

Another factor influencing the production of Tregs is HMGB1-chemoattractant from a group of non-gistonal B1 proteins, the levels of which in serum are significantly elevated in patients with oral and oropharyngeal cancer. And a chemokine like CCL22 is an intermediary in the migration of Tregs to the tumor site. Its corresponding receptor, CCR4, is elevated in patients with oral and oropharyngeal cancer [17].

The enhanced Tregs tumor infiltration promotes the expression of HMGB1 recognition receptor toll-like receptor 4 (TLR4) [24]. Tregs produce a lot of TLRs, because they play an important role in identifying molecules that are different from host molecules. A high expression of these receptors - TLR4, TLR6, TLR9 and TLR10 - was detected in patients with oral and oropharyngeal. Linking TLR to Tregs increases their suppressive activity, which promotes tumor-mediated immune suppression [23]. It has been determined that Tregs suppressive function is significantly higher with HSP60 or lipopolysaccharides.

In several studies of patients after the resection of the oral cavity and oropharyngeal tumors, in which there was no progression or relapse over the years, an increased number of identified Tregs was detected and that was not associated with the tumor stage. This shows that an oncotherapy contributes to the growth and spread of Tregs [21].

The intranuclear regulatory factor – FoxP3 controls regulatory activity Tregs. Tumor cells synthesize it themselves, so it is an independent prognostic indicator of the squamous cell carcinoma of the tongue. Its expression is associated with the differentiation and stage of cancer and is inversely proportional to survival rates [13].

An increased number of Tregs in the lymph nodes has already been observed in the presence of a dysplastic state or early stage of oral and oropharyngeal cancer. And their increase is accompanied by the growth of different populations of immune cells that exhibit a positive antitumor response. These cells include conventional T-cells (Tconv) – CD4 T-lymphocytes, T-helper 1 (Th1) and CD8+ T lymphocyte [12]. The total number of lymphocytes in patients with oral and oropharyngeal cancer is lower and on this background there is a decrease in the proportion of CD4+ T cells, CD8+ T cells, CD3- CD56+ CD16+ NK cells and CD3+ CD56+ NKT cells. However, the proportion of CD4+ CD25+ FoxP3+ Tregs with suppressor functions is still increasing [6].

The role of NK-cells in antitumor immunity in patients with oral and oral cancer.

NK-cells are the major cells of innate immunity, large granular lymphocytes and play a decisive role in the antitumor activity. They are capable of recognizing and destroying transformed malignant cells without a specialized MHC-antigen presentation. In particular, they carry out antibody-dependent cell-mediated cytotoxicity (ADCC). Their varieties - CD1d-restricted NKT cells (iNKT) play an important role in the activation of immune effector cells. It has been established that in patients with oral and oral cancers their number is significantly reduced, respectively, the low control of iNKT tumor cells in the regional collector, which correlates with low survival rates of these patients [17]. Functioning of NK cells is important for the cytokine environment, since activated NK cells secrete immunostimulating cytokines IFN-γ and TNF-α, which have their antitumor function.

Among the lymphocyte populations there is an increase in the relative and absolute number of innate immune cells - NK cells. NK cells occupy a central place in antitumor immunity and control the growth of the tumor at all stages (including metastasis) [3]. However, in some other studies, depressed NK-cytotoxic function is observed. It is believed to be associated with a decrease in the expression of cytotoxic molecules such as perforin, granzyme B and FasL in mononuclear cells of peripheral blood of these patients [6].

Tumor cells of the oral cavity and oropharynx produce a large amount of TGF-β1 that reduces the expression of NK-cell receptors (NKG2D is the primary cytotoxicity receptor), and CD16 (or Fcγ-receptor (Fcγ-R) III), suppressing the biological functions of NK cells [13]. The Fcγ receptor (Fcγ-R) III is a mediator of antibody-dependent cell-mediated cytotoxicity (ADCC).

Influence of macrophages on the development of oral and oropharyngeal cancer.

Macrophages are involved in both natural and acquired reactions of the immune system. These include induction of immunity, antigen presentation, cell cytotoxicity, tissue remodeling, inflammation regulation, thrombosis and endocytosis [10,13,25]. It has been established that macrophages contribute to the neovascularization, which is a compulsory requirement for the growth and spread of the tumor, that is, they have swollen functions. It has been shown that VEGF, a specific endothelial cell growth factor, is secreted by macrophages in patients with different carcinomas [13]. Thus, in patients with oral and oropharyngeal cancers, it has been proved that an increase in the number of tumor associated macrophages (TAMs) is a sign of tumor invasion, a greater intramatural density of micro vessels in the tumor and expression of VEGF [15] in patients with oral and oropharyngeal cancer, as well as more rapid tumor progression [13].TABs have been identified in fibrin deposition areas, indicating that they play an important role in stabilizing intramatural fibrin, as well as in promoting tumor matrix generation [11]. Tumor cells of the oral cavity and oropharynx can involve macrophages through secretion of monocytic chemotactic protein-1 (MCP-1) and TGF-β1. Then the macrophages secrete VEGF and IL-8, TNF-α and IL-1, which stimulate the release of tumor cells more than VEGF and IL-8 [13].

An interaction of systemic and local immunity in patients with oral and oropharyngeal cancer.

The interaction of systemic and mucosal immunities is important in protecting the mucous membrane from the action of the nonplastic process. There is a decrease in the total number of segmental neutrophils, monocytes, platelets in the blood of patients with oral and oropharyngeal cancer. Apoptosis indicators of lymphocytes are significantly lowered, which is considered a sign of the immune response to the tumor development, aimed at preserving and increasing the total number of lymphocytes [13].

Lactoferrin is involved in the antitumor protection of patients with oral and oropharynx cancer, but its amount in the peripheral blood does not change, which is the result of a decrease in the circulation of the producing cells of this protein (segmental proteins) [3].

The immunodeficiency of patients with oral and oropharyngeal cancer is shown by elevated indicators of circulating immune complexes (CICs). Also, it was retrospectively found that in patients with a favorable prognosis of the treatment is 2 times lower compared with patients who subsequently had a relapse [3].

In the medical literature there is an evidence that epithelial cells of the tumor of the oral cavity and the oropharynx are capable of producing nitric oxide and its derivatives. Analyzing the nitroxydergic regulatory system of blood in these patients, there was detected an increase in the index of end metabolites of NO - NO3 in 1.4 times. It somewhat affects the IFN-γ and antibodies to it, however, the way of its affecting is still being investigated.

Changes in TNF-α and IFN-γ on the salivatory level are also not detected, but the antibody level decreases to IFF-α in several times the, which has a negative effect on the local antitumor protection [3].

When comparing the state of systemic and mucosal immunity in patients with oral and oropharyngeal cancer before and after chemoradiotherapy, it has been found that after the treatment there is an enhanced synthesis of such cytokines as TNF-α in blood, TNF-α and INF-γ in saliva, and an excessive synthesis of terminal stable metabolites NO. The chemoradiotherapy has a negative effect on the systemic immunity. It causes the development of leukopenia, lymphopenia, a decrease in the number of major populations of lymphocytes - NK, CD3, CD4, CD8, CD22, and the number of cells with positive activation markers – CD25+, CD71+, HLA-DR+ [3].

Mucosal (local) immunity of patients with oral and oropharyngeal cancer.

An increase in the indicator of the state of innate immunity - mucin - is shown in the saliva, because it is further synthesized directly by epithelial malignant cells. Mucin has an immunosuppressive effect, that is, it promotes the anergy of T-lymphocytes, the induction of tolerance of cytotoxic lymphocytes, it also helps the antigen to avoid the immune response and reduces the synthesis of some cytokines [3].

An increased activity of the end component of complement C5 in saliva is determined due to the absence of its fixation in the membrane-attacking complex in the target cells, which is a cancerous cell. This can affect the formation of the immune response, the processes of the migration of macrophages and leukocytes at the site of development of the tumor.

In patients with oral and oropharynx due to the fixation of some subclasses of immunoglobulins on the surface of the tu-

mor, as well as a decrease in their synthesis by mucosal-associated lymphoid tissue in saliva, the reduction of the subclass of IgG4 is shown without altering the general population [3].

sIgA is an indicator of a local immunological response. IgA is synthesized locally by plasmatic cells in the interstitial tissue between the acinus of the salivary glands and in the subepithelial layer of the mucous membrane of the mouth. Then the IgA molecule forms a complex with a secretory component in the glandular epithelium – sIgA. In healthy people, the concentration of sIgA in saliva is 0.03-0.26 g/l. These numbers are lower in chronic smokers – 0,01-0,05 g/l, and in patients with carcinoma of the oral cavity and oropharynx, it is reduced by 45% [13].

Other salivary components of patients with oral cancer and oropharyngeal were evaluated: Amylase is 25% lower, IgG is 125%, albumin is higher than 108%, lactate dehydrogenase – 88%, insulin growth factor – 117%. Also, MMP-2 and MMP-9 are higher respectively by 75% and 35%. The indicator of the epidermal growth factor remains unchanged. There are also some changes in the electrolyte balance of saliva: K rates decrease by 155, Na – by 14%, Ca by 59%, P by 39%, Mg by 28%.

The mucous membrane of the oral cavity and oropharynx by enzymatic cleavage of the damaging agent, phagocytic reaction, the synthesis of antimicrobial substances fulfills its barrier function and provides natural immunity. APK (macrophages, dendritic cells, intergranular cells), some subpopulations of T lymphocytes, and polymorph nuclear neutrophils are cellular elements of nonspecific oral and oral defense that are responsible for the condition of local immunity. A study of functional activity of cells of granulocyte-macrophage (non-specific) links of immunity of patients with oral and oropharyngeal cancer was conducted. The bactericidal and fungicidal function of monocytes are significantly lowered. The relative number of polymorph nuclear leukocytes with phagocytic activity is lower compared with healthy ones, and the number of phagocytic monocytes does not change [3].

Conclusions.

1. There is an imbalance in the immune system in patients with oral and oropharyngeal cancer, but more specifically its role in initiating and progressing cancer of the oral cavity and oropharynx is only now, after a modern research becomes more understandable.
2. Mutated, atypical cells are eliminated by the immune system rather than they form a tumor as it is immune control, and the violation in it contributes to the immune avoidance of atypical cells, which can lead to cancer.
3. Tumor cells use the immune system in several ways to stimulate angiogenesis, proliferative signals and, in general, tumor progression. It can mask itself from the immune system by self-modification and immunosuppression of the patient's body.
4. Tumor synthesizes: cytokines, (TGF-β), interleukins (IL-6, IL-10), inflammatory factors of transcription (NF-kB), STAT3, suppressing cellular antitumor immunity.
5. A deep understanding of antitumor immune effects in cancer patients and their associated mechanisms for avoiding an immune response by a tumor cell prompts the search and usage of more targeted cancer therapy - immunotherapy in combination with standard methods.

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SUMMARY

ANALYSIS OF IMMUNE CHANGES AND THEIR ROLE IN THE DEVELOPMENT OF ORAL AND OROPHARYNGEAL CANCER

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Numerous studies of the immune system in cancer patients at the cellular and molecular levels indicate a persistent violation of natural and acquired mechanisms of immune defense.

This article reveals changes in the immune system of patients with cancer of the oral cavity and oropharynx. It was determined that the levels of cytokines IL-6, IL-10, HGF and VEGF in high concentrations in the serum of patients correlate with an unsatisfactory prognosis and are independent indicators of low survival and correlate with relapse. Different immune cells provide a complex defense system with effective communication through cytokines. The inflammatory component of the microenvironment of the tumor of the oral cavity and oropharynx is important in the immune response, because its main component is immunosuppressive cytokines. There is an imbalance of Th1 / Th2 cytokine types and increased levels of Tregs. Among Th1 types of cytokines - IFN-γ, IL-12, TNF-α, the levels of which are reduced, and Th2-cytokines - IL-4, IL-10 - are increased, while the norm is the opposite.

The tumor uses various mechanisms to induce changes in the system to avoid an immune response to its development. In fact, a malignant cell of the mouth or oropharynx suppresses the immune response by producing vascular endothelial growth factor (VEGF), prostaglandin E2 (PGE2), TGFβ, IL-6 and IL-10. The tumor environment also releases pro-inflammatory mediators, including a receptor such as IL-15 alpha subunit (IL15RA). It in combination with IL-15 carries out the strengthened synthesis of proinflammatory cytokines - IL-6, TNF-α and IL-17 that influences insufficiency of the immune response and accordingly low prognosis of survival.

It was found that the number of NK cells is reduced in patients with oral and oropharyngeal cancer, respectively, there is a low control of iNKT tumor cells in the regional collector, which correlates with low survival rates.

Increased concentration of dendritic cells in the blood correlates with a positive prognosis and greater survival of patients with cancer of the oral cavity and oropharynx, reduced metastasis to the cervical lymph nodes.

An effective antitumor immune response involves many components of the immune system, but T-cells remain the most important cells involved in antitumor immunity. Therefore, T-cell defects reduce the effectiveness of antitumor immunity. CD4 + CD25 + T-cells play a central role in initiating and maintaining the antitumor immune response. Detection of them and CD4 + CD69 +, CD3 + T cells in large numbers is associated with a good prognosis. More detailed changes in the cellular composition of immunity and the effector link are presented in the article.

Keywords: cancer, oral cavity, oropharynx, antitumor immunity.

РЕЗЮМЕ

АНАЛИЗ ИММУНОЛОГИЧЕСКИХ ИЗМЕНЕНИЙ И ИХ РОЛЬ В РАЗВИТИИ РАКА ПОЛОСТИ РТА И РОТОГЛОТКИ (ОБЗОР)

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Многочисленные исследования состояния иммунной системы у онкостоматологических больных на клеточном и молекулярном уровнях свидетельствуют о стойком нарушении природных и приобретенных механизмов иммунной защиты.

В статье раскрыты изменения в иммунной системе больных раком полости рта и ротоглотки. Определено, что уровни цитокинов IL-6, IL-10, HGF и VEGF в высокой концентрации в сыворотке крови больных указывают на неудовлетворительный прогноз лечения, являются показателями низкой выживаемости и коррелируют с рецидивом. Клетки иммунитета обеспечивают сложную систему защиты через цитокины. Воспалительный компонент микросреды опухоли полости рта и ротоглотки играет значимую роль в иммунном ответе, поскольку основным его компонентом являются иммунодепрессивные цитокины. Уровни Th1 цитокинов - IFN-γ, IL-12, TNF-α понижены, а Th2-цитокины - IL-4, IL-10 - повышены, тогда как в норме показатели противоположны.

Опухоль использует различные механизмы для индукции изменений в системе во избежание иммунного ответа на ее развитие, в частности злокачественная клетка полости рта или ротоглотки путем выработки фактора роста эндотелия сосудов (VEGF), простагландина E2 (PGE2), TGFβ, IL-6 и IL-10 подавляет иммунный ответ. Опухолевая среда высвобождает провоспалительные медиаторы, в том числе такой рецептор как IL-15 alpha subunit (IL15RA), который в сочетании с IL-15 осуществляет усиленный синтез провоспалительных цитокинов - IL-6, TNF-α и IL-17, влияет на недостаточность иммунного ответа и соответственно низкий прогноз выживаемости.

Установлено, что у больных раком полости рта и ротоглотки количество NK-клеток понижено, соответственно возникает низкий контроль iNKT опухолевых клеток в регионарном коллекторе, что коррелирует с низкими показателями выживаемости.

Повышенная концентрация дендритных клеток в крови коррелирует с позитивным прогнозом и большой выживаемостью больных раком полости рта и ротоглотки, уменьшением метастазирования в шейные лимфатические узлы.

Эффективный противоопухолевый иммунный ответ включает множество компонентов иммунной системы, однако Т-клетки остаются самыми значимыми клетками, участвующими в противоопухолевом иммунитете. Поэтому Т-клеточные дефекты снижают эффективность противоопухолевого иммунитета. CD4 + CD25 + Т-клетки играют центральную роль в инициировании и поддержке иммунного ответа. Наличие в большом количестве вышеуказанных и CD4 + CD69 +, CD3 + Т-клеток связано с хорошим прогнозом.

რეზიუმე

იმუნოლოგიური ცვლილებების ანალიზი და მათი როლი პირის ღრუს და პირხახის კიბოს განვითარებაში

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ივანო-ფრანკოვსკის ეროვნული სამედიცინო უნივერსიტეტი, [1]ონკოლოგიის კათედრა; [2]დიპლომისშემდგომი განათლების სტომატოლოგიის კათედრა; [3]ბუკოვინას სახელმწიფო სამედიცინო უნივერსიტეტი, ორთოპედიული სტომატოლოგიის კათედრა; [4]უჟგოროდის ეროვნული უნივერსიტეტი, უკრაინა

ონკოსტომატოლოგიური ავადმყოფების იმუნური სისტემის მდგომარეობის უჯრედულ და მოლეკულურ დონეზე ჩატარებული მრავალი კვლევა მიუთითებს იმუნური დაცვის ბუნებრივი და შეძენილი მექანიზმების მდგრად დარღვევაზე.

სტატიაში აღწერილია პირის ღრუს და პირხახის კიბოთი პაციენტების იმუნური სისტემის ცვლილებები. დადგინილია, რომ მაღალი დონის კონცენტრაციის ციტოკინების IL-6, IL-10, HGF და VEGF არსებობა პაციენტთა სისხლის შრატში მიუთითებს მკურნალობის არადამაკმაყოფილებელ პროგნოზზე, წარმოადგენს დაბალი გადარჩენის მაჩვენებელს და კორელაციაშია რეციდივთან. იმუნური უჯრედები უზრუნველყოფენ ციტოკინების მეშვეობით დაცვის კომპლექსურ სისტემას. პირის ღრუს და პირხახის სიმსივნის მიკროგარემოს ანთებითი კომპონენტი მნიშვნელოვანია იმუნური რეაქციის დროს, ვინაიდან მის ძირითად შემადგენელს წარმოადგენს იმუნოსუპრესიული ციტოკინები. Th1 ტიპის ციტოკინებს შორისაა IFN-γ, IL-12, TNF-α, რომელთა დონე დაქვეითებულია და Th2-ციტოკინები - IL-4, IL-10, რომელთა დონე მომატებულია, ხოლო ნორმაში ეს მაჩვენებლები საპირისპიროა.

პირის ღრუს ან პირხახის ავთვისებიანი უჯრედი თრგუნავს იმუნურ პასუხს სისხლძარღვთა ენდოთელიუმის ზრდის ფაქტორის (VEGF), პროსტაგლანდინის E2 (PGE2), TGFβ, IL-6 და IL-10 წარმოქმნით. სიმსივნის გარემო გამოყოფს ანთებისსაწინააღმდეგო მედიატორებს, მათ შორის ისეთ რეცეპტორს, როგორიცაა IL-15 alpha subunit (IL15RA), რომელიც IL-15- თან ერთად ახორციელებს ანთებისსაწინააღმდეგო ციტოკინების - IL-6, TNF-α და IL-17 გაძლიერებულ სინთეზს, გავლენას ახდენს იმუნური პასუხის დეფიციტზე და, შესაბამისად, გადარჩენადობის დაბალ პროგნოზზე.

აღმოჩნდა, რომ პირის ღრუს და პირხახის კიბოთი დაავადებულ პაციენტებში NK უჯრედების რაოდენობა შემცირებულია; შესაბამისად, რეგიონულ კოლექტორში ვლინდება სიმსივნის უჯრედების დაბალი iNKT კონტროლი, რაც კორელაციაშია გადარჩენადობის დაბალ მაჩვენებლებთან.

დენდრიტული უჯრედების მომატებული კონცენტრაცია სისხლში კავშირშია პირის ღრუს და პირხახის კიბოს მქონე პაციენტების დადებით პროგნოზთან და გადარჩენის მაღალ მაჩვენებელთან და კისრის ლიმფურ კვანძებში მეტასტაზირების შემცირებასთან.

ეფექტური სიმსივნისსაწინააღმდეგო იმუნური პასუხი მოიცავს იმუნური სისტემის მრავალ კომპონენტს, თუმცა Т-უჯრედები რჩებიან უმნიშვნელოვანეს უჯრედებად, რომლებიც მონაწილეობენ სიმსივნის საწინააღმდეგო იმუნიტეტში. ამიტომ, Т უჯრედების დეფექტები ამცირებს სიმსივნისსაწინააღმდეგო იმუნიტეტის ეფექტურობას. CD4 + CD25 + Т უჯრედები ცენტრალურ როლს ასრულებენ იმუნური პასუხის ინიცირებასა და შენარჩუნებაში. მათი და დიდი რაოდენობით CD4 + CD69 +, CD3 + Т- უჯრედების გამოვლენა კარგ პროგნოზს უკავშირდება.