and development mechanisms of periodontal tissue diseases at gastroesophageal reflux disease, bibliographic, analytical research methods and the method of systematic approach were used.

Results. Recent publications show that the development of periodontitis is often caused by pathology of internal organs. High dental morbidity is observed at presence of the gastroduodenal zone diseases (chronic gastritis and duodenitis, duodenal ulcer). Inflammatory processes in the oral cavity may be the first clinical signs of disorders at diseases of the digestive system. The presence of somatic diseases in the human body makes a significant difference in the etiopathogenesis of periodontal diseases. Combined pathology is characterized by a mutually burdened course of diseases due to presence of close functional relationship between the affected organs. A number of researchers suggest that generalized periodontitis, despite sufficient monomorphism of clinical manifestations, is an etiologically and pathogenetically heterogeneous disease. Motor-tonic disorders of the esophagus against the background of lower sphincter dysfunction cause violation of the mineral composition and viscosity of saliva with the development of acidification (pH < 5.0) and, according to many scientists, trigger a cascade of dental damage at GERD.

Conclusions. Thus, after analyzing the literature, it can be concluded that periodontal tissue lesions associated with gastroesophageal reflux disease have a wide range of clinical manifestations and an upward trend. Therefore, for the development of preventive measures, it is important to study in-depth the cause-and-effect relationships and mechanisms of periodontal tissue diseases at gastroesophageal reflux disease.

Key words: gastroesophageal reflux disease, inflammatory processes, periodontitis, combined pathology, prevention.

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MODERN VIEW ON THE ISSUES OF IMMUNOLOGICAL TOLERANCE OF THE ORAL MUCOSA

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Modern molecular biology and genetics make it possible to consider the epithelium of the mucosal system through the prism of immunology and expand the understanding of the implementation mechanisms immune' response upon contact with the microflora of the oral cavity.

The purpose of the research is to analyze literature sources based on Scopus, Web of Science, MedLine, PubMed, NCBI databases, the study of which does not exceed 10 years, including literature reviews and the results of clinical studies.

Being part of the mucous membrane system, the buccal and gingival epithelium takes an active position in relationships with irritating factors from the external and internal environment. This allows it to be used to study the physiology and reactivity of mucous membranes, including as an indicator of local and general disorders of homeostasis. Oral mucosa is in a state of tolerance, which is only occasionally broken in the presence of certain "danger signals". Typically, regulatory T cells are considered a key player in this tolerance.

The oral mucosa is a site of intense immune activity where a wide variety of immune cells occur to provide the first line of defense against pathogenic organisms.

Key words: *immune response, mucosa, dendritic cells, effector sites.*

Connection of the publication with planned research works.

The work is a fragment of the research work of Dental Therapy Department of I. Horbachevsky Ternopil National Medical University "Development and implementation of differentiated approaches to the diagnosis, treatment and prevention of periodontal and oral mucosa diseases", state registration number 0123U100071.

Introduction.

The rapid development of molecular biology and genetics at the present stage has allowed us to expand our understanding and was marked by a significant increase in interest in the "immunological functions" of the epithelium of the mucosal system. This is due to the recognition of its coordinating position in the reactions of the mechanisms of nonspecific and specific immunity, in the initiation and stabilization of inflammatory processes, which occupy a leading place in the pathology of the digestive tract, periodontal tissues and oral mucosa [1, 2].

Features of the anatomy of the oral cavity emphasize its importance in ensuring the digestive process. At the same time, villages note that the oral cavity is the site of the body's primary meeting with the microbial factor, which ensures its active immune response. The implementation and maintenance of immune reactions is ensured by the coordinated interaction of inductive and effector sites. The term inductive sites refers to the anatomical sites where the majority of lymphocytes are activated when stimulated by antigenic structures, while effector sites are the sites where activated lymphocytes migrate to mediate the immune response. In the oral mucosa, effector sites include the epithelium, lamina propria and salivary glands. Inductive sites include tonsils and lymph nodes [3, 4]. The above information actualizes the issue of harmonious interaction of epithelial cells and lymphocytes of the lamina propria of the oral mucosa as a component of lymphoid tissue associated with mucous membranes and makes it possible to characterize the tolerogenic mucous ability.

The aim of the study.

Analyze literary sources based on Scopus, Web of Science, MedLine, PubMed, NCBI databases, the study of which does not exceed 10 years, including literature reviews and results of clinical studies in which keyword searches were used to optimize the identification of published materials using the advanced search function regarding the role of epithelial cells in the implementation of the function of immunological tolerance of the oral mucosa.

Main part.

Epithelial cells, as components of effector sites, constitutively express, and when activated, enhance the secretion of proinflammatory cytokines, chemokines, growth, differentiation and hematopoietic factors, endothelin and other peptide mediators, inhibitors of proinflammatory agents, cytokines [5].

These cytospecific properties provide the possibility of interaction and cooperation of epithelial cells with professional inducers and effectors of inflammation and immunity. This is due to the fact that, being under the influence of exogenous and endogenous factors, epithelial cells are able to change their functional status, becoming involved in the formation of vicious circles that support chronic pathology in the oral mucosa system [6, 7].

Being part of the mucous membrane system, the buccal and gingival epithelium takes an active position in relationships with irritating factors from the external and internal environment. This allows it to be used to study the physiology and reactivity of mucous membranes, including as an indicator of local and general disorders of homeostasis. Like other epithelial cells, buccal and gingival cells are capable of producing a number of cytokines and chemokines (IL-6, IL-8, granulocyte-macrophage colony-stimulating factor [8], IL-18 and γ-interferon), prostaglandins PG-E2 and leukemia antigen-presenting (HLA-1, HLA-2), coadhesive (CD-54) and colony-stimulating (CD-40) molecules. Their formation depends on the functional state of the cells and changes under the influence of various factors [9, 10, 11, 12, 13].

Experiments showed [14] that buccal epithelial cells are able to enhance the secretion of PG-E2 and increase the level of intracellular calcium when co-cultivated with live E. coli strains. The presence of cationic peptides with the properties of defensins in buccal epithelial cells is documented by direct histochemical and functional analyzes [15, 16].

K. Papadimitriou in his works [17] showed the activation of the synthesis of IL-8 (one of the most powerful chemoattractants for neutrophils) upon adhesion of Streptococcus bovis to human buccal epithelial cells. The same effect was obtained when exposed to antigens extracted from the cell wall of S. bovis [18, 19].

Buccal epithelial cells are sensitive to the action of interferons, and according to M. Tsukasaki et al. [20], they constitutively express genes for IL-8; incubation with α-interferon is accompanied by an increase in the level of RNA transcripts for IL-8. Incubation of buccal epithelial cells with α- and β-interferons is accompanied by increased gene expression for RANKL-15 [21].

E. Bojang et al. [22] observed this in experiments with buccal cells infected with C. albicans. Secretion of β-interferon (observed in the early phase of infection) contributed to the appearance of the active form of IL-18, an inducer of β-interferon. Its mRNA and precursor protein are constitutively expressed by epithelial cells of the oral mucosa, but the active form is formed upon adequate stimulation and is associated with IL-1β-convertible protease. Stimulation with lipopolysaccharide was sufficient to activate IL-18 but did not induce interferon-γ production.

Like other epithelial cells, the functional status of buccal and gingival cells depends on their degree of maturity. As part of multilayered squamous epithelium, buccal epithelial cells are at different stages of morphofunctional differentiation – from poorly differentiated precursors in the basal layer, providing epithelial regeneration, to highly specialized cells, which, as they differentiate, are shifted to the surface layers subject to desquamation. Some of them have signs of keratinization. Differentiation and proliferative processes, as well as the functional parameters of mature cells are regulated by factors of local and central origin. Therefore, it is not surprising that the state of the epithelial cells of the oral mucosa reflects the nature of destabilizing processes at the local and systemic (distant) levels [23, 24].

The implementation of the activity of effector sites is ensured as follows. Antigens captured by the oral mucosa are recognized by lymphocytes in the proximal associated lymphoid tissues. At the base of tonsillar crypts (the formation of multilayered epithelium of the tonsils, significantly increasing the surface of the epithelium) there are specialized cell micropores that facilitate the transport of these antigens to the tonsils. There, antigens are taken up by dendritic cells and presented to T helper cells and B cells, which form the germinal centers of the tonsils. The germinal centers produce antibodies that initiate the adaptive immune response [25, 26]. In addition, resident dendritic cells are likely to capture antigens in non-keratinized parts of the oral mucosa and migrate to the tonsils or proximal lymph nodes to initiate an immune response there. Subsequently, B and T cells migrate to effector sites (i.e. the epithelium or, in the case of B cells, various secretory structures such as immunoglobulin-producing plasma cells) [27].

However, antigens by themselves cannot provoke a protective immune response without additional “danger signals.” In fact, the tonsils constantly receive antigens from food and resident bacteria without causing inflammatory reactions. Thus, the oral mucosa is likely to be in a standard state of tolerance, which is only occasionally broken in the presence of certain “danger signals.” Typically, regulatory T cells are considered a key player in this tolerance.

Typically, CD4+T is considered the basis of the immune response. This is due to their unique ability to polarize immune responses, mainly towards tolerance or inflammation. There are several types of T cells with regulatory activity, but the most important and numerous group of Treg cells in the oral mucosa consists of CD4 + T cells expressing CD25 and a major transcription factor and characterized by the secretion of the cytokine IL-10 along with (TGF)β and IL-35 [28, 29, 30, 31]. These cytokines promote immune suppression by inhibiting the synthesis and secretion of proinflammatory factors, reducing the expression of MHC II and costimulatory molecules, and suppressing T cell proliferation [32]. To summarize, Treg cells are key for maintaining immune homeostasis and controlling immune responses in the oral mucosa and associated lymphoid tissue. However, the presence and genesis of Tregs in the oral mucosa requires the intervention of dendritic cells [33].

Changes in epithelial differentiation, recorded morphologically (cell size, nature of nuclei and granules, signs of cytolysis), their electrokinetic potential are proposed to be taken into account when screening assessing health status under conditions of stress, harmful environmental factors, somatic pathology, biological age of a person [34].

Buccal epithelial cells may be an indicator of disorders of oral, including solivar, homeostasis. Changes in the differentiation of buccal epithelial cells are observed in inflammatory diseases of the oral mucosa [35].

The experiments showed that incubation of buccal cells with nickel, cobalt and palladium chlorides, as well as triethylene glycol dimethacrylate, was accompanied by a multiple increase in the secretion of PG-E2, IL-6 and IL-8. The most intense was the induction of IL-6. The production of cytokines was stimulated by non-toxic or low-toxic dosages of drugs, and an increase in PG-E2 secretion correlated with the cytotoxic effect [36].

A number of researchers [37] have identified the influence of hormonal levels on the adhesiveness of the buccal epithelium in women during the menstrual cycle: the most active adhesion of candidal cells to epithelial cells was observed in the follicular phase of the cycle. This phenomenon, like the effect of corticosteroids, according to some scientists [38, 39], may be associated with increased keratinization – keratinization of cells under the influence of estrogenic hormones.

According to F. R. Kirchner [40], it is keratinized buccal cells that have the maximum ability to adhere to C. albicans. However, increased keratinization is not the only change in the buccal epithelium during hormonal changes; the mechanisms of its functional modifications may be more complex and require detail. They may be the result of changes in cell receptors at the stage of epithelial differentiation, competitive interactions between microorganisms, and the influence of oral secretion products. Having sensitivity to various exogenous and endogenous influences, buccal epithelial cells undergo functional changes in various disturbances of local and systemic homeostasis [41]. From the point of view of microbiocenosis, the oral cavity is divided into several ecological niches, and buccal cells are one of them, no less discrete than epithelial cells of the pharynx, the dysbiosis of which is proposed to be classified as an independent clinical and microbiological category. Previous works [42] proposed two indicators: the index of natural colonization of buccal epithelial cells and the degree of their adhesiveness to C. albicans. The natural colonization index is a diagnostically significant and universal indicator in pediatric practice; it makes it possible to characterize the activity and predict various diseases, including those of an allergic and infectious nature. The resistance of buccal cells in Candida albicans changes more selectively. These observations indicate the reactivity of the mucosal epithelium in the general system of homeostasis, which allows the use of the most accessible of its elements in clinical and laboratory practice, in particular, buccal and gingival epithelial cells [43].

Conclusions.

The oral mucosa is a site of intense immune activity where a wide variety of immune cells occur to provide the first line of defense against pathogenic organisms. Interestingly, the oral mucosa is exposed to a large number of antigens coming from food and commensal bacteria. The mechanisms mediating such tolerance are not yet fully defined. Much work has focused on active immune mechanisms involving dendritic and regulatory T cells. However, epithelial cells also make a major contribution to tolerance, influencing both innate and adaptive immunity. Therefore, the tolerogenic mechanisms operating in the oral mucosa are intertwined.

The prospect of further research.

In the future, it is planned to consider the role of dendritic cells in the implementation of immune tolerance of the oral mucosa.

References

1. Molero-Abraham M, Sanchez-Trincado JL, Gomez-Perosanz M, Torres-Gomez A, Subiza JL, Lafuente EM, et al. Human Oral Epithelial Cells Impair Bacteria-Mediated Maturation of Dendritic Cells and Render T Cells Unresponsive to Stimulation. Front Immunol. 2019;10:1434. DOI: 10.3389/fimmu.2019.01434.
2. Sanchez-Solares J, Sanchez L, Pablo-Torres C, Diaz-Fernandez C, Sørensen P, Barber D, et al. Celiac Disease Causes Epithelial Disruption and Regulatory T Cell Recruitment in the Oral Mucosa. Front Immunol. 2021;12:623805. DOI: 10.3389/fimmu.2021.623805.
3. Pelaez-Prestel HF, Sanchez-Trincado JL, Lafuente EM, Reche PA. Immune Tolerance in the Oral Mucosa. Int J Mol Sci. 2021;22(22):12149. DOI: 10.3390/ijms222212149.
4. Park JY, Chung H, DiPalma DT, Tai X, Park JH. Immune quiescence in the oral mucosa is maintained by a uniquely large population of highly activated Foxp3+ regulatory T cells. Mucosal Immunol. 2018;11(4):1092-1102. DOI: 10.1038/s41385-018-0027-2.
5. He X, Koenen HJ, Slaats JH, Joosten I. Stabilizing human regulatory T cells for tolerance inducing immunotherapy. Immunotherapy. 2017;9(9):735-751. DOI: 10.2217/imt-2017-0017.
6. Zhang X, Olsen N, Zheng SG. The progress and prospect of regulatory T cells in autoimmune diseases. J Autoimmun. 2020;111:102461. DOI: 10.1016/j.jaut.2020.102461.
7. Guo X, He C, Xin S, Gao H, Wang B, Liu X, et al. Current perspective on biological properties of plasmacytoid dendritic cells and dysfunction in gut. Immun Inflamm Dis. 2023;11(9):e1005. DOI: 10.1002/iid3.1005.
8. Ushach I, Zlotnik A. Biological role of granulocyte macrophage colony-stimulating factor (GM-CSF) and macrophage colony-stimulating factor (M-CSF) on cells of the myeloid lineage. J Leukoc Biol. 2016;100(3):481-489. DOI: 10.1189/jlb.3RU0316-144R.
9. Pinheiro-Rosa N, Torres L, Oliveira MA, Andrade-Oliveira MF, Guimarães MAF, Coelho MM, et al. Oral tolerance as antigen-specific immunotherapy. Immunother Adv. 2021;1(1):ltab017. DOI: 10.1093/immadv/ltab017.
10. Farzam-Kia N, Lemaître F, Carmena Moratalla A, Carpentier Solorio Y, Da Cal S, Jamann H, et al. Granulocyte-macrophage colony-stimulating factor-stimulated human macrophages demonstrate enhanced functions contributing to T-cell activation. Immunol Cell Biol. 2023;101(1):65-77. DOI: 10.1111/imcb.12600.
11. Guilliams M, Thierry GR, Bonnardel J, Bajenoff M. Establishment and Maintenance of the Macrophage Niche. Immunity. 2020;52(3):434-451. DOI: 10.1016/j.immuni.2020.02.015.
12. Francisco-Cruz A, Aguilar-Santelises M, Ramos-Espinosa O, Mata-Espinosa D, Marquina-Castillo B, Barrios-Payan J, et al. Granulocyte-macrophage colony-stimulating factor: not just another haematopoietic growth factor. Med Oncol. 2014;31(1):774. DOI: 10.1007/s12032-013-0774-6.
13. Becher B, Tugues S, Greter M. GM-CSF: From Growth Factor to Central Mediator of Tissue Inflammation. Immunity. 2016;45(5):963-973. DOI: 10.1016/j.immuni.2016.10.026.
14. Rodríguez M, Domingo E, Municio C, Alvarez Y, Hugo E, Fernández N, et al. Polarization of the innate immune response by prostaglandin E2: a puzzle of receptors and signals. Mol Pharmacol. 2014;85(1):187-197. DOI: 10.1124/mol.113.089573.
15. Zhang Z, Huang S, Wu S, Qi J, Li W, Liu S, et al. Clearance of apoptotic cells by mesenchymal stem cells contributes to immunosuppression via PGE2. EBioMedicine. 2019;45:341-350. DOI: 10.1016/j.ebiom.2019.06. 016.
16. de Castro LL, Lopes-Pacheco M, Weiss DJ, Cruz FF, Rocco PRM. Current understanding of the immunosuppressive properties of mesenchymal stromal cells. J Mol Med (Berl). 2019;97(5):605-618. DOI: 10.1007/s00109-019-01776-y.
17. Papadimitriou K. Novel insight into the pathogenicity of Streptococcus gallolyticus subsp. gallolyticus belonging to the Streptococcus bovis/Streptococcus equinus complex. Virulence. 2018;9(1):662-665. DOI: 10.1080/21505594.2018.1432932.
18. Jans C, Boleij A. The Road to Infection: Host-Microbe Interactions Defining the Pathogenicity of Streptococcus bovis/Streptococcus equinus Complex Members. Front Microbiol. 2018;9:603. DOI: 10.3389/fmicb.2018.00603.
19. Dekker JP, Lau AF. An Update on the Streptococcus bovis Group: Classification, Identification, and Disease Associations. J Clin Microbiol. 2016;54(7):1694-1699. DOI: 10.1128/JCM.02977-15.
20. Tsukasaki M, Komatsu N, Nagashima K, Nitta T, Pluemsakunthai W, Shukunami C, et al. Host defense against oral microbiota by bone-damaging T cells. Nat Commun. 2018;9(1):701. DOI: 10.1038/s41467-018-03147-6.
21. Kostik MM, Makhova MA, Maletin AS, Magomedova SM, Sorokina LS, Tsukasaki M, et al. Cytokine profile in patients with chronic non-bacterial osteomyelitis, juvenile idiopathic arthritis, and insulin-dependent diabetes mellitus. Cytokine. 2021;143:155521. DOI: 10.1016/j.cyto.2021.155521.
22. Bojang E, Ghuman H, Kumwenda P, Hall RA. Immune Sensing of Candida albicans. J Fungi (Basel). 2021;7(2):119. DOI: 10.3390/jof7020119.
23. Rohr P, da Silva GF, Vicentini VEP, Almeida IV, Dos Santos RA, Takahashi CS, et al. Buccal micronucleus cytome assay: Inter-laboratory scoring exercise and micronucleus and nuclear abnormalities frequencies in different populations from Brazil. Toxicol Lett. 2020;333:242-250. DOI: 10.1016/j.toxlet.2020.08.011.
24. Song L, Dong G, Guo L, Graves DT. The function of dendritic cells in modulating the host response. Mol Oral Microbiol. 2018;33(1):13-21. DOI: 10.1111/omi.12195.
25. Yamashita K, Ichimiya S, Kamekura R, Nagaya T, Jitsukawa S, Matsumiya H, et al. Studies of Tonsils in Basic and Clinical Perspectives: From the Past to the Future. Adv Otorhinolaryngol. 2016;77:119-124. DOI: 10.1159/000441902.
26. Brand A, Hovav AH, Clausen BE. Langerhans cells in the skin and oral mucosa: Brothers in arms? Eur J Immunol. 2023;53(7):e2149499. DOI: 10.1002/eji.202149499.
27. Liu Y, Xu T, Jiang W, Ma Y, Zhang Q, Chen N, et al. Single-Cell Analyses of the Oral Mucosa Reveal Immune Cell Signatures. J Dent Res. 2023;102(5):514-524. DOI: 10.1177/00220345221145903.
28. Moreau JM, Velegraki M, Bolyard C, Rosenblum MD, Li Z. Transforming growth factor-β1 in regulatory T cell biology. Sci Immunol. 2022;7(69):eabi4613. DOI: 10.1126/sciimmunol.abi4613.
29. Bertolini TB, Biswas M, Terhorst C, Daniell H, Herzog RW, Piñeros AR. Role of orally induced regulatory T cells in immunotherapy and tolerance. Cell Immunol. 2021;359:104251. DOI: 10.1016/j.cellimm.2020.104251.
30. Savage PA, Klawon DEJ, Miller CH. Regulatory T Cell Development. Annu Rev Immunol. 2020;38:421-453. DOI: 10.1146/annurev-immunol-100219-020937.
31. Tanaka Y, Fukumoto S, Sugawara S. Mechanisms underlying the induction of regulatory T cells by sublingual immunotherapy. J Oral Biosci. 2019;61(2):73-77. DOI: 10.1016/j.job.2019.02.001.
32. Hariyanto AD, Permata TBM, Gondhowiardjo SA. Role of CD4+CD25+FOXP3+ TReg cells on tumor immunity. Immunol Med. 2022;45(2):94-107. DOI: 10.1080/25785826.2021.1975228.
33. Chen C, Liang J, Yao G, Chen H, Shi B, Zhang Z, et al. Mesenchymal stem cells upregulate Treg cells via sHLA-G in SLE patients. Int Immunopharmacol. 2017;44:234-241. DOI: 10.1016/j.intimp.2017.01.024.
34. Hovav AH. Dendritic cells of the oral mucosa. Mucosal Immunol. 2014;7(1):27-37. DOI: 10.1038/mi.2013.42.
35. Zou H, Zhou N, Huang Y, Luo A, Sun J. Phenotypes, roles, and modulation of regulatory lymphocytes in periodontitis and its associated systemic diseases. J Leukoc Biol. 2022;111(2):451-467. DOI: 10.1002/JLB. 3VMR0321-027RRR.
36. Sanchez-Trincado JL, Pelaez-Prestel HF, Lafuente EM, Reche PA. Human Oral Epithelial Cells Suppress T Cell Function via Prostaglandin E2 Secretion. Front Immunol. 2022;12:740613. DOI: 10.3389/fimmu.2021. 740613.
37. Kravtsov EG, Anokhina IV, Rybas YA, Sachivkina NP, Ermolaev AV, Brodskaya SB. Effects of female sex hormones on adhesion of Candida albicans yeast-like fungi to the buccal epithelium. Bull Exp Biol Med. 2014;157(2):246-248. DOI: 10.1007/s10517-014-2536-7.
38. Hall RA. Dressed to impress: impact of environmental adaptation on the Candida albicans cell wall. Mol Microbiol. 2015;97(1):7-17. DOI: 10.1111/mmi.13020.

39. Cornejo Ulloa P, Krom BP, van der Veen MH. Sex Steroid Hormones as a Balancing Factor in Oral Host Microbiome Interactions. Front Cell Infect Microbiol. 2021;11:714229. DOI: 10.3389/fcimb.2021.714229.
40. Kirchner FR, Littringer K, Altmeier S, Tran VDT, Schönherr F, Lemberg C, et al. Persistence of Candida albicans in the Oral Mucosa Induces a Curbed Inflammatory Host Response That Is Independent of Immunosuppression. Front Immunol. 2019;10:330. DOI: 10.3389/fimmu.2019.00330.
41. Larsson L, Garaicoa-Pazmino C, Asa'ad F, Castilho RM. Understanding the role of endotoxin tolerance in chronic inflammatory conditions and periodontal disease. J Clin Periodontol. 2022;49(3):270-279. DOI: 10.1111/jcpe.13591.
42. Berni Canani R, Gilbert JA, Nagler CR. The role of the commensal microbiota in the regulation of tolerance to dietary allergens. Curr Opin Allergy Clin Immunol. 2015;15(3):243-249. DOI: 10.1097/ACI.00000000 00000157.
43. Lemberg C, Martinez de San Vicente K, Fróis-Martins R, Altmeier S, Tran VDT, Mertens S, et al. Candida albicans commensalism in the oral mucosa is favoured by limited virulence and metabolic adaptation. PLoS Pathog. 2022;18(4):e1010012. DOI: 10.1371/journal.ppat.1010012.

СУЧАСНИЙ ПОГЛЯД НА ПИТАННЯ ІМУНОЛОГІЧНОЇ ТОЛЕРАНТНОСТІ СЛИЗОВОЇ ОБОЛОНКИ ПОРОЖНИНИ РОТА

Білозецький І. І., Радчук В. Б., Дзецюх Т. І., Погорецька Х. В.

Резюме. *Вступ.* Стрімкий розвиток молекулярної біології та генетики на сучасному етапі дозволив розширити уявлення та ознаменувався значним підвищенням інтересу до «імунологічних функцій» епітелію системи слизових оболонок, які є місцем первинної зустрічі організму із мікробним чинником, що забезпечує її активну імунну відповідь.

Метою дослідження є аналіз літературних джерел на основі баз даних Scopus, Web of Science, MedLine, PubMed, NCBI, вивчення яких не перевищує 10 років, включаючи огляди літератури та результати клінічних досліджень на предмет ролі епітеліоцитів в реалізації функції імунологічної толерантності слизової оболонки порожнини рота.

Основна частина. Будучи частиною системи слизових оболонок, букальний та ясенний епітелій займає активну позицію у взаєминах з подразнювальними факторами із зовнішнього і внутрішнього середовища. Це дозволяє використовувати його для вивчення фізіології і реактивності слизових оболонок, у тому числі в якості індикатора місцевих та загальних порушень гомеостазу. Однак, антигени самі по собі не можуть спровокувати захисну імунну відповідь без додаткових «сигналів небезпеки». Епітеліоцити як складові ефекторних сайтів конститутивно експресують, а при активації посилюють секрецію прозапальних цитокінів, хемокінів, ростових, диференціаційних і гемопоетичних факторів, ендотеліну та інших пептидних медіаторів, інгібіторів прозапальних агентів, цитокінових рецепторів, молекул головного комплексу гістосумісності і міжклітинних взаємодій. Таким чином, слизова оболонка порожнини рота знаходиться в стані толерантності, який лише іноді порушується за наявності певних «сигналів небезпеки». Як правило, регуляторні Т-клітини вважаються ключовим учасником цієї толерантності.

Висновки. Слизова оболонка порожнини рота є місцем інтенсивної імунної активності, де зустрічається велика різноманітність імунних клітин, щоб забезпечити першу лінію захисту від патогенних організмів.

Ключові слова: імунна відповідь, слизова оболонка, дендритні клітини, ефекторні сайти.

MODERN VIEW ON THE ISSUES OF IMMUNOLOGICAL TOLERANCE OF THE ORAL MUCOSA

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Abstract. *Introduction.* The rapid development of molecular biology and genetics at the present stage has allowed us to expand our understanding and was marked by a significant increase in interest in the "immunological functions" of the epithelium of the mucous membrane system, which is the site of the body's initial meeting with the microbial factor that ensures its active immune response.

The purpose of the research is to analyze literature sources based on Scopus, Web of Science, MedLine, PubMed, NCBI databases, the study of which does not exceed 10 years, including literature reviews and the results of clinical studies, in which keyword searches were used to optimize the identification of published materials. using the advanced search function for the role of epithelial cells in the implementation of the function of immunological tolerance of the oral mucosa.

Main part. Being part of the mucous membrane system, the buccal and gingival epithelium takes an active position in relationships with irritating factors from the external and internal environment. This allows it to be used to study the physiology and reactivity of mucous membranes, including as an indicator of local and general disorders of homeostasis. However, antigens by themselves cannot provoke a protective immune response without additional "danger signals". Epitheliocytes, as storage effector sites, constitutively express, and upon activation, force the secretion of proinflammatory cytokines, chemokines, growth, differentiation and hematopoietic factors, endothelin, etc. our peptide mediators, inhibitors of proinflammatory agents, cytokine receptors, molecules of the head complex of histosuiciency and intercellular interactions. Thus, the oral mucosa is in a state of tolerance, which is only occasionally broken in the presence of certain "danger signals". Typically, regulatory T cells are considered a key player in this tolerance.

Conclusions. The oral mucosa is a site of intense immune activity where a wide variety of immune cells occur to provide the first line of defense against pathogenic organisms.

Key words: immune response, mucosa, dendritic cells, effector sites.

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PHYTODRUGS WITH ANABOLIC EFFECT

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Galenic and neogalenic phytodrugs, which were widely used in traditional medicine, have not lost their importance even today due to their lower cost, lower toxicity and wide spectrum of action and availability. Special attention began to be paid to medicinal phytozamobs, which can activate protein and nucleic acids associated with work capacity and are used not only for physical exertion, but also for military and clinical purposes, for diseases of internal organs, cardiovascular and nervous systems , during the period of viral and infectious diseases.

One of the first plants whose root extract was found to have an anabolic effect was creeping wheatgrass. Already in experiments on intact anesthetized rats, the level of total protein, which is associated with the activation of the level of nucleic acids, increased in the tissues of the liver, kidneys and heart when intramuscularly the extract of creeping tyria was administered. Pharmacological anabolic activity of creeping wheat extract was also confirmed in experiments on rats with food deprivation and hydro-induced cortisol-induced protein catabolism. Food deprivation was simulated by leaving animals without food for 7 days. Hydrocortisol suspension was administered intramuscularly to rats for 8 days. The anabolic effect of the creeping wheat extract exceeded the effect of the reference drug potassium orotate. It has been established that, in addition to the anabolic effect, the extract of creeping wheat also has an immunomodulatory, antioxidant, and anti-inflammatory effect, which is the basis for the possibility of its use in clinical practice.

Metabolic and anabolic activity was also established in the wild wolf. At the same time, attention was paid to wound-healing, immunomodulating effects. At the same time, anti-inflammatory, adhesive, hepatoprotective, diuretic, antioxidant, vasodilator, hypoazotemic activity was established.

Preparations of beet roots, along with anabolic activity, also show hypoglycemic, antichenobacterial effect, and also normalized blood pressure, revealed antioxidant, anti-ischemic, cardioprotective, neuroprotective and antioxidant activity, influencing the content of nitric oxide.

Due to the presence of phytosterols, organic acids and other biologically active substances, the extract of the roots of creeping wheatgrass, field wolfberry, prickly wheatgrass and beetroot has an anabolic, organoprotective, reparative, hepatoprotective, diuretic, antioxidant, vasodilator, anti-inflammatory, hyponitrogenous effect.

Key words: *extract of the roots of creeping wheat, extract of beet roots, extract of wild lupine, anabolic action.*

Connection of the publication with planned research works.

The presented article was carried out according to the research plan of the department of pharmacology «Experimental substantiation of the combined use of cardiotropic drugs» (state registration number 0111U009417).

Introduction.

In the clinic of internal neurological patients in surgical departments, especially in the postoperative period, it is necessary to carry out complex pharmacotherapy, including the inclusion of herbal preparations, which often enhance the main pharmacological effect of other means with more accessible, cheaper and less harmful analogues [1-3]. In addition, now, thanks to their anabolic and anti-stress activity, they are important in the combat