DOI 10.26886/2523-6946.1(1)2017.1

UDC 612.79:616.5-008

REGULATORY SYSTEMS OF STRUCTURAL-FUNCTIONAL UNITS OF SKIN IN NORM AND PATHOLOGY

V. V. Bocharov, PhD, MD, DSc, Professor

L. P. Zubkova, PhD, MD, DSc, Professor

Medical Center «ORTO-DENT/BIO-DERM», Ukraine, Odessa

V. V. Bocharova, PhD, MD

Odessa National Medical University, Ukraine, Odessa

The subject of the study is the regulatory systems of the structural and functional units of the skin and visible mucous membranes that contact the skin under conditions of physiological activity and pathophysiological changes. The aim of the study was to study molecular, subcellular, cellular, tissue and organ systems regulating the morphological features and functions of the skin. A modern approach to the evaluation of the formation and functioning of structural and functional units of the skin and its significance for the diagnosis, treatment and prevention of diseases associated with their damage by various etiological factors are proposed.

Keywords: regulatory systems of different levels of the skin.

[1]В. А. Бочаров, доктор медицинских наук, профессор; [1]Л. П. Зубкова, доктор медицинских наук, профессор; [2]В. В. Бочарова, кандидат медицинских наук. Регуляторные системы структурно-функциональных единиц кожи в норме и патологии / [1]Медицинский центр «ORTO-DENT/BIO-DERM», Украина, Одесса; [2]Одесский национальный медицинский университет, Украина, Одесса

Предмет исследования – регуляторные системы структурно-функциональных единиц кожи и видимых слизистых, контактирующих с кожей в условиях физиологической

деятельности и патофизиологических изменений. Цель исследования – изучить молекулярные, субклеточные, клеточные, тканевые и органные системы, регулирующие морфологические особенности и функции кожи. Предложен современный подход к оценке формирования и функционирования структурно-функциональных единиц кожи и его значения для диагностики, лечения и профилактики заболеваний, связанных с их повреждением различными этиологическими факторами.

Ключевые слова: регуляторные системы различных уровней кожи.

The newest proposals of medical and biological science dictate the need to revisit the very purpose of the skin, and to revise the changes that occur in this or that type of damage in a new and sometimes unexpected way. Molecular biological methods of research allowed us to study the regulatory systems of the body not only on the systemic, tissue, cellular, but also at the subcellular levels. The interaction of these systems is most clearly manifested in the skin, since more than 33 types of its cells synthesize and secrete hormones, biogenic amines, retinoids, vitamin D, regulatory peptides, neurotransmitters, and a variety of mechanisms of their interactions (auto-, para-, neuroendocrine and others).

The discovery of a large number of biologically active chemically diverse "signaling" molecules, as well as the use of point immunocytochemistry, molecular cloning technologies, genetic engineering, have confirmed the unity of many systems in providing them with regulatory functions in the body (figure).

The basal membrane of the skin divides its two neuroimmunoendocrine units (epidermal and dermal), and as coordinators of their activity, Langerhans cells, melanocytes, mast cells, Merkel cells that closely contact

the nerve endings and direct the bi-directional flow of soluble factors and sensory signals act. The production of some signal molecules by the skin cells is short, but it is constant, and the biologically active peptides synthesized in the skin specifically activate the genetic apparatus of the cells.

Among the structural and functional units of the skin, the so-called "epidermal-melanin unit" is isolated, the main trigger factor for which is ultraviolet radiation. Melanocytes, in addition to melanin, secrete regulatory peptides that, with the help of mechanisms of auto- and paracrine regulation, affect both melanogenesis and melanization of keratinocytes.

Keratinocytes, in turn, belong to the cellular population, which is constantly updated (life expectancy averages 3 weeks). By the term "proliferative unit of the epidermis" is meant a structure that is formed by keratinocytes of different layers of the epidermis of different degrees of differentiation, and which comes from one stem cell of the basal layer that contacts the basal membrane and is located among the cells of the basal layer of the epidermis. Due to the fact that as the cells differentiate and multiply, the cells move to the surface in the epidermis, the above structural-functional unit is a column that occupies a certain area. Basal membrane due to hemidesmosomes provides a dense connection of cells of the basal layer of the epidermis with it, among themselves these cells are connected by desmosomes. This type of intercellular contacts is the most complexly organized specialized structure of cell adhesion. Both desmosomes and hemidesmosomes are often a pathophysiological target for the development of severe dermatoses, with damage to these structures in some cases leading to epidermal cell division (pemphigus); in others, the connections between cells become extremely dense (alopecia). One of the newest discoveries of recent years is that the interleukin-1 isoform (like IL-1α) is normally produced in the skin, and the IL-1β isoform is found only in

pathological conditions. Thus, IL-1α is almost exclusively epidermal cytokine, and it is very much in the epidermis (in the stratum corneum – about 6 thousand ng/g), but in blood – 3 million times less. The importance of this discovery is that if cytokines are normally produced by several species of cells, then this IL-1 isoform is autonomous and isolated from the rest of the body by a pool of cells. This cytokine is necessary for the formation of the epidermis, being the primary inducer of its growth, by affecting the dermal fibroblasts. Under the influence of this cytokine, dermal fibroblasts synthesize the essential growth factors for keratinocytes and their differentiation (the mechanism of the double-loop paracrine) that are essential for the formation of the epidermis. This cytokine not only has a critically important role in the process of formation and renewal of the epidermis, but also the role of an important regulator of the life cycle of collagen and elastin. In addition, this cytokine performs at least 5 effects of the preparatory stages of triggering melanogenesis with the participation of an additional signal (alpha-melanostimulating hormone). When the integrity of the surface of the skin in the epidermis is disturbed, the production of IL-1α immediately increases, especially in young people, as it stimulates the synthesis of lipids in the epidermis, normalizes its stratified structure, which increases the skin's ability to retain moisture. It can also simultaneously inhibit the proliferation of the cells of the epithelial matrix of the hair follicle without inhibiting the growth of the hair itself.

In addition to the known regulatory functions of keratinocyte for calcium homeostasis (synthesis and secretion of vitamin D3), these cells synthesize, serify and regulate acetylcholine, produce dopamine and adrenaline, express vasoactive intestinal peptide, neuropeptide-γ, somatostatin (in allergic dermatitis), metabolize steroid hormones in active andro- and estrogens. These mechanisms play a huge role in acne, as well as other dermatoses associated with the age aspects of developing

pathology. Under the action of damaging agents, keratinocytes activate and acquire features of immunocompetent cells: they release chemokines, cytokines, attractants, perform an activating role against neutrophils, monocytes, and release colony-stimulating factors. These functions of keratinocytes reflect their unique ability to "launch" the mechanisms of primary (antigen-independent) inflammation. Moreover, keratinocyte can acquire a function that is not characteristic of it – an unprofessional antigen-presenting cell.

Physiological or pathological changes in the vessels of the skin (especially capillaries of the superficial vascular plexus and papillae of the dermis and, above all, postcapillary venules) largely determine the appearance on the skin of primary and secondary morphological elements of the rash, which form a clinical picture of more than 3 thousand different diseases and syndromes of its damage.

A unique structure in the skin is its papillae – conical protrusions of the dermis into the epidermis, consisting of loose connective tissue and containing not only blood but also lymphatic capillaries and nerve endings. The mesh layer of the dermis is formed by a dense fibrous connective tissue, and the hypodermis – by lobules of adipose tissue, which are separated by interlayers of loose fibrous tissue. All this provides mobility of the skin, its thermal insulation and, in addition, the hypoderma plays the role of a depot of vitamins, hormones, various nutrients.

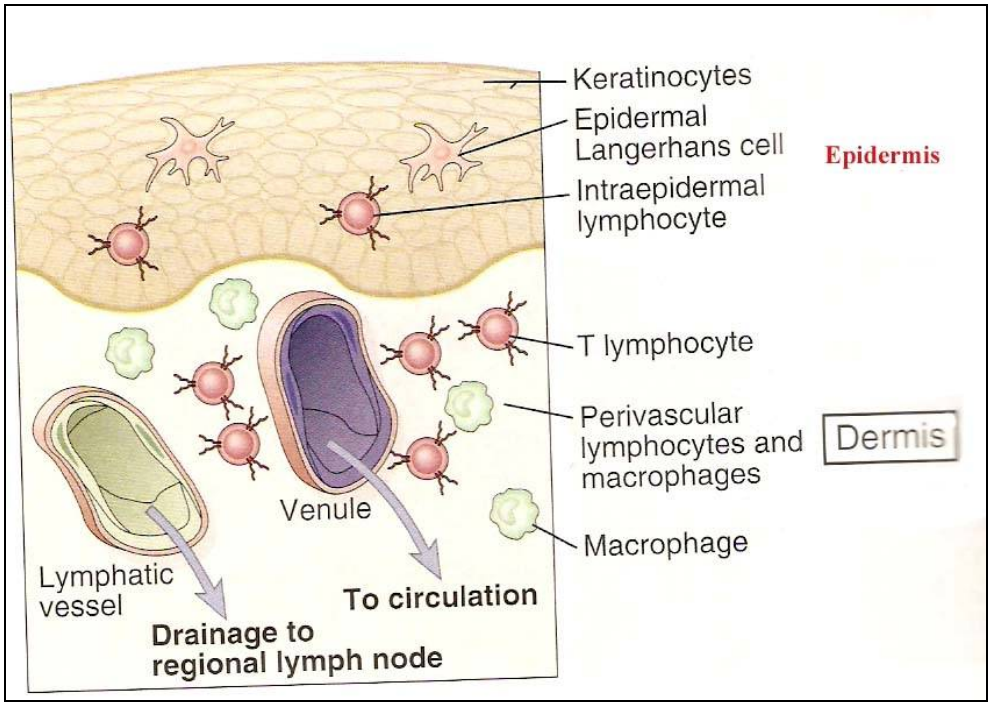
An important function in the skin (as in other organs and tissues) is played by Langerhans cells, which make up 3-5% of epidermal cells and are localized mainly in its prickly layer. Their main function is antigen presentation, which is realized due to the fact that these cells carry MHC I and II class proteins on their membrane, and the spectrum of receptors necessary for recognition of molecular patterns and antigens of immune complexes is evolutionarily behind them. Under the influence of cytokines,

substances of bacterial and viral origin and some other factors, Langerhans cells migrate from the epidermis to the dermis, and during this migration they already lose their phagocytic activity in the dermis, and they begin to express HLA-DR antigen and co-stimulating molecules in almost 100 times stronger than monocytes of blood. In lymphatic vessels they acquire the properties of "veile" cells, then penetrate into the paracortical (thymus-dependent) zone lymphatic node, where they form a pool of interdigitating cells, the processes of which are captured by lymphocytes. Langerhans cells thus not only present the antigen to naive T-lymphocytes, but also stimulate their differentiation into effector T-cells. Later, T-effectors from the lymph node enter the bloodstream and are transferred to the skin of the pathogen with the blood flow. At the same time, the evolutionarily formed interactions of partner cells "work" (in norm): 1) T-lymphocytes and endotheliocytes "recognize" each other (with the help of cadherins); 2) the migration of T-lymphocytes "stops" in the bloodstream; 3) endotheliocyte and T-lymphocyte "stick" to each other; 4) a gap contact is formed to transmit signals from the cell to the cell, either by diffusing molecules or by the interaction of the ligands of one cell embedded in the membrane with the receptors of the partner cell; 5) cell "ensembles" are formed and (6) cells interact in the ensemble with each other and (7) with other cells and the extracellular matrix. The appendages of the skin include her glands (eccrine and apocrine sweat, greasy), hair, nails, and according to some information – and the mammary gland. Sensitive innervation of the skin is branched. From the nerve plexus most expressed in the hypodermis, numerous nerve fibers leave for the hair and glands of the skin, and also for the plexus nerve plexus. Between the cells of the deep layers of the epidermis there are branched termals of thermoreceptors, in the basal layer – a complex of Merkel cells with nerve terminals is localized. Under the epidermis, in the papillary layer of the dermis, Meissner's corpuscles are

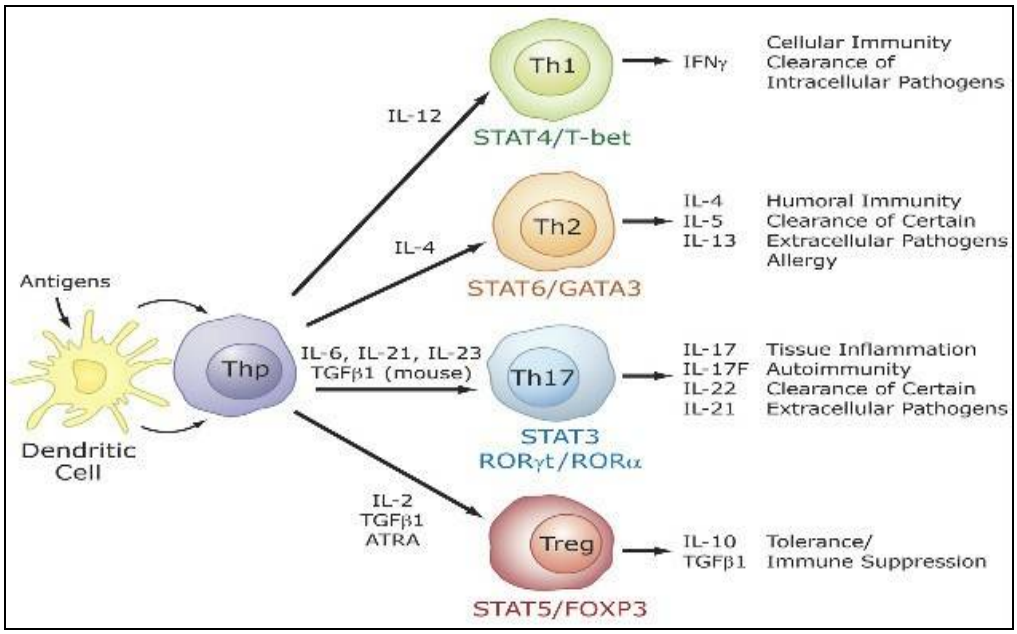
present, in the reticulate there is Ruffini's calf and Krause's flask, and Pacini's bodies are located both in the mesh layer of the dermis and hypodermis. These free nerve endings play the role of mechanoreceptors, thermoreceptors, nociceptors, etc. Fibers of the autonomic nervous system terminate on smooth muscle cells and skin glands cells, regulate blood supply and sweating, take part in thermoregulation.

Principal provisions for the development of the inflammatory process in the body are also applicable to the skin. In the process of inflammation, "cascades of biologically active compounds" (biogenic amines, eicosanoids, cytokines, etc.) that can both protect against pathological development and function as a damaging factor are "born". The cascade principle of their coordinated work allowed to formulate many new concepts with reference to the inflammatory process – "autocatalytic system of inflammation", "inflammatory-reparative process" (from the very beginning of damage, work and processes aimed at repair), 4 important principles of cell-molecular ensembles inflammation (necessary diversity, antagonism, feedback, duplication). Clearly formed the idea that the vascular-mesenchymal reaction to damage is a unique form of response of terminal vessels and connective tissue and is the essence of inflammation. The chronic pathogenesis of the inflammation is caused by the emerging pathological self-sustaining system (vicious circle), which, to a certain extent, gets out of the control of the organism and often behaves aggressively. At the same time, attention is drawn to the fact that it is the reparation that is the strategic "task" of the body, and for this inflammation interacts with immunity, and this connection is ensured by the participation of all body defense systems. According to modern data, there is a single non-immunoendocrine regulatory system in the body, but more and more data suggest that a system of tolerance can be attributed to the regulatory systems, which depends not only on the relationship of the macroorganism

and its microbiota in different biotopes (especially in the skin and intestines), but also from many genetic factors. Thus, in the pages of the new journal, priority will be given to the problems of interpreting data obtained in practice and in research laboratories on skin problems (dermatovenereology, cosmetology) from the standpoint of modern achievements in the field of basic sciences and in other biomedical and clinical branches.



(http://biosiva.50webs.org/organs.htm)



(http://www.brainimmune.com/chronic-urticaria-linked-th2th17-shift-skin-lesions)

Figure. Components of the SALT (Skin-Associated Lymphoid Tissue)

Literature:

1. Пальцев М. А. Руководство по нейроиммуноэндокринологии / М. А. Пальцев, И. М. Кветной. – М.: Медицина, 2006. – 384 с.

2. Основы клинической иммунологии / Э. Чепель, М. Хейни, С. Мисбах, Н. Сновден; пер. с англ. – М.: ГЭОТАР-Медиа, 2008. – 416 с.

3. Siebenhaar F., Sharov A. A., Sharova T. Y. [et al.] Substance p as an immunomodulatory neuropeptide in a mouse model for autoimmune hair loss (alopecia areata) // Journal of Investigative Dermatology. – 2007. – Vol. 127(6). – P. 1489-1497.

4. Кошевенко Ю. Н. Кожа человека. Том 1. Структура, физиология и предназначение функциональных элементов кожного органа человека / Ю. Н. Кошевенко. – М.: Медицина, 2006. – 360 с.

5. Гистология. 2-е изд., перераб. и доп. / ред. Э. Г. Улумбекова, Ю. А. Челышева. – М.: ГЭОТАР-МЕД, 2002. – 672 с.

6. Zaba L. C., Fuentes-Duculan J., Eungdamrong N. J. [et al.] Identification of TNF-related apoptosis-inducing ligand and other molecules that

distinguish inflammatory from resident dendritic cells in patients with psoriasis // J. Allergy. Clin. Immunol. – 2010. – Vol. 125(6). – P. 1261-1268.

7. El-Ramly A.Z., Fawzi M.M.T., Mahmoud S.B. et al. Assessment of serum levels of cathelicidin and vitamin D in acne vulgaris // Journal of the Egyptian Women's Dermatologic Society. – 2016. – Vol. 13(2). – P. 99-105.

8. Furci L., Baldan R. Bianchini V., Trovato A., Ossi C., Cichero, P., Cirillo, D. M. New role human α-defensin 5 in the fight against hypervirulent Clostridium difficile strains // Infection and Immunity. – 2015. – Vol. 83(3). – P. 986-995.

9. Iwasaki A., Medzhitov R. Control of adaptive immunity by the innate immune system // Nat. Immunol. – 2015. – Vol. 16 (4). – P. 343-353.

10. Kim S. Y., Hyun M. Y., Go K. C., Zouboulis C. C., Kim B. J. Resveratrol exerts growth inhibitory effects on human SZ95 sebocytes through the inactivation of the PI3-K/Akt pathway // International Journal of Molecular Medicine. – 2015. – Vol. 35(4). – P. 1042-1050.

11. Menha A. I., Manal E. H., Hanan H. S. et al. Evaluation of biomarkers of oxidant–antioxidant balance in patients with acne vulgaris // Journal of the Egyptian Women's Dermatologic Society. – 2015. – Vol. 12(2). – P. 136-141.

12. Orion E. Psychological factors in skin diseases: stress and skin factors and controversies / E. Orion, R. Wolf // Clin. Dermatol. – 2013. – Vol. 31(6). – P. 707-711.

13. Scudiero O., Nigro E., Cantisani [et al.] Design and activity of a cyclic mini-α-defensin analog: a novel antimicrobial tool // Int. J. Nanomedicine. – 2015. – Vol. 10. – P. 6523-6539.

14. Simpson R. C. What's new in acne? An analysis of systematic reviews and clinically significant trials published in 2010-2011 / R. C. Simpson, D. J. Grindlay, H. C. Williams // Clin. Exp. Dermatol. – 2011. – Vol. 36(8). – P. 840-843.

15. Toll-like receptor 2 activation and comedogenesis: implications for the pathogenesis of acne / Joanne Louise Selway, Tomasz Kurczab, Terence Kealey, Kenneth Langlands // BMC Dermatology. – 2013. – Vol. 13:10 doi:10.1186/1471-5945-13-10.

16. Wang G. Human Antimicrobial Peptides and proteins // Pharmaceuticals. – 2014. – Vol. 7(5). – P. 545-594.

17. Zeichner J. A. Inflammatory Acne Treatment: Review of Current and New Topical Therapeutic Options / J. A. Zeichner // J. Drugs Dermatology. – 2016. – Vol. 15 (Suppl. 1). – P. s11-s16.

18. Zhao X., Wu H., Lu H. [et al.] LAMP: A Database Linking Antimicrobial Peptides // PloS One. – 2013. – Vol. 18(8), N. 6. – P. 1-6.

19. Zouboulis C. C. Neuroendocrine regulation of sebocytes – a pathogenetic linkbetween stress and acne / C. C. Zouboulis // Exp. Dermatol. – 2004. – Vol. 13 (Suppl. 4). – P. 31-5.

References:

1. Paltsev M. A., Kvetnoy I. M. (2006). *Rukovodstvo po neyroimmunoendokrinologii.* Moscow: Medicina. [in Russian].

2. Chepel` E., Hejni M., Misbah S., Snovden N. (2008). *Osnovy klinicheskoj immunologii [Essentials of Clinical Immunology]; per. s angl.* Moscow: GEHOTAR-Media. [in Russian].

3. Siebenhaar F., Sharov A. A. , Sharova T. Y. et al. (2007). Substance p as an immunomodulatory neuropeptide in a mouse model for autoimmune hair loss (alopecia areata). *Journal of Investigative Dermatology,* 127(6), 1489-1497. [in English].

4. Koshevenko Yu. N. (2006). *Kozha cheloveka. Tom 1. Struktura, fiziologiya i prednaznachenie funkcional`nyh ehlementov kozhnogo organa cheloveka.* Moscow: Medicina. [in Russian].

5. Ulumbekov Eh. G., Chelyshev Yu. A. (2002). *Gistologiya [Histology]; 2-e izd., pererab. i dop.* Moscow: GEHOTAR-MED. [in Russian].

6. Zaba L. C., Fuentes-Duculan J., Eungdamrong N. J. et al. (2010). Identification of TNF-related apoptosis-inducing ligand and other molecules that distinguish inflammatory from resident dendritic cells in patients with psoriasis. *J. Allergy. Clin. Immunol.,* 125(6), 1261-1268. doi: 10.1016/j.jaci.2010.03.018.

7. El-Ramly A. Z., Fawzi M. M. T., Mahmoud S. B. et al. (2016). Assessment of serum levels of cathelicidin and vitamin D in acne vulgaris. *Journal of the Egyptian Women's Dermatologic Society,* 13(2), 99-105. [in English].

8. Furci L., Baldan R. Bianchini V., Trovato A., Ossi C., Cichero, P., Cirillo, D. M. (2015). New role human α-defensin 5 in the fight against hypervirulent Clostridium difficile strains. *Infection and Immunity,* 83(3), 986-995. doi: 10.1128/IAI.02955-14.

9. Iwasaki A., Medzhitov R. (2015). Control of adaptive immunity by the innate immune system. *Nat. Immunol.,* 16,(4), 343-353. doi: 10.1038/ni.3123.

*10.*Kim S. Y., Hyun M. Y., Go K. C., Zouboulis C. C., Kim B. J. (2015). Resveratrol exerts growth inhibitory effects on human SZ95 sebocytes through the inactivation of the PI3-K/Akt pathway. *International Journal of Molecular Medicine,* 35(4), 1042-1050. doi: 10.3892/ijmm.2015.2098.

*11.*Menha A. I., Manal E. H., Hanan H. S. et al. (2015). Evaluation of biomarkers of oxidant–antioxidant balance in patients with acne vulgaris. *Journal of the Egyptian Women's Dermatologic Society,* 12(2), 136-141. [in English].

*12.*Orion E., Wolf R. (2013). Psychological factors in skin diseases: stress and skin factors and controversies. *Clin. Dermatol.,* 31(6), 707-711. doi: 10.1016/j.clindermatol.2013.05.006.

13. Scudiero O., Nigro E. Cantisani et al. (2015). Design and activity of a cyclic mini-α-defensin analog: a novel antimicrobial tool. *Int. J. Nanomedicine,* 10, 6523-6539. [in English].

14. Simpson R. C., Grindlay D. J., Williams H. C. (2011). What's new in acne? An analysis of systematic reviews and clinically significant trials published in 2010-2011. *Clin. Exp. Dermatol.,* 36(8), 840-843. [in English].

15. Joanne Louise Selway, Tomasz Kurczab, Terence Kealey, Kenneth Langlands (2013). Toll-like receptor 2 activation and comedogenesis: implications for the pathogenesis of acne. *BMC Dermatology,* 13, 10. doi:10.1186/1471-5945-13-10.

16. Wang G. (2014). Human Antimicrobial Peptides and proteins. *Pharmaceuticals,* 7(5), 545-594. doi:10.3390/ph7050545pharmaceuticals.

17. Zeichner J. A. (2016). Inflammatory Acne Treatment: Review of Current and New Topical Therapeutic Options. *J. Drugs Dermatology,* 15(1), s11-s16. [in English].

18. Zhao X., Wu H., Lu H. et al. (2013). LAMP: A Database Linking Antimicrobial Peptides. *PloS One,* 18;8(6), 1-6. doi: 10.1371/journal.pone.0066557.

19. Zouboulis C. C. (2004). Neuroendocrine regulation of sebocytes – a pathogenetic linkbetween stress and acne. *Exp. Dermatol.,* 13(Suppl. 4), 31-5. [in English].

Dermatovenerology and Cosmetology**.** – 2017. – 1(1). – p. 4- 16