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GUT MICROBIOTA IN PATIENTS WITH AUTOIMMUNE DISEASES


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АУТОИММУН КАСАЛЛИКЛАРИ БЎЛГАН БЕМОРЛАРДА ИЧАК МИКРОБИОТАЛАРИ

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МИКРОБИОТЫ КИШЕЧНИКА У ПАЦИЕНТОВ С АУТОИММУННЫМИ ЗАБОЛЕВАНИЯМИ

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Резюме. *Аутоиммун касалликлар - бу инсон иммунитет тизимининг ишлашини бузиш билан боғлиқ касалликлар бўлиб, у ўз тўқималарини бегона деб таний бошлайди ва уларга зарар етказади. Бундай ҳолда, нафақат маълум бир тизим, балки бутун тизим ёки ҳатто бутун инсон танаси таъсир қилиши мумкин. Шу муносабат билан бундай касалликлар тизимли деб ҳам аталади. Ушбу касалликларнинг аксарияти сурункали бўлиб ҳисобланади. Танадаги содир бўлаётган жараёнларни тушуниш замонавий технологиялар туфайли сезиларли даражада ўзгарди, бу эса ичакнинг одамнинг асаб, эндокрин ва иммун тизимлари билан яқин алоқасини аниқлашга имкон берди. Мултифакториал табиатнинг сурункали касалликларининг аксарияти ичак микробиотасининг тур хилма-хиллигидаги ўзгаришларга асосланган бўлиб, бу макроорганизм гомеостазининг қайтарилмас бузилишига олиб келади. Ичак микробиотасининг сифат ва миқдорий таркибининг бузилиши билан боғлиқ дисфункция метаболик фаолликни ўзгартиради ва сурункали яллиғланишнинг ривожланишига ёрдам беради.*

Калит сўзлар: *ичак микробиотаси, аутоиммун касалликлар, микробиоценозлар.*

Abstract. *Autoimmune diseases are diseases associated with disruption of the functioning of the human immune system, which begins to recognize its own tissues as foreign and damage them. In this case, not only a specific system can be affected, but also the entire system or even the entire human body is affected. In this regard, such diseases are also called systemic. Until today, scientists have not fully identified the reason for the negative reaction of the human immune system to its own cells or tissues. Most of these diseases are chronic.Understanding of the processes occurring within the body has changed significantly due to modern technology, which has allowed us to reveal the close relationship of the intestine with the nervous, endocrine, and immune systems of the human body. It is believed that the majority of chronic diseases of multifactorial nature are based on changes in the species diversity of the intestinal microbiota, which lead to irreversible breakdowns in the homeostasis of the macroorganism. Dysfunction associated with disturbances in the qualitative and quantitative composition of the gut microbiota alters metabolic activity and promotes the development of chronic inflammation.*

Key words: *intestinal (gut) microbiota, autoimmune diseases, microbiocenoses.*

Introduction: Currently, the intestinal microbiota (IC) is of great interest to researchers as a biological ecosystem, which has an extremely complex organization, living with humans throughout life and affecting the functioning of all organs and systems. Microbiotic communities and macroorganism are Tereshchenko L. P., Voloshina N. P., 2020 in a constant dynamic equilibrium and through signaling pathways connect the intestine and the central nervous system [1]. The brain is in close relationship with the intestinal community, and MC is important for the normal functioning of the brain [2]. More than 100 million nerve cells are located between the esophagus and the intestine (this is the so-called "intestinal nervous system") - the second most complex cluster of nerve cells in the human body after the brain, related to it by common origin. The process of communication between the brain and the "gut-brain" has been called the Gut-Brain Axis (GBA). The interaction between brain and gut is regulated including MC in two directions through a molecular network, informing the central nervous system about the components passing through the gut (proteins, fats, carbohydrates and vitamins) [3]. The bidirectional nature of the interaction was confirmed in experimental studies in mice with acute brain injury leading to dysbiosis, intestinal barrier dysfunction, and decreased gastrointestinal motility. MC acts as a central

regulator of immune homeostasis, influencing the neuroinflammatory process and residual neurological deficits [4]. MC is considered as a set of multiple microbiocenoses, which are characterized by a certain species composition and occupy a particular biotope in the human body. According to modern concepts, there are four main biotopes: skin, respiratory tract, urogenital system and symbiotic microbiocenosis of the gastrointestinal tract (60% of all microbiota), which is the most complex and significant for humans [5]. The historical priority of studying the role of intestinal microbiota in human health belongs to the Russian scientist I.I. Mechnikov, Nobel Prize Laureate (1908) In his works he first drew attention to the role of MC in the pathogenesis of a number of chronic diseases: "The microbes that inhabit us determine to a due degree our spiritual and physical health" ... "the large intestines, which serve as a shelter for harmful microbes, become a source of poisoning from within" [6]. An important circumstance was the fact that more than 80% of human MC representatives do not grow on nutrient media. These are unculturable bacteria that could not be identified by conventional culture methods, so the study of this issue was suspended for a long time [7]. Significant changes in the understanding of the processes occurring inside the organism occurred in the early 21st century, thanks to modern omics technologies - genomics, transcriptomics, metagenomic sequencing, and metabiomics. Metagenome sequencing has made it possible to decipher the nucleotide sequences of bacterial 16S rRNA genes of microorganisms, which made it possible to formulate modern ideas about the interaction between micro- and macroorganisms [8-10]. In order to study the human microbiome in norm and pathology, as well as its relationship to health and disease, the US National Institute of Health initiated the Project (2008-2013). [11].

Work in this direction was continued (HMP2 - Human Microbiome Project), its goal was to further study the mechanisms of influence of the maternal microbiome on pregnancy outcomes using multi-omics strategies Multi-Omic Microbiome Study: Pregnancy Initiative (MOMS-PI). Another project (Meta-HIT Project - Metagenomics of the Human Intestinal Tract) was initiated by the European Commission (www. metahit.eu). As a result of large-scale research it was found out that there are 10 million cells, 100 trillion bacteria and a quadrillion viruses in the human body. The total mass of all human microbiota is from 1 to 3% of the body weight. The population composition exceeds 7 thousand strains. Of all human biocenoses, the intestinal microbiocenosis is characterized by the most pronounced individual differences and diversity. The species composition of the MC changes in different periods of life, while the type composition is quite stable and genetically determined. At the same time, the general functionality is preserved, which is necessary to maintain the basic set of physiological functions [12]. The human genome has 23 thousand genes (1%), and the intestinal metagenome contains more than 8 million unique bacterial genes (99%), i.e. there are 360 times more bacterial genes in humans than human genes [13, 14]. Thus, "humans should be considered in a complex way, not as one organism, but as a complex biological system - a "superorganism" or "supraorganism" - a hybrid of human and non-human cells. The gut microbiota has been recognized as a major source of health that influences the immune, nervous, endocrine systems and metabolism of humans" - from M. Oden's book, "The Genesis and Evolution of Homo Sapiens, 2017 [15]. In studies of healthy humans, taxonomic changes in the composition of the microbial community in different anatomical sites of the same person, as well as significant changes in the same-named loci in different individuals were found. There are also significant differences in the quantitative composition of the microbial community. и качественном составе МК у мужчин и женщин [16]. Differences in the composition and changes in the ratios of MCs in European and Asian populations of Bacteroides/ Firmicutes (B/F) have been revealed [17]. According to the dominance of phyla, we can speak about the existence of three enterotypes: Bacteroides, Prevotelia and Ruminococcus. The human organism is represented by prokaryotic cell communities to a greater extent than eukaryotic cells. In humans, 80% of all energy is formed in the mitochondria of eukaryotic cells and 20% of all energy is provided by intestinal microorganisms. Thus, 90% of the energy required for the functioning of the cells of the digestive conveyor belt is provided by intestinal bacteria. In the works of some authors the role of MC as a "metabolic reactor" is defined, and also the violation of the ratio of "harmful" and "useful" bacteria in the development of a number of human diseases is shown [18]. The composition of human MC is strictly individual, just like fingerprints. Most of the microbiota consists of bacteria belonging to the Phula Lactobacillum types (51 %), including coccoids and Clostridium leptum of the genus Bacteroides Prevotella (48 %), which participate in the regulation of lipid and bile acid metabolism and maintain the homeostasis of energy metabolism [19, 20]. The Bacteroides/Firmicutes (B/F) ratio in the European population changes with age [1]. Other less densely populated types are Proteobacteria, Actinobacteria (including the genera Bifidobacteria), Fusobacteria, Spirocheetes, Verrucomicrobia Lentisphaerae [2]. The microbiota is dominated by Actinobacteria, Bacterioidetes, Firmicutes, Proteobacteria, and many unique bacterial genes, resulting in a high degree of functional redundancy [6]. The inner surface of the adult intestine is 400 m2 and contains 80% of all immunocompetent cells, and each

meter contains 108 lymphocytes. The microbiomes of the various niches of the body are interconnected with each other and with MCs, actively fighting for survival. Commensal bacteria can displace pathogenic bacteria and create a barrier that blocks pathogens from reaching the intestinal epithelium. In addition, commensal microorganisms produce antimicrobial compounds, including immune compounds that are detrimental to pathogens and harmful compounds, as well as neurotransmitters that interact with the nervous system and participate in the regulation of transport in the epithelium [2,7]. MC biodiversity increases the resistance of microbial communities to various kinds of environmental factors, both abiotic and biotic, including anthropogenic ones. The stability (stability) of the MC is largely determined by the state of its "key" species that constitute the so-called "core microbiota" [8]. Colonization with avirulent strains of bacteria suppresses the ability of virulent strains to infect. This strategy can effectively prevent the progression of infection. With different localization of the infectious process, differences in cytokine expression are determined. In addition to bacteria (1014), viruses (1015), fungi and protozoa make up the MC, whose representation is still poorly understood. Viral communities (herpes groups, papillomaviruses, bacteriophages) have been found in healthy and diseased individuals. Fungi are also an integral part of the human microbiome. A variety of fungal communities have been identified throughout the human body that play an important role in maintaining immune function. The microbial ecosystem possesses a high degree of functional redundancy, the biological meaning of which is the maintenance of functional stability of the microbiota, providing it with the ultimate evolutionary advantage in mutuallistic relationships with the host organism. This position is fully consistent with the theory of functional systems of academician P. K. Anokhin: "A functional system is a dynamically forming wide distributed system of heterogeneous physiological formations, all parts of which contribute to obtaining a certain useful result", i.e. when one link loses the ability to self-regulation, it is covered by this functional redundancy of other representatives of the microbiota. The MC is responsible for a variety of physiological activity, neurological development, energy homeostasis, immune regulation, digestion and synthesis of a number of vitamins (groups B, A, D, E, K, folic acid, biotin, pantothenic acid) [3, 6]. Under normal physiological conditions, the stability and diversity of MC are maintained by symbiotic relationships between hundreds of bacterial species and the cells of the macroorganism, forming a kind of eubiotic system of the body (integration of the metabolism of the human body and its microbiota) [7]. Due to the detailed study of the role of individual representatives of the intestinal microbiocenosis, as well as the mechanisms of their combined effects on the homeostatic processes of the macroorganism, MC is considered as a unified system of the intestinal microbial-tissue complex, which is formed by all microorganisms, living in the intestine, dietary fiber, mucus, glycocalyx, mucosal stromal cells (fibroblasts, leukocytes, lymphocytes, neuroendocrine cells), as well as cells of the microcirculatory channel, connective tissue and nerve endings of the autonomic nervous system. Healthy MC, by producing neuroactive mediators (serotonin, butyrate, and others), help maintain the integrity of the intestinal barrier. In light of current understanding, control of epithelial cell barrier function occurs through regulation of tight contact protein expression and is a potential new target for the treatment of a number of chronic diseases of multifactorial nature [9]. The integrity of the intestinal barrier is crucial for the proinflammatory response and is ensured by the tight junction proteins claudin and occludin, which play an important role in the function of the intestinal mucosal barrier wall in preventing inflammation [1]. Modern researchers consider the MC as an additional multicellular, metabolically active neuroendocrine-immune "organ" capable of self-repair under changes caused by external factors and maintaining human health [40]. The interaction of microbiota with the intestinal epithelium normally occurs through the mucosal barrier (a kind of "damper" - biofilms), and its damage leads to direct contact of microbiota with the intestinal epithelium. This disrupts mucociliary clearance (biofilm destruction), damages the intercellular space and activates immunocompetent cells with the subsequent development of inflammation [40]. Correlations between microdamage of the intestinal mucosa, its permeability, activity of mast cells, interepithelial lymphocytes, gene and protein expression of intercellular tight contacts have been revealed [4,11]. Intercellular dense contacts are the most important component of epithelial cell construction representing barrier function. They regulate the permeability of the barrier and are able to tightly seal the junctions between cells [2]. Disruption of these tight contacts leads to bacterial translocation, disruption of the blood-brain barrier and triggering a cascade of inflammatory reactions. The severity of the resulting symptoms depends on the degree of damage to the epithelial barrier [13]. A healthy microbiome has a number of mechanisms preventing the development of pathological processes. In particular, the symbiotic microbiota is able to destroy foreign proteins due to its enzyme systems, reduce inflammatory reactions, strengthen the barriers between microbiota habitats and the internal environment of the body, and regulate the immune system in the directions of its adequate reactions.

In a physiological state (eubiosis), when infections caused by invasive Enterobacteriaceae occur,

factors of innate immunity effectively eliminate these pathogens, which promotes healing of damaged mucosa. In dysbiosis, macro- and microorganism interactions are disrupted and lead to a whole cascade of consequences: dysregulation of the inflammatory process, imbalance of energy homeostasis, and development of neuroinflammation [4]. At the same time, MC species diversity decreases, pathobiont dosage becomes higher due to symbionts and abundance of pro-inflammatory strains that reduce butyrate production. This promotes chronic, low-grade inflammation that affects the cellular infrastructure of the mucosa and leads to apoptosis in both the gut and brain. Signal transduction initiated by MC and its metabolites disrupts the delicate intracellular balance. Signaling cascades contribute to the pathorenesis of many chronic diseases, including autoimmune diseases [4, 15]. It has been revealed that pathogenic strains form the so-called "pathogenicity islands" - large genomic regions that encode the main spectrum of pathogenicity of microorganisms. The intensity of the host's innate response to infection, disease severity, and propensity for recurrence are determined by Toll-like receptors (TLRs) - special cellular structures located on the cell membrane in all organs and systems [6]. Tissue defense factors (IgA, mucin, defensins, cathelicidin) form exosomes - temporary immune effectors that contribute to host tissue defense. The formation of inflammasomes (NLRP3), pro-inflammatory cytokines IL-1β and IL-18 plays a crucial role in the development of infection. Inflammasome is a special protein complex in macrophages and neutrophils, which leads to the triggering of an inflammatory response when a cell comes into contact with microorganisms [11]. Modulation of inflammasome formation is initiated by bacterial and viral effectors. It is this mechanism that can prevent the development or eliminate infection [7]. Signals of infection entering the cell are recognized by TLRs, whereby they activate caspase-1 and trigger the formation of pro-inflammatory cytokines IL-1β and IL-18. Inflammasome maintains inflammation even after regression of clinical symptoms. As a result, the main lesion is not only and not so much related to the action of bacteria, but to the development of a local inflammatory response with the presence of inflammasomes [8]. MC alteration can be considered as one of the triggers for the formation of autoimmune inflammation. It is assumed that the development of autoimmune inflammation may be associated with impaired functional activity of regulatory T-lymphocytes (Treg). The increased functional activity of Th-1 and Th-17 lymphocytes, which subsequently produce such cytokines as IFN-γ, TNF-α and IL-23, plays a significant role.

The key defect is impaired recognition of bacterial molecular markers by dendritic cells, which leads to activation of Th-1, Th-2, and Th-17 adaptive lymphocyte subpopulations [4,6]. There are data on the influence of individual microorganisms on the functional activity of various adaptive subpopulations of T-lymphocytes. For example, the genus Candidatus Arthromitus, a Gram-positive microorganism belonging to the class Clostridium, can stimulate the differentiation of Th-17 lymphocytes, which, in turn, by secreting IL-17, attract neutrophils and macrophages to the intestinal mucosa. On the other hand, these bacteria also stimulate plasma cells that synthesize IgA, which blocks bacterial antigens in the intestinal mucosa and prevents possible infiltration and local inflammation by maintaining a balance of bacteria-commensals. It has also been shown that the presence of the Gram-negative bacterium Bacteroides thetaiotaomicron leads to a reduction in inflammation by enhanced release from the nucleus of RelA, a subunit of nuclear factor kappa B (NF-κB), which has proinflammatory properties that increase gene transcription with intranuclear localization . This protein complex relates to the receptor responsible for the anti-inflammatory properties of 5-aminosalicylic acid. In turn, microorganisms such as Lactobacillus, Bifidobacterium, Bacteroides fragilis induce the maturation of regulatory T lymphocytes in the intestinal lamina propria, stimulating the production of the immunosuppressive cytokine IL-10 [18]. A significant association of low levels of Faecalibacterium prausnitzii with high levels of pro-inflammatory cytokines has been proved. Faecalibacterium prausnitzii has an anti-inflammatory effect because it produces metabolites that inhibit the activity of factor NF-κB, which controls the expression of immune response genes and is responsible for the production of cytokines, which leads to a decrease in the secretion of proinflammatory cytokines such as IL-8, IL-12, and IFN-γ, and increases the secretion of the anti-inflammatory cytokine IL-10 . Currently, the role of genetic factors determining the predisposition to their development, which leads to the formation of chronic inflammation, is actively discussed in the pathogenesis of autoimmune diseases. In the work of Caspi R. R., et al., 2015, it is shown that MC is a trigger of severe inflammatory diseases of the ocular vasculature - autoimmune uveitis, often with a chronic recurrent course, leading to vision loss and blindness. The paradox of the disease lies in the fact that the eye, being a "barrier" organ, is isolated from the immune system of the body by the blood-ophthalmic barrier, so it has no immunogenic potential. The results of studies on animals with autoimmune uveitis showed that the activation of uveoretinal T-lymphocytes in the intestine correlates with the development of autoimmune uveitis

Conclusions: Thus, accumulation of knowledge about MC is important for understanding its functions in the organism. With pronounced changes in species diversity irreversible breakdowns

of macroorganism homeostasis occur, leading to the development of a number of chronic diseases with a severe course. The study of dynamic changes in MC is the basis for the development of promising therapies aimed at restoring the biodiversity of microorganisms. Lifestyle modification aimed at balanced nutrition and motor activity, as well as the inclusion of symbiotic microflora recovery agents with proven efficacy in the composition of complex therapy can significantly increase the effectiveness of treatment and alleviate the condition of patients with autoimmune diseases and reduce the rate of disease progression.

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МИКРОБИОТЫ КИШЕЧНИКА У ПАЦИЕНТОВ С АУТОИММУННЫМИ ЗАБОЛЕВАНИЯМИ

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Резюме. *Аутоиммунными заболеваниями являются заболевания, связанные с нарушением функциональной работы иммунной системы человека, которая начинает распознавать собственные ткани как чужеродные и повреждать их. При этом поражению может подвергаться не только конкретная система, но и поражается целая система или даже весь организм человека. В связи с этим, такие заболевания еще и называются системными. Большинство подобных заболеваний имеют хронический характер. Считается, что в основе большинства хронических заболеваний мультифакторной природы лежат изменения видового разнообразия микробиоты кишечника, которые приводят к необратимым поломкам гомеостаза макроорганизма. Дисфункция, связанная с нарушением качественного и количественного состава микробиоты кишечника, изменяет метаболическую активность и способствует развитию хронического воспаления.*

Ключевые слова: *микробиота кишечника, аутоиммунные заболевания, микробиоценозы.*