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Immunological Function of Intestinal Microflora, Morphological Features, Its Disorders and Correction Possibilities

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ABSTRACT

The article presents modern data indicating that normal microflora plays an important role in the development of the intestinal immune system. Intestinal microorganisms stimulate the maturation of intestinal lymphoid tissue, the synthesis of secretory immunoglobulin A, activate phagocytosis, stimulate the cytokine and interferon system. It is of interest to discuss the phenomenon of tolerance, which is of great importance for the formation of a stable micro-biocenosis. Probiotics are increasingly being used for the controlled formation or restoration of abnormal micro-biocenosis. Confirmation of the beneficial properties of each strain of probiotic culture in controlled clinical trials is recognized as one of the key requirements for probiotics.

Currently, a lot of data has been accumulated that in addition to the physical and chemical barriers created by the intestinal epithelium, microflora and mucous membrane, immunological protection is a functional part of the intestinal barrier apparatus [1, 2, 3, 4, 5, 6, 7, 8, 9, 10]. Of interest is the discussion of current data on gut-associated lymphoid tissue (gut–associated lymphoid tissue - GALT), where up to 80% of immunocompetent cells are localized and which is conditionally divided into two zones: inductive (grouped) and effector (diffuse).

Grouped lymphoid tissue is represented in Peyer's plaques of the small intestine, follicular formations of the vermiform process, solitary lymph follicles, mesenteric lymph nodes. The follicle zones contain mature lymphocytes at different stages of differentiation, macrophages, and dendritic cells. T cells have mainly CD4+ phenotype with the function of enhancing the synthesis of class A immunoglobulin (IgA) and to a lesser extent CD8+ phenotype mediating cytotoxicity. In the B-cell zones of the follicles, there are both precursors of IgA producers and mature cells with CD19, CD20, CD21 markers, as well as surface immunoglobulins of classes M (sIgM) and D (sIgD). The inductive zone is characterized by such stages of the immune response as antigen presentation, antigen recognition and the formation of antigen-specific clones of lymphoid cells. It is from the inductive zone that the T- and B-lymphocytes are dispersed along the mucous membrane of the digestive system and other mucous membranes.

Currently, it is more than obvious that Peyer's plaques – organized lymphoid structures – are of particular importance for the initiation of intestinal immune reactions. Their precursors are found in the fetus at the 16th week of antenatal development, differentiation into separate T and B cells occurs before the 19th week of antenatal development. They are well developed already at the

5th month of intrauterine life and continue to develop after the birth of a child [11]. There is a domed section in each Peyer plaque. Its epithelium is devoid of villi and crypts, contains a small number of goblet cells and specific M cells that are in close contact with lymphocytes and macrophages [11]. Microorganisms bind to M cells and get inside Peyer's plaques, where they are captured by antigen-presenting cells, in particular, dendritic cells [2, 3]. After activation, dendritic cells migrate from the surface of the mucous membrane through high endothelial venules and transfer the antigen to the mesenteric lymph node, where the antigen is presented to immature T cells. Along the way, costimulating molecules are produced, the spectrum of which is determined by regulatory cytokines [12, 13]. It has been established that dendritic cells from their own intestinal plate with the help of outgrowths (protrusions) of the cytoplasm penetrate through gaps in the epithelial barrier and capture the antigens present there. At the same time, the layer of polarized epithelium remains intact [10, 14].

Two main groups of dendritic cells are discussed. The first group includes cells localized in the subepithelial layer of Peyer's plaques, the marginal zone of the spleen and the subcapsular sinus of the lymph nodes belonging to the myeloid subpopulation (CD11c+CD11b+) associated with the induction of a Th2-type reaction. The second group includes lymphoid dendritic cells (CD11c+CD8a) found in the T–cell regions of lymphoid organs associated with Th1 inflammatory response. It is believed that these subpopulations of dendritic cells are characterized by functional plasticity, which depends on the dose of antigen, immunoregulatory mediators and the state of surrounding tissues [15].

The second zone (effector) consists of its own lamina propria and epithelial cells of the intestinal mucosa, provides a direct immune response of specialized cells (cellular response through T cells, local humoral response by B cells) [4, 6]. Lamina propria mucosae contains CD3+ T cells carrying ab receptors, CD4+, CD8+ T cells, NK cells, as well as B1 lymphocytes involved in the synthesis of low-affinity antibodies, B-cell subpopulations CD11b+, CD5+, SIGMA+, macrophages and dendritic cells. IdA synthesis is one of the main functions of this department. Nonspecific cells – macrophages – are diffusely distributed in their own plate, but are mainly concentrated in the area of Peyer's plaques. In the intestines of the fetus, they are detected from the 12th week of antenatal development. Macrophages occupy key positions in all forms of immune response: in the production of the Almanac of Clinical Medicine. 2015 August-September; 40: 35-46 36 Actual problem of antibodies, induction of cellular immune reactions, formation of immune memory and tolerance.

Currently, it is generally recognized that by capturing the antigen, the macrophage cleaves and processes it, and then presents the immunogenic fragment of the antigen as a peptide on its surface together with the molecules of the main histocompatibility complex of class II. Only under such conditions will the antigen be recognized by T-lymphocytes. Interesting and rather unexpected results were obtained when studying the regional characteristics of these myeloid cells. It turned out that the macrophages of their own plate lack the CD14 surface receptor, which has the ability to bind to lipopolysaccharides. Presumably, macrophages with such hyporeactivity in relation to endotoxin prevent excessive activation during the transmission of inflammatory response signals to gram-negative bacteria that are constantly present in the intestine and have the potential to overcome the epithelial barrier [16].

Mast cells, which are present in large numbers in the intestinal mucosa, belong to effector cells. They take part in allergic reactions mediated through IgE, perform a protective function against intestinal parasites and chronic bacterial pathogens. When exposed to allergens, activation of mast cells leads to the release of biologically active substances (histamine, serotonin, tryptase, etc.) that cause the development of an early phase of an allergic response. Interleukins (IL)-4, 13, 9 support the proliferation of mast cells.

The epithelial layer of the mucous membrane is considered as another section of the effector zone. Two main components of this area are involved in immune mechanisms: intraepithelial lymphocytes and intestinal epithelial cells (enterocytes). Most intraepithelial lymphocytes are CD8+ T cells with homomeric form of molecules (CD8aa), unlike CD8ab heterodimers of peripheral blood. Their ability to eliminate infected or defective cells with the help of cytolytic perforins and granzymes is assumed. Today, enterocytes are discussed as an innate component of the protection of the gastrointestinal tract and as antigen-presenting cells. When stimulated, enterocytes can produce a wide range of chemokines and cytokines. Recent scientific papers report on the isolated SIGIRR protein, which is present on the surface of intestinal mucosa cells and suppresses the natural nonspecific immune response of these cells to commensal bacteria, which ensures a comfortable existence for the latter. The researchers caused damage to the intestinal epithelium in mice genetically devoid of the SIGIRR gene by oral administration of bacterial pathogens (Escherichia coli, Salmonella typhimurium). In defective animals, more massive lesions of the intestinal epithelium, severe violations of microbiocenosis, pronounced symptoms of food poisoning were recorded compared to wild-type animals with a sufficient amount of SIGIRR protein. Thus, the activity of the SIGIRR protein helps intestinal commensal bacteria to win in competition with pathogenic microorganisms and may become a new target for therapeutic drugs used in the treatment of chronic inflammatory bowel diseases [17].

Literature data indicate that the introduction of commensal bacteria is accompanied by an immunological productive response, including an expansion of the population of intraepithelial lymphocytes with an increase in cell proliferation in crypts [18]. In the villi of the intestine, a pronounced reaction develops with the formation of numerous genes in enterocytes and even stimulation of angiogenesis. At the same time, various bacteria cause the expression of certain genes.

The immunomodulatory effect of the intestinal microflora is due to the effect on the differentiation of T-suppressors in Peyer plaques [2, 3]. The differentiation process depends on the antigen–presenting system (Human Leucocyte Antigens - HLA), on the amount and structure of the antigen, its exposure time and microenvironment. It should be emphasized that the mechanisms of immunoregulation at the level of the gastrointestinal tract involve T-helpers of two phenotypes - Th1 and Th2 [7]. The Th1 subpopulation determines the anti–infectious orientation of the immune response, Th2 - the polarization of the immune response along the path of atopy development. There are antagonism relations between Th1 and Th2, realized with the participation of their products – respectively, interferon (IFN)-γ, IL-4 or IL-10. That is why the emerging preponderance of one type of helpers is the Almanac of Clinical Medicine. 2015 August-September; 40: 35-46 Ursova N.I. The immunological function of the intestinal microflora, its disorders and the possibility of correcting one over the other is further consolidated, which determines the predominant form of the immune response.

According to a number of researchers, the Th1/Th2 divergence does not exhaust the differentiation diversity of T-helpers: subpopulations of Th17 cells and regulatory CD4+ T lymphocytes have been identified and studied. It is believed that Th17 cells secrete exclusively pro-inflammatory cytokines (tumor necrosis factor β, IL-17, etc.), which are able to activate neutrophils and mediate the development of an inflammatory T-cell immune response and, quite possibly, autoimmune processes. Differentiation of Th17 cells is supported by IL-6 and transforming growth factor β, but inhibits the key cytokines of Th1 (IFN-γ) and Th2 cells (IL-4, IL-5, IL-13) [19].

Of course, the question of the diversity of T cells is important from a practical point of view. It is known that some of them differentiate during normal T-lymphopoiesis in the thymus, they are called natural regulatory T cells (Treg). During the immune response, they form other variants of

regulatory T cells - Th3 and Tr1, while it is noted that Treg inhibit the development of allergic processes. A new concept is being discussed today, according to which the pathogenetic role of Treg in allergic processes is no less important than the role of the Th1/Th2 imbalance, the presence of an imbalance with a predominance of Th2 cells can be corrected by Treg cells and not lead to the development of an allergic process [20, 21].

The peculiarities of the immunity of the mucous membranes include the fact that along with T-helpers of the 1st and 2nd order, they contain regulatory T-helpers - CD3+CD4+CD25+ lymphocytes involved in immunological tolerance [7]. In the normal, physiological range, tolerance to representatives of the indigenous microflora is maintained, studies of the exact mechanisms of which have not yet been completed. As recently shown, Bifidobacteria and lactobacilli play a key role in them. At the same time, the species diversity and quantitative level of intestinal lactobacilli depend more on the control of the immune system compared to less immunogenic bifidobacteria. In addition, bifidobacteria and lactobacilli that determine microbiocenosis in children at the early stages of physiological adaptation are less capable of producing pro-inflammatory cytokines than those that dominate the biocenosis of older children [22, 23].

There is evidence that during the first two years of a child's life, the types of immune reactions that determine the nature of clinical phenotypes are established. As the results of a number of studies have shown, children with and without allergies have differences in intestinal flora [8, 9, 10]. If there is a shift towards the predominance of gram-positive microorganisms, this is interpreted as a risk factor for the development of food allergies, since there is no production of lipopolysaccharides (a product of the metabolism of gram-negative bacteria) responsible for the formation of food tolerance. The "hygienic hypothesis" was confirmed in the works that proved that an increase in contact with endotoxin is the most powerful protective factor against the appearance of atopy, possibly due to stimulation of specific CD14 receptors [24, 25]. In children who are naturally fed, the structure of microbial lipopolysaccharides is determined using the soluble sCD14 receptor supplied with breast milk, the concentration of which in breast milk is 20 times greater than in the plasma of women before pregnancy [26, 27].

Lymphoid tissue associated with the gastrointestinal tract is mainly committed to IgA production [28, 29]. The IgA molecules in the secretions are dimers connected in the tail part by a protein known as the J-chain, and also contain an additional secretory component that is acquired on the surface of epithelial cells. It is synthesized by the epithelial cells themselves and is first exposed on their basal surface, where it serves as a receptor for binding IgA from the blood. The resulting IgA complexes with a secretory component are absorbed by endocytosis, pass through the cytoplasm of the epithelial cell and are excreted on the surface of the mucous membrane. In addition to the transport role, the secretory component protects the IgA molecule from proteolysis by digestive enzymes. The functions of sIgA include binding of antigens of viruses and bacteria, blockade of adhesion of viruses and bacteria to mucous membranes, stimulation of antibacterial activity of phagocytes, lymphocytes against pathogenic bacteria, binding of food antigens and allergens capable of provoking allergic reactions. The Almanac of Clinical Medicine can give a child a full-fledged synthesis of sIgA. 2015 August-September; 40: 35-46 38 The actual problem is carried out starting from the age of 6 months, previously these functions are performed by IgD.

The main mechanism of interaction of normal microflora with the immune system of the body is the launch of the homing effect [30, 31]. Activated T-helper cells (CD4+), producing cytokines IL-4, IL-5, IL-10, are localized in the embryonic center of the follicles, where the process of T- and B-intercellular cooperation takes place. Subsequently, specific T- and B-lymphocytes are transported to the effector zone through the bloodstream and lymph flow [10]. The homing of

primed lymphocytes of the intestinal mucosa is directed using a4b7-integrin molecules [30]. The ability of lymphocytes to migrate from blood vessels to their own plate is achieved by the expression of a ligand to a4b7-integrin on endothelial cells of intestinal vessels. Chemokines produced by epithelial cells regulate the migration of lymphocytes into these tissues [30]. There is no doubt that there are ways of a primitive T-cell-independent IgA response to the commensal bacteria of the gastrointestinal tract. In any case, the very presence of bacteria has a permanent antigenic training effect.

As follows from the above, the immunomodulatory capabilities of the indigenous microflora are extremely large. At the same time, it is worth emphasizing: the intestinal microflora can be normal only with the physiological state of the body. As soon as pathological changes occur, the composition and properties of the intestinal microbiota change, its functions are disrupted.

Traditionally, the peak of scientific research and the maximum of clinical attention fall on problematic issues of intestinal dysbiosis. It has been established that significant changes in the biocenosis occur as a result of inflammatory diseases of the small and large intestine of both infectious and non-infectious nature [24, 25, 26]. A significant role is played by transient functional disorders of the biliary system, as well as fermentopathy and allergic damage to the intestinal mucosa. The influence of the age factor was noted: dysbiosis develops quite quickly in young children, which is associated with relative enzymatic insufficiency of the gastrointestinal tract and immaturity of the infant's immune system.

There are convincing data indicating the presence of cause-and-effect relationships between the state of the whole symbiotic endoecosystem of the organism and regional technogenic, natural and climatic factors. From the point of view of medical geography, the weakening of the last two phenomena is carried out through a certain sequence of compensatory and adaptive reactions, which are quite labile in childhood, depend on the intensity of technogenic toxicants and the duration of their action. There is evidence that serious violations of microbial colonization occur in the microbiotopes (nasopharynx, oropharynx, colon, genitourinary system) of children living in an unfavorable ecological and biogeochemical zone. They manifest themselves in a decrease and change in the properties of the indigenous microflora, modification of the total microbial contamination and the appearance of opportunistic microorganisms that are not characteristic of this biotope, a shift of microbial communities towards the associative growth of gram-negative bacteria. All this, undoubtedly, requires the development of a special program of correction and rehabilitation [28].

It is believed that ecopathogenic factors can initiate a number of mechanisms that ensure the expression of genetically determined atypical properties of microorganisms, increase the level of mutations, and lead to the creation of a new microecological equilibrium that does not always correspond to the concept of symbiosis. Against this background, further natural destabilization occurs, which is characterized by a change in the number and composition of bacterial populations in biocenotic niches (not only in the gastrointestinal tract, but also in other parts of open biological systems: nasopharynx, oral cavity, skin, genitourinary system, etc.) in the direction of associative growth of gram-negative bacteria, unusual for this biotope [27, 28]. Under these conditions, the evidence obtained is all the more important that gram-negative bacteria, compared with gram-positive ones, are stronger immunogens for the child's body and more resistant to the antibacterial action of not only the environment, but also broad-spectrum antibiotics. The point of view is stated, according to which, when a microecological imbalance occurs, strains of persistent potentially pathogenic bacteria are formed, capable of aggravating the course of a chronic disease when the defenses of the child's body weaken. Special attention should also be paid to the established fact of the formation of a deficiency of a number of microorganisms, primarily bifidobacteria and lactobacilli in the corresponding ecological niches.

As a result, this can lead to a significant decrease in the body's natural defense systems carried out by the following mechanisms: microflora and barrier effect, epithelium/mucus and immunity [28, 29].

It is well known that a large number of key mechanisms are involved in microflora disorders, which are represented by selective targets for various biological methods of exposure. One of the practical approaches to the restoration of regulatory systems is the use of microorganisms known as probiotics (from Greek. προ – "for", "for" and βιοτικ – "alive", which literally means "for life") [10,11,12,13,14,15,16]. The experts of the World Health Organization proposed the following definition: probiotics are living microorganisms that, when consumed in the required amount, have a beneficial effect on the health of the host organism [26]. According to the completed studies, the probiotic effect can be exerted not only by a viable, but also by a bacterial cell killed (for example, by irradiation), as well as non-viable structural components of bacteria (short sequences of deoxyribonucleic acid, peptidoglycan, lipoteichoic acid) [17,18,19,20,21]. It becomes obvious that there is a reason to expand the modern definition of probiotic.

Our interest in the problem of clinical use of probiotics is constantly growing, and the amount of knowledge is also increasing. The accumulated information convincingly shows that probiotics entering the intestine change not only its composition, but also the function of the microflora [13,14,17,21,23]. There are three areas of clinical and modeling research that can contribute to the study of the biological effects of probiotics. It should also be noted how important it is to strengthen the scientific base. Consequently, there is a high need for well-planned and organized studies, with the help of which it is possible to identify specific factors that are crucial in successful probiotic therapy. In the table. 1 the main directions of work in the field of determining the role of probiotic microorganisms in the development of antimicrobial effect, strengthening the barrier function of the epithelium and modulating the immune response are systematized [20].

A special place is occupied by studies studying the possibilities of probiotics to influence immunological recovery through such physiological processes as increasing the functional ability of phagocytic cells and cytostatic activity of macrophages, stimulation of intestinal-associated lymphoid tissue and effects on immunocompetent T and B cells [8, 9, 10].

Three ways of physiological immune response are being discussed today. The first is manifested in the fact that the adhesion of probiotic bacteria to the epithelial cells of the intestinal biotope causes the release of cytokines captured by dendritic cells. At the same time, intestinal epithelial cells are crucial in processing signals that act on common signaling pathways. Passage of probiotics in the intestinal lumen may be sufficient for the implementation of intercellular communications. The second way is also related to the mechanisms of cellular action and consists in the fact that M-cells in the follicle-associated epithelium on the surface of Peyer plaques provide delivery of probiotic bacteria to the subepithelial region for subsequent contact with immune cells (macrophages, dendritic cells). There they are recognized by receptors (Toll-like, lectin type C, NOD-like), which leads to their secretion of cytokines and expression of costimulatory molecules for T cells [3]. The third way involves the connection of microorganisms with the processes of dendritic cells extended into the lumen of the intestine, located on their own plate of the mucous membrane [3].

Of particular interest is the dialectic of the complex relationship between the state of the intestinal microflora and the production of secretory immunoglobulins. Analysis of data from a number of studies has shown that the stimulation of immunoglobulins is accompanied by an increase in the expression of adhesion receptors and bactericidal activity, thereby forming a specific protection. Secretory immunoglobulins play an important role in the implementation of a local immunological reaction. For example, IgA1 antibodies, due to heavy chains having

chemical affinity with mucosa, ensure the formation of a monolayer of immunoglobulins on the surface of the mucous membrane. Other Igs of the A2 subclass, having no affinity with the mucous membrane, migrate into the intestinal lumen and create the first line of the body's immune defense against infection. It should be noted that the process of specific adhesion of opportunistic and pathogenic microorganisms to the mucous membrane can be blocked, among other factors, by the presence of IgA and lysozyme, which, in turn, promote adhesion to the receptors of bifidobacteria and lactobacilli [26]. A detailed study of the role of IgA in preventing colonization of the mucous membrane by foreign bacteria allowed us to establish: 99% of bifidobacteria and lactobacilli are not covered with secretory immunoglobulins. On the contrary, the surfaces of enterobacteria, staphylococci, and other opportunistic and saprophytic microorganisms are completely lined with IgA. Presumably, this phenomenon is based on the phenomenon of immunological tolerance to normoflora. An important advantage of microflora in the development of an immune response should be considered its somewhat universal immunomodulatory effect, including both immunostimulation and immunosuppression [17, 18].

According to the results of recent experimental studies, probiotics can be attributed to anti-endotoxins. It has been convincingly shown that bifidobacteria have endotoxin-binding ability, reduce endotoxin-dependent induction and release of IL-8 [19]. There is a hypothesis according to which bacterial lipopolysaccharides and peptidoglycans, which are part of various strains of normoflora, have an immunoregulatory effect. In parallel, it was established that the key importance of anti-endotoxin immunity is not in the absolute protection of the body from endotoxin, but in limiting its concentration and biological activity to the level necessary for the realization of the physiological functioning of the immune system [19].

To date, many papers have been presented in which the mechanisms of action of probiotics are discussed in detail (Table. 2) [19,20,21,22,23,24,25].

In conclusion, we emphasize: intestinal microbiocenosis is formed for a long time, has an individual character and age characteristics, which is associated with the quality of the immune system. These properties should be taken into account when selecting promising probiotic strains for use in pediatrics. The rich arsenal of available probiotic drugs provides sufficient opportunities for their differentiated choice for the treatment of a certain nosology. There is an obvious need for further research related to the creation of individual probiotics based on autostamps and autoassociations of symbiotic microorganisms. To date, the importance of microbial exometabolites, which are actively involved in the restoration of human intestinal microflora, has been documented. It is these data that give a powerful impetus to the development of biotechnologies of a new class of standardized probiotic drugs.

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