

## THE RELATIONSHIP OF IMMUNITY AND INTESTINAL MICROBIOCENOSIS

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### Annotation

The role of symbiotic microbial flora for the human body has been proven since the 19th century. This is connected with the name of the great Russian scientist I. I. Mechnikov. Back in 1907, he wrote that the numerous associations of microbes inhabiting the human intestine largely determine his physical health. In recent years, reliable evidence has been obtained that the intestinal microflora performs important physiological functions, including supporting the immune properties of the body.

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The gastrointestinal tract (GI tract) of a person is colonized by a huge number of microorganisms (about 500 different species), which in number approach the total number of human cells. Normal microflora is a qualitative and quantitative ratio of various microbes of individual organs and systems that supports the biochemical, metabolic and immune balance of the macroorganism necessary to preserve human health.

Out of several hundred species of bacteria inhabiting the intestine, bifidobacteria and bacteroids prevail quantitatively, the proportion of which is 25% and 30%, respectively, in relation to the total number of anaerobic bacteria [18].

Before the birth of a child, his gastrointestinal tract is not populated with bacteria. At the moment of birth, the baby's intestines are rapidly colonized by bacteria that are part of the mother's intestinal and vaginal flora. As a result, a complex community of microorganisms is formed, consisting of bifidobacteria, lactobacilli, enterobacteria, clostridium and gram-positive cocci. After that, the composition of the microflora is subject to changes as a result of the action of several environmental factors, the most important of which is the nutrition of the child.

The microflora of an adult is represented by anaerobes and consists of bacteroids, bifidobacteria, eubacteria, clostridium, streptococci, E. coli and lactobacilli [3].

The predominance of bifidobacteria in the intestinal microflora of breastfed children is explained by the presence of certain components in breast milk, but the mechanism of this phenomenon is not fully known [21]. It is believed that such components of milk as whey, nucleotides and lactoferrin can have a bifidogenic effect. In addition, it has been proven that breast milk oligosaccharides are bifidogenic substances, which represent the second largest carbohydrate fraction of milk after lactose [10,13,16].

Breast milk oligosaccharides are not broken down by enzymes of the upper gastrointestinal tract and reach the large intestine unchanged. There they perform the functions of prebiotics, i.e. they are a substrate for the growth of bifidobacteria [2,4], contributing to the formation of a soft overcooked stool, similar to the stool of breastfed children [23].

The typical bifidodominant composition of the intestinal microflora of naturally fed children is associated with a number of positive effects, the main of which is the increased resistance of the child's body to intestinal infections [9,18]. Several properties of bifidobacteria may be associated with this effect. Firstly, bifidobacteria are able to secrete substances that inhibit the growth of pathogenic microorganisms. In addition, bifidobacteria create an acidic environment in the large intestine by producing acetate and lactic acid. Bifidobacteria also perform the function of modulating the mechanisms of the child's immune response [3,18]. Studies using probiotics have shown that as a result of the use of artificial feeding mixtures with the addition of bifidobacteria, the resistance of children to infectious diseases increases [17]. A recent study showed that in children with atopic diseases at the age of 12 months, clostridia are the predominant microorganisms in the intestinal microflora, and the number of bifidobacteria in such children is significantly lower than in their peers who do not suffer from atopic diseases [1]. All these studies show that there is a connection between the composition of the intestinal microflora and the maturity of the immune response of children.

The human intestinal microflora performs several basic functions, including metabolic adaptation processes [11]. One of them is the fermentation of previously unsplit food components, mainly carbohydrates, such as starch, oligo- and polysaccharides. The final products formed as a result of the fermentation process have various effects on human health.

For example, as a result of the activity of individual bacteria, toxic substances are formed – the breakdown products of proteins, while the fermentation of some carbohydrates produces products that have a positive effect on metabolism, such as lactic acid and short-chain fatty acids [3].

Short-chain fatty acids perform a trophic function and are used by the cells of the intestinal mucosa as an additional source of energy. Thus, the functioning of the protective barrier of the intestinal mucosa improves [18]. Moreover, certain carbohydrates can selectively stimulate the growth of bacteria beneficial to human health in the large intestine [3].

The intestinal microflora protects a person from colonization by exogenous pathogenic microorganisms and suppresses the growth of pathogenic microorganisms already present in the intestine. The mechanism of this phenomenon consists in the competition of microflora for nutrients and binding sites, as well as in the production of certain substances inhibiting the growth of pathogens by normal microflora [14]. Moreover, the bacteria inhabiting the large intestine are involved in the implementation of immunological defense mechanisms.

In case of a toxic or antigenic attack, enterocytes stimulate the expression of genes responsible for transcription and translation of cytokine molecules by certain activating signals. In addition, there is a release of growth factors necessary to stimulate proliferation and differentiation of the damaged area of the mucous membrane [22].

The differentiation process, which determines the nature of the immune response in the future, depends not only on the antigen-presenting system (HLA), but also on the amount, structure of the antigen, its exposure time, and microenvironment. The increased synthesis of Th1- CD4+ subpopulation, which determines the anti-infectious immune response, is due to mediators of intercellular interaction IL2, IL12 and IFN- $\gamma$ . The latter, in turn, blocks the production of the Th2 subpopulation responsible for the development of atopic allergy. The implementation of differentiation towards Th2 causes, thanks to IL4 (blocks the synthesis of Th1), IL13 and IL5, maturation, activation and an increase in the number of eosinophils, as well as an increase in the level of IgE. The Th3 subpopulation induced by *Lactobacillus rhamnosus* synthesizes tumor growth factor – TGF- $\beta$ , which prevents the development of atopy, and

anti-inflammatory IL10, which switches differentiation from Th2 to Th1 - immune response. I.e. according to the "hygienic theory" of the development of atopic allergy by David Sarchan, probiotics play a "compensatory" role of an infectious factor, contributing to the implementation of Th1 – immune response and preventing the development of atopy [6].

As noted earlier, 92-95% of the intestinal microflora consists of obligate anaerobes. The composition of the intestinal microflora is quite individual and is formed in the first days of a child's life. The most important factor in the formation of normal microflora is natural feeding, because women's milk contains a number of substances—prebiotics, which contribute to colonization of the intestine by certain types of microorganisms in certain quantities. Even minor problems in the first days of a child's life, especially pathological conditions of the gastrointestinal tract, can cause severe, difficult-to-correct violations of intestinal biocenosis in the future. Irrational antibiotic therapy can cause particular damage to the intestinal microflora during this period.

Violation of the microbial balance in the intestine is called dysbiosis or intestinal dysbiosis. The main causes of intestinal dysbiosis are late application to the breast, irrational nutrition of the child (especially in the first months of life), functional disorders of the gastrointestinal tract, diseases of the gastrointestinal tract, especially associated with malabsorption syndrome (lactase deficiency, celiac disease, cystic fibrosis, etc.), antibiotic therapy (especially in the first days of life) and features of the immune system.

Intestinal dysbiosis is a syndrome, always a secondary condition. According to the definition in the industry standard, "intestinal dysbiosis is a clinical and laboratory syndrome that occurs in a number of diseases and clinical situations, characterized by symptoms of intestinal damage, changes in the qualitative and/or quantitative composition of normal microflora, as well as translocation of its various species into unusual biotopes and their excessive growth." The root cause of intestinal dysbiosis is a change in the internal environment of the intestine, a violation of digestive processes, a damaging effect on the intestinal wall, malabsorption. Through intestinal dysbiosis, a pathogenetic vicious circle is closed, which must be broken both for the successful treatment of the underlying disease and the elimination of its consequences.

Correction of microecological disorders is based on the following principles: first, treatment of the underlying disease, then correction of dysbiotic disorders and, finally, correction of complications.

For this purpose, a targeted effect on the microflora is carried out with the selective destruction (antibiotics, bacteriophages) of undesirable microorganisms and colonization of the intestine with missing flora representatives, as well as a general effect on the microflora in order to create such conditions in the intestine that would be unfavorable for undesirable microorganisms, but favored colonization by missing ones.

It is necessary to note the imperfection of traditional dysbiosis therapy associated with the shortcomings of antibacterial therapy (suppression of microbiocenosis, growth of resistant forms), probiotic therapy (difficulty in selecting and inadequate doses of drugs for the purposes of their use) and phage therapy (narrow specificity of phages, rapid appearance of phage-resistant strains).

Recently, the prospects of using prebiotics – food ingredients that contribute to the selective stimulation of growth and metabolic activity of bacteria living in the colon have been shown. To normalize the intestinal microflora, probiotics are used – living microorganisms and substances of microbial origin that, with the natural method of administration, have a positive effect on physiological and metabolic functions, as well as biochemical and immune reactions of the host organism through optimization of its microecological status.

Several ways have been established by which probiotics realize a therapeutic effect:

1. Changing the immunogenicity of foreign proteins by proteolysis. Probiotic proteases destroy cow's milk casein. At the same time, its immunogenic properties change. Attention should be paid to the fact that casein enhances the production of the mediator of intercellular interaction of IL4 and  $\gamma$ -interferon in children sensitized to cow's milk. However, casein cleaved by *Lactobacillus rhamnosus* reduces IL4 production and does not affect the release of  $\gamma$ -interferon. This indicates the possibility of probiotics to inhibit the synthesis of IgE and the activation of eosinophils.

2. Decreased secretion of inflammatory mediators in the intestine. For example, the administration of *Lactobacillus rhamnosus* (ATCC 53103) reduces the level of tumor necrosis factor- $\alpha$  (TNF- $\alpha$ ) in the feces of patients suffering from atopic dermatitis and allergy to cow's milk.

3. Reduction of intestinal permeability.

4. The direction of the antigen to the Peyer plaques, where interferon promotes their capture, namely, IgA-producing cells are generated in them. Probably, lactobacilli, which increase the synthesis of interferon, contribute to this process. At the same time, an increase in systemic and secretory IgA is indicated with oral administration of lactobacilli. Taking *Lactobacillus casei* and *Lactobacillus bulgaricus* reduces phagocytic activity in children with food allergies. In non-allergics, probiotics enhance phagocytic activity.

Studies on the evaluation of the effectiveness of probiotics in allergy have revealed a reduction in the risk of developing atopic eczema by the first year of life in children at risk compared with the placebo group. At the same time, the level of general and specific IgE did not differ [8]. There was a decrease in the risk of developing atopic eczema during the first two years of life in children whose mothers received probiotics compared to the placebo group. An increase in the amount of tumor growth factor – TGF- $\beta$ 2 in milk was noted [7]. The use of probiotic drugs led to a decrease in the SCORAD index (the severity index of skin lesions in atopic dermatitis), a decrease in the level of tumor necrosis factor – TNF- $\alpha$ , the level of eosinophilic protein X and an increase in the level of IL10 [6,12,15].

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