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IMMUNOMODULATORY PROPERTIES OF THE HUMAN INTESTINAL MICROBIOTA AND PROSPECTS FOR THE USE OF PROBIOTICS FOR PROPHYLAXIS AND CORRECTION OF INFLAMMATORY PROCESSES

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Literature data and own author experiments concerning the influence of microbiota on the immune system are summarized. The mechanisms of the diversification of immune response to pathogenic and commensal microorganisms are described. Effect of microorganisms of normal flora on innate and adaptive immunity is characterized. Human inflammatory diseases associated with microbiota disorders are reviewed. Biological properties of probiotic preparations are discussed in context of its modulatory effect on inflammatory response. Prospects of use of immunomodulatory potential of probiotic microorganisms are being analyzed.

Key words: intestinal microbiota, immunomodulation, immunobiotics, inflammation.

Results of the research of the last decade regarding composition and functions of the human intestinal microflora caused a new wave of interest in the targeted use of probiotics and development of the new generation of these preparations for prevention and treatment of somatic diseases. Disturbance of microbiota is associated with the development of diseases of inflammatory etiology. A disorder of communication between cells of the immune system and microorganisms, caused by the change in composition of the microbial community, is the main reason of the development of such inflammation. Restoring the broken composition of microbiota promotes the establishment of a balanced immunoregulation and braking of inflammatory reaction of the immune system. Probiotics are known to be one of the most effective factors of recovery of the microbiota. Experts in medical technology position the development of probiotics as an efficient biotechnology (in terms of the ratio "cost — effect — safety"), which will be the best for prevention and cure of inflammatory diseases of the gastrointestinal tract (GIT) and beyond in the future [1–3]. However, despite the fact that the use of probiotics was put to preventive and therapeutic schemes for many diseases (necrotizing enterokolitis, antibiotic-asociated diarrheas, inflammatory bowel disease, urogenital infections, allergic pathologies, etc.), the potential of these drugs has only been partially implemented. The reasons for this is the multifactorial impact of probiotics on physiological and pathological processes in the body, and the lack of reliable criteria for the selection of one or another probiotic preparation for each specific pathology. Today several approaches to increase efficiency of probiotic preparations are described: a selection of the most effective strains, the combination of multiple strains, the combination of probiotic microorganisms with prebiotics, genetic modification of probiotic microorganisms [4–6]. However, usually numerous biological effects can be inherent in one probiotic microorganism. The problem of which of their properties are to be laid in the basis of choice for prophylaxis or treatment of each particular pathology, remains unsolved. An important mechanism of action of probiotic preparations is modeling of functions of the immune system both at the local and at the system level. Diseases associated with the disturbance of the microbiota, treatment of which involves the use of probiotics, is always accompanied

by disorders of immunologic reactivity of varying nature and severity. Due to this, the immunomodulatory activity of probiotics can be regarded as an informative criterium for targeted use of these preparations, which is aimed at an immunopathogenetic component of the pathological process, that is associated with disturbance of the intestinal microbiota.

Microbiota of the human intestine: formation stages and functions

Since 2006 the scientific community considers the gut microbiota as a new metabolically active organ, which consists of several trillion of commensal bacteria [7]. All coelomates have an additional genome — genome of gut microorganisms or microbiom. The number of microbial genes contained in the human intestine (about 540 000), more than 300 times higher than that in the human own genome. Intestinal microbial cells make up 90% of all cells in the body [1]. It is well recognized that the presence of normal microflora in the body is a prerequisite for the development of tissues, organs and physiological systems. Microbiota is necessary for food digestion and energy metabolism [8, 9]. The result of enzymatic degradation of dietary fiber by intestinal bacteria are the short-chain fatty acids (SCFA), the main ones are acetate, propionate and butyrate. SCFA are the additional source of energy and provide 10% of food energy in the body [10]. They also stimulate the growth and differentiation of enterocytes and colonocytes [11]. SCFA regulate peristalsis in the large intestine by stimulating the expression of 5-HT receptors in enteroendocrine cells, and induce inhibition of peristalsis in upper gastrointestinal tract [12]. The normal microflora prevents colonization of the intestine by pathobionts. Colonization resistance is provided by both direct effect on pathogenic microorganisms (change in pH, production of bacteriocins and other biologically active compounds with antimicrobial activity or a negative effect on the virulence factors of pathogens, competitive utilization of carbon and energy sources, etc.), and indirectly through its impact on morphofunctional characteristics of epithelium and local regulation of immunity [13]. Microbiota plays an important role in maintaining the barrier function of the intestinal wall. There are two levels of barrier defence in the intestine: the integrity of epithelium and neutralizing properties of mucus. The integrity of the epithelial barrier is provided by tight junctions between epithelial cells. Normal flora bacteria stimulate the synthesis of adhesion molecules that provide such junctions, as well as the secretion of cytoprotective trefoil factor 3 (TFF3), which prevents apoptosis of epithelial cells [14]. Symbiotic bacteria also contribute to the renewal of the intestinal mucus, which consists of two layers: inner and outer. Inner, thin layer of the intestinal mucus (another name apical glycocalix) consists of membrane-bound mucins and glycolipids. Outer, thick layer consists of three components: secreted mucins, sIgA and antimicrobial peptides. The outer layer of mucin performs the barrier function due to the presence of humoral factors of innate immunity, and neutralization of pathegenes. Normal flora bacteria use the secretory mucins as a source of energy, stimulating their production and continuous renewal of the mucin layer. In addition, symbiotic bacteria antigens stimulate the production of sIgA and antimicrobial peptides [15]. Microbiota promotes the development of intestinal vascular bed [16], the nervous system in early childhood and its functioning in adults [17, 18]. It is also a determining factor in the formation of mucosa associated lymphoid tissue (MALT), as well as gut associated lymphoid tissue (GALT) [19, 20]. According to the results of the recent years' researches, it has been suggested that a segmented filamentous bacteria (SFB) play the most important role in shaping the GALT and programming the interaction between the immune system and the microbiota. Like most (20 to 80%) intestinal microorganisms, SFB are non-culturable bacteria. SFB are spore-forming Gram-positive bacteria, which belong to a phyla of *Firmicutes*, order *Clostridiales*. Mainly they are localized in the ileum in humans and animals. SFB are the only intestinal bacteria, that form close contact with the epithelial cells. This partnership has been created evolutionary and was caused by SFB biological characteristics. SFB have virtually no metabolic cycles required for the production of amino acids, nucleotides, cofactors etc. SFB obtain all these compounds from the epithelial cells through a specialized transporting system [21]. Unlike animals, in which SFB are present throughout the whole life, in human these bacteria are only available in the early childhood (up to three years) — the period of formation of the relationship between the immune system and the microbiota. [22, 23]. Normal intestinal microflora exerts no less important effect on the immune system development in general. The main mechanism

of such action is a physiological translocation of living organisms, their metabolites and decay products to distant tissues and organs [24]. The ability of probiotics to enhance the immunogenicity of different vaccine preparations through the stimulation of antibody response in MALT is one of the evidences of the impact of bacterial flora on systemic immune reactivity. This phenomenon has been proved by the example of the use of Lactobacillus casei GG immediately before the vaccination of children with rotavirus vaccine and in the case of the use of Lactobacillus rhamnosus GG simultaneously with the polio vaccine. In both cases an increased titer of neutralizing antibodies and a significant growth rate of seroconversion were registered [6].

Formation of the intestinal microbiota depends on many factors: the way of birth, infant feeding and a treatment with antibiotics, especially in early childhood. According to current data, the first contact of the infant intestine with microorganisms occurs at the level of cord blood, placenta and amniotic fluid [25]. A distinctive feature of the microbiota is the age succession. Intestinal microflora of both term and preterm infants changes very quickly — every 2–7 days [1, 26]. In the 1–2 month of life bifidobacteria and enterobacteria appear and dominate, bacteroides colonize the intestine between 3 to 6 months after birth, and butyrate-producing bacteria, which belong to genera *Faecalibacterium* and *Roseburia*, appear at the end of the 1st year of life. Significant inter- and intrapersonal changes of the intestinal microflora last during this time period. Gradually intrapersonal changes cease and the foundation of adult microflora is being laid for the first three years of life [27, 28]. Although composition of the intestinal microbial communities is characterized by an individual variability, three main types of such community (enterotypes) are discovered. Each enterotype is characterized by a relatively high content of certain genus of microorganisms. The feature of enterotype I is an increased number of *Bacteroides*, enterotype II is enriched by the genus *Prevotella*, and high content of *Ruminococcus* is characteristic of the enterotype III. The distinctiveness of each enterotype is also based on the types of food chains of bacteria, their constituents. These food chains determine the sources of energy, the nature of its acquiring [29, 30]. Formation of enterotype is independent of age, gender, ethnicity or body weight, but largely depends on staying a long time on a particular diet [31]. Different age-related changes, which reduce the metabolic diversity of microorganisms are typical for the microbiota of the intestine, as well as for the other biotops of the human body. These changes affect the microbiota properties and are associated with an increased risk of a number of diseases.

Immunomodulatory properties of the normal microflora of human

The number of lymphocytes, localized in the MALT significantly exceeds the number of them in the bone marrow. About 70% of all the cells of the immune system are localized in this compartment, where they permanently provide the process of diversification of the reactions of the immune system on the pathogenic microorganisms and bacteria of the normal microflora [34]. The interaction between bacteria and MALT (GALT) occurs on three major levels: epitheliocytes, antigen-presenting cells and effector cells of the adaptive immune response. One of the fetures of GALT functioning is the need of equally effective generation of two different types of immune responses: immunoregulation/ tolerance towards food antigens and microorganisms of normal microflora and protective/aggressive immune response to pathogens. Such method of GALT functioning is ensured by the peculiarities of composition of immunocytes in the intestine and pattern of expression and functioning of recognizing molecules, which are responsible for interaction with foreign antigens. Formation of GALT and population composition of cells of the immune system are determined by the microbiota in the early postnatal period.

The first level of interaction of intestinal symbiotic microorganisms (i.e. normal human intestinal flora representatives) with the immune system of the host is the contact with the epithelium. Epitheliocytes of the intestine, as well as glandular goblet cells express a number of pattern recognition receptors (PRRs), responsible for the interaction with the antigens of microorganisms, generally known as microbes- or pathogen-assotiated molecular patterns (MAMPs or PAMPs). The nature of the interaction between the PRR of these cells and PAMP plays a great role in determining of the direction of the immune response to the source of these antigens. This phenomenon caused an evolutionary formation of multiple levels of regulation of activation of these receptors. PRR are divided into several families: the main, in particular TLR (Toll-like receptors), RLR (retinoic

acid inducible gene I (RIG-I)-like receptors), NLR (nucleotide oligomerization domain-(NOD)-like receptors) as well as C-type lectin receptors and cytosolic DNA sensors (DNA-dependent activator of IFN-regulatory factors (DAI), Interferon-inducible protein AIM2 also known as absent in melanoma 2 etc.). Genetically determined or acquired disorders of the expression and regulation of the PRR in the intestine are associated with the development of pathological conditions. For example, the NOD2 gene polymorphism that accompanies the Crohn's disease, is associated with reduced immunological reactivity in the intestine and impaired mechanisms of tolerance to the microbiota. Nowadays functioning in the stomach receptors of TLR family has the most detailed characteristic. Almost all TLRs are expressed at the level of mRNA in the intestine of the human. Thus the TLR4, 2 and 5 are expressed by cells in the follicle-associated epithelium, epithelium of the crypt and villi in the small intestine, and intraepithelial leukocytes, mainly localized in the large intestine. TLR4 and 2 are expressed at the low level. The regulation of the expression of TLR4 plays an important role, because the activation of this particular PRR is associated with the development of inflammatory diseases in the intestine. In connection with this a subtle mechanism of activation of TLR4 was evolutionarily created. The first contact of TLR4 on epitheliocytes of the intestine of an infant, with its specific ligand — LPS — induces the formation of small non-coding RNA (microRNA) miR-146a, which specifically inhibits the translation of a kinase associated with the interleukin-1 receptor (IRAK), which is one of the main components of the signaling pathway of TLR4 [35]. Follicle-associated epitheliocytes express TLR2 on the apical and basolateral surface. Pattern of the intracellular TLR9 expression is the same. TLR5 expresses only on basolateral surface of epitheliocytes, which is not in contact with the normal flora bacteria. All mature enterocytes in small and lagre intestine express TLR3. Functioning of TLR in an intestine has some peculiarities. For instance, the activation of TLR9 from apical and basolateral surfaces of the epitheliocyte initiates distinct signaling pathways. Apical activation initiates homeostatic response and tolerance to respective ligands. Basolateral stimulation causes the degradation of the I- B followed by the activation of the canonical NF-κB-dependent signaling. An increased expression of negative membrane-associated and intracellular regulators of signaling pathways (interleukin-1 receptor-associated kinase 3 - IRAK-M, inhibitory adaptor protein that interacts with the TLR -TOLLIP, etc.) as well as peroxisome proliferator-activated receptor gamma (PPARγ) is another feature of TLR functioning. It minimizes the risk of destructive immune response of immune system to MAMP of normal microflora [36]. An expression of soluble forms of TLR, which activate endocytosis or proteolytic disintegration of their membrane forms, is an additional tool of the control of the activation of these receptors. MicroRNA mediate posttranscriptional regulation of TLR-signaling in GALT. In response to the interaction with MAMP of microbiota epitheliocytes secrete a number of bioactive mediators that regulate the proliferation and migration of the cells of the immune system (CCL20, IL1β, 7, 8, 15, TGFβ, ADM), mediate switch-recombination in plasma B-cells to the synthesis of sIgA (APRIL, BAFF, TGFβ), activate the formation of dendrites in dendritic cells (DC, TSLP). In addition, the enterocytes produce antimicrobial peptides (defensins, cathelicidins, calprotectin, HIP/PAP, etc.), which provide the natural resistance of the intestine and detoxify potentially dangerous molecules of bacterial origin, such as lipopolysaccharides-LPS (alkaline phosphatase, ALPI). The interaction of the PRR of the epithelial cells PAMP of microbiota is needed not only for initiating immune responses and synthesis of antibacterial substances. No less important consequences of such interaction are the activation of epitheliocyte proliferation, preventing their apoptosis, as well as activation of the synthesis of molecules of intercellular adhesion, which ensure the integrity of the epithelial barrier [37].

In the *lamina propria*, located directly under the epithelial surface, cells of the immune system are localized: myeloid antigen-presenting cells (APC) — DC and macrophages, T- and B-lymphocytes, mastocytes, natural killer cell and a small number of leukocytes of other sub-populations. The next level of interaction between the microbiota and the immune system of MALT is the recognition of bacterial antigens by APC, first of all DK and macrophages. For the activation T-cells by DC three signals must be received: first one is a MHC complex: peptide, the second is the co-stimulatory molecule, which belong to B7 family. And a third signal is the one, that determines the polarization of the activation of naive T-cells (Th1, Th2,

Th9, Th17 or Treg). This molecular signal is extremely heterogeneous and may be soluble or membrane-associated: IL6, IL8, IL10, IL12, IFN-α, TGF-β, OX-40 ligand or retinoic acid [15]. The expression of these molecules is determined by the nature of the ligands (including PAMP), which activated DC. So the microorganisms are capable of causing differentiation of DC with different phenotypic and functional characteristics.

Macrophages play an important role in guiding the immune responses against bacteria as well. According to the Th1/Th2 dichotomy of the immune response, there are at least two tendencies in macrophage activations: classic (M1) and alternative (M2). Classic (M1) macrophage activation is accompanied by secretion of the proinflammatory cytokines, reactive oxygen species, nitrogen oxide, etc. In total, such macrophage activation leads to development of the inflammatory process and to induction of the Th1-type immune response. The alternative macrophage activations lead to development of the Th2- type immune response. Such macrophages practically lose cytotoxic activity. In spite of the MHCII-molecules formation, they are not capable of complete antigen-presentation. Instead of this, such cells accomplish the functions of regulatory cells [39]. M2 is the main type of macrophages in GALT. Intestinal macrophages are characterized by the so-called inflammatory anergy. They express anti-inflammatory cytokines (TFR-β and IL10). Expression of CD14, co-stimulating molecules (CD80/86), as well as FcR for IgA and CD89 is reduced in these cells. That's why their involvement in the activation of pro-inflammatory immune response, as well as in the antibody-dependent immune reactions is minimized. Instead, the expression of scavenger receptors, involved in the reaction of phagocytosis (Mannose receptor, CD36, CD13) is increased. Under homeostatic conditions macrophages of GALT are the regulatory cells. However, imbalance of gomeostatic equilibrium in the microbiome may cause their functional repolarization and involvement in the development of local and systemic inflammatory processes [40]. Macrophages, as well as DK play an exclusive role in diversification of the immune response to pathogenic and normal flora bacteria. Considering the overexpression of scavenger receptors in macrophages of GALT, the nature of the phagocytosis of bacteria as well as their metabolites and sub-cellular components is rather essential in this process [41].

Th17 and iTreg (induced regulatory $Foxp3^+$- cells) prevail among the T-lymphocytes in GALT. The first ones focus in the small intestine, the second — in the large one. Homìng of the lymphocytes of these populations and the functional differentiation of T-cells in various compartmentss of the intestine are regulated by microbiota. For example, differentiation of the naive T-cells on Th17 is mediated by the SFB, the differentiation of regulatory cells depends on the presence of bifidobacteria, lactobacilli and bacteroides of different genera [42]. Lymphocytes are also present in the structure of epithelium (intraepithelial lymphocytes).

As stated above, it is possible to initiate two oppositely directed immune reactions in the GALT: an aggressive immune response aimed at elimination of pathogens, and toleration/immunoregulation — to secure coexistence of immune system with microbiote. Antigens of normal flora bacteria are characterized by an unique ability to contribute to the development of tolerance/immunoregulation. For example, polysaccharides of a representative of the normal microflora of the intestine *Bacteroides fragilis* is a specific ligand for TLR2. The latter is one of the most important PRR in the GIT. Its ability to form heterodimers with different co-receptors provides rapid deployment of oppositely aimed programs of immune response, depending on the antigen stimulus (pathbionts or normal microflora) [43]. Recognition of *Bacteroides fragilis* polysaccharide by intestinal DC stimulates them to production of anti-inflammatory cytokines (IL10, TGF-β). It causes the differentiation of naive T-cells on Treg [44]. In addition, the lack of these polysaccharides in tha early childhood leads to the abnormalities of GALT and spleen development [45]. Supernatant of *Faecalibacterium prausnitzii* inhibits the activation of NFκB and expression of pro-inflammatory cytokines and chemokines, associated with this transcription factor [46]. *B thetaiotaomicron* in the microbiota composition are able to activate the PPARγ-dependent inhibition of NFκB-signaling [47]. A prolonged activation of TLR4 on the surface epitheliocytes and APC in the intestine by LPS of symbiotic bacteria determines the amplification of an expression of intracellular negative regulators of TLR-dependent signaling pathways [37]. GroEL (bacterial molecules, belonging to the family of heat shock proteins) of normal flora bacteria interact with TLR2 on the membranes of naive T-cells, activating their differentiation on $CD4^+CD25^+Foxp3^+$Treg [48]. SCFA play a very important immunoregulatory role.

Acetate, propionate and butyrate interact with specific G protein–coupled receptors: GPR41 (Ffar1), GPR109A and GPR43 (Ffar2). The latter is mostly expressed on the cells of the immune system. Acetate and butyrate stimulate synthesis of the secretory mucins. They also enhance the expression of proteins, providing tight junction between epitheliocytes: zonulin and occludin [49]. SCFA exert immunomodulating action only to the stimulated cells of the immune system, and do not cause any changes of the functions of resting immunocyte. The widest range of immunomodulatory activity was registered for the butyrate. SCFA have the ability to inhibit stimulated NFκB-dependent transcription of TNF-α and IL6, IL12, IL2, IFNγ and also stimulate the synthesis of IL10 moderately. They inhibit induced migration of neutrophils and their adhesion to the endothelium, inhibit the production of chemoattractants by myeloid cells and epitheliocytes, also they stimulate the synthesis of anti-inflammatory prostaglandin E2 [50]. Butyrate inhibits the stimulated proliferation of T-lymphocytes and negatively affects the differentiation of monocytes into tissue macrophages. It results in an inhibition of phagocytic function and production of reactive forms of oxygen [51].

Inflammatory diseases associated with disturbances of intestinal microbiota

There are many reasons of abnormalities in intestinal microflora: high-fat diet associated with an increased level of polyunsaturated fats (Western diet) [52], the treatment with antibiotics [1, 53], different types of stress [54], local (in the digestive tract) [55] and systemic inflammatory diseases [8], etc. In many cases, several factors act simultaneously. The consequences of disturbances in intestinal microflora are complex and can cause both local (bowel disease) [56, 57] and systemic (metabolic disease) pathological conditions [58, 59]. The imbalance of the intestinal microbiota in early childhood leads to disorders of GALT, negatively affects the homeostasis of the body and can be one of the causes of a number of immunodependent diseases including Crohn's disease, diabetes, obesity, atopic dermatitis, allergies and many others. Age-related changes in the microbiota are also associated with the development of neurodegenerative diseases.

The most common feature of disturbances of intestinal microflora is a shift in the *Firmicutes* to *Bacteroidetes* ratio. Most frequently detected pathological changes in the composition of the intestinal microbiota are an increase in the relative number of representatives of *Firmicutes* with a simultaneous decrease of *Bacterioidetes*. The shift of a balance in gut microflora in favor of *Firmicutes* is accompanied by a decrease in functional diversity of intestinal microbiota, a prevalence of metabolic cycles with a high amount of enzymes for the fermentation of nondegradable polysaccharides, and resulting in an increase of caloric content of food and increased lipogenesis [60]. The pathogenesis of diseases, that are associated with the disturbances of normal microflora, is always characterized by pathological changes in immune system, including GALT [8, 61]. For example, there are three major pathogenic factors of pathogenesis of diet-induced obesity, that are closely interconnected: abnormalities of intestinal microflora, development of local (in the gut) and system (in adipose tissue) inflammation and activation of endocannabinoid system [62–64]. The diet with a high content of carbohydrates and polyunsaturated fats causes the decrease of the relative amount of bifidobacteria and lactobacilli [65, 66]. An increased income of bile acids in the intestine, caused by the stimulatory effect of food with a high fat content on the process of biliary excretion is considered to be one of the reasons of the aforementioned phenomenon. Bile acids and cholates are charactrized by a bactericidal activity. Bacteroides, as well as bifidobacteria and lactobacilli, are more sensitive to the action of cholic acid and cholates [67]. Reducing the relative amount of bifidobacteria is accompanied by a decrease of the synthesis of proteins, that are involved in the formation of tight junctions between epithelial cells. The change of microbial community structure is also associated with increased expression of CB1 — one of the receptors of endocannabinoid system. The two main endocannabinoids are agonists of this receptor: N-arachidonoylethanolamine (anandamide) and 2-Arachidonoyl glycerol. Increased expression of CB1 is accompanied by the alterations in expression, distribution and localization of proteins of tight junctions. It results in an increased permeability of the intestinal wall. Increased lipogenesis is accompanied by a synthesis of chylomicrons and their release into the bloodstream. Increased permeability of intestinal wall leads to the translocation of PAMPs (LPS, peptydoglycan, flagellin, etc.) along with chylomicrons into the bloodstream, and activation of circulating effector cells of

immune system. From the bloodstream bacteria and PAMPs are spread to distant insulin-dependent tissues and organs, including adipose tissue, where they cause the development of inflammatory reactions. Th1 inflammation becomes a systemic. It is followed by the reduced sensitivity of peripheral tissues to insulin and obesity progression [68]. As noted above, the microbiota supports constitutive synthesis in the intestine ALPI. It is an enzyme,which is responsible for absorbtion of food lipids. In addition, this enzyme is thought to function in the detoxification of bacterial LPS by dephosphorylation of its lipid component. Disturbances of intestinal microflora lead to the derangement of alkaline phosphatase biosynthesis and decrease of LPS detoxification [44]. One of the most susceptible organs to the pro-inflammatory effect of PAMPs including LPS is the liver. Metabolic endotoxemia caused by intestinal microflora disturbances is one of the pathogenetic factors of nonalcoholic hepatic steatosis and other liver diseases [69]. PAMP-associated Th1-inflammation promotes insulin resistance and the development of diabetes mellitus type II [70, 17].

Changes in the composition of intestinal microflora lead to the development of malignant tumors in the large intestine and rectum [71]. Microbiota disturbance, that accompanies tumor growth in the large intestine and rectum is always associated with Th1-inflammation irrespective of the nature of dysbiosis.

Pathological change in intestinal microbiota accompanies the development of food allergies. A characteristic feature of this change is the reduction of proportion of *Firmicutes* spp. along with an increase of the number of proteobacteria [72]. Increased proportion of *Clostridium difficile* and *E. coli* as a part of the normal intestinal microflora is associated with the development of allergic colitis [73]. The development of Th2-inflammation is an important immunopathogenetic component of these diseases.

Disturbance of intestinal microbiota influences the development of diabetes mellitus type I. The increase in the relative amount of the three major groups of bacteria (*Actinobacteria*, *Proteobacteria* and *Bacteroidetes*) is the distinctive feature of such disturbance. Reduced relative amount of bacteria that produce butyrate and lactate is another feature of this dysbiosis [74]. Th1-inflammation is also present in the immunopathogenesis of type I diabetes.

Probiotics: general characteristics, biological effects and classification

Probiotics, in accordance with the definition of the World Health Organization (WHO), are the living microorganisms, the use of which in proper quantities improves the hosts health [75]. The main criteria of selection of probiotic microorganisms are resistance to hydrochloric acid of gastric juice and bile in the duodenum, the ability of the competitive replacement of pathobionts and modulating of the functions of MALT. Competitive replacement of pathogens by probiotic microorganisms is based on their ability to interact with the components of mucus due to the presence of specialized adhesins, such as MapA (mucous adhesion-promoting protein) in *L. reuteri* and *L. fermentum*, as well as the ability to stimulate the production of mucins by epitheliocytes [76]. Probiotics are characterized by a wide range of biological effects in the GIT and beyond. The use of probiotics is accompanied by a change in the luminal metabolism of intestine, which results in a decrease of the level of carcinogens, reduced production of sulfides and free radicals, which are potentially apoptogenic for epitheliocytes. SCFA, which are produced in an intestine as a product of metabolism of probiotic microorganisms, stimulate the vascularization of intestinal wall, proliferation and functional maturation of the epitheliocytes, that is necessary for the reparative processes. As a result, it reduces the risk of malignant transformation of these cells. Probiotic microorganisms synthesize bacteriocins, hydrogen peroxide and lactate. It enables their use in the prevention of gastroenteritises and infectious diarrheas. The most important effects of probiotics are associated with their influence on the immune system. The result of it is the maintaining/ restoring of the neutral balance of cellular and humoral immunity factors, what means, that probiotics can be used as potential drugs for the control of inflammatory processes [77–79].

All probiotics are classified into three groups: probiotics (eubiotics) — drugs, biologically active dietary supplements and products of functional nutrition, based on the living microorganisms. Considering the large number of already existing probiotic preparations there are several approaches to their classification [80]. Depending on the composition of probiotics, they are divided into such groups: monocomponent (first generation probiotics, which contain just one strain of a microorganism, such as

«Colibacterin», «Lactobacterin», Probio-Tec ®, etc.); multicomponent (second generation probiotics, which contain several strains of microorganisms, «Bificol», «Linex», etc.); probiotics, that contain microorganisms, that are not symbiotes of an intestine (third generation probiotics, so called probiotics-antagonists, which do not colonize the intestine and self-eliminate, «Bactisubtyl», «Biosporin», «Enterol», Enterogermina ®); combined probiotics or synbiotics (fourth generation probiotics, that contain both probiotics and prebiotics, for example «Bifilis», «Normobact», etc.); genetically modified probiotics (fifth generation probiotics, which are composed of genetically modified organisms, for example «Subalin»). A new class of drugs — the multiprobiotics — is a separate group of multicomponent probiotics. This probiotics (for example, «Symbiter ®») contain different «symbiters». The peculiarity of such probiotics is the principle of combining of strains of probiotic microorganisms, which is based on the mutualistic multi-symbiosis of microorganisms with synergy by a number of biological properties. Also probiotics are classified by the state of microorganisms in the preparation: dry (most probiotic preparations, which contain lyophilically dried microorganisms, such as Bifidumbacterin dry), liquid (containing micro-organisms from the fermentation medium in which they were cultivated, such as «Bioflor») and sorbed (contain microorganisms, immobilized on the carrier, such as "Bifidumbacterin-forte»). Another way of classification of probiotic preparations is classification by their purpose, based on the biological effect. Today this classification divides probiotics into four subgroups: for the ensuring of functional nutrition (animals mostly), for rehabilitative therapy and recovery of microbiocenosis after prolonged use of antimicrobial drugs, for therapy of diseases of bacterial and viral etiology, and for immunocorrection during inflammatory diseases. The last subgroup of probiotic preparations is characterized by the ability to modulate functions of the immune system on the local and systemic levels. Almost all the probiotic microorganisms have the ability to modulate of immune responses, what makes a significant contribution to the mechanism of their curative and preventive effect. It prompted several research teams to offer an add a separate group of microorganisms to the classification of probiotics by their purpose, the main biological effect of which would be immunomodulation. This group would be given the name of «immunobiotics» [83, 84].

Mechanisms and perspectives of targeted use of immunomodulatory properties of probiotics

Biological effects of probiotic micro-organisms are strain-specific. Depending on the phylum, the genus and even the strain of probiotic bacteria they can exert immunostimulatory, immunodeviating (bipolar) and immunoregulatory / suppressive effect. This phenomenon can be demonstrated by the example of lactic acid bacteria. They are characterized by a wide range of immunomodulatory activity. The direction of this activity varies within the same genus or even within a species. The most numerous group of lactic acid bacteria is represented by bacteria belonging to the order *Lactobacillales*. A typical representative of this order is genus *Lactobacillus*. *Lactobacillus rhamnosus* is a most common component of probiotic preparations. All bacteria belonging to this species carry a high content of unmethylated CpG motifs in the genome. This DNA motif is recognized by TLR9 on epithelial cells and immune cells, that results in stimulation of secretion of anti-inflammatory mediators. However, the composition of the C-G-nucleotides varies in different strains of bacteria, defining their differences in the ability to activate inflammatory metabolism of intestinal epithelial cells and immune cells. The bacteria of this genus are characterized by both pro-inflammatory and anti-inflammatory immunomodulatory activity. For example, probiotic strain Lcr35 causes pro-inflammatory activation of immune cells in the GALT. These bacteria can stimulate macrophage to produce IL12 and thereby enhances Th1-immune response against resident intracellular pathogens [83]. This property of *L. rhamnosus* Lcr35 (as well as some other strains of this species) is realized only in case of use of high doses of probiotic microorganism. It also depends on the degree of degradability of bacterial cell wall in macrophage phagolysosome [84]. Pro-inflammatory immunomodulatory effect of *L. rhamnosus* Lcr35 is local. Representatives of other strains of this species (*L. rhamnosus* CRL1505) exert stimulatory (Th1) effect not only locally on the immune cells in GALT, but also systemically - on effector cells of the respiratory tract. Immunomodulatory effect of *L. rhamnosus* CRL1505 in respiratory tract is more expressed and promotes the prevention

of respiratory infections [85]. At the same time, immune cells of the respiratory tract are insensitive to immunomodulatory effect of bacteria of the same species, but another strains [86]. Strains L. rhamnosus Lr32 and GR-1 are characterized by opposite local immunoregulatory activity. These bacteria suppress Th1-immune response by stimulating the production of immunosuppressive IL10 by different populations of cells in the GALT and the reproductive tract. The use of L. rhamnosus Lr32 and GR-1 is effective in the treatment of inflammatory bowel disease and the prevention of miscarriages respectively [87, 88]. Anti-inflammatory immunomodulating action are also characteristic for *L. rhamnosus* GG [37].

The use of probiotic microorganism separately and in combination with other can have different effects on immunological reactivity. It is of great importance for composing of multiprobiotics. *Shida et al.* analyzed this phenomenon in details, using *Lactobacillus casei* Shirota as an example [89, 90]. *L. casei* Shirota is a multifunctional immunobiotic with a wide range of different immunomodulating effects. The direction and intensity of immunomodulating action depend on the presence and properties of additional probiotic components. *L. casei* Shirota stimulates the production of proinflammatory IL12 and virtually doesn't affect the production of IL10, when used separately. This property of *L. casei* Shirota, as in case of *L. rhamnosus* Lcr35, is determined by low degradability level of peptidoglycan of this probiotic microorganism in macrophage phagolysosome. If *L. casei* Shirota is used in combination with the bacteria, which has a high degree of peptidoglycan degradability by the enzymes of phagolysosome, for example, *L. johnsonii* JSM 2012, the stimulating effect on the production of IL12 virtually disappears. The same results were observed in the case of *L. casei* Shirota use along with peptidoglycan of other G^+ bacteria. A combination of *L. casei* Shirota and a teichoic acid of *L. plantarum* or lipoteichoic acid of G^+ bacteria, such as lactobacilli or *S. aureus*, resulted in the stimulation of the production of IL10.

Another example of the aforecited phenomenon is the nature of the immunomodulating activity of *S boulardii*.. A separate usage of this microorganism is accompanied by an increased production of IL10 by lymphocytes in the GALT. Its use in combination with *E. coli* EMO and *B. animalis* significantly increases antibody synthesis in the GIT and does not affect the production of IL10 [91].

The immunomodulating effect of some probiotic microorganisms has more unidirectional nature. It concerns, for example, numerous strains of *Bifidobacterium infantis* [92, 93]. According to Konieczna et al. data, the contact of epitheliocytes with *B. infantis* results in a decrease of the production of IL8 and chemokine CCL-20 in response to the activation by bacterial flagellin. DC of different origin and phenotype are able to directly bind and phagocytize *B. infantis* with the complete degradation of murein. As a result they are being stimulated to secrete IL10 and TGF-β and not produce TNF-α and IL12 *in vitro*. The use of *B. infantis* by healthy volunteers is associated with an increase of the proportion of $Foxp3^+$ Treg in peripheral blood. Circulating mononuclear leukocytes, isolated from the blood of these volunteers, after the stimulation *in vitro* increased expression of IL10, but not TNF-α, IFN-γ, IL2, or IL12. It means, that *B. infantis* are able to activate the anti-inflammatory (regulatory) type of immune response selectively [94].

Bacteroides fragilis and its metabolites exert preferably anti-inflammatory immunomodulating effects. This microorganism interacts with TLR2 on the surface of $CD4^+CD25^+FoxP3^+$Treg, increasing production of anti-inflammatory IL10 [15, 16].

Taking into account powerful immunomodulating potential of SCFA, prebiotics are an important factor, that potentiates the immunomodulating properties of probiotic microorganisms. Addition of immunobiotic preparations with prebiotics requires taking into account mechanisms of immunomodulating effect of SCFA. The immunomodulating effect of the butyrate is mostly realized locally, in the intestine. Butyrate is the main source of energy for the epitheliocytes of the large intestine. This SCFA reduces the risk of colon cancer, as it has the ability to inhibit the histone deacetylase. In addition, it induces the activation of PPARγ, which is effective in the inhibition of inflammation in the GIT [91]. Due to this, the usage of butyrate-producting bacteria separetely and in combination with corresponding prebiotics is considered to be a prospective component of the therapy of inflammatory bowel diseases [95, 96]. This combination might also be used for the treatment of obesity, considering the high level of SCFA receptors in the adipose tissue [97]. Unlike the butyrate, acetate (SCFA, which is produced in the intestine at high level) exerts a systemic immunomodulating effect, because

it gets into the bloodstream very quickly, where it reaches the high concentration and regulates the functions of both circulating cells of the immune system and tissue leukocytes. A positive immunomodulating (anti-inflammatory) effect of acetate in the treatment of systemic inflammatory diseases, such as asthma and arthritis has been revealed [91]. In addition to already examined SCFA, probiotic microorganisms also produce long-chained fatty acids, which have an anti-inflammatory effect. Bassaganya-Riera et al. showed that the use of multiprobiotic drug VSL#3, which containes four types of lactobacilli (*Lactobacillus casei*, *L. plantarum*, *L. acidophilus* and *L. bulgaricus*), three types of bifidobacteria (*Bifidobacterium longum*, *B. breve* and *B. infantis*) and *Streptococcus thermophilus*, is accompanied by local production of conjugated linoleic acid and associated with an inhibition of the development of experimental colitis in mice, mediated by the activation of PPAR-γ in myeloid cells [98].

Immunomodulating effects of probiotic bacteria are implemented through cells-associated mechanisms and production of biologically active substances with immunoregulating properties [99, 100]. For example, exometabolites of probiotic bacteria *Lactobacillus acidophilus* and *Bifidobacterum infantis* contain low-molecular faction (10–15 kDa) with anti-inflammatory effect [16]. Probiotic bacteria *Lactobacillus reuteri* 6475 utilize L-histidine, along with production of biogenic amine with immunomodulating properties — histamine. Histamine binds to histamine receptors of enterocytes and inhibits their synthesis of proinflammatory cytokine — TNF-α [100]. Immunomodulating effects are also characteristic for subcellular components of probiotic bacteria. For example, the systemic immunostimulating action of lipoteichoic acid of *L. rhamnosus* GG affects the skin immunity and reduces the risk of development of malignant tumours, induced by UV [101]. The ability of exometabolites and soluble constituents of probiotic bacteria to modulate immune reactivity is definitely noteworthy for further study, since the intake of living microorganisms is inappropriate to immunologically compromised persons, considering the risk of bacteremia, fungemia and sepsis [16, 102]. The usage of PAMP of normoflora bacteria as an alternative to the use of living microorganisms is a promising approach for the correction of disorders of immunological reactivity in early childhood, when the immune system is not yet formed [103].

In some cases, the same symptom complex but of different etiology requires the use of different probiotic preparations. For example, in the therapy of diarrheas caused by acute gastroenteritis of rotaviral etiology in children up to 1 year a combined use of certain strains of *Lactobacillus* and *Saccharomyces boulardii* would be the most effective [104]. Whereas antibiotic-associated diarrheas in children of the same age are treated by combination of *Bifidobacterium lactis* and *Streptococcus thermophilus* more effectively [105].

Many inflammatory diseases, in the pathogenesis of which disturbance of the microbiota is present (asthma, allergic rhinitis, inflammatory bowel diseases, etc.), are characterized by circadian rhythms of clinical course [106, 107]. The basis of this phenomenon is the subordination of the interaction of PAMP of microorganisms (both pathogenic and probiotic) with the PRR into GALT to circadian rhythms of expression of the receptors of different types [108]. Taking into account this fact in determining the schedule of the use of probiotic compounds can enhance the effectiveness of their immunomodulating effect — both therapeutic and prophylactic.

Direction and expressiveness of immunomodulating effect of probiotic bacteria depends on basal functional state of cells of the immune system. The same probiotic can activate the migration of functionally neutral cells and inhibit the movement of the effectors, which are polarized to a particular phenotype, or enhance proliferation of resident tissue leukocytes and inhibit induced proliferation of circulating cells of the immune system of different populations [109]. However, phenotypic and metabolic criteria for the evaluation of the functional state of immunocytes within the MALT is extremely limited by the existing number of methodological approaches. Unfortunately, the examination of circulating immunocytes does not always adequately represent the state of the resident cells of mucous membranes. So the choice of diagnostic strategies for the assessment of immunological reactivity in perspective of its correction with the use of probiotics largely determines the success of an application of these preparations [24].

Genetic factors play an essential role for the implementation of the immunomodulating effect of probiotics. First of all, it concerns a genetically determinined disorders of PRR expression, that are associated with the development of inflammatory diseases,

including the ones in GIT [110]. It is no less important to choose and prescribe a probiotic preparation taking into account the genetically determined susceptibility of person to certain diseases. For example, probiotic preparations are frequently used in early childhood after antibiotics therapy, mainly to restore the normal microflora, especially required for the formation of Th1-immune response within the GALT and at the level of the body. In this case the drugs with the appropriate nature of immunomodulating effect must be selected. However, in the case of hereditary predisposition of the child to allergic diseases it is advisable to supplement the chosen probiotic preparation with microorganisms, which are able to stimulate the differentiation of regulatory cells, that are necessary to prevent the development of, for example, atopic dermatitis [111].

Mechanisms of immunomodulating effect of probiotic bacteria are still intensively investigated. The results of these studies indicate that the stimulation of Th1-immune response by probiotics is a consequence of activation of (MyD88)-dependent and -independent signaling cascades (MyD88 is the myeloid differentiation primary response gene 88). The mechanisms of inhibition of Th1-immune response by probiotic microorganisms are more complicated and less examined. It is known that the interaction of bifido- and lactobacteria with TLR2 enhances synthesis of negative regulators of TLR-signaling pathways both in epitheliocytes and in the APC, as well as the synthesis of regulatory miRNA; a phagocytosis of probiotic bacteria is accompanied by activation of cytosolic PRRs, such as NOD2, and causes activation of the synthesis of anti-inflammatory cytokines [112, 113]. The presence in the genome of probiotic microorganisms immunoregulating CpG-sequences, that activate TLR9 of naive T-cells, causing the formation of Treg, is very important for the anti-inflammatory immunomodulating activity of these preparations [114]. However, these studies relate to the activation separately taken PRRs only. According to modern concepts, both pathogenic bacteria and probiotic microorganisms interact with cells-participants of the immune response simultaneously through both soluble (metabolites and subcellular components, which exposed as a result of the destruction of bacterial cells) and membrane-associated patterns, that are recognized by various PRR and PRR-complexes. A complex receptor mosaic is formed as a result. Even a minor difference in this mosaic can lead to the development of a diametrically opposite reactions [100, 115].

Thus, modulation of immunologic reactivity is one of the most important mechanisms of effect of probiotic microorganisms that can be used as a basis of targeted use of probiotic preparations in prevention and treatment of human diseases. The strategy for the effective use of the immunomodulating activity of probiotics consists of three components. The first one is the knowledge of the composition and functions of the microflora of different compartments, including enterotype, age and individual characteristics of metabolome of microbiota, causes and nature of disbiosis. The second is the evaluation of the state of systemic and local immunological reactivity, immunopathogenic components of the pathological process, circadian dynamics of its progress. The third is the detailed analysis and consideration of all of the properties and mechanisms of action of probiotic microorganism (-s), specially the nature and direction of immunomodulating effect. A comprehensive assessment of all components will lead to the determination of the nature of the required immunomodulation, composition of apropriate probiotic, the schedule of its use. It will allow to realize preventive and therapeutic potential of probiotic preparations purposefully and effectively.

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ІМУНОМОДУЛЯТОРНІ ВЛАСТИВОСТІ МІКРОБІОТИ КИШКОВИКА ЛЮДИНИ ТА ПЕРСПЕКТИВИ ВИКОРИСТАННЯ ПРОБІОТИКІВ ДЛЯ ПРОФІЛАКТИКИ І КОРЕКЦІЇ ЗАПАЛЬНИХ ПРОЦЕСІВ

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Узагальнено дані літератури та власних досліджень автора стосовно впливу мікробіоти на імунну систему. Розглянуто механізми диверсифікації імунної відповіді на патогенні та симбіотичні мікроорганізми. Охарактеризовано вплив мікроорганізмів нормофлори на вроджений і адаптивний імунітет. Наведено чинники запальних захворювань людини, асоційованих із порушеннями мікробіоти. Біологічні властивості пробіотичних препаратів розглянуто в контексті їх модуляторного впливу на запальну імунну реакцію. Висвітлено перспективи застосування імуномодуляторного потенціалу пробіотичних мікроорганізмів.

Ключові слова: мікробіота кишковика, імуномодуляція, імунобіотики, запалення.

ИММУНОМОДУЛЯТОРНЫЕ СВОЙСТВА МИКРОБИОТЫ КИШЕЧНИКА ЧЕЛОВЕКА И ПЕРСПЕКТИВЫ ИСПОЛЬЗОВАНИЯ ПРОБИОТИКОВ ДЛЯ ПРОФИЛАКТИКИ И КОРРЕКЦИИ ВОСПАЛИТЕЛЬНЫХ ПРОЦЕССОВ

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Обобщены данные литературы и собственных исследований автора относительно влияния микробиоты на иммунную систему. Рассмотрены механизмы диверсификации иммунного ответа на патогенные и симбиотические микроорганизмы. Охарактеризовано влияние микроорганизмов нормофлоры на врожденный и адаптивный иммунитет. Приведены факторы воспалительных заболеваний человека, ассоциированных с нарушениями микробиоты. Биологические свойства пробиотических препаратов рассматриваются в контексте их модуляторного влияния на воспалительную иммунную реакцию. Освещены перспективы применения иммуномодуляторного потенциала пробиотических микроорганизмов.

Ключевые слова: микробиота кишечника, иммуномодуляция, иммунобиотики, воспаление.