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Environmental Problems

Environmental Determination of Indigenous Bifidobacteria of the Human Intestine

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Abstract—The environmental determination of indigenous (constantly present) bifidobacteria of the human large intestine is considered in this review. Environmental determination (from the Latin *determinere*, "I determine") is understood as a set of natural phenomena of a habitat (biotope) that determine the role of indigenous microorganisms in the microbiocenosis. Using the symbiotic approach, an attempt is made to identify the environmental conditions for the habitat of bifidobacteria and their physiological effects in the microsymbiocenosis. The features of indigenous bifidobacteria in terms of their nature have been established: evolutionary–genetic (phylogenetic remoteness, genome conservation, metabolic specialization), biochemical (lysozyme resistance, constitutive acetate production), and physiological (microbial "friend–foe" identification, immunoregulation), which are important in adaptation (persistence) and the provision of mutualistic effects and stability of the bifidoflora in the population.

Keywords: symbiosis, bifidobacteria, persistence, lysozyme resistance, acetate production, antipeptide activity, microbial "friend–foe" identification, review

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Considering that determination in the classical meaning is based on the objective causation of phenomena [1], we approached the study of indigenous bifidobacteria of the human intestine from the standpoint of *environmental determination*. In the context of microbiology, it was the Dutch microbiologist M.V. Beijerinck who at the beginning of the 20th century proposed the principle of environmental determination, specified in 1934 by his compatriot L.B. Becking. Initially, it was presented as the maxim "everything is everywhere." Then this approach was significantly limited, and an understanding was formed that environmental conditions determine the population of the biotope [2] and, hence, the range of their physiological manifestations. The consequence of this was the existence of a finite number of more or less stable zones of optimum adaptation in the multidimensional space of the evolutionary fitness landscape [3]. This approach is also applicable to microorganisms inhabiting the digestive tract [4].

The intestinal microsymbiocenosis is rightfully considered one of the most diverse in composition. The extreme complexity of the microflora inhabiting humans and animals is evident from the fact that the absolute number of bacteria in the large intestine is comparable to the number of cells in the host organism. In recent decades, the use of modern metagenomic approaches has made it possible to expand our understanding not only of the composition of the microbiota but also of its dynamics and ecology, which reflects the evolutionary side of the formation of mutualistic relationships in the "parasite–host" system [5, 6].

The great biochemical diversity and dynamism of the contents of the large intestine significantly complicate the search for the most important dependencies and relationships in the microbiocenosis and the establishment of the influence of certain factors that determine its composition and the result of interaction with the host organism [7]. Considering that the microbiota produces substances that have a significant neuroendocrine regulatory effect on the body, the intestinal microbiota can be viewed as a full-fledged

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microbial organ that takes part in ensuring the host's homeostasis [8].

The role of indigenous bifidobacteria in the human intestine is still a subject of inquiry. It has been shown that they are one of the few reliable human mutualists that do not have pathogenic properties, regardless of the state of the host organism [9]. Factual materials have been accumulated, indicating that some types of bifidobacteria have stably settled in the large intestine and remain our faithful helpers, participating in the maintenance of homeostasis [10]. Note that the relatively small number of bifidobacteria in adults and the relatively small size of the genome do not reflect their functional role in microsymbiocenosis. Thus, the specific environmental niche of bifidobacteria in the intestinal microsymbiocenosis and the respective main adaptability criteria remain unclear. In this regard, we tried to identify the most significant characteristics of bifidobacteria that determine their place in the human intestinal microbiocenosis and the mechanisms of their persistence. The features were grouped into three categories with account for the available factual material and their nature: evolutionary–genetic, biochemical, and physiological.

Evolutionary–genetic parameters of the adaptability of bifidobacteria. According to the modern taxonomy, the genus *Bifidobacterium* belongs to the family Bifidobacteriaceae, order *Bifidobacteriales*, subclass Actinobacteridae, class Actinobacteria, phylum *Actinobacteria*. The specific and quantitative paucity of representatives of this taxonomic branch, established by the results of microbiome studies, indicates the *phylogenetic remoteness/isolation* from most pathogenic and opportunistic intestinal bacteria, which complicates the process of horizontal transfer of pathogenicity and antibiotic resistance genes between them [11]. No islands of pathogenicity have been identified in bifidobacteria to date, despite several cases of their fixation (together with other microorganisms) in some infectious and inflammatory diseases [10]. The number and diversity of intra- and extrachromosomal mobile genetic elements in bifidobacteria are small, and the peculiarities of their organization do little to facilitate their transfer to other microorganisms [12, 13].

To date, a significant number of bifidobacteria genome sequences have been published and described [10, 14]. However, their reasons for living in the human gut throughout life, their adaptation and survival in the gastrointestinal environment, and their physiological effects require further study. Bifidobacteria as free-living forms of prokaryotes have a *relatively small and conservative genome*, which, in light of the trend towards its reduction [15], may reflect a steady trend of their evolution towards specialization to a particular type of biotopes by fixing the physiological capabilities. Comparative analysis of the genomes of bifidobacteria and typical representatives of the obligate anaerobic link of the intestinal microsymbiocenosis, based on the assessment of the genome size and the set of genes of two-component systems, allowed us to perform the following ranking of taxa: *Bifidobacterium* spp. (less than 2.5 million base pairs (bp), 5–19 proteins) < *Propionibacterium* spp. (2.5–3.5 million bp, 6–34 proteins) < *Prevotella* spp. (2.6–3.6 million bp, 4–22 proteins) < *Clostridium* spp. (4.1 ± 0.06 million bp, 14–32 proteins) < *Peptoclostridium* spp. (4.1 ± 0.7 million bp, 51 proteins) < *Bacteroides* spp. (5.0–6.26 million bp, 50–86 proteins) [12].

Conservation of the bifidobacteria genome is confirmed by the results of a comparative analysis of a cluster of orthologous genes specific for Bifidobacterium, the core genome, which made it possible to establish the presence of ten different phylogenetic groups partially correlated with environmental niches. For example, representatives of the *B. adolescentis* (*B. catenulatum, B. pseudocatenulatum*, and *B. adolescentis*), *B. longum* (*B. breve* and *B. longum*), *B. pseudolongum* (*B. animalis* subsp. *Lactis*), and *B. bifidum* groups are typical of the human intestinal tract and are commercially used as probiotic strains [16].

An evaluation of the adaptive potential of the microbial genome by calculating the absolute and relative indicators of the "signal census"—the number of genes for two-component signal systems [17]—showed that, on average, the bifidobacterial genome encodes more determinants of signal systems than lactobacilli and is superior in the relative regulatory efficiency to both lactobacilli and bacteroids. Next, we turned to the known determinants of intercellular communication systems through "quorum-sensing" autoinducers and found that all sequenced strains carry genes that provide both pathways for the synthesis of the key autoinducer-2 precursor, dihydroxy-2,3-pentanedione, both from S-ribosyl-L-homocysteine (luxS gene) and from ribulose-5-phosphate [18]. No homologues of known determinants of autoinducers of the homoserine lactone family, or receptors for autoinducer-2, have been found in bifidobacteria. Although bifidobacteria form a mediator of the "general bacterial presence," no specific signal systems of intermicrobial interaction have been identified in them. Considering the exceptional biochemical diversity of the intestine as a habitat in comparison with other biotopes of the human body, it can be assumed that these conditions impose specific requirements on the *regulatory and adaptive potential of the genome* of its inhabitants. This leads to the conclusion that bifidobacteria are characterized by the pronounced adaptive potential of their genome [12].

Recent advances have shown that bifidobacteria coevolved with their hosts and that many of their physiological characteristics may depend on where they live. Bifidobacteria are thought to have undergone *specific genetic and metabolic adaptations* to facilitate colonization of the human gut [19]. In particular, *in*

silico analysis of bifidobacteria genomes revealed a large arsenal of genes encoding enzymes involved in the breakdown of complex carbohydrates that cannot be metabolized by enzymes of the host or most microorganisms of the intestinal microbiota [20, 21]. The specific genetic and metabolic adaptation of bifidobacteria ensured their colonization of the human intestine and determined the actualization of their mutualistic effects as an indigenous symbiont. An analysis of a number of evolutionary genetic parameters of bifidobacteria has shown that the properties of their genome reflect the fairly long and narrow specialization of prokaryotes to a well-defined environmental host niche—the large intestine.

Biochemical parameters of bifidobacteria adaptability. The high trophic activity of the species (as one of the signs of environmental determination) can be used to analyze the role of intestinal microsymbionts involved in the processes of digestion and metabolism in the host organism. In terms of the gene composition, the microbiota has a significant individual component since two-thirds of the genes are present in only 20% of people [22]. Thus, we can say that the host transferred part of the metabolic functions to its microbiota [10]. The survival of any organism in any biotope is determined primarily by adaptation to the most common physicochemical factors that shape the environmental conditions of a particular habitat.

One of the key factors determining the possibility that prokaryotes colonize and persist in the biotopes of the host organism is their resistance to the natural antiseptic lysozyme. It has been established that this indicator in indigenous species of bifidobacteria exceeds the level of lysozyme production in the intestine by orders of magnitude [23]. Resistance to it in bifidobacteria is provided by modification of peptidoglycan, as well as resistance to its nonenzymatic action [24, 25]. High resistance to lysozyme in bifidobacteria both in the intestine and in breast milk is a selection factor for the *Bifidobacterium* spp. species indigenous to humans [26].

As is known, the adhesive activity of bifidobacteria (as one of the important factors of biotope colonization) is characterized by the variability (species and strain specificity) of both the set and structure of individual molecular determinants of adhesion to intestinal epithelial cells and the intestinal mucus [27]. It has been established that only sortase-dependent fimbriae (pili) are found in all types of indigenous bifidobacteria [28] and have an immunomodulatory effect on the production of TNF-α cytokine. The FimA gene, which encodes the main pilin subunit at the pil2 locus, has the highest variability [29].

The next factor contributing to the colonization of the intestinal biotope by bifidobacteria is the presence of various specific anaerobic biochemical transformations of substances in them [30]. Bifidobacteria are detected mainly in the parietal region of the oxygenated intestine [31], but they retain viability and metabolic activity at atmospheric oxygen concentrations up to 15% or more [32] owing to antioxidant defense mechanisms (peroxidase, NADH oxidase, the presence of the SIR2 regulator factor in the genome) [33].

The processes of metabolism in the intestine involve a wide variety of metabolic phenotypes of the microbiota, each of which can become a priority in various biochemical processes and be important both for the human body and for maintaining the microbial community in the biotope [34]. At the same time, many processes of microbial fermentation of substrates in the human body are actualized in combination since microorganisms can have only part of the metabolic pathway. Microorganisms uniting in associations methodically perform metabolic functions at the stage of fermentation and utilization of substrates. Bifidobacteria and bacteroids through "cross-feeding" interactions consistently participate in the breakdown of polysaccharides to monosaccharides with the formation of final substrates, short-chain fatty acids. Compared to the human genome, which encodes only 17 glycoside hydrolases, the bifidobacteria genome contains about 56 carbohydrase determinants that ferment oligosaccharides to monosaccharides [35]. Acetate formed by bifidoflora acts as the main joint substrate to produce butyrate and as a growth factor for a number of obligate anaerobic bacteria [36]. Thus, acetate (anion of acetic acid and its soluble salts) becomes the final metabolite of obligate anaerobes in the intestine [37].

The formation of acetate by bifidobacteria occurs through the so-called "bifid shunt" of the enzyme fructose-6-phosphate-phosphoketolase (F6PPK). An increase in the oxygen concentration in the medium does not reduce the level of acetate production either. It was found that a high intensity of acetate production can be ensured if the bifidobacteria have genetic determinants of carbohydrate membrane transport [38]. The ability to secrete acetic acid in indigenous bifidobacteria is highly conserved, constitutive in nature, being the result of their basic catabolism pathway. It is known that bifidobacteria acetate, by stimulating the anti-inflammatory function of host enterocytes, can block Shiga toxin absorption [39] and reduces the ability of salmonellae to adhere and invade [40]. In the course of our work, it was shown that the acetate concentrations created by indigenous bifidobacteria of the intestine (both in vitro and in vivo) can reduce the resistance to lysozyme of gram-positive bacteria nonresident for the human microbiota and modify their peptidoglycan by *N*-deacetylation [38]. Thus, the acetate production of bifidobacteria serves as a selection factor for nonindigenous gram-positive microbiota. The mechanism of persistence of indigenous bifidoflora through an alternative modification of microbial peptidoglycan was revealed, where acetate plays the role of the key regulator, which determines the dominant role of bifido-

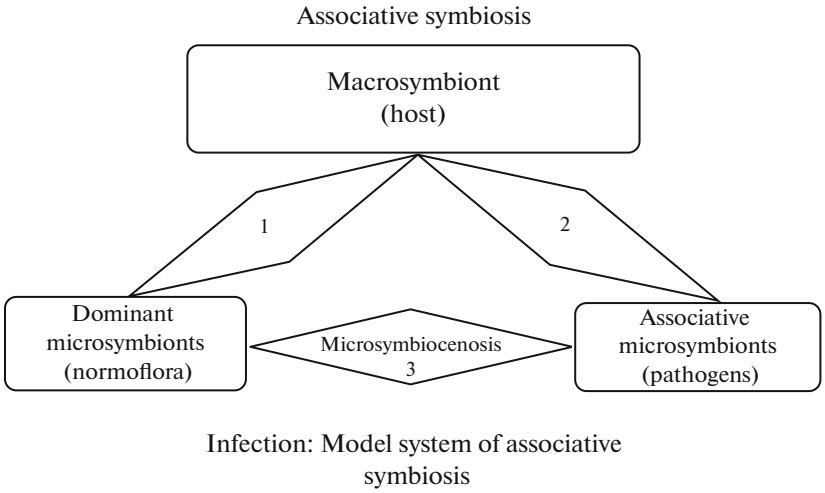

Fig. 1. Human associative symbiosis [6].

bacteria in the intestinal biotope of the host, providing both primary discrimination of nonindigenous intestinal associates through blocking de-*N*-acetylation of their peptidoglycan and preservation of the indigenous gram-positive microbiota with *O*-acetylation of peptidoglycan.

Physiological effects of indigenous bifidoflora in symbiosis. The interactions of the indigenous bifidoflora with the host and with the associative link that has entered the intestine are due to *associative symbiosis*. The term *associative symbiosis*, proposed by E.S. Lobakova, a Professor at Moscow State University, has taken root in infectious symbiology owing to its versatility. This is a multicomponent system that includes the host as the macropartner, a stable dominant microsymbiont (normal, indigenous microflora), and minor associated microsymbionts with multidirectional action. Infection is a model system of associative symbiosis with the participation of three vectors of this composition: dominants, associates, and microsymbiocenosis. The first two groups of symbionts do not require explanation for the reader, while the third term—*microsymbiocenosis*—means "sharing" (from the Greek). Microbes come together to "communicate" and "make a decision" to determine their future fate in the biotope. Surprisingly correct conclusions may follow that bacteria can remain in the biotope since there is no danger for them. Otherwise, a signal will be transmitted through the gut–brain axis to produce a homeostasis regulator, the neurohormone oxytocin of the posterior lobe of the pituitary gland, to normalize the situation [41]. This is the main point of the today's sensation: "microbes control us." We used these criteria in subsequent work as a backbone factor of microsymbiocenosis (see Fig. 1).

What is microsymbiocenosis after all? This is a single dynamic system consisting of multispecies consortia that form symbiotic bonds between themselves and the macroorganism in conditions of biocommunication to create homeostasis for the life of the host and their own. If we recognize that microsymbiocenosis is a "control panel" that allows us to regulate the situation to maintain the homeostasis of the intestinal biotope, then we acquire a new powerful ally. Maybe it is time to use oxytocin for the treatment of patients with a severe form and complications of the new coronavirus infection COVID-19? Perhaps, we have overlooked still another naturelike technology?

Returning to the ecological determination of indigenous bifidobacteria, let us give another example of the obvious usefulness of microorganisms that are directly involved in the diagnosis of the microflora of the intestinal biotope. What is it—your own or someone else's? We tried to answer this question with the help of the same indigenous bifidobacteria with account for the experience gained in working with them.

The study of the "parasite–host" relationship made it possible to formulate an algorithm for "friend–foe" microbial identification in the human intestinal microsymbiocenosis based on the experimentally revealed opposite phenomenon (intensification/suppression) of reproduction and adaptation of microsymbionts of the "dominant–associate" pair [6]. As a fundamental discovery, this pair immediately began to be used in the selection of bifidobacteria for probiotic purposes. If we add to this that bifidobacteria, in addition to discriminating against foreign material, are involved in the initial stage of "signaling," i.e., regulation of host immune homeostasis [41], it becomes clear why so much attention is paid to them.

After revealing the differences in the dynamics of the adaptive potential of bifidobacteria in criteria such as antilysozyme activity (ALA), biofilm formation (BFF), and growth properties (GP, CFU), it became clear that with a decrease in these parameters (adaptive potential and GP) of the strains studied, the input

for them closed. They simply do not take root in this environment. If microbes feel uncomfortable, their growth and reproduction are inhibited. However, if the strain is "one's own," the parameters only grow, reflecting the favorable nature of the ecological environment and the acceptance of the strain by the environment. We described this methodical technique using the "dominant–associate" pair and tested it for a number of years with positive results.

The "friend or foe" method has become widespread in the selection of promising microbial strains for the creation of new probiotics, which became the basis for the registration of these strains in both domestic (State Collection of Microorganisms of Normal Microbiota, GKNM) and international collections. New probiotic strains were proposed, such as *B. bifidum* ICIS-202 (GKNM no. 1257), *B. bifidum* ICIS-310 (GKNM no. 1258), and *B. bifidum* ICIS-643 (GKNM no. 1259) (deposited in the GKNM and registered in the NCBI BioProject database), awarded in 2017 with a gold medal at the Bioindustry International Competition Exhibition in St. Petersburg (RF patent nos. 2670054, 2726653, 2704423, and 2678123).

The use of antilysozyme activity and biofilm formation of microorganisms as a biotarget made it possible to form a line of indicator cultures of microorganisms suitable for assessing the biological activity of new target-directed probiotics. The use of these properties in connection with the new coronavirus infection COVID-19 is very relevant today since the problem of biofilm formation of microorganisms and their role in the development of inflammatory pathology of visceral organs and systems of the human body are becoming no less important.

The list of criteria to assess new probiotic strains included the antipeptide (anticytokine) activity of bifidobacteria, which we discovered for the first time [10], in relation to pro- and anti-inflammatory cytokines—signaling mediators. Using an original technique, promising strains with a pronounced immunoregulatory effect were identified, which can be used as a basis for creating new generation anti-inflammatory drugs. The results obtained created the prerequisites for the introduction of a new interpretation of understanding the mechanisms of the inflammatory response and the initial stages of adaptive immunity. An applied aspect of the study of bifidobacteria with their bivalent effect has been established: on the one hand, they regulate immunity, and on the other hand, they reduce the persistence potential of pathogens, which can be used to create combined biological products (synbiotics, probiotics). This is relevant in addressing issues of combating persistent and antibiotic-resistant pathogens.

Other studies relate the anti-inflammatory properties of bifidobacteria to the presence of anti-inflammatory proteins such as the serine protease inhibitor serpin [42], as well as extracellular macromolecules, exopolysaccharides (EPS), which form a layer of glycan mucus in the intestinal lumen [43]. Among the determinants of serine-threonine protein kinases, the gene for the cytokine receptor FN3, which specifically binds tumor necrosis factor TNF-α, has been identified [44]. In *Bifidobacterium longum*, exposure to proinflammatory cytokines (TNFα and interleukin 6) caused the expression of a number of genes, the products of which have an anti-inflammatory effect [45]. At the integral phenotypic level, the effect of such mechanisms reflects the complex participation of bifidobacteria in the regulation of innate immunity factors, maintaining the balance of cytokines and microbicides in the biotope of the human large intestine [10].

Thus, we can state that the study of environmental determination significantly expands our understanding of the mechanisms of the persistence of an invaluable assistant in the human body—the intestinal microbiota, which is on guard for our health.

* * *

The considered characteristics of the microbiota represent a set of conditions necessary for the environmental determination of indigenous bifidobacteria in the human large intestine. The evolutionary reliability of microorganisms as symbionts is ensured by their genetic features, which in intestinal bifidobacteria are characterized by *phylogenetic remoteness, genome conservation*, and *metabolic specialization*. The phylogenetic remoteness from most intestinal bacteria makes it difficult for bifidobacteria to acquire pathogenicity and antibiotic resistance factors. The conservatism of the genome and the small number of genes of signal systems evidence that bifidoflora has a simpler adaptive behavior in the microsymbiocenosis and specializes to the biotope occupied. Along with this, the parameters of bifidobacteria listed above are *strain specific* and serve as an individual strain marker ("fingerprint"), contributing to the understanding of the adaptive strategy of prokaryotes during associative symbiosis with humans.

Direct fixation of the bacterium in the biotope of the host organism occurs, as a rule, in the presence of the appropriate persistence factors. At the surface of the intestinal mucosa, bacteria should have a pronounced ability to adhere and be resistant to at least lysozyme, a universal natural antiseptic. This explains why bifidobacteria exhibit pronounced *lysozyme resistance* and demonstrate the ability for *specific adhesion* to mucus components and the surface of intestinal epithelial cells. It is possible that the *biochemical specialization* of bifidobacteria, expressed in the ability to secrete acetic acid, which is constitutive in nature, being a product of the basic catabolism pathway, is additional evolutionary evidence and a factor of such stability.

The evolutionarily long coexistence of the symbionts is facilitated by their unique properties valuable for the host, that is, special *mutualistic effects*. Understanding the role of indigenous bifidoflora in interacting with the host and microsymbiocenosis is illustrated by associative symbiosis. It has been established that the microbiota provides for the primary selection of microsymbionts, and this is done by dominant microorganisms—bifidobacteria. Primary discrimination of foreign material by bifidobacteria is the initial stage of signaling in the regulation of host immune homeostasis. Further stages of regulation are carried out by activation of dendritic cells directly by bifidobacteria and their metabolites, followed by influence on the differentiation of naive $CD4^+$ T-lymphocytes towards regulatory lymphocytes and maintaining the optimal cytokine balance of the human intestinal biotope. The listed constitutive features of indigenous species of bifidobacteria determine them as a mutualistically reliable mediator in the intestinal microsymbiocenosis and a regulator of homeostasis (health) of the host.

The material presented expands our understanding of the survival conditions and mechanisms of persistence of indigenous bifidobacteria of the human intestine, revealing their ecological features and new physiological effects in the body, which contributes to understanding the pathogenetic role of bifidoflora. The unique strains of bifidobacteria identified during this study and which are deposited in domestic and international collections and are suitable for therapeutic purposes as effective pro- and symbiotics are also of practical importance.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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