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From the Researcher's Notebook

Persistence Features of Indigenous Strains of the Human Intestine Bifidobacteria

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Abstract—In the present review, the authors draw attention to the indigenous bifidoflora, which is not always used in the selection of natural bifidobacteria to replenish the human intestinal microflora with effective strains. At the same time, the use of indigenous bifidoflora actually expands the possibilities for obtaining new strains suitable for probiotic purposes. Nature has rationally organized the constant improvement of the normal human intestinal microflora, our main assistant, thereby prolonging our life. Finding a replacement for this process is quite difficult, but quite feasible.

Keywords: indigenous bifidobacteria, persistence, probiotics, lysozyme

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Mankind lives in a vast world of various microorganisms, both useful and pathogenic for us, challenging in the form of epidemics and even pandemics (an example of this is the flu). At the Orenburg Research Institute for Cellular and Intracellular Symbiosis, Ural Branch of the Russian Academy of Sciences, work is constantly in progress to solve the question: where to get such microbes that will be our helpers, that is, where to find such probiotics that will protect our body from foreign strains? Else I.I. Mechnikov isolated such microbes from the human intestine and knew about their protective qualities. But today it is no longer the 19th century, and we have at our disposal the knowledge of our predecessors, obtained in the course of great and painstaking work.

Having established a "friendship" with the microbial world, we realized that we are interested in everything that relates to our "inmates." At the suggestion of Mechnikov, we engaged in bifidobacteria living in the human intestine. It is known that they are one of the few human symbionts that do not have pathogenic properties [1], regardless of the state of the host's immunity. They can by rights be attributed to the indigenous (own) microbiota, which has already received "education" in the human body. Indigenous microflora—bifidobacteria—is constantly present in the human intestine, helps us and protects us, in fact – this is the guarantee of our health. The indigeneity of microorganisms is closely related to their long-term survival in the host organism—persistence. This is a widespread phenomenon in infectology, a consequence of parasite-host relations [2, 3]. Persistence attracts the attention of researchers both for its little study, and for those new approaches that are revealed thanks to this phenomenon in infectology[1]. The review discusses the physiology features of indigenous strains of human intestinal bifidobacteria with the identification of a large number of unexplored issues of persistence.

Today, understanding the basics of bifidobacteria persistence, its mechanisms, and participation in the formation of the role of these strains in the host organism remain little-studied. We analyzed extensive experimental and clinical material and modern published data on the factors and mechanisms of prokaryotic persistence on the example of indigenous strains of human intestinal bifidobacteria.

THE PERSISTENCE OF MICROORGANISMS IS THE RESULT OF MUTUAL ADAPTATION OF PROKARYOTES AND THE HOST

Both bacteria and host have a remarkable plasticity that serves as a basis of their complex evolutionary

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[1] The above terms came from Latin: Indigena, aef—indigenous, natural, local [4]; persistentia, aef—preservation of the previous state, perseverance, constancy [5]; persistere—to be persistent, persistent [5].

relationships. It is this property of microbial cells in relation to environmental stress exposure that allowed them to develop various survival mechanisms in a particular specific biotope, as well as general mechanisms [6]. The dormancy of bacteria is a universal form of their adaptation to changing environmental conditions, when the microbial cell undergoes reversion with the preservation of its biological potential [7], aimed at the preservation and survival of its own population. The dormancy of prokaryotes can also be seen as a manifestation of persistence.

As one of the important mechanisms of mutual adaptation of symbionts, one can consider the universal principle of self-regulation with the formation of feedback from prokaryotic cells, where the varying feature of microorganisms is the ability to persistence, and in the case of the host, immunocompetence. It is these characteristics of symbionts that become decisive at the stage of their mutual adaptation in a specific ecological niche of the host [2, 8].

Over the past decades, the study of the persistence of prokaryotes within the "parasite–host" system has made it possible to determine the key function of bacterial peptidoglycan [2, 9], present an original classification of persistence mechanisms, and reveal new microbial secreted factors that inactivate host defense (anti-isozyme, anti-lactoferrin, anti-complementary, anti-carnosine activity), as well as factors of their regulation of various nature [9, 10]. It was found that persistent properties were universal both for pathogens and representatives of the indigenous microbiota of the host [2, 9]. Bifidobacteria as indigenous human symbionts have a wide range of secreted persistence factors [11, 12]. These features have also been established in such representatives of our microbiota as lactobacilli, enterococci, *Escherichia coli*, corynebacteria, etc. [9, 13].

A distinctive feature of the persistence potential of bifidobacteria is the presence of moderate values of traits in comparison with highly persistent pathogens [14, 15]. Probably, for the indigenous microbiota, persistent properties provide, first of all, protection of the microbial cell in the conditions of the large intestine, where the host's innate immunity factors constantly affect microorganisms. That's why, when describing the persistence potential of the indigenous microbiota, it is more correct to characterize the secretory factors not as "antifactors," but rather as signs that determine their resistance (stability) to the host's antimicrobial proteins.

It is known that the protein components of innate immunity, including lactoferrin, lysozyme, β-defensins, immunoglobulins, and cytokines, can have a direct or indirect effect on microorganisms [12, 16]. Both enzymatic and cationic properties of type C lysozyme are involved in antibacterial activity [17]. Degradation and lysis of bacteria by lysozyme, a natural antiseptic, enhance the release of bacterial products, including peptidoglycan, this process activates receptors of pattern recognition in immunocompetent cells of the human body. Paradoxically, lysozyme is also important at the stage of suppression of the inflammation process in mucosal areas [18]. The antimicrobial activity of lactoferrin against bifidobacteria is observed with a limited content of iron in the medium. Reduced β-defensins with sulfhydryl groups exhibit pronounced antimicrobial activity against bifidobacteria [19]. It has been shown that many protective proteins of the human body, having different origins and structures, posses a number of similar ligands and fixation mechanisms, which provides a synergistic (increasing) antimicrobial effect [16].

Microorganisms through secreted factors inactivate antimicrobial proteins in their microenvironment and escape from the action of protective proteins, creating optimal conditions for colonizing the host niche. However, the persistent potential of indigenous bifidobacteria does not contribute to the formation of local insufficiency of factors of the host innate immunity, while maintaining the physiological state of the intestinal biotope [20]. This is evidenced by the results of a study in the "lysozyme–lysozyme resistance" system, which made it possible to conduct a correlation analysis of the expression of persistent characteristics of bifidobacteria and the corresponding factors of local immunity of the human intestine [12]. Thus, persistent indigenous strains of bifidoflora have secreted factors that contribute to overcoming the natural barrier of the mucous membranes of the body and do not disturb its homeostasis in the microsymbiocenosis.

For indigenous bifidobacteria, a number of mechanisms have been shown to overcome the antimicrobial activity of the cationic peptides of the host, which is subsequently used for their own growth and reproduction. Carbohydrate chains associated with lactoferrin can serve as a carbon source for bifidobacteria [19]. Bioactive peptides of breast milk (α-lactalbumin, lactoferrin, IgA, osteopontin, lysozyme) have a bifidogenic effect [12]. All of the above allows us to conclude that the indigenous microbiota of the intestine was formed as a result of mutual adaptation of the host organism and bacteria, as a result, microbial cells, using host antimicrobial proteins as a nutrient substrate, acquired an important selective advantage in the occupied biotope.

No less important in the adaptation of symbionts is the fact that the indigenous microbiota, its components and metabolites, interacting with pattern recognition receptors and antimicrobial molecules, play a regulatory role in the implementation of physiological processes in the body, in maintaining the balance of cytokines and microbicidal substances [12]. Such a complex and balanced interaction between the microbiota and immunity, aimed at maintaining the integrity of the intestinal barrier under constantly changing environmental factors [21], ensures the maintenance of intestinal homeostasis and the persistence of indigenous strains of bifidoflora.

Thus, the phenomenon of persistence of indigenous microorganisms should be considered as a special case of the adaptive potential of prokaryotes in the human body formed during evolution, which does not have a pathogenetic basis and aimed exclusively at defense the microbial cell from the protective factors of the host. The presence of secreted principles in strains can provide a selective advantage for the indigenous population of bifidobacteria in the large intestine, as well as determine their regulatory role in maintaining the balance of cytokines and mucosal microbicidal substances.

PERSISTENT POTENTIAL IS A SET OF CHARACTERISTICS OF COLONIZATION BY MICROORGANISMS IN THE CONDITIONS OF THEIR ADAPTATION TO THE HOST

The human large intestine as an ecological niche provides an ideal habitat for various microorganisms. Indigenous representatives of the intestinal microsymbiocenosis, participating in the metabolic, protective and structural processes of the human body, persist throughout life and maintain its health [22]. Colonization by bifidobacteria species of various ecological niches supports the idea of anthropogenic influence, which could promote the horizontal transmission of strains between hosts. Thus, certain species (for example, *B. asteroides, B. bohemicum, B. bombi* and *B. indicum*), which were previously considered highly specialized insect colonizers, are widely distributed among various mammals [23]. However, bifidobacteria are characterized by predominantly vertical transmission, which occurs between mother and newborn during childbirth and subsequent breastfeeding. It has been established that identical strains are present in the intestinal microbiota of both the mother and child, and their prevalence and abundance are affected by both the method of delivery and the type of feeding, and the impact of antibiotics. *B. brevis, B. longum subsp. longum, B. bifidum* are most often vertical transferred from mother to child [1, 23]. This amazing phenomenon is observed not only in humans, but also in other species of mammals.

The question of the correlation between the factors of colonization and persistence of microorganisms may be of importance at the stage of determining the evolutionary and ecological features of prokaryotic indigeneity in the microsymbiocenosis of the host. This also allows to identify some adaptive features of indigenous strains that ensure their colonization and long-term survival in the conditions of the human large intestine. This topic has not been sufficiently investigated, multifaceted, and different approaches can be applied to it.

Today, in order to determine the indigeneity of bacteria, it is necessary to identify a number of genophenotypic features of microbial cells associated with the structural components of their cell surface and the processes of anaerobic fermentation of substrates. This was done by means of the example of indigenous strains analysis of *Lactobacillus ruminis*, which made it possible to establish the determinants that provide their fundamental nature in the intestines of humans and animals [22]. Strains of bifidobacteria have undergone specific genetic and metabolic adaptations in the course of evolution in order to facilitate the adaptation and colonization of the host intestine [1, 23]. Thus, the genomes of bifidobacteria encode different types of pili,[2] known as sortase-dependent pili and pili type IVb, Tad, that are of paramount importance in intestinal colonization and are able to modulate the immature immune system of the newborn [23, 24]. In addition, the role of indigenous bifidobacteria in the fermentation of glycan resources of the intestine through the building of trophic links between microsymbionts, associated with the production of biologically active substances (fatty acids, γ-aminobutyric acid, biotin, B and K vitamins, spermidine, tryptophan, tyrosine) was established [12, 25].

The complex of their persistent characteristics also contributes to the successful colonization of the human intestinal biotope by indigenous strains. Using a factor analysis of the complex of biological properties of more than 200 indigenous strains of bifidobacteria from a healthy contingent, two stable parameters of these microsymbionts were identified that determined a high level of viable cells in the intestine—lysozyme resistance (LR) and biofilm formation (BFO) (Table 1, load values greater than 0.8 by factor 1, 44.5% of the total variance). To specify the obtained data, another method of statistical processing was additionally used—a system-forming factor [25], which made it possible to confirm the information content of these features and use them in the selection of indigenous strains of bifidobacteria.

Among the persistent characteristics of bifidobacteria, significant for factor 2, the ability of strains to influence the level of key mediators Th1- (TNFα and IFNγ) and Th2-immune response of the host (IL-10) was established. The revealed activity of bifidobacteria can be associated with the presence of such proteins as the serine protease inhibitor serpin, as well as extracellular macromolecules, exopolysaccharides (EPS) [12]. Among the determinants of serine-threonine protein kinases, cytokine receptor FN3 gene, which specifically binds tumor necrosis factor (TNF)α, was identified. All this suggests that indigenous strains, colonizing the intestinal mucosa, regulate the level of mediators through secretory persistence factors, affecting cell differentiation and the direction of immune responses.

The detection of lysozyme resistance and biofilm formation allows us to conclude that they contribute to the processes of fixation and long-term survival of indigenous strains in the body as a result of the evolu-

[2] Pili are filamentous protein structures located on the surface of the cells of many bacteria.

Table 1. Factor loading of biological traits of indigenous strains of bifidobacteria of the human large intestine

Biological parameter strains	Factor 1 (44.5% total variance)	Factor 2 (24.7% total variance)	Factor 3 (11.7% total variance)	Factor 4 (19.1% total variance)
LR	**0.914129**	0.063617	0.082075	0.029637
BF	**0.865975**	0.063564	0.091068	–0.084630
AA	0.779277	–0.071679	–0.094985	0.109659
AK	0.734464	–0.035133	–0.242782	0.121949
AIgA	0.611673	–0.000551	0.007377	0.245118
PC TNFα	0.440550	0.333862	–0.085242	0.089914
ALfA	0.363192	–0.059483	0.287917	–0.000440
PC IL-17	0.180594	0.037218	0.075754	0.128385
PA	0.172401	0.088339	–0.257906	0.693880
BA	0.121607	–0.050960	–0.067217	0.690104
isoBA	0.118812	–0.130645	–0.157501	0.148003
APA IL-17	0.100890	0.257735	0.106234	–0.074004
APA IL-1Ra	0.050419	–0.065830	–0.099429	0.148489
APA IFN-γ	0.034010	**0.797927**	0.008107	0.142177
APA IL-10	0.018538	**0.840131**	–0.065623	0.031689
APA IL-6	0.016045	0.551067	–0.020170	–0.106414
PC IL-1Ra	0.011463	0.113173	0.007635	–0.017154
VA	–0.011166	0.189828	**–0.773116**	–0.008328
PC IL-6	–0.040552	0.086985	0.229670	**0.769763**
isoBA	–0.102351	–0.009125	–0.546565	0.088066
APA TNFα	–0.107663	**0.712618**	0.024176	–0.052118
PC IFN-γ	–0.163375	0.140905	–0.072830	–0.063293
KA	–0.191348	–0.109181	**–0.801704**	–0.018657
PC IL-10	–0.341917	0.354778	0.058292	–0.012347

The level of acetic (AK), propionic (PA), butyric (BA), isobutyric (isoBA), valeric (VA), caproic (KA) and isocaproic (isoKA) acids produced by strains; biofilm formation (BF), lysozym resistance (LR), anti-lactoferrin (ALfA), anti-immunoglobulin (AIgA) activity, anti-peptide activity (APA) against TNFα, IFN-γ, IL-6, IL-17, IL-10, IL-1Ra; antagonistic activity (AA) and the level of immunoregulatory activity—the ability of strains to influence the production (PC) of TNFα, IFN-γ, IL-6, IL-17, IL-10, IL-1Ra by lymphocytes.

tion of prokaryotes together with the host's immune system.

THE LIFE OF AN ADAPTED MICROORGANISM IN THE HOST ORGANISM IS A SERIES OF STEPS OF CELLULAR ACTIVATION IN RESPONSE TO THE COMPLEX ENVIRONMENTAL CONDITIONS OF THE HOST BIOTOPE

The persistence of prokaryotes underlies the formation of symbiotic interactions between bacteria and the host, where the main biotarget of immunity is the cell wall, its peptidoglycan (PG) [2, 9]. It is possible that the thesis about bacterial peptidoglycan as an immunological target can be supported by its sensitivity to many host defense factors, against which other bacterial components show high resistance. With this in mind, the main role of peptidoglycan in understanding the central issue of infectious immunology, i.e., recognizing "self" and "non-self" [2, 25], and, consequently, participation in the phenomenon of microbial persistence, becomes clear. It follows that any adaptive processes of a microbe aimed at protecting (or isolating) the peptidoglycan structure of the

cell wall can apparently be considered as persistence mechanisms.

Bifidobacteria are characterized by pronounced resistance to the universal host antimicrobial protein, lysozyme, known as lysozyme resistance [26]. Its key role in the preservation of the population of bifidobacteria in the human intestine allowed us to stop in more detail on the study of the processes of interaction between prokaryotes and lysozyme. Taking into account that the ability of bifidobacteria to show resistance to the bactericidal action of protein at concentrations 20–25 times higher than its physiological level in the intestine [27], it can be assumed that lysozyme resistance for bifidobacteria is the main strategy of their persistence. This is confirmed by the fact that the high resistance to lysozyme in bifidobacteria both in the intestine and breast milk is a selection factor for Bifidobacterium spp species indigenous to humans. On the contrary, non-residential bifidobacteria strains are sensitive to the lytic action of lysozyme [27], which may indicate a selective effect of the antimicrobial protein on the colonization and survival of prokaryotes in the host intestine. However, the mechanisms or processes involved in the formation and regulation of resistance of bifidobacteria to lysozyme are not well understood.

Among the currently known mechanisms of lysozyme resistance in prokaryotes, two main processes can be distinguished, implemented through the neutralization of muramidases with the help of lysozyme inhibitors (secretory and sorption factors), as well as through the modification of peptidoglycan of microorganisms, since this biopolymer acts as a powerful irritant of the immune system [2, 9].

Specific lysozyme inhibitors, such as proteins of the Ivy and Pli/Mli families, have been identified in Gram-negative bacteria (*Escherichia* spp., *Klebsiella* spp., *Salmonella* spp., *Pseudomonas* spp.), that correlates with their pronounced anti-lysozyme activity [25]. Enterotoxin type C of Gram-negative bacteria also has the ability to inhibit lysozyme as a non-specific factor [2]. Among gram-positive microorganisms (*Clostridium difficile, Bacillus subtilis, Enterococcus faecalis*), the presence of bacterial receptors is noted—a large and diverse family of σ-factors, in the absence of which strains become more sensitive to lysozyme and a number of host antimicrobial factors [28].

The analysis of known genomes of bifidobacteria has shown that these microorganisms are not carriers of specific lysozyme inhibitors. The identification of secreted principles in bifidobacteria made it possible to establish that their lysozyme resistance, in contrast to commensal and pathogenic microorganisms, is a nonspecific feature that may be associated with their metabolism and acetate production [29].

The metabolic activity of bifidobacteria, providing only a slight decrease in lysozyme in the microenvironment, creates the basis for the process of peptidoglycan modification—O-acetylation. In the genomes of bifidobacteria, two variants of the genes for N-acetylmuramic acid O-acetyltransferases are revealed. These determinants are present among all indigenous species of human intestinal bifidobacteria, are present in the genome of all strains sequenced by us, and are capable of providing resistance to its enzymatic action. The use of such a survival mechanism in the intestinal environment determines the advantage of bifidobacteria in comparison with a number of prokaryotes, which are characterized by the processes of de-N-acetylation of peptidoglycan [29].

Along with the modification of peptidoglycan in prokaryotes, the process of "shielding" of peptidoglycan, which is a mechanical protection of peptidoglycan using structural elements that allows bacteria to create a "camouflage" of the peptidoglycan polymer can be considered as one of the important mechanisms of persistence of indigenous strains of the human intestine. A feature of gram-positive microorganisms is their ability to form an additional capsule-like (immunoglobulin) cover upon contact with blood serum and human immunoglobulin [2, 9].

Among the surface structures of bifidobacteria, it is worth highlighting glycans involved in interaction with similar structures of the secretory component (SC) of immunoglobulin A [30]. Traditionally, secretory immunoglobulin A (sIgA) is regarded as a non-inflammatory factor that has a neutralizing effect on pathogens and their components. At the same time, the interaction between sIgA and indigenous strains of bifidoflora is characterized by low affinity, in contrast to pathogens. Bifidobacteria cells coated with sIgA contact the surface of the epithelium, helping to strengthen the intestinal barrier and reduce pro-inflammatory reactions. It has been shown that the relationship between intestinal microorganisms and sIgA is two-sided. Thus, the microbiota can modulate the distribution of sIgA in the intestine [30, 31].

All of the above opens up prospects in the study of new mechanisms of persistence of indigenous bifidoflora. Considering that various mechanisms of protection of peptidoglycan in bacteria are currently being actively studied, one can only regret that many more nature-like technologies have not been created, while infectious symbiology is the basis for solving such issues. In our work, we screened test cultures of both indigenous and non-indigenous and pathogenic human flora (*Shigella zonnei* 177b, *Shigella flexneri* 337, *Klebsiella pneumoniae* ICIS-278, *Escherichia coli* 157, *Staphylococcus aureus* 209, *Proteus mirabilis* 50/10) by agglutination reactions using a pool of human immunoglobulins to assess their immunological activity. This experiment made it possible not only to characterize the immunological activity of various microorganisms, but also to compare the results with the method for determining the foreignness of these cultures [32]. It has been established that the immuno-

logical activity of bifidobacteria is unexpressed; this may indicate a low affinity of immunoglobulins for peptidoglycan of these representatives of the normobiota, in contrast to pathogenic test cultures, which is confirmed by published data [30].

Thus, the main strategy for the persistence of indigenous bifidoflora is resistance to the action of the host lysozyme, realized through the modification of peptidoglycan, O-acetylation of peptidoglycan (the widespread occurrence of determinants of O-acetyltransferases in bifidobacteria), and the ability to nonspecifically inhibit the level of lysozyme in the medium. In addition, the formation of complexes of bifidobacteria with immunoglobulins may also be crucial for the persistence of indigenous microbiota in the human intestine. Revealing the characteristics of the persistence of microorganisms made it possible to answer the question: how to distinguish "self" microorganisms from "non-self" ones? This is quite difficult due to the lack of knowledge about the details of this process. It is possible that further study of the surface structures and secreted factors of microorganisms will help expand and replenish the persistence of representatives of the indigenous flora with new components.

THE SURVIVAL STRATEGY OF INDIGENOUS MICROORGANISMS IS BASED ON THE ABILITY OF PROKARYOTES TO REGULATE THE PHYSIOLOGICAL PATHWAYS OF THE VITAL ACTIVITY OF HOST CELLS

In works devoted to the study of the indigenous bifidoflora of the human intestine, it has been shown that bifidobacteria are a key link in the microbiota in the regulation of intestinal homeostasis, based on the formation of functional groups of strains:

- the first, regulating the balance of microbicidal proteins and cytokines;
- the second, discriminating the pathogens;
- the third, participating in maintaining the barrier function of enterocytes in the large intestine [33].

There is an idea of the role of bifidoflora in the formation of immune homeostasis of the intestinal biotope, where the primary discrimination of foreign material by bifidoflora is the initial stage of subsequent immunological signaling [34].

Considering the issue of persistence of indigenous cultures of bifidobacteria made it possible to establish the role of acetate in the discrimination of non-indigenous gram-positive microbiota by the mechanisms of lysozyme resistance. This is a new understanding of the physiological effects of prokaryotes in the body, an understanding of the protective role of bifidoflora in the host organism. However, the question of possible ways of interaction between bifidobacteria and non-indigenous bacteria, depending on the mechanisms of their persistence, has not yet been studied.

The role of acetate in the persistence of indigenous bifidobacteria in the intestinal biotope was determined through lysozyme resistance under model conditions of peptidoglycan acetylation–deacetylation. An experiment carried out on a model system showed the ability of a neutral salt of acetate at physiological concentrations created by bifidobacteria to reduce the resistance to lysozyme of bacteria with the mechanism of peptidoglycan deacetylation—*Listeria* (for example, the *Listeria monocytogenes* strain ICIS-280) [29]. The presence of acetate in the medium shifts the equilibrium of the reversible deacetylation reaction catalyzed by the de-N-acetylase of non-indigenous microbiota towards unmodified bacterial peptidoglycan [29]. This means that peptidoglycan remains sensitive to the action of lysozyme, returning to the elimination of prokaryotes from the intestinal biotope. Released by bifidobacteria in the process of catabolism, acetate affects the persistent potential of non-indigenous microorganisms, performing, in fact, the function of a regulator of lysozyme resistance in the biotope.

The data obtained by us are of particular interest from the point of view of studying the participation of persistence in the formation of the role of indigenous strains in the host organism. On the one hand, the formation of acetate by bifidobacteria is their metabolic activity; on the other hand, acetate in the parietal region of the intestine at created concentrations can indirectly act as an element of nonspecific antagonism through the inactivation of one of the key factors of persistence—resistance to lysozyme in non-indigenous microbiota. Obviously, acetate is a key regulator of the persistence of intestinal microsymbionts through the mechanism of lysozyme resistance, which is involved both in the discrimination of non-indigenous Gram-positive microorganisms (*Listeria*) by blocking the de-N-acetylation of their peptidoglycan, and in the preservation of the indigenous Gram-positive microbiota with O-acetylation of peptidoglycan.

* * *

Humanity is constantly facing with representatives of the microbial world. When they harm us by causing illness, we are forced to defend ourselves, but in a number of situations we need their assistance. Expanding the scope of knowledge of our assistants—the intestinal microbiota, we realized how competently Nature took care of a person, giving him his own, indigenous bacteria that help maintain homeostasis. That is why a healthy intestine is an indicator of the health of the whole organism. Of course, this discovery did not pass by the scientific community, and microorganisms began to be used to improve bowel function.

While systematically studying the symbiotic microorganisms of the intestine, we drew attention to the

fact that their persistence stays in the shadows. This prompted us to research in this direction, as well as to identify the nature of the relationship between bifidobacteria. At the same time, it is clear that, staying in the intestine for a long time, bacteria persist and play an important role in the functioning of the digestive tract.

FUNDING

We have access to a pantry of beneficial microorganisms that can strengthen our microbiota. The study of the persistence of indigenous bifidobacteria made it possible to select strains that will be included in the composition of probiotic preparations (registration patent application no. 2023109383), to develop a biocompatibility method (RF patent no. 2676910) of promising strains (RF patents nos. 2670054, 2704423, 2726653) for probiotic purposes registered in domestic and international collections.

CONFLICT OF INTEREST

The authors declare that they have no conflicts of interest.

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