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SYMBIOTIC GRAM POSITIVE BACTERIA: LECTIN SYSTEMS AND THEIR PROSPECTS

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ABSTRACT

Our results, suggestions and concepts regarding lectins of symbiotic/probiotic bacteria (LSB) underline their importance and future significance. LSB serve key regulators of the body's microbiocenoses. The results indicate participation of LSB in metabolic pathways of directions "Microbes—Microbes" and "Microbes—Human body". LSB is one of the key factors to converse any biotope into probiotic type. LSB support the probiotic microflora and biotope microbial infrastructure. LSB act as an anti-pathogenic cascade synergistic system that causes the destruction and then lysis of arrays and biofilms of potential pathogenic microbiocenoses such as "*Candida*, *Staphylococus* and/or *Candida* + *Staphylococus*". LSB will be especially effective (as factors resistant to antibiotics) in cases of absence of bifidobacteria and/or lactobacilli in the biotope. The synergy between LSB and other antimicrobial agents (antimycotics, phytolectins) allows the use of LSB in the design of both perspective alternative antimicrobial compositions and multipro/synbiotics. Thus, LSB are promising for medical biotechnology and agriculture.

KEYWORDS: lectins; lactobacilli; bifidobacteria; probiotics; synbiotics; conditional pathogens; microbiocenoses; systemic properties; biotopes; diagnostics; prognostic analysis.

Abbreviations

a acidic
b biotinyl
c cationic

CBD carbohydrate binding domains
CBS carbohydrate binding sites
CF cultural fluid
CPM conditionally pathogenic microbes
D optical density
GC glycoconjugates
IEF isoelectrofocusing
LB lectins of bifidobacteria
LL lectins of lactobacilli
LS lectin systems
LPB lectins of probiotic bacteria
LSM lectins of symbiotic microbes
PAA polyacrylamide (linear polymer soluble in water)
PAG polyacrylamide gel
PBS phosphate buffer saline pH 7

1. INTRODUCTION

On the one hand, probiotics as microbial cellular preparations useful for humans are represented by numerous examples of successful use to maintain a healthy body status. Most probiotics are represented by lactobacilli, bifidobacteria and their mixtures and consortia. Among them are *Acylact* (consortium of lactobacilli *Lactobacillus helveticus* NK1 and 100ash + *L. casei* K3III24), Lactobacterin (*L. plantarum* 8RA-3), Bifidin (*Bifidobacterium adolescentis* MC-42), Bifidumbacterin (including *B. bifidum* No. 1), Biovestin (*B. adolescentis* + *B. bifidum*), Biobacterin, Bifidum-Multi, Normospectrum and others refer to probiotics produced in Russia. These probiotics are based on probiotic strains originally isolated from the intestines of healthy adult individuals (Collection of Microorganisms at the *G.N. Gabrichevsky* Institute of Epidemiology and Microbiology). However, being living metabolically "changeable" cells, the survival and metabolism of probiotics cannot be reliably controlled, and in rare cases probiotic bacteria have a risk of use, manifestations of negative properties similar to those of opportunistic/ conditionally pathogenic microbes (CPM). Thus, the search and construction of non-cellular types of natural agents that mimic probiotic cells is important.

On the other hand, lectins, as carbohydrate-binding/recognizing/sensitive proteins of a non-immunoglobulin nature, are multifunctional and polydomain. They have at least one carbohydrate-binding domain (CBD) responsible for the binding of carbohydrates and glycoconjugates (GC) at the level of amino acid sequences, or a carbohydrate-binding site (CBS) – a spatial epitope, which explains the widespread distribution of lectins in nature.[1-9] Lectins can be involved in specific assemblies with various soluble or insoluble glycans, polysaccharides or GC (glycoproteins, glycolipids, other glyco-non-proteins containing exposed hydroxyl groups, as well as other targets with exposed GC) in certain stereo directions on solid, cellular or extracellular matrix surfaces.[10-15]

During the assembly process, lectin complexes: a) modulate their own multivalent and multifunctional CBS (including with the participation of CBD), and the appearance of new types of CBS and their corresponding metabolic and solid-phase targets is achieved; b) form a dynamic reversible (sometimes partial) network system of lectin associates (systemic multiple forms) that preserve or modify recognition carbohydrates, GC and their derivatives. At the same time, there is a spatial network changing location of the resulting common vector of recognition by the lectin system, which corresponds to adequate changes in the ranking of carbohydrate-containing targets by affinity and accessibility of GC sets to lectin. As a result, lectin in the biological environment is represented as: a) a lectin system (LS) of complexes and ensembles; b) a cascade of directed assembly and disassembly reactions; c) a cascade system.[16,17] For example, lectin-GC complexes and lectin oligomers are capable of exhibiting new specificities (as occurs at the junctions of lectin subunits[14]) or modulated former specificities to carbohydrates and GC. Thus, functioning cascades of the lectin type are possible, involving assembly supramolecular changes involving lectin-GC interactions and, thereby, forming a dynamic duty target recognition network.[18,19]

Lectins are represented by more than 20 families and large groups (based on structural features; classification work is ongoing) involved in the regulation of metabolism and widely used in biotechnology.[5,7,8,13,15,17,20] Lectins of symbiotic microbes (LSM) are important regulators of the relationships between microbes and eukaryotic organisms.[16] However, among LSM, probiotic bacterial lectins (PBL) are the least studied recognition factors.[8, 16, 21]

In 2004 year, we identified and partially characterized LPB systems using the example of human lactobacilli and bifidobacteria (LL and LB) lectins.[22] The present review paper expands the understanding and knowledge about LPB as a new class of natural symbiotic

compounds.[23] LPB play an important role (they have sets of important network activities) in the human superorganism in the regulation of inter- and intra-cellular population relationships between microbiocenoses in biotopes and in host microbiocenosis systems.[24, 25] The data obtained make it possible to assess the potential of LPB as factors co-functioning with other human defense systems produced by probiotics.[26, 27]

The purpose of the work is to review the current state of LPB research in terms of their prospects for biotechnology and medicine.

2. RESULTS

2.1. Purification and properties of LPB

Criteria for the choice of bacterial sources of LPB: a) probiotic lactobacilli and bifidobacteria, b) industrially significant strains, c) consortium variants with enhanced antagonistic activities against microbial reference variants. The probiotic *Acylact* met all these criteria. Thus, isolated LL are represented by a combination of lectins of all strains of lactobacilli of *Acylact*. Similarly, LB are represented by a combination of lectins of strains MC-42, No. 1 and GB (ingredients of a number of probiotics[28]). The lectins of probiotic lactobacilli and bifidobacteria originally isolated from the intestines of healthy adult individuals were studied.

The identification of LPB[24] was carried out using a set of biotinylated synthetic linear polymer water-soluble GC (pseudopolysaccharides) (www.lectinity.com). The advantages of such GC were homogeneity (determines the unambiguity of the interpretation of the specificity of lectins), polyvalence (the presence of multiple carbohydrate residues repeating in clusters in the form of lateral branches from the linear axis of polyacrylamide [PAA], providing strong binding to CBD or CBS); similarity with the cluster arrangement of carbohydrate residues in protein sequences in mucins – the dominant components of the mucosa of the human body cavities – objects of mucosal immunity; imitation of antigens; the possibility of using instead of insoluble polysaccharides (chitin, pectin, other dietary fibers); the possibility of interaction of a GC molecule with several lectin molecules (additional strengthening of the binding strength of lectins and GC in biotope infrastructures); the use of GC lectins as a matrix for supramolecular directional assemblies.

The critical stage of LPB identification is isoelectrofocusing (IEF) of protein fractions within a polyacrylamide gel (PAG) plate followed by electroblotting of lectin components onto the membrane. Membrane-bound lectins treated with GC-b were visualized by streptavidin

peroxidase conjugate in the presence of a chemiluminescent peroxidase substrate in the "Dark Room" of the *BioChemi System* (UVP, Calif., USA). To select the optimized mode and the corresponding picture, the kinetics of chemiluminescence of the blot was recorded in the form of a changing live image as a series/gallery of patterns with consistently non-linearly varying exposures of capture and accumulation by a bioluminescence detector controlled on a computer display. Major and minor areas of the LPB system arrangement were identified.

Lectins found in the acidic region of the pH gradient (in the range pI 4-4.5) were considered as acidic (a) LPB (aLL and aLB preparations), and lectins found in the alkaline (cationic) region (in the range pI 7.6-8) were considered as cationic (c) LPB (preparations cLL and cLB). Additional LPB were identified as slightly acidic (in the range of pI 5-6)[29] or near-neutral. Synthetic mannan [GC as poly-Man]- or (mucin-like [GC as poly-GalNAc])-binding LPB were considered as LL-binding (mucin-like binding was observed) and LB-binding (preferential binding of α-D-mannan). The preparations of LL (aLL or cLL) of *Acylact* reflected the contribution of the corresponding aLL or cLL of ingredient strains of *Acylact*. Similarly, LB preparations included aLB and cLB contributions of MC-42, No. 1 and GB strains complemented each other.

LPB were localized on the surface of bacteria as part of complexes that were desorbed in the presence of 1-3 M LiCl (but not NaCl).[24] The system of cell surface LL (as more protected) was represented by an increased number of forms compared with the system of secreted LL (as more dissociated and accessible to environmental hydrolases) into the culture fluid (CF).[30] The maximum number of forms of LL was obtained as a result of boiling the preparations in the presence of sodium dodecyl sulfate (DDS) and 2-mercaptoethanol (ME).

LPB purification

Being a part of complexes on the bacterial cell surface, LPB can be easily desorbed *in vitro* and naturally (under the influence of endogenous compounds similar to the action of detergents) partially transform into CF. This occurs in the presence of chaotropic agents in combination with surfactants (endogenous biosurfactants or exogenous agents added to the medium), as well as in the presence of metal chelated substances. The method of purification of active LPB is protected by a patent.[31] The LPB purification procedure takes about 3 days. The obtained LPB preparations were characterized as colorless, transparent, tasteless and odorless liquids, stable when stored in eppendorfs in the freezer in the form of small stock portions.

Physico-chemical properties of LPB

LPB exhibit the properties of hydrophobic proteins and can be represented as aggregated (with the properties of nanoparticles) assembly forms with partially exposed aromatic amino acid residues, spectrophotometrically controlled in the cases of Tyr, Trp and Phe and their derivatives. The protein stability of LPB required the presence of a cocktail of protease inhibitors ("Complete", R& D) of all four Enzyme Classification (EC) subclasses of proteinases EC 3.4.[15] The disappearance of the detectable protein in the cLB preparation was observed when stored in glass penicillin vials (compared with storage in polypropylene tubes) for a long time (several months), which indicated sorption of the protein onto the glass. LPB contained metal cations. Thus, the major forms of LPB of NK1 (the strain that is the dominant contributor to *Acylact* in terms of lectin diversity) contained 2 Ca^{2+} atoms in the molecule. The fluorescent properties of LPB (especially in the case of LB) were enhanced in LPB complexes including endogenous exopolymers (soluble, in the composition of CF).

The above data allow to classify LPB.[5,7,8,16,17] LPB can be considered as: cell surface protein recognition complexes; (Ca^{2+} and/or cations of other metals)-containing and binding proteins; proteins with a relatively poorly organized secondary structure (a decrease in the level of randomly organized structure was observed during refolding procedures, as part of complexes, including on surfaces); predominantly mono- or bivalent substances (with one exposed CBS in the subunit and an additional CBS within the region between the protein molecules of the complex) with weakly pronounced hemagglutination, like pan-agglutinins[32] (highly sensitive sensitized homogeneous cellular systems are required to work with LPB); agents with the ability to create non-covalent complexes and cascades, oligomers, aggregated (nano)particles and assemblies; members of functional superfamilies.[16]

Biological properties of LPB

LPB mimic the main activities of probiotic cells: antimicrobial, antagonistic, immunocorrective, supporting the functioning of the consortium, stabilizing the healthy status of biotopes in the Microbes—Microbes and Microbes—Host directions. In addition, LPB exhibit unique properties that complement probiotic cells and convert them into synbiotics with an expanded range of beneficial activities (as combinations of Probiotics + LPB).[28]

LPB were represented by four types of preparations. LL (acidic and cationic) and LB (acidic and cationic) were isolated and studied in detail. In addition, in the case of slightly acidic LL identified on the blots after transfer from IEF-PAG, their potential co-functioning with the

oxidoreductase system within the potential combined lactobacillar consortium of *Acylact* and *L. plantarum* 8RA-3 was assumed (the strain 8RA-3, according to our data, can serve the source of a pronounced lectin system.[22][29] The role of such LL may be manifested in the regulation of the protection of probiotic consortia in biotopes from peroxide stress (excess of peroxides). Examples of regulation (including in cascades) of oxidoreductases by lectins are well known.[15] However, other possible functions of near-neutral LL remain poorly understood.

***Interactions between LPB and GC*[14, 20, 22, 24, 33, 34, 36-39]**

The major forms of the obtained soluble LPB are mainly represented by molecules and their complexes with at least one CBS. Such LPB require adequate highly sensitive test cell systems, for example, prepared using optimized hydrolase treatments of erythrocytes - to visualize LPB-induced hemagglutination in a color reaction.[32,33-35] In the hemagglutination reaction of human erythrocytes of the AII(+) blood group treated with *Clostridium perfringens* sialidase, the interaction between LPB and GC proceeds as equimolar (1 : 1, M/M).

Using a set of GC, we identified various lactobacilli and bifidobacteria-secreted lectins using mainly the following three methods: a) dot-bloting of concentrates and fractions of the CF supernatant on the hydrophobic membrane *Immobillon P* (Millipore), b) bloting of proteins after IEF-PAG separation of concentrated fractions of the CF supernatant, c) sorption of lectins on sialidase or trypsin-treated human erythrocytes of the AII(+) blood group (with exposed GalNAc residues mimicking the mucin surface).[5,31,33,36,40]

For screening and identification of CF lectins of an expanded number of promising strains of lactobacilli and bifidobacteria, sets of synthetic GC (0.5-5 mcg/ml, in PBS) containing repeatedly exposed short carbohydrate antennas (1-3 carbohydrate residues in antenna) departing from the biotinylated (b) PAA chain or not biotinylated (www.lectinity.com), imitating natural glycopolymers (on the right in parentheses):

*$(Fuc\alpha1)_n$-PAA-b [α-L-fucan-like],

*$(Gal\beta1)_n$-PAA-b [β-D- galactan-like],

*$(Gal(3\text{-}Sulfate)\beta1)_n$-PAA-b [$(3\text{-}HSO_3Gal\beta1\text{-})_n$; β-D-galactan-3-$SO_3$ polymer],

*$(GaNAc\alpha1)_n$-PAA-b [$(Tn\text{-like antigen})_n$ polymer],

*$(GalNAc\alpha1,3Gal\beta1)_n$-PAA-b [$A_{di}$ as $(blood\ group\ AII\text{-like antigen})_n$ polymer],

*$(GalNAc\alpha1,3GalNAc\beta1)_n$-PAA-b [Fs as $(antigen\text{-Forsman-like})_n$ polymer],

*(GalNAcα1,3GalNAcα1)$_n$-PAA-b , [(cervical cancer marker antigen)$_n$ polymer]
*(Galα1,3GalNAcα1)$_n$-PAA-b [($T_{αα}$-like antigen)$_n$ polymer],
*(GalNAcβ1)$_n$-PAA-b [desialylated mucin-like],
*(Galβ1,4GlcNAcβ1)$_n$- PAA-b [(LacNAc)$_n$-containing mucin-like],
*(GlcNAcβ1)$_n$-PAA-b [soluble linear chitin-like],
*(Manα1)$_n$-PAA-b [α-D-mannan-like],
*(Man(6-H_2PO_3)α1)$_n$-PAA-b [(6-H_2PO_3Manα1-)$_n$ polymer; α-D-phosphomannan],
*((MurNAc-L-Ala-D-isoGln)β1)$_n$-PAA-b [MDP-; (muramyl-dipeptide)$_n$ polymer; (bacterial peptidoglycan)-like],
*(Rhaα1)$_n$-PAA-b [α-L-rhamnan-like].

The chemiluminescence patterns of LL and LB separated by IEF-(PAG plate) and blotted differed and required additional individual optimized modes of registration of blot parts. The study showed that: a) the patterns of LPB systems are unique and depend on the nature of the strain, b) the dominant types of LPB are represented as mucin- and/or mannan-binding; b) LPB of the probiotic consortium (*Acylact*) include LPB of ingredient strains. Mannan-binding lectins of *L. plantarum* 8RA-3 had increased chemiluminescence intensities.[22] These results were confirmed by a study of the specificity of LPB to GC in hemagglutination reactions.[5,33] Dissociation of LPB—agglutinates (hydrolase-treated erythrocytes of the AII blood group) was observed after the addition of adequate GC (0.5-1 mcg/ml, final concentration). The effectiveness of GC decreased in the following order: (poly-GalNAc-PAA as mucin-like or pseudomannan-PAA) > pseudogalactan-PAA >> pseudochitin(soluble chitin analog)-PAA (no influence).

In other series of experiments, the set of probiotic strains was expanded, as well as the set of GC for the identification of new types of LPB using dot-blotting analysis.[36, 40] It has been shown that LL and LB are able to recognize chemiluminescent images/patterns of GalNAc-containing GC in a live (kinetic) image (images containing multiple GalNAc residues repeated as clusters of short side chains - exposed, masked or duplicated [two GalNAc residues in each side chain]), including in the composition of glycoantigens Adi-, Fs- or Tn-, depending on the nature of the probiotic strain and the consortium. There was no binding of LPB to antigen-like GC of type $T_{αα}$. LPB also recognized (distinguished) synthetic peptidoglycans, mannans, and mucins. Due to the fact that LPB are represented and function as LS[16], effects are possible when two or more forms of LPB (major and minor forms) vary

in specificity, similarity (part of the mosaic of the LPB pattern of different strains is visible on a blot with the same specificity) and differences (mosaic of the strain lectin pattern, in general, as a unique one, with a ranking of the intensity of lectin components with similar specificity, and some components simultaneously recognize two [or more] types of GC targets), the recognition potential of species and genera (lactobacilli and bifidobacteria) can be established.

Using the dot-blotting method, at least 7 types of drugs were identified in the case of an expanded set of promising strains of lactobacilli and bifidobacteria that occur in the human intestine. Among them, LS were represented by lectins, which largely recognized synthetic α–D-mannans (phosphorylated or not, similar to yeast), α-L-fucan (similar to fucan from brown algae), peptidoglycans (similar to bacterial), mucins (similar to intestinal); antigens of Tn (tumor), Forsman (Fs, an interspecific specific antigen present on erythrocytes of many species, as well as on the surface of some microorganisms), a substance of the AII blood group. Such lectins have been identified as mosaic (systemic) within the mainly acidic protein array.

The above data on the interaction of LPB and GC indicate that LPB can serve as an important functional characteristic of both the microbiocenosis in a biotope and the relationship of microbiocenosis with the human body. LPB can serve as a basis for the study of biotope metabolic relationships involving probiotic/synbiotic bacteria as antagonistic factors against CPM in order to maintain the status of a healthy biotope. In addition, LPB are a promising basis for the design of co-functioning LPB systems together with plant ingredients (yeast and from higher plants).

Antimicrobial activities of LPB against clinical microbial strains and isolates[23, 26, 29, 41-50] included such as,

* inhibition of CPM growth:

- biodegradation (including delayed lysis):

-- synergistic effects of LL and LB:

--- against staphylococci (efficacy: LL > LB);

--- against micromycetes (effectiveness: LB > LL);

-- synergistic effect of LPB and antibiotics:

--- LB and antimycotics: against species of the genus *Candida* (prospects for reducing therapeutic relatively high doses of antibiotics and their side effects; the possibility of

alternatives to antibiotics if necessary; alternating types of antimicrobial agents due to the multi-resistance of pathogens).

-- cascade and prolong antimicrobial action (action of aLPB followed by action of cLPB);

-- competitive use of CPM resources (for example, in conditions of an excess of lactobacilli in the vagina) during the stages of CPM life cycles;

-- LPB-induced "incorrect" assemblies of CPM biofilms with their subsequent accelerated and directed degradation;

-- effects of LPB as metabolombiotics (selection and/or switching of metabolomic pathways/networks).[51, 52]

-- increased synergistic degradation of CPM populations up to their lysis in conditions of stress.

Important generalizations regarding the antimicrobial activity of LPB should be noted. The action of LPB (LB and LL) is directed against colorectal (the use of a combination of LB and LL is promising) and urogenital (the inclusion of LB is especially advisable due to the absence of bifidobacteria) clinically significant strains of human biotopes. LPB act as members of a new functional class of biofilm destructors.[23] The anti-staphylococcal and anti-*Candida* effects of LPB reveal a multi-stage territorial synergy (differing areas of action between aLL and cLL, aLB and cLL, aLL and aLB, antibiotics-like action, delayed lysis) and over time (early antibiotics-like action, later lytic action of aLPB, followed by lysis by cLPB). There is a multi-synergism of the anti-*Candida* action of LPB and antimycotics (azoles, amphotericin B, nystatin). In general, LPB mimic the antistaphylococcal and anti-*Candida* effects of probiotic cells - lactobacilli and bifidobacteria[53, 54], have selective affinity for target cells and can be used in the treatment of candidiasis and staphylococcosis.[47]

It should also be noted that LPB have advantages over other antimicrobial agents: prolonged action; cascading synergistic effect at low subcytoagglutinating doses; independence from antibiotics used in treatment (while probiotic cells can be inactivated by antibiotics). In addition, ketoconazole and some other antibiotics are poorly soluble in PBS and other aqueous compositions, which often reduces their resulting final effectiveness and their control capabilities.

LPB activity in relation to the probiotic compartment of the biotope[55-57]

LPB exhibit a number of communicative activities, including in relation to populations of lactobacilli isolated from the same biotope (urogenital).[55] The results indicate that LL

maintain a healthy status of the biotope's normoflora by implementing surveillance and signaling functions, participating in *Quorum Sensing* (QS)[50,55] and *Cross Talking* [58, 59]. There is reason to believe that when delivered to the body (for example, into the biotopes of the rectal and/or vaginal cavities) LPB will strengthen the synbiotic biotope compartment (lead to a positive shift in the existing negative balance) against the background of general positive events in the direction of the Host—Microbes, opposed to the CPM compartment in the biotope and the body.

Other biological activities of LPB

LPB activity in relation to mammalian defense system cells

*inducing the production of tumor necrosis factor-α (TNF) by leukocytes from peripheral blood cultures of patients[59,59];

*modulating migration of intraperitoneal macrophages in a manner different from action of GC (including LPB-specific ones)[23];

*protection/preservation of eukaryotic cell metabolism (erythrocyte metabolism).

Predicted LPB activity based on similarity to LSM[16], other bacterial probiotic lectins, animal lectins and phytolectins.

*LPB as ingredients of dosage forms in cases of pathologies of the rectum and colon (potential efficacy: LB > LL) or urogenital pathology (potential efficacy: LL > LB, against the background of the absence of bifidobacteria); at the same time, additional effects of LPB are realized such as support for the probiotic compartment of the biotope, stabilization of the relationship of probiotic-oriented microbiocenosis with the infrastructure of the human biotope;

*Direct and indirect (action of LPB through complexation and as carriers of GC effectors) antitumor effects: against altered human cellular systems with impaired GC decor (similar to the action of LPB against eukaryotic CPM as foreign to the body) (potential efficacy: LB > LL); through enhanced affinity of LPB to [(poly-LacNAc)-PAA]-like targets as the basic basis of a family of potential tumor antigens[14] (potential efficacy: LL > LB);

*Against *Protozoa* pathogens (similar to the prolonged action of LPB against micromycetes – another type of eukaryotic pathogens – yeast-like fungi on the examples of *Candida*);

*Against viruses (similar to the effect of *Acylac*t against rotavirus infection in children; similar to mannan-binding phytolectins with activity against human immunodeficiency virus-1 [HIV-1, glycoprotein 120 kD]);

*Intracellular sorting into organelles and vesicles (due to the ability of LPB to recognize [(poly-Man-6-P)-PAA]-like natural GC on the surface of targets similar to Man-6-P-binding lectins of animal lysosomes, including humans);
*Biocompatibility and synergism of LL and/or LB together with other probiotic microbial lectins and their associates as antimicrobial systemic agents;
*Biocompatibility and synergism of LPB together with other types of antimicrobial agents with mechanisms of action other than LPB (antibiotics and others);
*Possible formation of an additional antimicrobial pool – active fragments of LPB (including those with lectin activity against limited sets of GC) in the presence of host and/or microbial hydrolases of limited/restrictive hydrolysis in the general interactive environment of the biotope.

The above data demonstrate the wide potential of LPB and LSM for medical biotechnology and microbiology.

The prospects for wider use of LPB and LSM are shown below.

Promising areas of application of LPB and LSM.
*for cell cultures (auto- and heterostimulators, support for pro/synbiotic bacterial and eukaryotic cultures, including mixed, in the presence of CPM, etc.);
*in diagnostics (microanalysis; for typing and standardization of CPM strains; for detection of disturbed normal cell surface and biotopes or the metabolomic network of the interactome of the organism)[42, 43, 46];
*in the design of biological additives and dosage forms (systemic drugs with synergistic and selective action as anti-CPM agents, as well as factors supporting the probiotic compartment of biotopes)[56, 57];
*in the construction of predictable lactobacilli and bifidobacteria-based pro/synbiotic-like consortia using algorithmic approaches and ranked prognostic and diagnostic patterns:
- maintaining the status of the metabolome network;
- switching (on/off, modulating) microbial networks and cascades;
- control of the functioning of microbiocenoses; provision and implementation of "training"/ adaptation of surrounding cells, including in the composition of biofilms;
- in designing pro/synbiotic microbiocenoses;
- directed anti-pathogenic action (against initiated/activated CPM) through external LPB-dependent changes in the ontogenesis of pathogens and CPM[23];

- helpers (active helpers) in the construction of cellular, cytokine-like and mixed gradients and cascades on the solid phases[33];
- synergistic and synbiotic factors in mixed cultures of microorganisms or host biotopes[46];
- stabilizers of poorly growing pro/synbiotic microorganisms[55];
- co-functioning with other LPB-like and different from LPB antimicrobial agents produced by the pro/synbiotic compartment of the biotope (bacteriocins, antimicrobial peptides and biosurfactants)[31, 60];
- co-functioning (synergism) with: human cytokines (including LPB, as cytokine inducers, for example TNF-α), defensins, antibiotics, antibodies[9, 58, 59];
- synergy between LPB signaling and signaling proteinases/(oligo)peptidases and (oligo)peptides of the environment;
- screening, selection and typing/ standardization of strains;
- ingredients of cell-free therapeutic ointments and cosmetic creams (to improve formulas).[60];
- in recombinant lectin technologies[20];
- carriers for the delivery of the GC type drugs, low molecular weight highly hydrophobic heterocyclic effectors (antibiotics, antitumor agents, inducers of apoptosis, others)[3, 20];
- ingredients of multifunctional biological additives;

*in the design of cascade biosensors based on assembly composition and organization [for monitoring a healthy balance in the biotope; for screening strains, their mixtures, microbiocenoses and consortia antagonistic to CPM, including as part of associates and biofilms on solid (as a special case, interfacial) surfaces (sensitized membranes, polystyrene or polypropylene);

*in systemic therapy, when added LPB (LL and BL) will modulate the spectrum of systemically important activities;

*in landscape microecology and microbiological architecture of functioning homo- and hetero-massives of microbes and microbiocenoses (LPB as direct participants and organizers of landscapes and architectures[46]);

*in the study of the hierarchical glycome of an organism ordered into a network.[19]

It is obvious that solid-phase and cellular surfaces are of primary importance for directional assembly (and hence disassembly/degradation in case of reversibility of events) initiated by LPB (increased accumulated interphase concentrations of reactants will more efficiently and faster initiate/launch directional assemblies on the immobilized first components of cascades

to obtain extended and branched asymmetric products). That is why LPB accumulated in the pores of hydrophilic PAG or hydrophilic multilayer membranes (such as *Durapore*, Millipore), LPB on hydrophobic polyvinylidene fluoride (PVDF) membranes (such as *Immobillon P*), at the bottom of polystyrene wells of micropanels or the surface of latex and other (nano)particles are particularly promising.

3. CONCLUSION

Aforementioned results, suggestions and concepts regarding LSB indicate importance of LSB and their further significance. LSB reveal themselves multifunctional regulators within the body's mucosal microbiocenoses. LSB are involved in cell-cell and cell-metabolic directions "Microbes—Microbes" and "Microbes—Human body". LSB serve one of the key factors of conversion of biotope into the system with probiotic action. LSB support the probiotic microflora and participate in organization and functioning of biotope infrastructure. LSB can act as an anti-pathogenic cascade synergistic system (the system with prolonged action) that causes the destruction and then lysis of arrays and biofilms of sensitive species of genera *Candida* (for examples *C. albicans*, *C. tropicalis*) and *Staphylococus* (for example *S. aureus*). LSB can be used instead of (in cases of absence of bifidobacteria and/or lactobacilli in the biotope) and together with probiotic cells. The synergy between LSB and antimycotics and phytolectins allows the use of LSB in the design of new antimicrobial compositions. The properties and activities of LSB isolated from industrial strains of human probiotic lactobacilli and bifidobacteria can be used in the design of multipro/synbiotics. That is why LSB are promising for medical biotechnology and agriculture.[61]

Disclosure of conflict of interest

The authors declare no conflict of interest.

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