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Mucosal Opened Cavities as the Organ of Increased Resistance and Effectiveness

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Authors' contributions

This work was carried out in collaboration between all authors. All authors read and approved the final manuscript.

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ABSTRACT

New aspects of human mucosal cavity protection systems are under consideration. On the basis of own data it was suggested that mucosal cavities function as mucosal organs. New players of mucosal organ were proposed. They included system probiotic lectins and probiotic microorganisms, and system synthetic polymeric multivalence pattern glycoconjugates. Resulting interacting biotope pro/synbiotic system of microbes, lectins and glycoconjugates (mucin-like or imitating, antigens and others) was suggested to communicate to other glycoconjugates-recognizing molecules and receptors of the human higher hierarchic protection systems. Conception of functioning mucosal organs is supported by own proposals, strategies, approaches, methods and algorithms. The data are also useful for constructing biotope pro/synbiotic microbiocenoses for application in medical biotechnology.

Keywords: Mucosal organ; mucosal barrier; biotope; microbiocenosis; probiotic; lectin; glycoconjugate; antimicrobial; synbiotic system; leader microorganism; pathogen.

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ABBREVIATIONS

GC : Glycoconjugates
MGC : Mucin type glycoconjugates
MO : Mucosal organ
L : Lectins
LL : L of lactobacilli
LB : L of bifidobacteria
LS : Lectin system
LSPB : LS of PB
PA : Polyacrylamide
PAG : Polyacrylamide gel
PB : Probiotic bacteria
SLS : Super lectin systems
QS : Quorum sensing

1. INTRODUCTION

A lot of diseases is connected to altering processes in human organism involving changes in glycome [1].

On one hand, a number of human recognition systems protect interactome of organism [2,3]. Such systems involve a lot of examples of recognition between lectins and glycoconjugates (GC) [2,4]. Indeed, some cytokines, defensins, pattern recognition receptors and molecules, components of complement and blood clotting, protein hormones and their receptors are important participants of human metabolome network and reveal addirional properties of true lectins [2,3]. Lectins act as universal cofunctioning recognition system regulating human interactome involving GC. On the other hand, microbiocenoses are important part of any human biotope. Together with complement and other human recognition systems, microbiocenoses are also involved in protection against diseases. Pro/synbiotic compartments of microbiocenoses, biotope, mucus and mucosal opened cavities counteract relatively pathogenic compartments at different levels of structure-functional organization of human organism. Synbiotic biotope compartments involve complementary network of GC interacted to probiotic lectin systems (LS) [4-6]. Intestinal mucus is under consideration as potential target organ [7]. However protection aspects of mucosal opened cavities which may act as mobile mucosal organs (MO) are not investigated enough.

The aims were to use mainly own data for a) development of conception of functioning human opened cavities as MO involving recognition of GC (one player) supported by probiotic lectins together with probiotic microorganisms or probiotics (another player); b) description of biotechnological resources of MO which simplify applications of MO against pathological processes in organism for goals of medical microbiology.

2. CONCEPTION AND STRATEGIES

Conception of functioning mucosal opened cavities of organism as its MO includes the following general positions.

1. Universality of structure-functional organization of mucus, individuality of biotope mucus, tropism of local mucus, state of locally changeable mucus in on duty regime.
2. Phenotypes of local MO depend on relationships between probiotic compartment and relatively pathogenic compartment of biotope [8].
3. Due to contribution of interactions between mucins and between lectins and GC, mucus as MO is characterized by 3D-architecture organization of host cells and microbiocenoses [9,10]. Directed organization of MO is programmed by evolutionary molecular, cellular and other mechanisms including biorhythmic assembling-disassembling (periodical abruption and changing of mucus; inducing biosynthesis and degradation).
4. MO reveals itself as multifunctional organ possessing different adaptive network properties. MO reveals itself as trapping, delivering, adjuvant, stabilizing, preventive, immune modulating, vaccinating, and therapeutically reacting instrument in its replies on any form of stress.
    - MO is opened one to such communications as quorum sensing (QS) and cross-talking.
    - MO repairs and corrects protection processes of recognition/ isolation/ conservation/ elimination/ prolongation in regime of retaining and keeping functioning on duty reversible relationships together with surroundings.
5. Main structures of MO are ranged as synchronized in direct supervising supported with opposite control in relationships: MO—Mucosal layer (external, intermediate, inner)—Cell barrier—Epithelial cell surface—Membrane mucins [9,11,12]. It takes play multilevel regulation of mucosal barrier by human and microbiocenoses' systems.

6. MO reflects microbiocenoses balance, antagonistic relationships between probiotic and potentially pathogenic microbiota [8,13,14]. MO orders mucosal and cellular barrier for localization, submission, fixation and inactivation of pathogens, exclusion of pathogens distributed all over the organism, prevention of cellular transformation of epithelial cells into cancer cells [1,8]. Gradient disposition of microorganisms in MO must be taken into consideration [12].
7. Interactome network reveals of coupling relationships between antioxidant, antimicrobial, antiviral and antitumor activities of MO [3,5,6,15,16].
8. Sensitivity of eukaryotic pathogens (yeast like mediators between bacterial compositions and associates of microbiocenosis and tissues of the host biotope) to antimicrobials (LSPB, antibiotics, mucin like substances) serves one of important infrastructural indicators of communicative potential of MO [10,17-21].
9. In cases of appearance of tumor like cells possessing decreased level of cell surface differentiation, MO functions in accordance to the strategy of reversible compensation and immediate reparation when changed mucosal surrounding medium and cellular decors are rebuilt in direction of original healthy status (images of normally functioning MO) [22]. As a result MO will prevent further “cell surface steps”-depended amplification of tumor like cells and development of tumors. Resources for reparation and stabilization of changed MO can be presented by therapeutically active free and solid phased LS and GC (for example, from nutrients, bioactive additives, therapeutics, specially directed compounds).
10. MO serves the library/ catalog/ memory and source of spectra of mucin type GC (MGC) of human and microbiocenosis origin, as well as diagnostic indicator and sensor accumulator and amplifier of tumor antigenic signals of diagnostic and prognostic significance.
11. MO (natural or artificial) can be used for delivery of metabiotics, depositing and further release of therapeutic agents (therapeutic Ab against tumor antigens, antimicrobial agents of pathogen suppression).
12. Current recognition by mucus and local binding to molecular-cellular targets within MO pass by ways on duty regime involving super LS (SLS). SLS of MO influence organization (net of pores of regulated size, permeability into gel) and regulation of MO.
13. SLS adapts architecture of MO for successful operations including delivery of therapeutic and signal MGC, their retaining and further release by portions (system SLS-MO as macro adjuvant device). SLS increases and supports antipathogenic control within MO.
14. SLS act as metabolomebiotics [22a]. SLS initiates, stabilizes, supports (provides deeper resistance due to increasing “buffer reactivity”) and conserves microbiocenoses of healthy status of biotopes within MO.
15. Biotopes of MO function as synbiotic biotopes (synbiotopes) supporting biotope probiotic microbial compartment [7,23].
16. Diversity of MGC and probiotic LS provides latitude of adaptive mobile adequate replies of MO on stress [6,16,22, 24,25]. The choice of compositions of MGC depends on mucosal biotope phenotype, current healthy status of individual and diagnosis of patient.
17. On duty network of SLS-MGC increases potential of MO against viral and other inducers of tumors [1]; supports MO as reliable source of therapeutic GC and their cascades.
18. LSPB act against relatively pathogenic microbiocenoses as against communicative “bodies” of pathogenic massives [24]. In extended terms, MO and its microbiocenoses function as hierarchic communicative “bodies” which are exchanged by signals with surroundings including other protective systems of organism.
19. SLS serve the necessary affinity macro scaffold in action of such protective systems as complement, blood clotting, pattern recognition receptors and molecules, protein hormones and their receptors.

2.1 Strategies Based on Conception of MO

Aforementioned above conception of MO possesses resources and can serve the basis for

further development, choice and application of proposals against pathogenic factors.

2.1.1 Strategies based on probiotic microbial cells and probiotics

It is of reason to use probiotic combinations of lactobacilli and bifidobacteria together because of lactobacilli stimulate bifidobacteria (the reverse influence is possible). In addition, LS of probiotic bacteria (LSPB) (lectins of lactobacilli and bifidobacteria: LL and LB) as imitators of probiotic cell activities can be used together with PB that provides support of balance, resistance and reliability of molecular-cellular recognition processes in biotopes of MO) [23,25].

Probiotic leader microorganisms influencing biotope metabolically coupled microbial populations of MO can be used. For example, leader strains *of L. acidophilus, L. casei/ paracasei, L. helveticus, L. brevis* against *Candida* species [15,26-30].

2.1.2 Strategies based on metabolic imitators of probiotic microbial cells

LSPB act as relatively high molecular mass polymeric probiotic effectors (in contrast to low molecular mass acidic cultural agents and bacteriocins). LSPB act as members of new class of destructors of biofilms of pathogens, and signal regulators of communications of QS type [4,5,17,22a,31,25]. Examples of LSPB include the following probiotic microbial sources investigated: *Lactobacillus* sources such as multistrain probiotic Acilact, *L. casei* K_3III_{24}, *L. helveticus* NK1, *L. helveticus* 100_{ash}, *L. paracasei VKPM B-6253, L. plantarum* 8R-A3; *Bifidobacterium* probiotic strains of human origin such as *B. adolescentis spp. longum* MS-42, *B. bifidum* No 1, *B. infantis* 302-87, *B. breve* 23, *B. longum* B 379 M, *B. angulatum OV-15*, *B. pseudocatenulatum* OV-2 [31,32].

Strategies of using free (non-cellular) LSPB against eukaryotic and Gram positive pathogens can be of interest [5,17,18,19,21,33,34]. Antimicrobial strategies of MO using LSPB can include the following dominating synergistic combinations of LL and BL: a) against pathogenic yeast like fungi (*Candida albicans*, BL > LL) and pathogenic Gram positive bacteria (*Staphylococcus aureus*, LL > BL); b) anti-*C. albicans*-cascade “Acidic BL—Alkaline LL”; c) anti-*C. albicans*-combinations of LSPB and phytolectins, BL and azoles. Advantages of such system combinations are in non-dependence on the presence of PB (PB need special conditions for survival including the absence of a lot of types of antibiotics and other antimicrobials); possibility to use BL in the vagina which is not comfortable for bifidobacteria. Disadvantage is inability to use PB-barrier immediately within MO (later events are possible).

Protective microbial synergistic SLS involving reversible LSPB—MGC systems possess extended antipathogen potential [8,16,17,20,33]. This position is supported by the facts that complexed LSPB retain spectrum of lectin recognizing activities (increased or decreased, or modulated as quite new).

In case of delivery of LSPB into MO, constructions of LSPB—MO will increase structure-functional stability (in term of deeper “buffer“ reply reactions) of healthy status of biotope, its resistance to changes in surroundings (for example, in respect of appearance and amplification of pathogenic microbes and viruses, appearance of pathogen-induced tumor like cells, their associates and tissues) [33].

It is expected that exogenic delivery of constructed ”Artificial MO based on LSPB“ into altered biotope will promote exchange between MO and altered mucus (similar to process for mucus saturating with MGC from surroundings) that will allow redistribution of processes to support healthy status of biotope (for example, in cases of vaginal and rectal ones).

Supersystem LSPB—GC possesses ability of distant control of landscape surroundings [17]. Delivery of constructed LSPB—“Chosen panel of GC” into MO will increase not only current state of biotope but also allow using construction as source of addressed antimicrobial and antiviral preparations and vaccine ingredients which are based on participation of MGC. For example, sulfated GC reveal activity against human immunedeficit virus (HIV) and chitosans (soluble imitators of chitin) as carriers of therapeutic effectors themselves contribute to sum of antimicrobial actions.

It is possible that upon their delivery, constructions LS—(Chosen panel of GC) will cofunction to therapeutic Ab, antigens, enzymes, antibiotics and bacteriophages [4,5,15,18].

Cofunctioning Ab-independent network LSPB—MGC together with on duty complement system using C3- and C4-subsystems of protection against pathogens (in normal states and upon systemic diseases) is additional possibility to increase effectiveness of MO against pathogens [3,35].

Adequacy of chosen model system "LS of probiotic bacteria in polyacrylamide (PA) gel (LSPB-PAG)—Mucin glycoconjugates-PA" in respect of MO (its mucosal layer, cell surface mucins and epithelial membranes) serve the reliable basis for development of constructions for medical biotechnology and medical microbiology [1,34].

Table 1. Biotechnological resources for MO application

No	Subconceptions, strategies, approaches, algorithms, methods
	LSPB, symbiotic lectins, GC – as effectors
1	Sc. LSPB as regulators of QS in microbiocenoses and cross talking in human interactome [25]. A and M. Identified expressed major and minor components of probiotic LS as potential therapeutics and signals [6,32].
2	Sc. LSPB as a new class of imitators of probiotics and synbiotics [5,23]. S, A and M. Antimicrobial synergistic LSPB revealing synergy together with other type antimicrobials and factors [36]. C and M. Cofunctioning LSPB and (exo)polymeric GC in themselves' assembled porous hydrophilic swelling gels [16]. S. LSPB as inducers of cytokines [5].
3	Sc1. LSPB as a new class of metabolomebiotics distinct from biotics and metabiotics [4, 17]. Sc2, S, A and M. LSPB as navigator in early assembling and later degradation [19]. S and A. *Lactobacillus* system of LSPB and antioxidants as antifungal potential factor [37]. M. Maximal and minimal LS of PB cultures for screening desire combinations of probiotic effectors [32]. M. A number of different LS (GC type depended LS) among the same proteome as functionally active kinetic sequential cascades [32]. M. Recognition of GalNAc-containing artificial polymeric soluble glycoantigens by LSPB [5,32].
4	Sc. LSPB as a new class of pathogen biofilm destructors [17]. A and M. Space and time cascade synergistic actions of antimicrobials and other antipathogenic factors involving LS [17].
5	Sc and A. Functional superfamily of symbiotic lectins as prognostic instrument for revealing new properties of LSPB [38].
6	Sc1. Therapeutic potential of artificial GC systems imitating natural glycopolymers [33]. Sc2. Polymeric GC as inducers of increased antimicrobial protection [20]. Al. Algorithm of Screening and choice of Probiotic Strains and Their Consortia Possessing New Antimicrobial Potential for Constructing Multistrain Probiotics [20a].
	Biotope microbiocenoses
7	Sc. Support of biotope functionally balanced antagonistic microbiocenoses [8,23].
8	Sc. Microbial massive as communicative body possessing one or more centers [24]. S. Multipoint organized attack of antimicrobials (firstly in sensor regions, and secondly in internal regions of exposed pathogenic mixed communicative body) [17].
	Synbiotopes
9	Sc. The presence of mobile synbiotopes involving in organism protection [23]. S. Support of probiotic microbiocenoses in analytical small volumes (1 ml- insulin syringes) [38]. M. Synbiotic Screening System Involving Participation of Lectins of Probiotics and Synthetic Glycopolymers [38a].
	Leader strains of multiknot biotope
10	Sc. Multiknot functioning biotope characterized with leaders of functionally coupled microbial populations [29]. C. Leader strains as supervisor microbes in cofunctioning microbiocenoses [30]. Al. Identification of leaders among coupled microbial populations [26]. Al. Calculation of the coupled system "*Lactobacillus-Candida*" of balanced multispecies knot of biotope network depending on biofilm forming [29]. Al. Identification of group of *Candida* possessing increased potential of pathogenicity [27]. Al. Search of compositions of consortia-like strain pools which provide biotope stability [28].
	Cases of use of antibiotics
	Sc. The presence of biotope biomarker biosensor coupled communicative antagonistic microbial populations systems increasing biotope resistance in the presence of antibiotics [15].
11	Sc. Antibiotics act as selective agents rearranging current hierarchic distribution of taxonomic pools within biotope coupled microbiocenoses [39]. A. Prognostic relationships between probiotic bacteria, yeast-like fungi and antibiotics in urban population biotope [40].
	Collaboration of protective microbiocenoses together with higher protective systems of human organism
12	Sc. Complement as a prognostic model system for any innate ptotective system involving "lectin-GC" recognition [41]. C and S. Prediction of human interactome based on communications between innate GC-recognizing systems [2,3]. A and M. Potential usefulness of lectin-like subisotypes of C4A and C4B of human complement in diagnostics of autoimmune and infectious diseases [35].

Comments: A= Approach, Al= Algorithm, M= Method, S= Strategy, Sc= Subconception

2.1.3 Strategies of molecullar-cellular systems of probiotic cells/ probiotics and LSPB involving in functioning MO

MO functions at the level of synbiotic biotopes [23]. LSPB can act as carriers and adjuvants of different GC (artificial GC as metabiotics: therapeutics and prebiotics). Prebiotic GC will increase synbiotic action of MO and final resulting target-dependent effectiveness of the delivered molecular-cellular probiotic system. Some food phytolectin glycoproteins can reveal additional prebiotic properties towards probiotic microbiota.

Delivery of recombinant therapeutics (glycoprotein hormones, monoclonal Ab, other GC) into or within synbiotope using probiotic microbes regulated with bacteriophages is of perspective significance (cases for lactobacilli) [42].

3. BIOTECHNOLOGICAL RESOURCES FOR APPLICATION OF CONCEPTION OF MO

Subconceptions, additional strategies, approaches, algorithms and methods supporting MO application are summarized in Table 1.

The structure-functional principles of the complement system (the highest achievement of evolutionary innate protective systems) can be used as a prognostic model system for organization and functioning of any other protective system involving LS—GC recognition. In our opinion, any recognizing biosystem (known and unknown) in human organism partially function according to LS—GC recognition.

4. CONCLUSION

Aforementioned conception of MO, strategies and results indicate importance of prospects of pro/synbiotic systems (LSPB, SLS and their cellular producers) and GC system (MGC and others, natural and artificial ones) in supporting antipathogenic and antitumor resistance of MO biotopes (intestinal, urogenital, others). Methodological approaches, methods and algorithms which support MO to increase mucosal immunity of organism are indicated. Conception of MO uses principles of balanced application of probiotic lectins and probiotics that increase natural resistance to stress. Strategies against pathological processes in organism underline prospects of MO constructing for improved therapy of system and chronic diseases. Conception of MO may be useful for further development of experimental approaches in biomedical engineering. Super system LSPB—MGC opens further new possibilities of innate protection in organism. Synbiotic SLS integrate known molecular-cellular protection systems. Conception of MO can serve the basis to create new combinative ways against pathogens and tumor like cells as well as to develop new approaches for constructing and using new hierarchic systems of drugs in terms of medical biotechnology.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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APPENDIX

Definitions

- Biotope - structure-functional organized local space (3D-solid phased landscape together with internal and external surroundings) of mucus of opened cavities in organism (examples of our interest: rectal and vaginal ones as suitable biotopes for delivery of therapeutics).
- Glycoconjugates (GC) – covalently bound carbohydrate/ glycoside-containing polymeric compounds of artificial or natural origin (glycoproteins, proteoglycans, glycolipoproteins, glycolipids, lipopolysaccharides, other natural or artificial modified and synthetic polysaccharides and glycoantigens); GC as metabiotics (therapeutic agents, prebiotics);
- Leader microorganisms – biotope microorganisms when, for example, isolated strains of one taxonomic group significantly influence ranging/ ordering biofilm forming of another taxonomic group in mixed cultures (for example, probiotic bacteria versus yeast-like fungi).
- Consortium microorganisms - microorganisms which reveal themselves as normally coexisted monotaxonomic or mixed functionally coupled groups in balanced biotope (similarly to multistrain pro/ synbiotics).
- Lectins (L) – carbohydrates- and GC-binding/ recognizing proteins/ (oligo)peptides-containing compounds and their complexes. Limitations: a) L are of non-immunoglobulin or enzyme of carbohydrate metabolism nature (with exceptions of enzymes containing CBM [carbohydrate binding modules]); b) L reversibly bind to target without chemical altering contact covalent structure.
- Lectin systems (LS) – multiple lectin forms possessing different biological and physiological activities.
- Maximal LS – maximal number of identified visualized lectin forms (LS represented by major and minor forms; the latter are responsible for signal or firstly expressed minor biological activities observed).
- Metabolomebiotics – SLS of organism which influence human metabolome according principle “SLS network—Interactome network”.
- Metabiotics – compound possessing standard known or established structures of therapeutic significance.
- Microbiocenosis – cofunctioning microbiota; sum of microorganisms placed and functionally ordered in biotope; it always consist of antagonistic compartments (pro/synbiotic and relatively pathogenic one; both compartments function in balanced manner.
- Minimal LS – minimal number of identified visualized lectin forms (LS represented by major forms which are responsible for major biological activities observed).
- Mucosal Organ (MO) – structure-functional organized actively exposed mucus of opened cavities of organism.
- Probiotic L – L of different origin revealing useful properties for human (LSPB, phytolectins, food L, LS of human protective systems).
- Super LS (SLS) – sum of LS of all type protection systems of organism (integrated SLS of MO; SLS as “coordinative hierarchic sum of LS of organism” plus network of GC [free and in complexes with LS]; SLS as carriers of GC).
- Superorganism – human organism together with microbiota which function as inherent constituent of human body.
- Synbiotope – synbiotic biotope supporting probiotic microbiota.
- Synbiotope (synbiotic biotope) - biotope possessing properties of preferential support of probiotic microbiota (for example by prebiotics of glycoconjugate and non-glycoconjugate origin).

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