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THE ROLE OF THE LEADER STRAINS OF SOME SPECIES IN THE ORDERING, INITIATION AND SWITCHING OF SUBPOPULATIONS OF MICROORGANISMS OF OTHER SPECIES COEXISTING IN THE BIOTOPE: PROGNOSTIC CALCULATION OF THE SERIES OF STRAINS OF MICROORGANISMS RANKED BY THE ABILITY TO BIOFILM FORMATION IN *LACTOBACILLUS-CANDIDA* MIXTURES

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ABSTRACT

The concept of the role of the strain leaders of some species (on example of lactobacilli) in the order, initiation, and switching of microbial subpopulations of another species (on example of *Candida*) coexisting in biotopes has been developed. A view on the role of biofilm formation and its potential application in predicting the behavior, co-functioning, and antagonism of microbes in mucosal biotopes is expanded (using urogenital biotope as an example), as well as assessment of the protective and combat status of microbiocenoses is presented (using *Lactobacillus* species versus *Candida* species). For the first time, results of prognostic calculations and analysis of a series of strain microorganisms ranked by their ability to form biofilms in human biotic mixtures are presented along with the proposed concept. The concept and methodological approaches are applicable to any type of organism biotope and any taxonomic groups of microorganisms in human biotopes (populations and subpopulations of genera, species, subspecies and strains), and are key when considering aspects of microbial ecology. Further prospects for application of results in medical microecology are discussed.

KEYWORDS: microecology, biotope, microbiocenose, *Lactobacillus, Candida*, mixed cultures *Lactobacillus—Candida*, biofilm forming, ranging formulas, subpopulations, leader strains, antagonism, synergism, probiotic-like lactobacilli, human, patients.

ABBREVIATIONS

Aci	*Lactobacillus acidophilus*
Alb	*Candida alicans*
Bre	*Lactobacillus brevis*
Cas	*Lactobacillus casei*
BF	biofilm formation
Kru	*Candida krusei*
lac	lactose
MRS	nutrient microbial medium (de Man, Rogossa and Sharpe)
raf	raffinose
Tro	*Candida tropicalis*

1. INTRODUCTION

We conducted studies of representatives of microorganisms microbiocenosis of biotopes of open body cavities of patients observed in the *Clinical Diagnostic Center* at the Institute named after *G.N. Gabrichevsky*. As a result, among the tested microorganisms of the genera *Lactobacillus* and *Candida*, leader strains were identified, a prognostic calculation of the series of strains of microorganisms ranked by their ability to biofilm formation (BF) was developed, calculations of nodes of metabolically linked pools of microorganisms were carried out, and the concept of multi-node network functioning of the biotope was proposed.

The aim is, based on our own results[1-27], to develop ideas about the functional significance of BF in potentially antagonistic subpopulations of microorganisms in human biotopes, as well as about the role of leader strains in the species and interspecific relationships of such microorganisms in the same biotope.

2. MATERIALS AND METHODS

Clinical strains from the *Gabrichevsky* Institute Collection of human microorganisms were used. We used the methodology developed by us for comparative ranking of BF with *Lactobacillus* and *Candida* cultures mixed in optimized ratios and conditions. After 2 days of strain growth (separately and in mixtures) in MRS at 37°C, the biofilms formed in the wells of the micropanels were stained with a gentian violet, which was extracted and the absorption of extracts in the region of 600 nm was measured.

The used *Lactobacillus acidophilus* (Aci) strains 106, 124, 183a; L. brevis (Bre) strains 104, 109, 143; L. casei (Cas) strains 124b, 183; *Candida albicans* (Alb) strains were studied 3, 23, 26, 45, 116, 147, 161, 320; *C. krusei* (Kru) strains 5, 60, 125, 135, 185, 309; *C. tropicalis* (Tro) strains 97, 112, 144, 162, 417, 433, 438, 897 - all were of the human urogenital biotope origin. The effect of pools of 6-8 *Lactobacillu*s strains on the BF of each *Candida* strain was calculated (and, conversely, the effect of pools of 6-22 *Candida* strains on the BF of each *Lactobacillus* strain). Strains of *Candida* (or *Lactobacillus*) were ranked/ ordered according to the severity of BF in the form of rows. The degree of ordering of a species within a series was estimated by the number of strains of a given species continuously arranged in a row.

3. RESULTS

3.1. *BF in monocultures*

BF has decreased randomly in cases of *Lactobacillus* and *Candida* monocultures.

3.1.1. Genus *Candida*

Tro 438 > Alb 23 > Tro 144 > Alb 116 > Kru 135 > Kru 5 > Tro 897 > Tro 97 > Alb 147 > Kru 309 > Alb 3 > Tro 162 > Alb 26 > Alb 320 > Kru 185 > Kru 60 > Alb 161, Kru 126, Tro 417, Tro 433 > Alb 45, Tro 112.

3.1.2. Genus *Lactobacillus*

Cas 183 > Bre 143> Aci 183a > Bre 109 ≥ Aci 106 > Bre 104 > Cas 124b > Aci 124.

3.1.3. Characteristics of the leader strains of bacteria and fungi

The leader strains of lactobacilli (Aci 124 and Cas 124b) were characterized by minimal values of BF, which indicated their relatively high original metabolic enzyme (hydrolase) activity.

In general, leader strains in the studied pools of microorganisms (Aci 124, Cas 124b, Kru 309, Alb 320) in mixed cultures differed from other strains by the maximum spread of position in the compared ranked sequences according to signs of growth in MRS and the severity of BF, including in comparison with monocultures.

3.2. *Influence of Lactobacillus pools of 6-8 strains in respect of Candida pools of strains (calculated BF rows of Candida strains in the presence of Lactobacillus)*

3.2.1. *The system [Aci + Bre + Cas]—[Alb + Tro] (16 strains)*

The row of *Candida* BF observed

Alb 23 > Alb 161 > Alb 320 > Alb 147 >
Tro 144 > Tro 97 >
Alb 45 >
Tro 438 > Tro 897 > 112 > Tro 417 > Tro 162 > Tro 433 >
Alb 116 > Alb 3 > Alb 26.

The above series shows: a) 2 subpopulations of *C. albicans* (Alb-a [23, 161, 320 and 147] and Alb-b [116, 3 and 26]) – 3-4 strains per block, b) an increase in species-dependent (not random) clustering in both populations, especially in Alb- a.

Without Alb45, complete species-dependent (not random) cohesion of the *C. tropicalis* population is achieved. This maximum block size includes 8 strains, and the cohesion of *C. tropicalis* is distinctly different from that of *C. albicans*. Strain Alb45 functions as a disorganizer of *Candida* sorption.

Blocks Alb-a and Alb-b were not differed in antimycotic type resistance (Alb-a as more sensitive to antimycotics). Noncapability to utilize Sac (Alb-b), Lac and Raf (Alb-b) was observed. Blastopore germ tubes were early registered (Alb-a>Alb-b). So, population Alb-a (as more higher in BFF) reveals relatively higher pathogenic potential.

3.2.2. *The system [Aci(without Aci124) + Bre + Cas]—[Alb + Tro] (16 strains)*

Alb 23 > Alb 161 > Alb 320,
Tro 144 > Tro 97 >
Alb 147 >
Tro 112 ≥ Tro 438 ≥ Tro 897 > Tro 417 > Tro 433 > Tro 162,
Alb 116 > Alb 3, Alb 26 > Alb 45.

In the above rows, one can see: a) strong block organization of C. tropicalis (a sequence of 6 strains in a row), b) switching within Alb to an increase in the block organization of the Alb-b subpopulation.

3.2.3. ***The system [Aci(without Aci124b) + Bre + Cas]—[Alb + Tro] (16 strains)***

Alb 23 > Alb 45 > Alb 329 > Alb 147 > Alb 161,
Tro 438 > Tro 144 > Tro 97, Tro 897 > Tro 162 > Tro 417 > Tro 433 > Tro 112,
Alb 116 > Alb 26 > Alb 3.

It can be seen that: a) the species are completely organized as blocks (maximally organized and, apparently, the subpopulations of both species are maximally protected), b) interspecies boundaries are smoothed, c) the order of species and the composition of the subpopulations Alb-a and Alb-b have not been changed.

3.2.4. ***The system [Aci(without 124) + Bre + Cas(without 124b)]—[Alb + Kru + Tro] (16 strains)***

Alb 23 >
Tro 438 > Tro 144 > Tro 417,
Alb 320 >
Tro 112, Tro 433 >
Alb 116 >
Tro 97 > Tro 162, Tro 897 >
Alb 26 > Alb 161 > Alb 3 > Alb 147 > Alb 45.

Interspecies switching is visible (indicating the co-functioning of *Candida* species in the biotope): a) Tro subpopulation instead of Alb-a subpopulation (as switching of Alb-a leader function to Tro in the biotope), b) extended Alb-b subpopulation (Alb 26 > Alb 161 > Alb 3 > Alb 147 > Alb 45).

Alba and All-b show independent signs of switching of close species of the same group of yeast-like fungi (Alb and Tro).

3.2.5. ***The system [Aci(without 124) + Bre + Cas]—[Alb + Kru + Tro] (22 strains)***

Tro 144 > Tro 97 >
Alb 147 >
Kru 135 ≥ Kru 5 ≥
Tro 112 >Tro 438 >
Kru 60,
Tro 897 > Tro 417 > Tro 433 > Tro 162,

Alb 116 > Alb 3, Alb 26 >
Kru 185 > Kru 125 >
Alb 45.

It can be seen that: a) 2 subpopulations of Kru (Kru-a: Kru 135 ≥ Kru 5; Kru-b: Kru 185 > Kru 125) are revealed, b) preservation of the Tro core (Tro 897 > Tro 417 > Tro 433 > Tro 162) takes place, c) smoothing of BF at the boundaries between Tro (preservation nuclei – 4 strains) and Kru (from the side of reduced BF Tro 162 > Alb-b) is observed.

The strain Aci 124, unlike Cas 124b, showed the ability to restructure the functioning of the *Candida* pool of the Alb+Tro group – interspecies switching. Both leader strains of lactobacilli seem to be linked to the metabolism of *Candida* pools (affect the metabolism of *Candida*) at different points of the multi-node biotope.

3.3. The influence of pools of 6-22 *Candida* strains on lactobacilli (8 strains)

3.3.1. *The system [Alb+Tro] (16 штаммов)—[Aci+Bre+Cas]*

Cas 124b > Aci 124 > Cas 183 > Bre 143 > Aci 183a > Aci 106 > Bre 109 > Bre 104.

The sequence is a "random" row (not a single species block).

3.3.2. *The system [Alb(without Alb 320)+Tro] (15 штаммов)—[Aci+Bre+Cas]*:

Cas 124b > Aci 124 > Cas 183 > Bre 143 > Aci 183a > Aci 106 > Bre 109 > Bre 104.

Removing the Alb320 leader strain orders the BF ranking (2 blocks of BF appear: *L. acidophilus* > *L. brevis*).

3.3.3. *The system [Alb + Tro + Kru] (22 strains)—[Aci + Bre + Cas]*

Cas 124b > Aci 124 >
Cas 183 >
Bre 143 >
Aci 183a > Aci 106 >
Bre 109 > Bre 104.

One can see: a) the emphasis on the important (main, root) contribution of the leader strains of lactobacilli as opposed to *Candida*), b) the tendency to species convergence in cases of Bre and Aci.

3.3.4. *The system [Alb(without 320) + Tro + Kru(without 309)] (22 strains)—[Aci + Bre + Cas]*

Cas 124b > Aci 124 >
Cas 183 >
Bre 143 >
Aci 183a > Aci 106 >
Bre 109 > Bre 104.

One can see: a) the emphasis on the important (main, root) contribution of the leader strains of lactobacilli as opposed to *Candida*), b) the tendency to species convergence in cases of Bre and Aci.

3.3.5. *The system [Alb (8 strains)]—[Aci + Bre + Cas]*

Cas 124b ≥ Aci 124 >
Cas 183 > Aci 124 >
Bre 143 > Aci 106 >
Bre 104 ≥ Bre 109, Aci 183a.

Visible: a) an increased capacity to arrange lactobacilli as the block (4 strains of two co-functioning species Aci and Cas) is revealed, b) the emphasis is on the important (main, decisive) contribution of both leading strains of lactobacilli (Cas 124b and Aci 124) in countering *Candida*, c) pool Alb orders the combination of Bre > Aci (combination of lactobacillus species as a likely synergistic opposition/ counterweight to *C. albicans*), d) a tendency of BF to be represented as a sequence of Bre strains.

3.3.6. *The system [Tro (8 strains)]—[Aci + Bre + Cas]*

Cas 124b > Cas 183 >
Aci 124>
Bre 143 >Bre 109,
Aci 183a > Aci 106 >
Bre 104.

There are trends towards species BF equally in all lactobacillus species under the influence of Tro, including the Cas block with the leader strain (Cas 124b). There may be an intraspecies enhancement of the potential of the Cas 124b (leader strain) in response to exposure from *C. tropicalis.*

3.3.7. *The system* [Kru (6 strains)]—[*Aci* + *Bre* + *Cas*]

Cas 124b > Aci 124 > Cas 183 >
Bre 143 > Bre 104 ≥
Aci 183a > Aci 106,
Bre 109.

Kru switches as well as Tro.

In general, Tro and Kru pools (but not Alb 320 and/or Kru 309 personally) seem to be able to interchangeably switch the functioning of Bre—Aci. In the "Alb + Tro” group, pool Tro (but not pool Alb) is functionally linked to Cas. Strains 320 and 309 did not significantly affect the species ordering of the *Lactobacillus* pool when ranking BF.

4. CONCLUSION

The possible role of the leader strains of the genera *Lactobacillus* and *Candida* in the human urogenital biotope has been investigated. It has been established that the presence of leader microorganisms (using the examples of leader strains of the genus *Lactobacillus*) contributes to the destruction of the ordering (BF, cohesion, sorption, unity) of subpopulations of opportunistic microorganisms (using the example of strains of fungi of the genus *Candida*). The leader strains (both as lactobacilli and *Candida*), apparently, in the places of their appearance and action, transfer the biotope into a temporarily chaotic/ random unstable state of species relationships, making their representatives weakened and unprotected.

The algorithm of ranked assessment of the role of leader strains in the biotope for various variants of interactions in the *Lactobacillus*—*Candida* system is applied. Conditions for increasing species cohesion according to BF have been found, indicating increased stability of subpopulations of microorganisms.

The leader strains of lactobacilli are able to switch the functioning of subpopulations of *Candida* species pools (including weakening the general pathogenicity of fungi), as well as influence the distribution of microecological niches between *Candida* species in the biotope.

The leader strains of lactobacilli (Cas 124b and Aci 124) are promising as candidates into probiotic strains, new synergistic ingredients of probiotics.

In turn, the leader strains of *Candida* are able to reduce the protective effect of probiotic-like subpopulations (lactobacilli). Thus, by identifying the leader strains of *Candida* (including taking into account BF), it is possible to focus/ emphasize antifungal effects on them, including taking into account the contribution of probiotics (*Lactobacillus* and *Bifidobacterium* strains as important or key ingredients).

New evidence has been obtained for the functional community of the *C. albicans* and *C. tropicalis* in group I (the group I is the first of the three epidemiological categories on significance in terms of the ability to cause diseases in humans *en masse*).

When analyzing a specific biotope (using the example of an urogenital one) with specific pools of microorganisms (with beneficial *Lactobacillus* and *Bifidobacterium* species close to probiotic factors agaimst opportunistic *Candida* species), the results obtained have prognostic value, may allow predicting the influence of the present established leader strains on the taxonomic and metabolic unity of the biotope microbiocenosis.

Additional factors of conditional pathogenicity of *Candida* are characterized. They include *Candida* species, subspecies and strain resistance at the level of BF and coupled other morphological and metabolic features (*Candida* ability to rapidly form a communication body resistant to destruction).

The results provide additional characteristics for standardization and assessment of the potential of taxonomically different pools of the interacting biotope microorganisms, prediction of dynamic mutual resistance of antagonistic subpopulations of microorganisms.

The possibilities of experimentally shifting the balance in the biotope microbiocenosis in the direction of improving health status are emphasized.

The results indicate that the leader strains of lactobacilli are capable of eliminating some dysbiotic conditions in biotopes, for example, in mucosal biotopes of open body cavities.

The universality of the experimental data presented above lies in the possibilities of applying a methodological approach for any type of biotope and any pair of selected pools of microorganisms (not necessarily antagonistic or taxonomically different).

Disclosure of conflict of interest

The authors declare no conflict of interest.

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