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Biological Regulation of Human Microbiota: from Basic Research to Innovation.

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The detection in bacteria of new factors of host defense substrate inactivation is the most "novel" sphere of studies. These are many secreted proteases that provide survival for micro-organisms in the "human–bacteria" ecosystem. The anti-cytokine activity (the ability of bacteria to inactivate pro- and anti-inflammatory cytokines) (Bukharin O.V. et al., 2011), the "anti-interferon" activity of bacteria, the anti-complementary activity, the anti-histone activity (Sokolov, 1993), the anti-carnosine activity (Bukharin et al., 1999), the anti-lactoferrine activity (Bukharin et al., 2000; Valysheva, 2005) and subsequently anti-hemoglobin activity (Khanina, 2006) have been found to the factors of persistence.

In our work we detected of anti-lysozyme activity in bacteria that specifically inactivates the host lysozyme and revealed a wide frequency of occurrence of this sign. The experimental–clinical materials permitted assigning the anti-lysozyme test (ALA factor) to markers of bacterial persistence (Bukharin, 1999). The anti-lysozyme activity as a "biological target" biological regulation of microbiota was found. Thereby, the strain of Klebsiella pneumoniae (Bukharin O.V., Perunova N.B. et al.) (RF Patent № 2321632) was created as an innovative product. Use of the anti-lysozyme activity of this strain can justify the effectiveness of the combination of oxytocin with antimicrobials in surgical infection. The result is a ointment for the treatment of septic wounds (in wound healing phase II), consisting of oxytocin-antibiotic complex with a hydrophilic ointment base "Silativit" (application № 2011107059 from 24.02.2011). Efficiency of the developed drug combination was confirmed in experiments in vitro and in vivo. By the model of a purulent wound infection in mice, it was shown that application of the developed ointment decreased persistence (the anti-lysozyme activity and biofilm formation) and antibiotic resistance of bacteria, to stop release of purulent exudate and stimulation of reparative processes in the wound, which, ultimately, contributed to a more rapid recovery of animals.

Estimating an infectious process as a result of parasite–host relationships, one can use it as a model (analog) describing associative symbiosis. This is further confirmed by the existence of three functional vectors of interactions between symbionts: host–dominant partner; host–associative micro-organisms; and dominant micro-flora–associative micro-organisms (micro-symbiocenosis). Interactions between symbionts in micro-symbiocenosis (dominant–associative micro-flora) in infection have been intensely studied in recent years. We considered that micro-symbiocenosis is a single open self-regulating system which is a complex of populations of micro-organisms of different (autochthonous and alloch-

thonous) species from which interactions of the host homeostasis depend. Changes in the biological characteristics of micro-symbiocenosis participants and their quantitative estimation are reflected in the progress of the disease in the presence of opportunistic micro-flora in the body. A lot of experimental data on this issue have been accumulated recently.

Studies of the antagonistic activity of normal flora (Bifidobacterium) under the effect of autochthonous and allochthonous microorganisms showed that allochthonous species stimulated the antagonism of Bifidobacterium against themselves, but "self" micro-flora did not change the expression of the character in dominants under the conditions of interspecific recognition of micro-symbionts. The study of microbial recognition makes it possible to find the system-forming factor of micro-symbiocenosis functioning, which includes the main functions of micro-symbiont survival: growth characteristics (GCs), universal markers of persistency of microorganisms, anti-lysozyme activity (ALA), and biofilm formation (BFF). We developed the algorithm that gave the possibility to obtain results of this microbial recognition. The data showed a different changes in the course of the studied functions of associants under the effects of exo-metabolites of the Bifidobacterium (preliminarily incubated with the supernatant of this associant). More precise data were obtained in tests with Bifidobacterium longum and Bifidobacterium adolescentis. The developed method of microbial self - non-self recognition gave the possibility to make such a recognition not only at the interspecific level but also at the intraspecific one. Lactose-negative E. coli (typical of dysbiosis) activated antagonism of Bifidobacterium against itself by decreasing GCs, ALA, and BFF of the associants. Lactose-positive E. coli (typical of eubiosis) did not change the antagonistic activity of Bifidobacterium against itself but promoted to the increase of the studied parameters. Thus, the results showed that not only the host itself in an associative symbiosis has the ability to organize defense against associants using PRR. But its normal flora also has the capacity for microbial recognition of associants in the self – non-self system. In other words, the phenomenon of opposite (enhancement/inhibition) effects of micro-organisms at their biological characteristics (antagonistic/persistent) inside a pair of micro-symbionts (dominant–associant) in micro-symbiocenosis has been found. This phenomenon may have a biological sense of host defense through its colonial resistance, which occurs in micro-symbiocenosis due to the host normal flora. The data offer the prospect for new methods for diagnosis of infection and developing the innovation of drugs (pre-, pro-, synbiotics).