The role of microbiota in the regulation of homeostasis in the human body during infection

Oleg V. Bukharin, Natalia B. Perunova✉

Institute for Cellular and Intracellular Symbiosis of the Orenburg Federal Research Center, 460000, Orenburg, Russia

The review considers the regulatory capabilities of the human microbiota to preserve human health. The problem is not new, but it has expanded with the inclusion of new "findings" since the time of I.I. Mechnikov, a staunch supporter of the useful (protective) function of the normal flora.

The study of the integration of human metabolism and microbes inhabiting human body revealed the participation of microbial metabolites — "signaling molecules" — in providing the homeostasis of the host. Particular attention is paid to the metabolic products – aromatic amino acids as regulators of the physiological functions of humans and microbes. "Signal" molecules regulate the microbial "quorum", the immune system (its cellular and humoral components). Opiates, hormonal peptides, in particular, natriuretic hormone, hypothalamic nonapeptides (oxytocin and vasopressin), which have both a direct antimicrobial and an indirect effect in the host's body, are not ignored. Researchers are also showing interest in the products of adipose tissue — "adipokines" (in particular, leptin), which turned out to be a multipurpose regulator showing a pro-inflammatory nature.

The category of "signaling" molecules also includes cytokines that interact with gram-positive bacteria, which is actively discussed in the literature.

In the evaluation of the material presented on various models of infections, a general pattern is observed: under the conditions of symbiosis, a "single regulatory environment" is formed, in which a variety of connections from immediate (direct) interactions are noted, i.e. the destruction of "signaling" molecules, induction of physiological functions due to the presence of similar receptors with ligands and, finally, modification of "signaling" molecules, i.e. expansion of the spectrum of action. The combination of this variety of integration mechanisms in this "single regulatory environment" (microorganism–host) probably leads to the formation of homeostasis, i.e. dynamic balance of the "signaling" systems of the microbiota and humans in the conditions of associative symbiosis, where an infection is its model system.

This concept fits well our method of intermicrobial recognition of friend–foe in the dominant–associate pair and the described triangle: microbiota–hypothalamic-pituitary neurosecretion–oxytocin, organically constituting the gut-brain axis.

Keywords: *homeostasis; microbiota; signaling molecules; infections; oxytocin.*

Роль микробиоты в регуляции гомеостаза организма человека при инфекции

Бухарин О.В., Перунова Н.Б.✉

Институт клеточного и внутриклеточного симбиоза ФГБУН «Оренбургский федеральный исследовательский центр» Уральского отделения РАН, 460000, Оренбург, Россия

В обзоре рассмотрены регуляторные возможности микробиоты человека для сохранения его здоровья. Проблема не нова, но она расширилась с включением новых «находок» со времен И.И. Мечникова — убежденного сторонника полезной (защитной) функции нормофлоры.

Изучение интеграции метаболизма человека и населяющих его микробов выявило участие микробных метаболитов — сигнальных молекул — в обеспечении гомеостаза хозяина. Особое внимание уделяется продуктам метаболизма — ароматическим аминокислотам как регуляторам физиологических функций человека и микробов. Сигнальные молекулы регулируют микробный «кворум», иммунную систему (ее клеточные и гуморальные звенья). Не обойдены вниманием опиаты, гормональные пептиды, в частности,

ОБЗОРЫ

натрийуретический гормон, гипоталамические нонапептиды (окситоцин и вазопрессин), оказывающие как прямое антимикробное, так и опосредованное действие в организме хозяина.

Интерес исследователи проявляют и к продуктам жировой ткани — адипокинам, в частности, лептину, который оказался многоцелевым регулятором, проявляя при этом провоспалительный характер.

К разряду сигнальных молекул отнесены и цитокины, взаимодействующие с грампозитивными бактериями, что активно обсуждается в литературе.

При оценке представленного материала на различных моделях инфекций просматривается общая закономерность: в условиях симбиоза формируется единая регуляторная среда, в которой отмечается многообразие связей от непосредственных (прямых) взаимодействий (разрушение сигнальных молекул, индукция физиологических функций за счет наличия сходных рецепторов к лигандам и, наконец, модификация сигнальных молекул — расширение спектра действия) до косвенных воздействий, опосредованных активацией и регуляцией системы иммунитета через цитокиновую сеть и систему адипокинов. Вероятно, сочетание этого многообразия механизмов интеграции в единой регуляторной среде (микроорганизм–хозяин) и приводит к формированию гомеостаза, т.е. динамическому равновесию сигнальных систем микробиоты и человека в условиях ассоциативного симбиоза, где инфекция — его модельная система.

В эту концепцию хорошо вписывается разработанный нами метод межмикробного распознавания свой–чужой в паре доминант–ассоциант и описанный треугольник: микробиота–гипоталамо-гипофизарная нейросекреция–окситоцин, органично составляющий кишечно-мозговую ось.

Ключевые слова: *гомеостаз; микробиота; сигнальные молекулы; инфекция; окситоцин.*

The "parasite — host" interactions of microbes and humans are very diverse and often disrupt the homeostasis of the host; i.e., stable internal balance of the functioning body systems. On the other hand, there are many examples when microbial cells are useful for maintaining human health. However, this "union, inseparable from enmity", which has been going on for centuries, has its own "microbial organ", i.e. the microbiome that Nature has endowed the man with, protecting all his biotopes. How is this carried out, and what is in the "piggy bank" of researchers?

Metabolic integration and "signaling" molecules

The abundance of various "signaling" molecules and metabolites in the intestine allows the microbiota to influence the state of the host's body, the formation of its homeostasis and control of behavior. Regulatory metabolites of microorganisms include short-chain fatty acids, gamma aminobutyric acid, biotin, vitamin K, putrescine, spermidine, spermine, taurine, cadaverine, tryptophan, etc. [1–4].

The integration of human metabolism and its microbiota was substantiated on the basis of generalization of the results of studies with the participation of microbial metabolites in the development of critical conditions [5], where it was shown that the existing human–microbiome system contains all the necessary objective conditions for the formation of metabolic integration. The group of microbial exometabolites with an aromatic structure deserves special attention. Their analysis revealed about 50 aromatic compounds in the intestine of a healthy person; metabolites such as phenylacetic acid, hydroxyphenylacetic acid, phenylpyruvic acid, etc. were predominating in quantitative terms. The presence of most of these aromatic amino acids with a predominance of hydroxyphenylacetic acid was found in the blood serum of healthy people. The authors associate the change in the ratio of aromatic amino acids in the blood with their selective utilization by cells of tissue barriers, although it does not exclude the need for metabolites of the gut dominant microflora.

There are data confirming the role of opiates in the infectious process [8, 9]. Experimental data show that opiates appear in the intestinal lumen in laboratory animals under stress, which is accompanied by activation of *E. coli* virulence and impaired the barrier function of the intestinal epithelium [6]. It turned out that dynorphin, a representative of the opiate group, does not increase growth properties, but enhances the production of pyocyanin in pseudomonas. This is another proof of the influence of eukaryotic "signaling molecules" on the physiology of prokaryotes without changing their growth/reproduction [7]. A number of studies have also described a decrease in the virulence of microorganisms under the action of signaling molecules of the immune system through a violation of the microbial quorum, as was shown by the example of dynorphin and interferon (INF) -γ [8–10]. The study

of M.W. Bader et al. [11] presents data on the effect of peptide hormones having structural homology to antibacterial peptides on microorganisms. These molecules are believed to have secondary antimicrobial activity in addition to their target-specific interactions with eukaryotic cells.

Natriuretic peptides are currently also considered as peptides with antimicrobial action that can affect the microbiota during the infectious process [10]. This is supported by data on the formation of pores in the bacterial membrane under the action of C-type natriuretic peptide and an increase in the concentration of brain natriuretic peptide in septic shock. A number of studies have shown that natriuretic hormones of B and C types stimulate the virulent properties of pseudomonas without affecting their growth characteristics, but changing the intracellular concentration of cAMP. The mechanism of this action of natriuretic hormones is believed to be mediated by the Vfr protein, which binds cAMP and controls the production of various virulence factors in *P. aeruginosa*. Studies of strains of pseudomonas have shown the presence of receptors for different subtypes of natriuretic hormones, acting both through cAMP and cGMP [12-14].

Hypothalamic nonapeptides

The general research interest in oxytocin and vasopressin is not accidental. As a product of hypothalamic-pituitary neurosecretion (HHNS) of the brain, its supraoptic and paraventricular nuclei, oxytocin, like vasopressin, has a wide range of physiological actions and is directly involved in the regulation of the adaptive reactions of the human body [15]. This is especially evident during infection, where oxytocin protects the host from the pathogen. Earlier, it was believed that the drug does not have a direct protective effect, although its ability to enhance the antimicrobial effect of antibiotics used in combination with oxytocin was found [16].

So what is the secret of the protective effect during the infectious pathology? What does it do with the pathogen? To understand it, let us return to the early studies on the regulation of the persistent potential of bacteria by O. L. Chernova (1989), who, studying the effect of various antiseptic pharmacological agents on the anti-lysozyme activity of *S. aureus* and *S. epidermidis*, showed that oxytocin was the leader in the top ten studied antiseptics — drugs that suppress the anti-lysozyme activity of bacteria, which made it possible to draw attention to the inhibition of this persistent feature of microorganisms. Further, D. A. Kirillov (2004), using the method of clonal analysis of various pathogen populations showed that oxytocin rearranges the persistent potential of clones in the pathogen population until its elimination from the host organism.

These studies "paved the way" to the XXI century — the age of infectology (from microbiology and immunology) that studies the parasite–host relationship during infection based on the symbiotic platform and clonal analysis of the persistent potential of the pathogen population. It was found that oxytocin promoted "restructuring", i.e. a sharp decrease in the number of clones of microbial cells with a high persistent potential until the elimination of the pathogen from the host body. Thus, the clonal rearrangement of the pathogen population, which reduces its adaptive abilities, is the essential mechanism of host protection realized with the help of oxytocin.

It is not unlikely that this mechanism of protecting the host against infections is another illustration from the category of "nature-like technologies" that we have yet to master. But this is a matter of time and courage of mind. Whereas there are reasons for this.

Immunologists also contributed to the study of the protective effect of oxytocin during infection, they described other mechanisms of the mediated protective effect of oxytocin during infection: phagocytic function of macrophages, increased blast transformation of lymphocytes, inhibition of pathogen biofilm formation [17].

When discussing this problem, one cannot fail to mention the insulin-like effect of oxytocin, based on an increase in the synthesis of glycogen from glucose. Surgeons make good use of this technique, using oxytocin in the context of diabetes mellitus in patients with purulent necrotic lesions of feet and purulent inflammatory diseases of soft tissues [17, 19].

The universal regulatory effects of nonapeptides have found their application in pancreatic necrosis, destructive pancreatitis, and systemic lesions of the pancreas [20, 21].

Researchers do not lose interest in fundamental problems of medicine. This fully applies to the problem of the body's homeostasis. How can we help the patient?

The best evidence of this is the study performed at the "school" of Academician Yu.V. Natochin, where a new mechanism of the multipurpose regulator of homeostasis, i.e. oxytocin, was identified, which determined a new functional role of the nonapeptide, namely its participation in osmoregulation of the body. When studying the regulation of renal water excretory function, it was noted that, after water load at overhydration in rats, the secretion of oxytocin by HHNS increased, which enhanced water diuresis and led to a faster renal water excretion and restoration of the osmotic homeostasis [22].

Adipokines and cytokines

Many studies of the mechanisms of the relationship between metabolic disorders and inflammatory processes have led to the recognition of the fact that the adipose tissue functions as an endocrine organ, releasing various biologically active substances (adipokines). The study of adipokines showed that the imbalance of these pro- and anti-inflammatory mediators leads to various metabolic dysfunctions, which indicates the

role of adipokines in the formation of the host's homeostasis [23]. Taking into account the involvement of adipokines in inflammation, these peptides were divided into pro-inflammatory (leptin, resistin, interleukin (IL)-6, tumor necrosis factor (TNF)-α) and anti-inflammatory (adiponectin, IL-1 receptor antagonist, IL-10) [24].

Leptin has multiple effects and affects the hypothalamus, carrying out hormonal regulation associated with the supply of nutrients and energy metabolism, and also affects the metabolism of glucose, lipids, and other human functions [25]. One of the important functions of leptin is the regulation of the immune response, which suggests a role for these peptides in the integrative mechanisms of the associative symbiosis between humans and microorganisms.

This issue is currently being actively studied. The protective role of adipokines in colon infection with the participation of leptin, which induces mucin production by stimulating the epithelial cells of the colon, and thus provides a static external barrier against pathogens, has not yet been clarified. However, the bacterial invasion of *S. typhimurium*, the presence of endotoxin from *Salmonella* or *E. coli* did not affect the level of leptin in the blood. On the contrary, administration of the *C. difficile* toxin to laboratory animals caused a significant increase in the level of leptin in the blood plasma and increased the expression of lectin receptors on the cells of the mucous epithelium, which suggests a direct pro-inflammatory effect of leptin in the intestine [26, 27].

It is known that diarrhea arising from bacterial intestinal infection is associated with the effect of microbial lipopolysaccharides on the immune system and impaired motility of the gastrointestinal tract. *In vivo* experiments revealed that in mice treated with ghrelin, motor impairment caused by the presence of endotoxin in the blood was corrected by inhibiting the level of nitric oxide in the gastrointestinal tract and reducing the production of proinflammatory cytokines IL-1β and TNF-α and by the induction of the anti-inflammatory cytokine IL-10 as well [28, 29].

The integration of the microbiota with the host body can be carried out using cytokines, i.e. the "signaling" molecules of the human immune system, the balance of which is one of the conditions for the formation of human homeostasis, since cytokines are directly involved in the regulation of the immune response during infection [30]. In this case, a change in the cytokine balance occurs not only due to the interaction of the microbiota with immune cells, but also due to the direct influence of bacteria on cytokines (antipeptide activity). The influence of the cytokines themselves on the biological properties of microorganisms is also known. *In vitro* experiments showed stimulation of the bacterial growth properties under the action of IL-1, IL-2, IL-6, INF-γ, TNF-α. In the culture of *Yersinia pestis*, there were found membrane receptors (F1 capsule assembly antigen) that bind IL-1β, and in *P. aeruginosa* a protein that specifically binds to INF-γ, which led to the activation of the "quorum sensing" mechanisms [31–35].

Data were obtained on the enzymes of bacteria degrade many types of organic macromolecules, including cytokines IL-2, INF-γ [36], which may indicate that the inactivation of cytokines produced by immune cells (lymphocytes, macrophages, etc.), can lead to defective mechanisms of both innate and adaptive immunity. The modification of cytokines and their receptors is confirmed by materials indicating that the aureolysin of *Staphylococcus aureus*, which is a metalloprotease, can cause the degradation of cell receptors to IL-6, the cysteine protease of *Streptococcus pyogenes* degrades IL-1β, and serine protease — IL-8. In addition, the cysteine protease of *Porphyromonas gingivalis* can degrade a whole group of cytokines, including IL-8, -1β, -6, -12, INF-γ, TNF-α, and the metalloprotease of *Pseudomonas aeruginosa* is able to degrade IL-2, IL-6 [37, 38].

Thus, the "findings" obtained illustrate the ability of the microbiota not only to influence the cytokine production of immune cells, but also to use certain cytokines as growth factors and mediators of the "quorum sensing", as well as to manifest antipeptide activity, contributing to the formation of cytokine balance in the human body.

Undoubtedly, the interaction of the microbial "signaling" metabolites and the human immune system is of interest from the standpoint of the integration of molecular systems of pro- and eukaryotes in the human associative symbiosis. A number of studies have shown that various homologues of acylhomoserine lactones (AHL) accelerate the apoptosis of macrophages and neutrophils, inhibit the lymphocyte proliferation and the production of TNF-α and IL-12, inhibit the T-cell response, and induce the apoptosis in dendritic and CD4+ T lymphocytes. The role of AHL is confirmed by the presence of mechanisms that limit the number of "signaling" molecules in the medium, which is called "quorum suppression". The decrease in AHL concentration is controlled by both the microbiota and the host. For example, in response to an increase in the amount of AHL, bacilli produce an enzyme that inactivates a broad spectrum of AHL by cleaving the lactone ring. Respiratory epithelial cells in mammals also produce AHL-inactivating enzymes (paraoxonase) that degrade AHL of *Pseudomonas aerugino*sa. Another study showed the existence of three families of paraoxonases located mainly in the liver in mammals and able to inactivate various AHLs [39–44].

When studying the mechanisms of integration between the microbiota and the host, the "signaling" molecules of microorganisms are also of interest. Their effect on the human immunity was shown on the example of alkyloxybenzenes homologues, where, under the influence of methylresorcinol, the functional activity and substrate specificity of lysozyme were changing. [45].

It is evident that "signaling" molecules are involved in the mechanisms of integration of the microbiota and humans: from the side of the microbiota — low-molecular metabolites, molecules of "quorum sensing", etc., and from the side of the host — hormones and immune "mediators". Apparently, under the conditions of symbiotic microbiota–host relationships, a single regulatory environment is formed, in which a variety of emerging bonds is observed: from immediate (direct) interactions –degradation of signaling molecules (inactivation of quorum molecules, degradation of antimicrobial immunity factors), induction of physiological functions due to the presence of similar receptors to ligands and, finally, modification of signaling molecules (broadening the spectrum of available antimicrobial enzymes, the appearance of antimicrobial activity in peptides that did not have this property before) — to effects mediated (indirect) by the activation and regulation of the immune system through the cytokine network and the adipokine system. Apparently, the combination of this variety of integration mechanisms in a "single regulatory environment" leads to the formation of homeostasis, which means a dynamic balance of the signaling systems of the microbiota and humans under the conditions of associative symbiosis [44].

Bifidoflora of the intestinal biotope — an "outpost" of human health

The role of the microbial "organ" (microbiome) can hardly be overestimated; as it is created by Nature and has been coexisting with the host for centuries, then all that remains is to understand its physiological purpose. The existence of hypothalamic-pituitary complex, i. e. a universal and ancient "command center" in mammals, producing nonapeptide neurosecretory hormones (vasopressin and oxytocin), suggests that they cannot remain out of work [46, 47].

It was found that the gut microflora protects the body from wound infection by stimulating the host's immune defense. On the one hand, this protection can be carried out due to the translocation of the beneficial microflora of the host, as was shown on the example of bacilli [48]. On the other hand, microbial components (cells and metabolites), forming the gut-brain axis, can influence the production of the hypothalamic hormone, i.e. oxytocin. Studies on the effect of bacteria on the secretion of oxytocin are few in number and have been carried out on a model of lactobacilli. It was found that lactobacilli stimulate the production of oxytocin, which had a beneficial effect on the healing of infected wounds in the experiment [49]. It is noted that *Lactobacillus spp.* stimulates oxytocin that regulates the expression of IFN-γ and CD-25 for the immune tolerance. All these efforts prevent excessive reactivity of both own and external environmental factors, which contribute to the premature aging of the body. The efficacy of T-reg induced by lactobacilli and their cell lysates with

the participation of the neuropeptide hormone oxytocin was shown in mouse models [49-51].

The above materials, together with our data described indicate that the microbiome enhances the regulation of oxytocin, thereby improving the course of wound infection by contributing to the fastest wound healing [17].

In light of the issue under discussion, the data obtained by Orenburg researchers from the Institute of Cellular and Intracellular Symbiosis, Ural Branch of the Russian Academy of Sciences, who study the biological characteristics of bifidoflora as a key regulator of human health, are of certain interest.

A systematic study of the microsymbiocenosis of the intestinal biotope in humans allowed revealing the phenomenon of microbial recognition friend–foe under the conditions of interaction between dominant (bifidoflora) and associative microsymbionts [44].

It is known that, regardless of the level of complexity, any living organism (from prokaryotes to higher eukaryotes) has different mechanisms of defense against foreign information, since the concept of "friend" is closely related to self-identification and self-regulation of any biological system [52].

The microbial recognition and mechanisms of self-identification of bacteria are being actively studied. L.M. Wenren et al. [53], as a result of studying the growth of *Proteus mirabilis* cultures on the surface of agar media, noted that the relationships of microorganisms in a broth culture may differ from those in the "agar medium" model, since microbial metabolites are important in this process. A.E. Shank et al. [54] associated the regulatory interactions of microorganisms with the presence of "signal" molecules in the supernatant. It is obvious that the change in the phenotype of microbial populations during the intermicrobial interaction is carried out with the help of various molecules, which are further used by the microbiota as inducers of new intermediary metabolites, and it ultimately affects the formation of antagonistic or synergistic relationships between microorganisms [44].

The method of induction by microbial metabolites under the conditions of a dominant–associate pair revealed the phenomenon of the opposite (enhancement/suppression) effect of microsymbionts on their biological properties (antagonistic, persistent potential and the ability to form biofilms) that allow implementing the principle of "friend–foe" in microsymbiocenosis. Further development of studies in order to determine the "foreignness" of strains of microorganisms allowed determining the "biocompatibility" of bacteria in the microbial composition and evaluating the effectiveness of probiotic drugs [44].

Using a symbiotic approach on the platform of the new "infectious symbiology" direction, it was determined that not only the host organism identifies and destroys "foreign" strains of bacteria and fungi by various mechanisms of innate and adaptive immunity, but

ОБЗОРЫ

also the microorganisms themselves (representatives of the dominant microbiota) are able to detect "own" and "alien" types of microsymbionts as part of microsymbiocenosis. Thus, a kind of restructuring of the human "microbial organ" allows the microbiota to form symbiotic ties to maintain the stable functioning of the microsymbiocenosis at an optimal level in order to ensure the survival of normal flora in the human ecological niche that they occupy.

Conclusion

Assessing the retrospect of the issue under consideration, we can conclude that it is advisable to continue accumulating data about the clarification of the protective mechanisms of the host body using microbial cells and their products. The possibility of using "signal molecules", hormones and cytokines as regulators of homeostasis in the human body is being actively studied. This is a very interesting and promising topic for the identification of new "nature-like" technologies that we have yet to discover, but it is not shameful to learn from Nature.

The emergence of the infectology science in the third millennium has significantly expanded the scope of studying the parasite — host relationship by involving the symbiotic approach at the organismal and clonal levels of the persistent potential of pathogens.

This allowed revealing the role of the gut microbiota in the regulation of the host homeostasis through the gut microbiota — HHNS — oxytocin triangle [17]. This can be supplemented with data that clarify the bioeffects of this universal key regulator of homeostasis:
1) faster wound healing;
2) maintaining the human body's musculoskeletal mass;
3) improving mental health;
4) psychotropic effect, regulation of social memory and cognitive functions;
5) reduced risk of obesity;
6) increased reproductive activity, etc.

The described triangle of microbiota — HHNS — oxytocin is confirmed by experimental and clinical data and fits organically the concept of the gut-brain axis, which describes a number of the most important physiological functions of the host and substantially completes them.

REFERENCES

1. Zheng X., Xie G., Zhao A., Zhao L., Yao C., Chiu N.H., et al. The footprints of gut microbial-mammalian co-metabolism. *J. Proteome Res.* 2011; 10(12): 5512–22. https://doi.org/10.1021/pr2007945
2. Le Gall G., Noor S.O., Ridgway K. Metabolomics of fecal extracts detects altered metabolic activity of gut microbiota in ulcerative colitis and irritable bowel syndrome. *J. Proteome Res.* 2011; 10(9): 4208–18. https://doi.org/10.1021/pr2003598
3. Beloborodova N.V., Olenin A.Y., Fedotcheva N.I., Shubina V., Teplova V.V. Effect of phenolic acids originating from microbes on mitochondria and neutrophils. *Crit. Care.* 2012; 16(Suppl. 3): 26.
4. Matsumoto M., Kibe R., Ooga T., Aiba Y., Kurihara S., Sawaki E., et al. Impact of intestinal microbiota on intestinal luminal metabolome. *Sci. Re:* 2012; 2: 233. https://doi.org/10.1038/srep00233
5. Beloborodova N.V. Integration of metabolism in man and his microbiome in critical conditions. *Obshchaya reanimatologiya.* 2012; 8(4): 42–54. (in Russian)
6. Wu L., Holbrook C., Zaborina O., Ploplys E., Rocha F., Pelham D., et al. *Pseudomonas aeruginosa* expresses a lethal virulence determinant, the PA-I lectin/adhesin, in the intestinal tract of a stressed host: the role of epithelia cell contact and molecules of the quorum sensing signaling system. *Ann. Surg.* 2003; 238(5): 754–64. https://doi.org/10.1097/01.sla.0000094551.88143.f8
7. Zaborina O., Lepine F., Xiao G., Valuckaite V., Chen Y., Li T., et al. Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa*. *PLoS Pathog.* 2007; 3(3): 1–15. https://doi.org/10.1371/journal.ppat.0030035
8. Hooi D.S., Bycroft B.W., Chhabra S.R., Williams P., Pritchard D.I. Differential immune modulatory activity of *Pseudomonas aeruginosa* quorum-sensing signal molecules. *Infect. Immun.* 2004; 72(11): 6463–70. https://doi.org/10.1128/iai.72.11.6463-6470.2004
9. Pritchard D.I. Immune modulation by *Pseudomonas aeruginosa* quorum-sensing signal molecules. *Int. J. Med. Microbiol.* 2006; 296(2-3): 111–6. https://doi.org/10.1016/j.ijmm.2006.01.037
10. Lesouhaitier O., Veron W., Chapalain A., Madi A., Blier A.S., Dagorn A., et al. Gram-negative bacterial sensors for eukaryotic signal molecules. *Sensors (Basel).* 2009; 9(9): 6967–90. https://doi.org/10.3390/s90906967
11. Bader M.W., Sanowar S., Daley M.E., Schneider A.R., Cho U., Xu W., et al. Recognition ofantimicrobial peptides by a bacterialsensor kinase. *Cell.* 2005; 122(3): 461–72. https://doi.org/10.1016/j.cell.2005.05.030
12. Vila G., Resl M., Stelzeneder D., Struck J., Maier C., Riedl M., et al. Plasma NT-proBNP increases in response to LPS administration in healthy men. *J. Appl. Physiol. (1985).* 2008; (105): 1741–5. https://doi.org/10.1152/japplphysiol.90442.2008
13. Veron W., Lesouhaitier O., Pennanec X., Rehel K., Leroux P., Orange N., et al. Natriuretic peptides affect *Pseudomonas aeruginosa* and specifically modify lipopolysaccharide biosynthesis. *FEBS J.* 2007; 274(22): 5852–64. https://doi.org/10.1111/j.1742-4658.2007.06109.x
14. Veron W., Orange N., Feuilloley M.G., Lesouhaitier O. Natriuretic peptides modify *Pseudomonas fluorescens* cytotoxicity by regulating cyclic nucleotides and modifying LPS structure. *BMC Microbiol.* 2008; 8: 114. https://doi.org/10.1186/1471-2180-8-114
15. Stadnikov A.A., Bukharin O.V. *Hypotalamic Neurosecretion and Structural-Functional Homeostasis of Pro- and Eukaryotes [Gipotalamicheskaya neyrosekretsiya i strukturno-funktsional'nyy gomeostaz pro- i eukariot].* Orenburg; 2012. (in Russian)
16. Stadnikov A.A. *The Role of Hypothalamic Neuropeptides During Interactions of Pro- and Eukaryotes (Structural-Functional Aspects) [Rol' gipotalamicheskikh neyropeptidov vo vzaimodeystvii pro- i eukariot (strukturno-funktsional'nye aspekty)].* Ekaterinburg; 2001. (in Russian)
17. Bukharin O.V., Stadnikov A.A., Perunova N.B. *The Role of Oxytocin and Microbiota in Regulation of Pro- and Eukaryote Interactions in Infection [Rol' oksitotsina i mikrobioty v regulyatsii vzaimodeystviy pro- i eukariot pri infektsii].* Ekaterinburg; 2018. (in Russian)
18. Widmaier U., Shah P.R., Lee G. Interactions between oxytocin, glucagon and streptozotocininduced diabetic rats. *Regul. Pept.* 1991; 34(3): 235–49. https://doi.org/10.1016/0167-0115(91)90182-g
19. Bukharin O.V., Kurlaev P.P., Perunova N.B., Skorobogatykh Yu.I. Experimental study of ciprofloxacin and oxytocin

combination on formation of biofilms by opportunistic bacteria. *Zhurnal mikrobiologii, epidemiologii i immunobiologii.* 2010; (6): 3–7. (in Russian)

20. Kostyuchenko A.L., Filin V.I. *Emergency Pancreatology [Neotlozhnaya pankreatologiya].* St. Petersburg: Dean; 2000. (in Russian)

21. Demidov V.M., Demidov S.M. Prospects for intrabursal use of dalargin and sandostatin in laparoscopic interventions in patients with pancreatic necrosis. *Annaly khirurgicheskoy gepatologii.* 2002; 7(1): 200. (in Russian)

22. Natochin Yu.V., Golosova D.R., Shakhmatova E.I. New functional role of oxytocin — participation in osmoregulation. *Doklady Akademii nauk.* 2018; 479(6): 712–5.
https://doi.org/10.7868/S0869565218120228 (in Russian)

23. Greenberg A.S., Obin M.S. Obesity and the role of adipose tissue in inflammation and metabolism. *Am. J. Clin. Nutr.* 2006; 83(2): 461–5. https://doi.org/10.1093/ajcn/83.2.461s

24. Toussirot E., Streit G., Wendling D. The contribution of adipose tissue and adipokines to inflammation in joint diseases. *Curr. Med. Chem.* 2007; 14(10): 1095–100.
https://doi.org/10.2174/092986707780362826

25. El Homsi M., Ducroc R., Claustre J. et al. Leptin modulates the expression of secreted and membrane-associated mucins in colonic epithelial cells by targeting PKC, PI3K, and MAPK pathways. *Am J. Physiol. Gastrointest. Liver Physiol.* 2007; 293(1): G365–73.
https://doi.org/10.1152/ajpgi.00091.2007

26. Jenkins N.L., Turner J.L., Dritz S.S., Durham S.K., Minton J.E. Changes in circulating insulin-like growth factor-I, insulin-like growth factor binding proteins, and leptin in weaned pigs infected with *Salmonella enterica* serovar *Typhimurium.* *Domest. Anim. Endocrinol.* 2004; 26(1): 49-60.
https://doi.org/10.1016/j.domaniend.2003.09.001

27. Mykoniatis A., Anton M., Wilk M., Wang C.C., Ungsunan L., Blüher S., et al. Leptin mediates *Clostridium difficile* toxin A-induced enteritis in mice. *Gastroenterology.* 2003; 124(3): 683–91. https://doi.org/10.1053/gast.2003.50101

28. Chen Y.T., Tsai S.H., Sheu S.Y. et al. Ghrelin improves LPS-induced gastrointestinal motility disturbances: roles of NO and prostaglandin E2. *Shock.* 2010; (33): 205–212.

29. Waseem T., Duxbury M., Ito H., Tsai L.H. Exogenous ghrelin modulates release of pro-inflammatory and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. *Surgery/* 2008; 33(2): 205–12.
https://doi.org/10.1097/shk.0b013e3181ae841b

30. Lambert G. Stress-induced gastrointestinal barrier dysfunction and its inflammatory effects. *J. Anim. Sci.* 2009; 87(14 Suppl.): E101-8. https://doi.org/10.2527/jas.2008-1339

31. Zav'yalov V., Chernovskaya T.V., Navolotskaya E.V., Karlyshev A.V., MacIntyre S., Vasiliev A.M., et al. Specific high affinity binding of human interleukin 1 beta by Caf1A usher protein of Yersinia pestis. *FEBS Lett.* 1995; 371(1): 65–8.
https://doi.org/10.1016/0014-5793(95)00878-d

32. Wu L., Holbrook C., Zaborina O., Ploplys E., Rocha F., Pelham D., et al. *Pseudomonas aeruginosa* expresses a lethal virulence determinant, the PA-I lectin/adhesin, in the intestinal tract of a stressed host: the role of epithelia cell contact and molecules of the quorum sensing signaling system. *Ann. Surg.* 2003; 238(5): 754–64.
https://doi.org/10.1097/01.sla.0000094551.88143.f8

33. Romanova Yu.M., Alekseeva N.V., Stepanova T.V., Razumikhin M.V., Tomova A.S., Shilov I.A., et al. Influence of tumor necrosis factor on the growth of vegetative and nonculturable forms of *Salmonella. Zhurnal mikrobiologii, epidemiologii i immunobiologii.* 2002; (4): 20–5. (in Russian)

34. Kanangat S., Meduri Gu., Tolley E.F., Patterson D.R., Meduri C.U., Pak C., et al. Effects of cytokines and endotoxin on the intracellular growth of bacteria. *Infect. Immun.* 1999; 67(6):

2834–40.
https://doi.org/10.1128/iai.67.6.2834-2840.1999

35. Wilson M., Seymour R., Henderson B. Bacterial perturbation of cytokine networks. *Infect. Immun.* 1998; 66(6): 2401-9.
https://doi.org/10.1128/iai.66.6.2401-2409.1998

36. Potempa J., Pike R.N. Corruption of innate immunity by bacterial proteases. *J. Innate. Immun.* 2009; 1(2): 70–87.
https://doi.org/10.1159/000181144

37. Sheets S.M., Robles-Price A.G., McKenzie R.M., Casiano C.A., Fletcher H.M., et al. Gingipain-dependent interactions with the host are important for survival of *Porphyromonas gingivalis. Front. Biosci.* 2008; 13: 3215–38. https://doi.org/10.2741/2922

38. Leidal K.G., Munson K.L., Johnson M.C., Denning G.M. Metalloproteases from *Pseudomonas aeruginosa* degrade hyman RANTES, MCP-1, and ENA-78. *J. Interferon. Cytokine. Res.* 2003; 23(6): 307-18.
https://doi.org/10.1089/107999003766628151

39. Tateda K., Ishii Y., Horikawa M., Matsumoto T., Miyairi S., Pechere J.C., et al. The *Pseudomonas aeruginosa* autoinducer N-3-oxododecanoyl homoserine lactone accelerates apoptosis in macrophages and neutrophils. *Infect. Immun.* 2003; 71(10): 5785–93.
https://doi.org/10.1128/iai.71.10.5785-5793.2003

40. Telford G., Wheeler D., Williams P., Tomkins P.T., Appleby P., Sewell H., et al. The Pseudomonas aeruginosa quorum-sensing signal molecule N-(3-oxododecanoyl)-L-homoserine lactone has immunomodulatory activity. *Infect. Immun.* 1998; 66(1): 36–42. https://doi.org/10.1128/iai.66.1.36-42.1998

41. Boontham P., Robins A., Chandran P., Pritchard D., Cámara M., Williams P., et al. Significant immunomodulatory effects of *Pseudomonas aeruginosa* quorum- sensing signal molecules: possible link in human sepsis. *Clin. Sci. (Lond.)* 2008; 115(11): 343–51.
https://doi.org/10.1042/cs20080018

42. Stoltz D.A., Ozer E.A., Ng C.J., Yu J.M., Reddy S.T., Lusis A.J., et al. Paraoxonase-2 deficiency enhances *Pseudomonas aeruginosa* quorum sensing in murine tracheal epithelia. *Am. J. Physiol. Lung. Cell. Mol. Physiol.* 2007; 292(4): L852–60.
https://doi.org/10.1152/ajplung.00370.2006

43. Bar-Rogovsky H., Hugenmatter A., Tawfik D.S. The evolutionary origins of detoxifying enzymes: the mammalian serum paraoxonases (PONs) relate to bacterial homoserine lactonases. *J. Biol. Chem.* 2013; 288(33): 23914–27.
https://doi.org/10.1074/jbc.m112.427922

44. Bukharin O.V., Perunova N.B. *Microsymbiocenosis [Mikrosimbiotsenoz].* Ekaterinburg; 2014. (in Russian)

45. Evdokimenko A.Yu., Dosadina E.E., El' Registan G.I., Belov A.A. Effect of alkyloxybenzene on the enzymatic activity of some hydrolases under different conditions. *Uspekhi v khimii i khimicheskoy tekhnologii.* 2016; 30(9): 10–2. (in Russian)

46. Gordon J.I. Honor thy gut symbionts redux. *Science.* 2012; 336(6086): 1251–3.
https://doi.org/10.1126/science.1224686

47. Bukharin O.V. Adaptive strategies for the interaction of the pathogen and host with infection. *Vestnik Rossiyskoy akademii nauk.* 2018; 88(7): 637–43.
https://doi.org/10.31857/S086958730000087-3 (in Russian)

48. Tarasenko V.S., Fadeev S.B., Bukharin O.V. *Surgical Infection of Soft Tissues (Clinical and Microbiological Aspect) [Khirurgicheskaya infektsiya myagkikh tkaney (kliniko-mikrobiologicheskiy aspekt)].* Ekaterinburg; 2015. (in Russian)

49. Poutahidis T., Kearney S.M., Levkovich T., Qi P., Varian B.J., Lakritz J.R., et al. Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. *PLoS One.* 2013; 8(10): e78898.
https://doi.org/10.1371/journal.pone.0078898

50. Poutahidis T., Springer A., Levkovich T., Qi P., Varian B.J., Lakritz J.R., et al. Probiotic microbes sustain youthful serum testosterone levels and testicular size in aging mice. *PLoS One.*

2014; 9(1): e84877.
https://doi.org/10.1371/journal.pone.0084877

51. Poutahidis T., Kleinewietfeld M., Smillie C., Levkovich T., Perrotta A., Bhela S., et al. Microbial reprogramming inhibits Western diet-associated obesity. *PLoS One.* 2013; 8(7): e68596. https://doi.org/10.1371/journal.pone.0068596

52. Lopez-Larrea C., ed. *Self and Nonself.* New York: Springer; 2012.

53. Wenren L.M., Sullivan N.L., Cardarelli L., Septer A.N., Gibbs K.A. Two independent pathways for self-recognition in proteus mirabilis are linked by type VI-dependent export. *mBio.* 2013; 4(4): e00374-13.
https://doi.org/10.1128/mbio.00374-13

54. Shank A.E., Kolter R. New developments in microbial interspecies signaling. *Curr. Opin. Microbiol.* 2009; 12(2): 205–14.
https://doi.org/10.1016/j.mib.2009.01.003

Л И Т Е Р А Т У Р А

1. Zheng X., Xie G., Zhao A., Zhao L., Yao C., Chiu N.H., et al. The footprints of gut microbial-mammalian co-metabolism. *J. Proteome Res.* 2011; 10(12): 5512–22.
https://doi.org/10.1021/pr2007945

2. Le Gall G., Noor S.O., Ridgway K. Metabolomics of fecal extracts detects altered metabolic activity of gut microbiota in ulcerative colitis and irritable bowel syndrome. *J. Proteome Res.* 2011; 10(9): 4208–18. https://doi.org/10.1021/pr2003598

3. Beloborodova N.V., Olenin A.Y., Fedotcheva N.I., Shubina V., Teplova V.V. Effect of phenolic acids originating from microbes on mitochondria and neutrophils. *Crit. Care.* 2012; 16(Suppl. 3): 26.

4. Matsumoto M., Kibe R., Ooga T., Aiba Y., Kurihara S., Sawaki E., et al. Impact of intestinal microbiota on intestinal luminal metabolome. *Sci. Re:* 2012; 2: 233.
https://doi.org/10.1038/srep00233

5. Белобородова Н.В. Интеграция метаболизма человека и его микробиома при критических состояниях. *Общая реаниматология.* 2012; 8(4): 42–54.

6. Hooi D.S., Bycroft B.W., Chhabra S.R., Williams P., Pritchard D.I. Differential immune modulatory activity of *Pseudomonas aeruginosa* quorum-sensing signal molecules. *Infect. Immun.* 2004; 72(11): 6463–70.
https://doi.org/10.1128/iai.72.11.6463-6470.2004

7. Pritchard D.I. Immune modulation by *Pseudomonas aeruginosa* quorum-sensing signal molecules. *Int. J. Med. Microbiol.* 2006; 296(2-3): 111–6. https://doi.org/10.1016/j.ijmm.2006.01.037

8. Wu L., Holbrook C., Zaborina O., Ploplys E., Rocha F., Pelham D., et al. *Pseudomonas aeruginosa* expresses a lethal virulence determinant, the PA-I lectin/adhesin, in the intestinal tract of a stressed host: the role of epithelia cell contact and molecules of the quorum sensing signaling system. *Ann. Surg.* 2003; 238(5): 754–64.
https://doi.org/10.1097/01.sla.0000094551.88143.f8

9. Zaborina O., Lepine F., Xiao G., Valuckaite V., Chen Y., Li T., et al. Dynorphin activates quorum sensing quinolone signaling in *Pseudomonas aeruginosa. PLoS Pathog.* 2007; 3(3): 1–15. https://doi.org/10.1371/journal.ppat.0030035

10. Lesouhaitier O., Veron W., Chapalain A., Madi A., Blier A.S., Dagorn A., et al. Gram-negative bacterial sensors for eukaryotic signal molecules. *Sensors (Basel).* 2009; 9(9): 6967–90.
https://doi.org/10.3390/s90906967

11. Bader M.W., Sanowar S., Daley M.E., Schneider A.R., Cho U., Xu W., et al. Recognition ofantimicrobial peptides by a bacterialsensor kinase. *Cell.* 2005; 122(3): 461–72.
https://doi.org/10.1016/j.cell.2005.05.030

12. Vila G., Resl M., Stelzeneder D., Struck J., Maier C., Riedl M., et al. Plasma NT-proBNP increases in response to LPS administration in healthy men. *J. Appl. Physiol. (1985).* 2008; (105): 1741–5. https://doi.org/10.1152/japplphysiol.90442.2008

13. Veron W., Lesouhaitier O., Pennanec X., Rehel K., Leroux P., Orange N., et al. Natriuretic peptides affect *Pseudomonas aeruginosa* and specifically modify lipopolysaccharide biosynthesis. *FEBS J.* 2007; 274(22): 5852–64.
https://doi.org/10.1111/j.1742-4658.2007.06109.x

14. Veron W., Orange N., Feuilloley M.G., Lesouhaitier O. Natriuretic peptides modify Pseudomonas fluorescens cytotoxicity by regulating cyclic nucleotides and modifying LPS structure. *BMC Microbiol.* 2008; 8: 114.
https://doi.org/10.1186/1471-2180-8-114

15. Стадников А.А., Бухарин О.В. *Гипоталамическая нейросекреция и структурно-функциональный гомеостаз про- и эукариот.* Оренбург; 2012.

16. Стадников А.А. *Роль гипоталамических нейропептидов во взаимодействии про- и эукариот (структурно-функциональные аспекты).* Екатеринбург; 2001.

17. Бухарин О.В., Стадников А.А., Перунова Н.Б. *Роль окситоцина и микробиоты в регуляции взаимодействий про- и эукариот при инфекции.* Екатеринбург; 2018.

18. Widmaier U., Shah P.R., Lee G. Interactions between oxytocin, glucagon and streptozotocin induced diabetic rats. *Regul. Pept.* 1991; 34(3): 235–49.
https://doi.org/10.1016/0167-0115(91)90182-g

19. Бухарин О.В., Курлаев П.П., Перунова Н.Б., Скоробогатых Ю.И. Экспериментальное изучение комбинации ципрофлоксацина с окситоцином на образование биоплёнок условно-патогенными бактериями. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2010; (6): 3–7.

20. Костюченко А.Л., Филин В.И. *Неотложная панкреатология.* СПб.: Деан; 2000.

21. Демидов В.М., Демидов С.М. Перспективы интрабурсального применения даларгина и сандостатина при лапароскопических вмешательствах у больных с панкреонекрозами. *Анналы хирургической гепатологии.* 2002; 7(1): 200.

22. Наточин Ю.В., Голосова Д.Р., Шахматова Е.И. Новая функциональная роль окситоцина — участие в осморегуляции. *Доклады Академии наук.* 2018; 479(6): 712–5.
https://doi.org/10.7868/S0869565218120228

23. Greenberg A.S., Obin M.S. Obesity and the role of adipose tissue in inflammation and metabolism. *Am. J. Clin. Nutr.* 2006; 83(2): 461–5. https://doi.org/10.1093/ajcn/83.2.461s

24. Toussirot E., Streit G., Wendling D. The contribution of adipose tissue and adipokines to inflammation in joint diseases. *Curr. Med. Chem.* 2007; 14(10): 1095–100.
https://doi.org/10.2174/092986707780362826

25. El Homsi M., Ducroc R., Claustre J. et al. Leptin modulates the expression of secreted and membrane-associated mucins in colonic epithelial cells by targeting PKC, PI3K, and MAPK pathways. *Am J. Physiol. Gastrointest. Liver Physiol.* 2007; 293(1): G365–73. https://doi.org/10.1152/ajpgi.00091.2007

26. Jenkins N.L., Turner J.L., Dritz S.S., Durham S.K., Minton J.E. Changes in circulating insulin-like growth factor-I, insulin-like growth factor binding proteins, and leptin in weaned pigs infected with *Salmonella enterica* serovar *Typhimurium. Domest. Anim. Endocrinol.* 2004; 26(1): 49-60.
https://doi.org/10.1016/j.domaniend.2003.09.001

27. Mykoniatis A., Anton M., Wilk M., Wang C.C., Ungsunan L., Blüher S., et al. Leptin mediates *Clostridium difficile* toxin A-induced enteritis in mice. *Gastroenterology.* 2003; 124(3): 683–91. https://doi.org/10.1053/gast.2003.50101

28. Chen Y.T., Tsai S.H., Sheu S.Y. et al. Ghrelin improves LPS-induced gastrointestinal motility disturbances: roles of NO and prostaglandin E2. *Shock.* 2010; (33): 205–212.

29. Waseem T., Duxbury M., Ito H., Tsai L.H. Exogenous ghrelin modulates release of pro-inflammatory and anti-inflammatory cytokines in LPS-stimulated macrophages through distinct signaling pathways. *Surgery.* 2008; 33(2): 205–12.
https://doi.org/10.1097/shk.0b013e3181ae841b

30. Lambert G. Stress-induced gastrointestinal barrier dysfunction and its inflammatory effects. *J. Anim. Sci.* 2009; 87(14 Suppl.): E101-8. https://doi.org/10.2527/jas.2008-1339

31. Zav'yalov V., Chernovskaya T.V., Navolotskaya E.V., Karlyshev A.V., MacIntyre S., Vasiliev A.M., et al. Specific high affinity binding of human interleukin 1 beta by Caf1A usher protein of Yersinia pestis. *FEBS Lett.* 1995; 371(1): 65–8. https://doi.org/10.1016/0014-5793(95)00878-d

32. Wu L., Holbrook C., Zaborina O., Ploplys E., Rocha F., Pelham D., et al. *Pseudomonas aeruginosa* expresses a lethal virulence determinant, the PA-I lectin/adhesin, in the intestinal tract of a stressed host: the role of epithelia cell contact and molecules of the quorum sensing signaling system. *Ann. Surg.* 2003; 238(5): 754–64. https://doi.org/10.1097/01.sla.0000094551.88143.f8

33. Романова Ю.М., Алексеева Н.В., Степанова Т.В., Разумихин М.В., Томова А.С., Шилов И.А. и др. Влияние фактора некроза опухоли на размножение вегетативных и некультивируемых форм сальмонелл. *Журнал микробиологии, эпидемиологии и иммунобиологии.* 2002; (4): 20–5.

34. Kanangat S., Meduri Gu., Tolley E.F., Patterson D.R., Meduri C.U., Pak C., et al. Effects of cytokines and endotoxin on the intracellular growth of bacteria. *Infect. Immun.* 1999; 67(6): 2834–40. https://doi.org/10.1128/iai.67.6.2834-2840.1999

35. Wilson M., Seymour R., Henderson B. Bacterial perturbation of cytokine networks. *Infect. Immun.* 1998; 66(6): 2401-9. https://doi.org/10.1128/iai.66.6.2401-2409.1998

36. Potempa J., Pike R.N. Corruption of innate immunity by bacterial proteases. *J. Innate. Immun.* 2009; 1(2): 70–87. https://doi.org/10.1159/000181144

37. Sheets S.M., Robles-Price A.G., McKenzie R.M., Casiano C.A., Fletcher H.M., et al. Gingipain-dependent interactions with the host are important for survival of *Porphyromonas gingivalis*. *Front. Biosci.* 2008; 13: 3215–38. https://doi.org/10.2741/2922

38. Leidal K.G., Munson K.L., Johnson M.C., Denning G.M. Metalloproteases from *Pseudomonas aeruginosa* degrade hyman RANTES, MCP-1, and ENA-78. *J. Interferon. Cytokine. Res.* 2003; 23(6): 307-18. https://doi.org/10.1089/107999003766628151

39. Tateda K., Ishii Y., Horikawa M., Matsumoto T., Miyairi S., Pechere J.C., et al. The *Pseudomonas aeruginosa* autoinducer N-3-oxododecanoyl homoserine lactone accelerates apoptosis in macrophages and neutrophils. *Infect. Immun.* 2003; 71(10): 5785–93. https://doi.org/10.1128/iai.71.10.5785-5793.2003

40. Telford G., Wheeler D., Williams P., Tomkins P.T., Appleby P., Sewell H., et al. The *Pseudomonas aeruginosa* quorum-sensing signal molecule N-(3-oxododecanoyl)-L-homoserine lactone has immunomodulatory activity. *Infect. Immun.* 1998; 66(1): 36–42. https://doi.org/10.1128/iai.66.1.36-42.1998

41. Boontham P., Robins A., Chandran P., Pritchard D., Cámara M., Williams P., et al. Significant immunomodulatory effects of *Pseudomonas aeruginosa* quorum-sensing signal molecules: possible link in human sepsis. *Clin. Sci. (Lond.)* 2008; 115(11): 343–51. https://doi.org/10.1042/cs20080018

42. Stoltz D.A., Ozer E.A., Ng C.J., Yu J.M., Reddy S.T., Lusis A.J., et al. Paraoxonase-2 deficiency enhances *Pseudomonas aeruginosa* quorum sensing in murine tracheal epithelia. *Am. J. Physiol. Lung. Cell. Mol. Physiol.* 2007; 292(4): L852–60. https://doi.org/10.1152/ajplung.00370.2006

43. Bar-Rogovsky H., Hugenmatter A., Tawfik D.S. The evolutionary origins of detoxifying enzymes: the mammalian serum paraoxonases (PONs) relate to bacterial homoserine lactonases. *J. Biol. Chem.* 2013; 288(33): 23914–27. https://doi.org/10.1074/jbc.m112.427922

44. Бухарин О.В., Перунова Н.Б. *Микросимбиоценоз*. Екатеринбург; 2014.

45. Евдокименко А.Ю., Досадина Э.Э., Эль Регистан Г.И., Белов А.А. Влияние алкилоксибензолов на ферментативную активность некоторых гидролаз при различных условиях. *Успехи в химии и химической технологии.* 2016; 30(9): 10–2.

46. Gordon J.I. Honor thy gut symbionts redux. *Science.* 2012; 336(6086): 1251–3. https://doi.org/10.1126/science.1224686

47. Бухарин О.В. Адаптивные стратегии взаимодействия возбудителя и хозяина при инфекции. *Вестник Российской академии наук.* 2018; 88(7): 637–43. https://doi.org/10.31857/S086958730000087-3

48. Тарасенко В.С., Фадеев С.Б., Бухарин О.В. *Хирургическая инфекция мягких тканей (клинико-микробиологический аспект).* Екатеринбург; 2015.

49. Poutahidis T., Kearney S.M., Levkovich T., Qi P., Varian B.J., Lakritz J.R., et al. Microbial symbionts accelerate wound healing via the neuropeptide hormone oxytocin. *PLoS One.* 2013; 8(10): e78898. https://doi.org/10.1371/journal.pone.0078898

50. Poutahidis T., Springer A., Levkovich T., Qi P., Varian B.J., Lakritz J.R., et al. Probiotic microbes sustain youthful serum testosterone levels and testicular size in aging mice. *PLoS One*. 2014; 9(1): e84877. https://doi.org/10.1371/journal.pone.0084877

51. Poutahidis T., Kleinewietfeld M., Smillie C., Levkovich T., Perrotta A., Bhela S., et al. Microbial reprogramming inhibits Western diet-associated obesity. *PLoS One.* 2013; 8(7): e68596. https://doi.org/10.1371/journal.pone.0068596

52. Lopez-Larrea C., eds. *Self and Nonself.* New York: Springer; 2012.

53. Wenren L.M., Sullivan N.L., Cardarelli L., Septer A.N., Gibbs K.A. Two independent pathways for self-recognition in proteus mirabilis are linked by type VI-dependent export. *mBio.* 2013; 4(4): e00374-13. https://doi.org/10.1128/mbio.00374-13

54. Shank A.E., Kolter R. New developments in microbial interspecies signaling. *Curr. Opin. Microbiol.* 2009; 12(2): 205–14. https://doi.org/10.1016/j.mib.2009.01.003

Information about the authors

Oleg V. Bukharin — Dr. Sci. (Med.), Full Member of RAS, main researcher, Institute for Cellular and Intracellular Symbiosis, Orenburg Federal Research Center, 460000, Orenburg, Russia.
ORCID ID: http://orcid.org/0000-0002-6039-5265.
E-mail: ofrc@list.ru

Natalia B. Perunova✉ — Dr. Sci. (Med.), Professor of RAS, leading researcher (with the duties of the head of the laboratory), Laboratory of biomonitoring and molecular genetic research, Institute for Cellular and Intracellular Symbiosis, Orenburg Federal Research Center, 460000, Orenburg, Russia.
ORCID ID: http://orcid.org/0000-0002-6352-8879.
E-mail: perunovanb@gmail.com

Contribution: the authors contributed equally to this article.

Информация об авторах

Бухарин Олег Валерьевич — д.м.н., акад. РАН, г.н.с. Института клеточного и внутриклеточного симбиоза ФГБУН «Оренбургский федеральный исследовательский центр» УрО РАН, 460000, Оренбург, Россия.
ORCID ID: http://orcid.org/0000-0002-6039-5265.
E-mail: ofrc@list.ru

Перунова Наталья Борисовна✉ — д.м.н., проф. РАН, в.н.с. (с исполнением обязанностей зав. лабораторией) лаб. биомониторинга и молекулярно-генетических исследований Института клеточного и внутриклеточного симбиоза ФГБУН «Оренбургский федеральный исследовательский центр» УрО РАН, 460000, Оренбург, Россия.
ORCID ID: http://orcid.org/0000-0002-6352-8879.
E-mail: perunovanb@gmail.com

Участие авторов: все авторы сделали эквивалентный вклад в подготовку публикации.