Обзоры
Reviews

ПЕРСПЕКТИВЫ СОЗДАНИЯ НОВЫХ ЛЕЧЕБНО-ПРОФИЛАКТИЧЕСКИХ СРЕДСТВ НА ОСНОВЕ СИМБИОТИЧЕСКИХ ШТАММОВ БАКТЕРИЙ ДЛЯ КОРРЕКЦИИ НАРУШЕНИЙ ИММУННОЙ РЕГУЛЯЦИИ, ОПОСРЕДОВАННОЙ КИШЕЧНОЙ МИКРОБИОТОЙ ПРИ COVID-19

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Резюме. Современные исследования роли кишечной микробиоты у животных и человека показывают, что микроорганизмы являются важным фактором, определяющим здоровье хозяина, и участвуют в патогенезе различных инфекционных и неинфекционных заболеваний. В настоящее время активно исследуются механизмы формирования функциональной оси «кишечник — легкие» при новой коронавирусной инфекции COVID-19, где желудочно-кишечный тракт может являться входными воротами инфекции, указывая на вовлечение кишечной микробиоты в инфекционный процесс. С одной стороны, изменение микробиоты пациентов (дисбиоз), инфицированных вирусом SARS-CoV-2, является одним из факторов развития вторичной бактериальной инфекции, сепсиса, системного воспаления и полиорганной недостаточности. С другой стороны, нарушение микробиоты кишечника способствует развитию тяжелого течения и летального исхода у пациентов из-за двунаправленной связи кишечной микробиоты через систему иммунитета посредством цитокинов. Показана связь степени тяжести COVID-19 у пациентов с уровнем цитокинов и выявлением в кишечном биотопе опре-

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деленных видов «провоспалительных» или «противовоспалительных» бактерий. Иммунологические нарушения у пациентов с COVID-19 также опосредованы изменением профиля метаболома на фоне дисбиотических нарушений микробиоты. Связь между составом микробиоты кишечника, уровнями цитокинов и воспалительными маркерами позволяет предположить, что микробиом кишечника влияет на развитие и течение коронавирусной инфекции, а «симбиотический потенциал» нормобиоты может быть использован для разработки мер профилактики и реабилитации пациентов. Этому может способствовать развитие исследований в направлении проблемы симбиоза человека и микробиоты. Ряд ключевых механизмов изучения интеграции бифидобактерий и лактобацилл с хозяином, опосредованные системой иммунитета, гормонов и нейромедиаторов, открывают новые перспективы для медицины, включая получение новых пробиотических штаммов различной целевой установки для лечебно-профилактической коррекции нарушенных функций организма. Изучение микросимбиоценоза, как одного из векторов ассоциативного симбиоза, позволило разработать метод межмикробного распознавания «свой-чужой», где в качестве тестовой распознающей культуры используются бифидобактерии, т. к. для «своих» штаммов характерен синергизм (поддержка), тогда как при встрече с «чужой клеткой» — антагонизм. Именно этот фундаментальный механизм можно использовать при отборе «своих» для хозяина штаммов, пригодных для создания пробиотической композиции.

PROSPECTIVES OF NOVEL THERAPEUTIC AND PROPHYLACTIC MEDICATIONS BASED ON SYMBIOTIC BACTERIAL STRAINS FOR CORRECTION OF IMMUNE DISORDERS MEDIATED BY INTESTINAL MICROBIOTA IN COVID-19

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Abstract. Recent studies on the role of intestinal microbiota in animals and humans show that the microorganisms are an important determinant of host health, participating in the pathogenesis of various infectious and non-infectious diseases. Currently, the effects of functional gut-lung axis are being actively investigated in the new coronavirus (COVID-19) infection. Gastrointestinal tract may be the point of entry for infection, suggesting involvement of intestinal microbiota in the infectious process. On the one hand, the changes in gut microbiota (dysbiosis) in SARS-CoV-2 patients may be among the factors contributing to development of secondary bacterial infection, sepsis, systemic inflammation and multi-organ failure. On the other hand, impaired gut microbiota contributes to severe clinical course and mortality in patients due to bidirectional coupling of the gut microbiota with immune system via cytokine network. The studies have shown a link between the severity of COVID-19 in patients, cytokine levels, and presence of distinct types of pro- and anti-inflammatory bacteria in the intestinal biotope. Immune abnormalities in COVID-19 patients are also mediated by altered metabolome profile associated with dysbiotic microbiota. The relations between gut microbiota composition, cytokine levels and inflammatory markers suggests that the gut microbiome may influence the progression of coronavirus infection. Therefore, the "symbiotic potential" of normobiotic microbiota may be used to develop prevention and rehabilitation strategies for the patients. This approach may be facilitated by the studies of human-microbiota symbiosis. A number of key mechanisms for studying the

integration of *Bifidobacteria* and *Lactobacilli* with the host mediated by the immune system, hormones and neurotransmitters are opening new perspectives for medicine, including development of differently targeted probiotic strains for therapeutic and preventative correction of impaired functions within the organism. The studies of microsymbiocenosis, being a vector of associative symbiosis have enabled a technical approach for intermicrobial "friend or foe identification", where bifidobacteria are used as a diagnostic culture, since "friendly" strains are characterised by synergism (support). By contrary, encountering the "foreign cells" leads to antagonism. This fundamental mechanism may be used for choosing the "host-friendly" bacteria strains eligible for design of a probiotic compositions.

Keywords: COVID-19, microbiota, gut-lung axis, symbiosis, Bifidobacteria, immune response, probiotic

Introduction

The emergence of the new COVID-19 coronavirus infection has posed the problems connected to quick diagnostics and provision of health care to patients. Currently, intensive study of the clinical and epidemiological features of the disease and the development of new means of its prevention and treatment continues. In this regard, it is of interest to discuss the role of microbiota in the new COVID-19 coronavirus infection and the possibility of using symbiotic relations between humans and microbiota in the development of therapeutic and preventative measures.

The relation of patients' gut microbiota with new COVID-19 coronavirus infection

Currently, the association of the gut microbiota with various human pathologies is receiving particular attention from researchers [20, 61, 62] due to the COVID-19 pandemic. A number of recent publications indicate that the severity of the course and consequences of COVID-19 are associated with the intestinal microbiota of infected patients [2, 16, 71].

SARS-CoV-2 virus can travel from the lungs to gastrointestinal biotopes [58]. It was found that coronavirus RNA was detected not only in respiratory secretions but also in the faeces of patients for more than one month after the onset of the disease [75]. In addition to acute respiratory syndrome, many patients with COVID-19 had extrapulmonary manifestations (nausea, vomiting, loss of appetite, diarrhoea) [14, 63], liver dysfunction and exacerbation of chronic inflammatory bowel disease [32]. Moreover, in some cases, signs of intestinal disorders in patients appeared even before pneumonia was detected [42].

The gastrointestinal tract is thought to play a key role in the development of infection, in particular through higher expression of ACE2 receptors on intestinal enterocytes compared to lung tissue cells [28, 40, 57, 76]. The binding of the virus to human ACE2 indicates that significant amounts of SARS-CoV-2 virus capable of regulating amino acid transport, affecting the quantitative and qualitative composition of the intestinal microbiota and inducing inflammation may be present in the intestine, especially in colonocytes [30, 64]. All this confirms that the gastrointestinal tract may be the point of entry of infection and indicates the involvement of the intestinal microbiota in the infectious process in the new COVID-19 coronavirus infection and the formation of a functional gut-lung axis [4, 65]. The link between the gastrointestinal tract and the respiratory tract has also been shown in studies on the effect of respiratory viral infections on the composition of the intestinal microbiota with the subsequent development of intestinal dysbiosis [27]. Thus, patients with COVID-19 had significant microecological disorders in the large intestine compared to the control group, characterised by an increase in the proportion of opportunistic microorganisms associated with a decrease in the level of representatives of normal microbiota [21, 74]. It is noted that the composition of the gut microbiome was significantly altered in patients with COVID-19 compared to patients without the coronavirus infection, regardless of whether they were taking medication. Gut dysbiosis persisted even after SARS-CoV-2 was eliminated, and respiratory symptoms disappeared. A pilot study by Chinese scientists found changes in the gut microbiome in patients with COVID-19 compared with the control group, characterised by an increase in the number of fungal pathogens of the genus Candida and Aspergillus [3, 82].

To date, disruption of the gut microbiota is thought to contribute to the severe course and fatal outcome of novel COVID-19 coronavirus infection because of the bidirectional coupling of the gut microbiota with the immune and respiratory systems [3]. The formation of microecological disorders leads to increased permeability of the large intestine and, as a consequence, appears to be one of the factors in the development of secondary bacterial infection, sepsis, systemic inflammation and multi-organ failure [24, 52, 56]. Large intestinal dysbiosis has also been found to be associated with various chronic human

conditions such as asthma, arthritis, obesity and type 2 diabetes [4, 31, 67]. Previously, bacterial translocation from the gut to the lungs has been identified in sepsis and acute respiratory distress syndrome [17].

Immune regulation impairment mediated by intestinal microbiota in COVID-19

Changes in the microbiota of patients infected with SARS-CoV-2 virus are naturally accompanied by immunological rearrangements and the suppression of T-cell immunity [66, 81]. A number of researchers have shown a correlation between the severity of COVID-19 in patients and the level of cytokines, which, in turn, have been associated with the detection of certain types of "pro-inflammatory" or "anti-inflammatory" bacteria in the intestinal biotope [37, 43, 46, 51, 78], confirming the role of the microbiota in immune dysregulation. The composition of patients' gut microbiota has been found to be associated with plasma concentrations of aspartate aminotransferase (AST), chemokine receptor (CXCL10), CRP and lactate dehydrogenase (LDH) [78]. On the other hand, the induction of mediators of the inflammatory cascade further aggravates gut dysbiosis by disrupting the immune homeostasis of the biotope and the relationship between the resident microbiota and the gut immune system, leading to excessive pathological inflammation or chronic inflammatory diseases. This is supported by a study of blood samples from COVID-19 patients which showed a correlation between gut dysbiosis, the increased quantity of inflammatory mediators and the severity of systemic inflammation [5, 36, 78].

Immunological disorders in patients with COVID-19 are also mediated by changes in the metabolome profile that occur naturally against the background of dysbiotic microbiota disorders [19]. Short-chain fatty acids (SCFAs), bile acids, amino acids, carbohydrates, and neurotransmitters are known to be among the significant immunoregulatory metabolites of the microbiota [34, 48]. Recent studies have demonstrated the ability of butyrate produced by the gut microbiota to affect the membrane receptor ACE2, inactivate viral spike protein and inhibit SARS-CoV-2 virus replication [41]. A decrease in or disappearance of butyrate-producing bacteria in the biotope, along with an increase in pro-inflammatory mediators (C-reactive protein, IL-6 and sIL2R), has been found in patients in severe and critical conditions [59]. Other studies have shown the ability of ursodeoxycholate produced by bacteria of the genus Collinsella to block virus attachment to ACE2 receptors [53] and inhibit pro-inflammatory cytokines [38], preventing the development of cytokine storm [1]. The blocking of cytokine storm was also found on the model of Bacteroidetes bacteria

through inhibition of toll-like receptor 4 (TLR4) and signalling pathways related to the ACE2 receptor [22, 70]. The disruption of the biosynthesis of SCFAs and L-isoleucine, associated with high levels of CRP and CXCL10 in plasma, was attributed to the disappearance of the bacterium Faecalibacterium prausnitzii [44, 77, 79]. It was found that amino acids produced by bacteria were positively correlated with high levels of pro-inflammatory cytokines (CXCL9, CXCL10, IFNγ and IL-6) and negatively correlated with low levels of cytokines IL-9 and IL-17 in COVID-19. The content of biogenic amines had a positive correlation with low levels of cytokines CCL22, IL-12 and IL-13, but negatively correlated with high levels of pro-inflammatory cytokines (IL-6 and IL-10) [48]. Other microbial neurotransmitters such as tryptophan and polygammaglutamic acid (gamma-PGA) stimulated dendritic cells to polarise CD4+ cells towards Th1 [29].

L.B. Giron et al. found a decrease in citrulline (a marker of intestinal function), an increase in succinic acid (a marker of dysbiosis) and an increase in the kynurenine/tryptophan ratio in severe COVID-19. Citrulline was inversely correlated with IL-6, while succinic acid level and kynurenine/tryptophan ratio were positively correlated with IL-6 concentration [26].

Disruption of intestinal barrier integrity is considered to be one of the key inducers of systemic inflammation in COVID-19, as it promotes translocation of microbial cells or their components into the systemic bloodstream and stimulation of proinflammatory cytokine secretion, and may lead to the development of a cytokine storm [55, 72]. Lipopolysaccharides (LPS), peptidoglycan (PGN), zonulin, β-glucan and lipopolysaccharide binding protein (LBP) have been found to be indicators of intestinal barrier dysfunction in the plasma of COVID-19 patients associated with the regulation of immune response [25]. It is known that zonulin, β-glucan and LBP are positively correlated with factors of systemic inflammation and immune activation, including CRP, IL-6 and IL-10. In addition, increased permeability and microbial translocation may contribute to microbiota-mediated myeloid inflammation. As expected, levels of monocyte and neutrophil inflammatory markers (soluble CD14 (sCD14) and myeloperoxidase (MPO)) were elevated in the group of patients with severe COVID-19 compared to the group of patients with mild COVID-19 and the control group. In addition, plasma concentrations of pro-inflammatory cytokines IFNγ, IL-6, IL-8, MCP-1, macrophage inflammatory protein MIP-1α, MIP-1β, and TNFα were elevated in COVID-19 patients [55].

Role of normal microbiota in the formation of biotope immune homeostasis

It is known that the physiological role of the gut microbiota, and, first of all, of the normal microbiota (bifido- and lactobacilli) is largely related to the ability of prokaryotes to regulate the development and function of the innate and adaptive human immune system [49]. Intestinal microsymbionts influence the secretion of antimicrobial peptides, pro- and anti-inflammatory cytokines, compete for nutrients and habitat, thus contributing to the maintenance of homeostasis [47]. One of the mechanisms of microbiota immune regulation is the ability to influence the production of a certain type of regulatory molecules — cytokines as growth factors and stimulation/suppression of their synthesis [15, 39]. Some pathogenic and opportunistic bacteria secrete enzymes that allow microorganisms to cleave basic types of organic macromolecules. It is known that signalling molecules of the intestinal microbiota (short-chain fatty acids such as butyrate, acetate, propionate, and secondary bile acids) are able to regulate pro- and anti-inflammatory responses in the human body [50]. Immune homeostasis of the intestine is regulated by T-reg cells which are ultimately controlled by members of the normal human microbiota (bifido- and lactobacilli) through the toll-like receptor (TLR) system and nucleotide binding receptors (NOD) [60]. Inactivation of cytokines (antipeptide activity) [3], which are the product of activated T-lymphocytes, macrophages, dendritic cells, may entail significant disturbances in the mechanisms of innate and adaptive immunity. The balance of these regulatory molecules is important for human homeostasis, as cytokines participate in the regulation of the immune response during infection [12]. The production of cytokines in response to the presence of microorganisms implies not only indirect (through the regulation of immunity), but also direct contact of bacteria with these signalling molecules. This fact has significance in the development of complications in the new COVID-19 coronavirus infection, since one of the mechanisms of pathogenesis is the generation of a cytokine storm. The excessive immune response to the virus (cytokine storm) eventually causes multi-organ failure and patient mortality; therefore, a balanced immune response is needed, where an over- or under-reactive immune system response may equally exacerbate complications such as pneumonia and ARDS in new COVID-19 coronavirus infection. Healthy gut microbiome may be critical for maintaining optimal immune system function.

The management of microecological disorders of intestinal microbiota via bifidobacteria and lactobacilli normalises immune reactions and may be one of the ways to prevent complications, as well as reduce the risks of SARS-CoV-2 disease. Thus, administration of probiotic strains such as Bifidobacterium lactis to healthy elderly volunteers resulted in a significant increase in the proportion of mononuclear leukocytes and NK cells [23]. It is known that the composition of intestinal microbiota, primarily normobiota (bifido- and lactobacilli), has a great influence on the effectiveness of pulmonary immunity [6]. Animal experiments have shown that the ability to eliminate pathogens in the lungs was impaired in mice deprived of gut microbiota [18]. Disruption of the gut microbiota (dysbiosis) by the widespread use of antibiotics may also have an effect similar to that observed in population studies showing that inappropriate and uncontrolled use of antibacterial drugs such as penicillins, cephalosporins, macrolides and quinolones correlates with an increased risk of lung cancer in humans [7].

The use of probiotic medicines based on Lactobacillus and Bifidobacterium cultures has demonstrated positive results in the realisation of anti-inflammatory and immunoregulatory response of the organism [73]. It was found that the administration of some strains of probiotic bacteria (*Lacticaseibacillus rhamnosus, Bifidobacterium lactis* and *Bifidobacterium breve*) to experimental animals promotes the proliferation of T-reg-lymphocytes, suppressing inflammatory and allergic reactions in the organism [20], and administration of lactobacilli (*Lacticaseibacillus casei Shirota* or *Lacticaseibacillus rhamnosus GG*) to patients with cystic fibrosis leads to improvement of their condition [73].

Prospects for the development of targeted probiotics

It is now assumed that probiotic bacteria can be used for preventative or therapeutic purposes of inducing hormonal and immune changes in the body, since the participation of normobiotics (on the model of lactobacilli) in the regulation of the production of the neuropeptide hormone, oxytocin, has been proved [54, 69]. These studies are of interest because oxytocin is considered to be one of the possible candidates for the treatment of COVID-19. Oxytocin is known to be able to exert a dual action: to mobilise the immune defence potential and suppress excessive reactions of innate immunity, to limit pro-inflammatory (cytokine storm) and oxidative stress reactions by reducing cytokine levels. It has been suggested that even if oxytocin does not have a direct antiviral action, it still has sufficient mechanisms that may make it effective against COVID-19 through immunomodulatory, cardioprotective, antidiabetic and anabolic functions [35]. A number of studies have shown that some strains of normobiota (living cells

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and their components) are able to stimulate oxytocin and have immunoregulatory activity [54].

Of particular interest for COVID-19 treatment and prevention is nitric oxide (NO), which is a key signalling molecule that acts as a modulator of the host response in viral infections [68, 80]. At the same time, the microbiota is one of the sources of nitric oxide production directly [45] or indirectly through the induction of immune cells [10].

One of the problems arising in the use of biological medicines (synbiotics, probiotics, etc.) is the gradual decrease in the level of their antagonistic activity [11, 26], which ultimately affects the therapeutic and preventive efficacy of drugs. Also, one of the reasons for the low levels of effectiveness or its absence of probiotics is their foreignness to microorganisms [13]. Currently, as an alternative, for the correction of human dysbiosis, it is proposed to use one's own strains of bifidobacteria (autostrains), that are biocompatible, due to which they effectively form a biofilm with other representatives of the indigeneous microbiota under the conditions of microsymbiocenosis, in contrast to industrial strains of bacteria, which are not always able to colonise the human intestine [33].

When creating a consortium of microorganisms of probiotic action, bacterial strains are also selected without taking into account their biocompatibility in the composition, which can lead to suppression of microorganism viability and loss of their practically significant properties.

Two described biological universal phenomena of a fundamental nature contribute greatly to the solution of these problems: 1) associative symbiosis [9]; 2) bacterial persistence [8].

The study of microsymbiocenosis as one of the vectors of associative symbiosis allowed developing a method of intermicrobial "friend or foe" identification, where bifidobacteria are used as a diagnostic culture, since "friendly" strains are characterised by synergism (support), whereas encountering a "foreign cell" leads to antagonism. This fundamental mechanism may be used for choosing the "host-friendly" bacteria strains eligible for the creation of a probiotic composition. In this regard, one of the priority directions in the design of microbial compositions of pro- and synbiotics may be the use of the phenomenon of microbial "friend or foe" identification, which has proven itself well for the assessment of foreignness of *E. coli* strains [12].

As for another fundamental phenomenon, persistent potential of bacteria which fulfils the role of a "microbial biotarget", these adaptation characteristics may be used to solve an equally important task, the assessment of biocompatibility of microbial cultures, since preliminary studies have shown their full suitability for the specified purpose. Based on the method of intermicrobial identification, the principle of biocompatibility of probiotic cultures of microorganisms was formulated based on the oppositional (amplification/suppression) phenomenon of regulatory relations of microsymbionts, where it is possible to apply quantitative determination of the degree of biocompatibility of cultures based on the adaptive potential (biofilm formation and anti-lysozyme test) of bacteria. Such a two-in-one combination — inclusion of biocompatibility assessment of microsymbionts with simultaneous determination of "friend-foe" — can form the basis for selection of probiotic strains and formation of new drug compositions based on them [10, 12].

Conclusion

Thus, modern studies of the role of intestinal microbiota in animals and humans show that the intestinal microbiota is an important factor determining health, influencing immunity, participating in the pathogenesis of various infectious and non-infectious diseases. The pronounced contribution of the intestinal microsymbiocenosis is realised through the maintenance of a number of physiological functions and the formation of homeostasis of the host organism. The association between gut microbiota composition, cytokine levels and inflammatory markers in COVID-19 patients suggests that the gut microbiome influences the severity of the course of coronavirus infection. A number of key mechanisms for studying the integration of bifidobacteria and lactobacilli with the host, mediated by the system of immunity, hormones and neurotransmitters, open new perspectives for medicine, including obtaining new probiotic strains of different targeting for therapeutic and prophylactic correction of disturbed body functions.

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