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Intestinal microbiota as a fundamental basis for homeostasis, general pathology and aging

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ABSTRACT

Intestinal microbiota is a kind of satellite organ that performs digestive and protective functions, a supplier of molecules vital for homeostasis processes, involved in metabolic processes and determining the activity level of adaptive systems, including immunity. Immunity works both for and against the host, which is predetermined by the very nature of adaptive immunity and its interaction with the innate link of the immune system. The key element of this interaction is endotoxin molecules, or lipopolysaccharides, the concentration of which in the general bloodstream determines the activity level of adaptive (mediated by innate) immunity, which operates in a stochastic mode. This provides both antitumor protection and self-destruction of the body based on autoimmune damage. Over the past 35 years, there has been a powerful breakthrough in the field of understanding the mechanisms of interaction between the intestinal microbiota and the host organism. Interesting data have been obtained and published that have not yet been fully systematized and understood. The methodology for studying the biological role of lipopolysaccharides in clinical settings developed by Russian scientists was based on the ability of agents for reducing their blood levels to increase the effectiveness of the treatment and preventive process. In particular, it made it possible to establish the involvement of the lipopolysaccharide factor in the pathogenesis of a number of diseases. The phenomenon of systemic endotoxinemia discovered by Russian researchers is a process of controlling the activity of adaptive systems (including the immune system) with the participation of the hypothalamic-pituitary-adrenal system by means of intestinal endotoxins. We see the following issues for wide discussion in the clinical community: (1) determining the directions for finding agents for normalizing systemic endotoxinemia indicators as the basis of preventive medicine, including pro- and prebiotics, entero- and hemosorbents, hepatoprotectors, immunopreparations, chaotropic effects (plasmapheresis, blood irradiation); (2) clinical and experimental models for studying diseases associated with intestinal microbiota; (3) creation of a research protocol to establish the age range of integral indicators of systemic endotoxinemia (the level of lipopolysaccharides and the activity of antiendotoxin immunity that resists endotoxin aggression); (4) ways to understand the mechanisms of development of endotoxin tolerance accompanying aging and its overcoming.

Keywords: intestinal microbiota; lipopolysaccharides; endotoxins; adaptive immunity; innate immunity; systemic endotoxinemia; endotoxin aggression.

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Кишечная микробиота как фундаментальная основа гомеостаза, общей патологии и старения

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АННОТАЦИЯ

Кишечная микробиота — своеобразный орган-сателлит, выполняющий пищеварительную и защитную функции, поставщик жизненно важных для процессов гомеостаза молекул, участвующих в процессах метаболизма и определяющих уровень активности адаптивных систем, в том числе иммунитета. Иммунитет работает как во благо, так и против хозяина, что предопределено самой природой адаптивного иммунитета и его взаимодействием с врождённым звеном иммунной системы. Ключевым элементом этого взаимодействия служат молекулы эндотоксинов, или липополисахаридов, концентрация которых в общем кровотоке определяет уровень активности адаптивного (опосредованно врождённого) иммунитета, работающего в стохастическом режиме. Это обеспечивает как противоопухолевую защиту, так и самоуничтожение организма на основе аутоиммунного повреждения. За последние 35 лет произошёл мощный прорыв в области познания механизмов взаимодействия кишечной микробиоты и организма хозяина. Получены и публикованы интереснейшие данные, которые в полной мере ещё не систематизированы и не осмыслены. Созданная российскими учёными методология изучения биологической роли липополисахаридов в клинических условиях основана на способности средств для снижения их уровня в крови повышать эффективность лечебно-профилактического процесса. Она позволила констатировать, в частности, участие липополисахаридного фактора в патогенезе ряда заболеваний. Открытое отечественными исследователями явление системной эндотоксинемии представляет собой процесс управления посредством кишечных эндотоксинов активностью адаптивных систем (в том числе иммунной) при участии гипоталамо-гипофизарно-надпочечниковой системы. Среди вопросов для широкого обсуждения в клиническом сообществе нам видятся следующие: (1) определение направлений поиска средств для нормализации показателей системной эндотоксинемии как основы профилактической медицины, среди которых про- и пребиотки, энтеро- и гемосорбенты, гепатопротекторы, иммунопрепараты, хаотропные воздействия (плазмаферез, облучение крови); (2) клинические и экспериментальные модели изучения ассоциированных с кишечной микробиотой заболеваний; (3) создание протокола исследований по установлению возрастного диапазона интегральных показателей системной эндотоксинемии (уровня липополисахаридов и активности антиэндотоксинового иммунитета, противостоящего эндотоксиновой агрессии); (4) пути познания механизмов развития сопутствующей старению эндотоксиновой толерантности и её преодоления.

Ключевые слова: кишечная микробиота; липополисахариды; эндотоксины; адаптивный иммунитет; врождённый иммунитет; системная эндотоксинемия; эндотоксиновая агрессия.

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INTRODUCTION

For several decades now, the brilliant hypothesis of Ilya Mechnikov about the leading role of the gut flora, also called "gut microbiota," in the aging process remains unproven. Several expeditions to regions with a high prevalence of people with relatively long lives and the removal of the large intestine in some individuals did not support the desired result, revealed no special characteristics of the gut microbiota structure, and did not increase the life expectancy of the volunteers after the surgical removal of their large intestine.

These events led to research apathy and a loss of interest in the subject for almost half a century. Then, in 1988, the first scientific evidence of the ability of intestinal endotoxins [or lipopolysaccharides (LPS)] to induce systemic inflammation without any apparent cause or need was reported. This discovery was not accepted by the medical community because it contradicted one of the fundamental principles of general pathology, which classified inflammation as a protective reaction of the body in response to damage, and also because there was no methodology to test this bold assumption [1].

In addition, the role of LPS in the adaptation processes was discovered by using innovative laboratory methods in clinical settings, which was confirmed by foreign colleagues who discovered an LPS receptor of innate immunity in humans at the end of the 1990s [1]. This TLR4 receptor regulates the activity of all parts of the immune system, which formed the basis for an endotoxin theory of human physiology and pathology and introduced new scientific terminologies such as "systemic endotoxinemia" and "aggressive endotoxins" [2].

SYSTEMIC ENDOTOXINEMIA AS A MANDATORY COMPONENT OF HOMEOSTASIS AND GENERAL PATHOLOGY

Systemic endotoxinemia is the process of controlling the activity of adaptive systems (including the immune system) by intestinal endotoxin, involving the hypothalamic-pituitary-adrenal axis [2]. Stress induces its adaptive effect involving LPS with increased systemic blood levels due to shunting of the portal blood flow and its release from an adipose tissue depot as a result of stress-induced lipolysis, which can be observed in the neonatal period during the development of early adaptive responses [2].

LPS essentially serve as exohormones of adaptation (since they have their TLR4 receptor) and they can activate almost all adaptive systems and protein kinase C, which releases repression from the genome. This is an extremely necessary phenomenon for the body under extreme (or near-extreme) conditions. However, the role of systemic endotoxinemia is not limited to its involvement in the homeostatic processes, rather it extends to general pathology.

Russian researchers developed a methodology for studying the biological role of LPS in clinical conditions based on ways to reduce blood LPS levels, which also enhances the effectiveness of treatment and prevention. This event allowed the following [1–7]:

– Confirmation of the LPS ability to induce disseminated intravascular coagulation associated with multiple organ dysfunction syndrome,

– Assumption of the involvement of the LPS factor in pathogenesis of female infertility, broncho-obstructive syndrome in children with acute respiratory viral infections, chronic hepatitis B and C, human immunodeficiency virus infections (and acquired immunodeficiency syndrome), SARS-CoV-2,[1] atherosclerosis and acute myocardial infarction, diet-induced obesity and type 1 diabetes mellitus, endogenous iridocyclitis and endophthalmitis, autoimmune diseases, and endogenous psychoses.

Based on these data, interdisciplinary definitions of inflammation and sepsis were developed and the new research concept of aggressive endotoxins (a disease-inducing form of systemic endotoxinemia) was introduced: "Aggressive endotoxins of intestinal or other origin are a disease-inducing trigger of systemic inflammation, a premorbid condition and/or a universal factor of general pathology, which manifests as one or another disease entity due to genetic and/or acquired predisposition" [2].

Aggressive endotoxins may develop due to the following factors:

– Stress (physical, psychoemotional, or other),

– High-fat diet,

– Liver and kidney disease, as these are the major LPS-secreting organs (endotoxin-releasing properties of the skin have not been evaluated),

– Intestinal dysbacteriosis and other factors that increase intestinal permeability.

ENDOTOXIN PERMEABILITY OF THE INTESTINAL WALL

The possible causes of increased intestinal permeability include damage to the intestinal mucosa (dietary, viral, bacterial, mechanical, parasitic, and autoimmune) and excessive bacterial growth (specifically, LPS-producing gram-negative gut microbiota) [8]. Experimental and modeling studies have been crucial in understanding the role of gut microbiota and LPS in general pathology.

For instance, Cani et al. [9] proposed a dietary model of chronic endotoxinemia called "metabolic endotoxemia" (we do not consider this to be the best term) and established a direct correlation between systemic LPS levels (i.e., chronic

[1] SARS-CoV-2 (severe acute respiratory syndrome-related coronavirus-2) is the second coronavirus associated with severe acute respiratory syndrome.

endotoxinemia), obesity and insulin resistance, as well as created a completely new approach to the prevention of type 2 diabetes mellitus and other metabolic disorders associated with decreased intestinal permeability.

The endotoxin theory of human physiology and pathology considers obesity and insulin resistance as direct consequences of chronic endotoxinemia [2]. These include the following [4]:

– The hydrophobic form of LPS (recirculating pool of the molecule along the intestine-blood-liver-intestine-blood route) passes through the intestinal wall as a part of chylomicrons; fatty food increases intestinal permeability and body weight (LPS probably activates lipogenesis),

– Obese patients tend to have slower inflammatory disease progression and elevated pro-inflammatory and blood LPS levels,

– Adipose tissue serves as a depot for LPS; therefore, therapeutic fasting and dietary use of a gastrointestinal lipase inhibitor not only reduces body weight but also normalizes the integral parameters of systemic endotoxinemia.

The first successful attempt to reduce intestinal permeability using a probiotic (a live culture of *Bifidum*) was made in 2004 in order to reduce the LPS levels in the patient's blood and the incidence of exacerbations of chronic diseases [10]. It was also discovered that *A. muciniphila* has an even greater ability to "strengthen the intestinal barrier" [11]. In our opinion, this should be considered one of the most important achievements of clinical microbiology, since the prevention and/or elimination of aggressive endotoxins are a mandatory component of treatment and prevention as it involves slowing down the rate of aging.

AGING AS A RESULT OF INFLAMMATION

One of the most significant achievements of our time has been Claudio Franceschi's concept of the inflammatory nature of aging [12] in contrast to the term "inflamaging" introduced by him since there are no fundamental age-based differences in chronic (low-intensity) inflammation.

Autoimmune inflammation accompanies us from birth (predetermined by the nature of the immune system, which simultaneously protects and destroys a host, ensuring self-renewal of the population and evolution of the species [2]) and intensifies with age, without acquiring any new characteristics. The main trend in maintaining health and prolonging life is to decrease the activity of adaptive immunity (which is controlled by innate immunity and its ligands) since life itself is a process of burning in the fire of chronic (including and, perhaps, primarily autoimmune) inflammation [13].

Notably, [2] blood LPS levels gradually increase with age along with the number and severity of chronic diseases, including arteriosclerosis, which is accompanied by a decreased activity of antiendotoxin immunity, decreased body's ability to respond to excess systemic LPS levels, and a high body temperature (i.e., increased metabolism). In other words, endotoxin tolerance increases with age, which is probably individually required in the short term to block excessive immune system activity (aggressiveness) in extreme conditions (such as sepsis or shock) and in the long term to ensure pool aging and self-renewal processes that is, species evolution. In this process, the gut microbiota plays a key role as a source of innate immunity ligands, primarily LPS.

GUT MICROBIOTA: A FRIEND AND FOE

At first glance, the interaction of the gut microbiota with the host organism seems paradoxical. On one hand, the gut microbiota is the guarantor of digestive processes and, the synthesis of compounds essential for homeostasis (including vitamins, signaling molecules, and innate immunity ligands). On the other hand, it is the primary enemy of its host, since it is involved in aging and self-destruction, which is predetermined by the nature of the immune system and its interaction with LPS, which is recognized not only as a marker but also as an inducer of systemic inflammation and the rate of aging [13].

Therefore, it is not unreasonable to say that life is a process of "burning in the fire of chronic inflammation" with periods of exacerbation induced by chronic and acute endotoxin aggression [13].

ANTIENDOTOXIN THERAPY AS A BASIS FOR NEW MEDICINE

There are several approaches to reducing the systemic LPS levels:

– The use of food products and enterosorbents to remove endotoxins from the intestine [14],

– Plasma purification with LPS filters [8],

– The use of bacteria with high adherence to the mucosa, as they reduce intestinal permeability, including bifidobacteria and *A. muciniphila* [10, 11],

– Consideration of dietary factors that affect the gut microbiota profile and natural bioantioxidants [15, 16],

– Adapting ways to increase the activity of antiendotoxin immunity, including various chaotropic effects [17],

– Potential consideration of selective enterosorption of endotoxin aggression sources [18].

CONCLUSION

The gut microbiota is a satellite organ that acts as a guardian, a supplier of vital compounds, and directly participates in homeostatic processes, thereby determining the level of activity of adaptive systems, including immunity. Immunity acts both for and against the host, as determined by the nature of adaptive immunity and its interaction with the innate part of the immune system. LPS is the key element in this interaction; its systemic levels determine the activity of adaptive

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(innate) immunity, which operates stochastically, providing both antitumor protection and autoimmune self-destruction of the body.

Over the past 35 years, there have been breakthroughs in understanding the mechanisms of interaction between the gut microbiota and the host organism. Some interesting facts related to this aspect have been reported in scientific publications, but they have not yet been systematized and are therefore not understood. Here, are some of the issues for discussion:

– Finding ways to normalize the parameters of systemic endotoxinemia as a basis for preventive medicine, including the use of probiotics and prebiotics, enterosorbents and hemosorbents, hepatoprotectors, immunological agents, chaotropic agents (such as plasmapheresis and blood irradiation),

– Clinical and experimental models to study gut microbiota-associated diseases,

– Development of a study protocol to determine the age range of integral parameters of systemic endotoxinemia (LPS levels and antiendotoxin immune activity),

– Ways of understanding mechanisms of age-related endotoxin tolerance and how to overcome it, which will be discussed at the next scientific forum in the Republic of Tatarstan (www.lpsexpo.ru).

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

Вклад авторов. А.С.С. — концептуализация, методология, редактирование рукописи, общее руководство; И.А.А. — методология, исследование, валидация; Р.И.Ж. — валидация, создание черновика, редактирование рукописи; М.М.М. — исследование, анализ, создание черновика; С.Г.М. — ресурсы, анализ, редактирование рукописи, общее руководство, финансирование.

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ADDITIONAL INFORMATION

Authors' contribution. A.S.S. — conceptualization, methodology, writing — review and editing, supervision; I.A.A. — methodology, investigation, validation; R.I.Zh. — validation, writing — original draft, writing — review and editing; M.M.M. — investigation, formal analysis, writing — original draft; S.G.M. — resources, formal analysis, writing — review and editing, supervision, funding acquisition.

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