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Gut Microbiome and Age-Related Diseases

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Abstract—The gut microbiome (community of microorganisms) has a great influence on human physiology both in a healthy state and in pathologies. It can affect human health either directly (by secreting biologically active substances such as vitamins, bacteriocins, essential amino acids, lipids, etc.) or indirectly (by modulating metabolic processes and the immune system). The composition of microbiota is determined by the genetic predisposition and microbiome received in childhood from the mother and from the environment, which can change during life under the influence of external and internal factors. The human microbiome undergoes the most noticeable deviations in infancy and then in old age, when the immune system is also in the weakest and most unstable state, which can lead to the development of different pathologies. The use of probiotics and prebiotics is recommended when correcting different pathological conditions and when used in a complex treatment of diseases. The development of test systems of biologically active substances affecting the human microbiome allows us to determine the biological activity of individual strains and to design new generation drugs to extend healthy longevity. Such developments are one more step towards personalized medicine.

Keywords: microbiome, anti-aging medicine, dysbiosis, intestinal microbiota, probiotics

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INTRODUCTION

Studying the state of healthy microflora of the gut and other human organs is one of the important topics in science and medicine. It is difficult to overestimate the role of prebiotics and probiotics in the organism. More than a hundred years ago, I.I. Mechnikov put forward the hypothesis about the relationship of the human microbiome with its diseases and longevity. He considered that multiple associations of microbes inhabiting the human gut largely determine a person's spiritual and physical development. "The intestinal flora is the main reason for the shortness of our life, fading away without reaching its limit" (Mechnikov, 1964). Thus, a human is a "superorganism" (a symbiotic community, which includes a wide variety of microorganisms). The microbiome of each human is unique (almost like fingerprints) and includes many species of fungi, archaea, viruses, and eubacteria. According to some estimations, the number of microbiome cells is 3–10 times greater than the number of cells in one's own body. More than 100 trillion microorganisms live in the human body. They form colonies on its surface (on the skin), in respiratory organs, eyes, mouth, urogenital tract, and gastrointestinal tract (GIT) (Sartor, 2008; Sender et al., 2016). In each of these areas, microorganisms are united into the communities called "microbiota" (microflora) of this area.

The aim of the review is a description of the composition of the human microbiome, its changes with age and with different pathologies, methods of its correction, and study of the ways in which biologically active substances affect the microbiome for creating new microbial preparations.

MAIN METHODS AND INTERNATIONAL DATABASES FOR STUDYING THE HUMAN MICROBIOME

Identification of microorganisms that cause infection is important for the efficient treatment of individuals. The traditional methods of pathogen identification include the culture method, serological detection, and molecular biology methods (such as nucleic acid amplification). However, not all bacterial species can be efficiently cultivated in a diagnostic laboratory, and new pathogens cannot be detected using nucleic acid amplification. Almost all modern data on microbiota diversity were collected by DNA sequencing as a result of studying bacterial ribosomal RNA (Nafea et al., 2024). The analysis of these data is carried out within the international scientific programs: Human Microbiome, MetaHIT, Metagenomics of the Human Intestinal Tract, MicroObes, Human Intestinal Microbiome in Obesity and Nutritional Transition, Data Analysis and Coordination Center, etc. There is a special program ELDERMET for studying the microbiota of elderly (≥65 years) individuals, funded by the Irish government. As a result of a large number of independent studies, a large amount of data on the composition of microbiota in individuals of different ages and with different pathologies were accumulated (Suvorov, 2017).

DEVELOPMENT OF MICROBIOME IN ONTOGENESIS

According to current concepts, a human is born almost free of microbiota. Aerobic and some anaerobic bacteria of the mother's intestine are the first colonizers of the child's intestines (in the case of natural childbirth); newborns receive them when passing through the birth canal (Prince et al., 2015). In the process of breastfeeding, anaerobes with a significant representation (10–15% of the total microbial number) of actinomycetes (Bifidobacteria family) begin to dominate in the microbiota. As a child develops, the diversity and stability of its microbiota increases: if *Bifidobacterium bifidum* and *Lactobacillus* predominate from the first days of life, then a relative decrease in the representation of lactic acid flora is observed, and *B. longum* and *B. breve* begin to predominate among *Bifidobacterium*. Subsequently, the microbiome changes in the case of refusal of breast milk, then during puberty, and it varies because of different diseases, diet, antibiotic use, stress, and aging. Both the composition of microbiota and the number of microbes in individual groups, as well as their ratio, are subject to change. From the age of two, microbiota is developed in a human with an approximately equal ratio of Firmicutes and Bacteroidetes typical for adults (Mackie et al., 1999). This phase is characterized by a relative stability of the microbial composition, which is almost preserved throughout the entire adulthood of an individual. Beginning with the primary colonization by microorganisms (which is affected by the way a child is born, the mother's use of antibiotics, the degree of fetal maturity, as well as the nature of his feeding), the composition of microbiota is extremely important for further human development, as well as for the treatment of diseases that will overtake him in adulthood (Rolhion and Chassaing, 2016).

Adult Microbiome

Microorganisms living in the intestine of a healthy individual form a normal microflora and are in the state of equilibrium both with the host organism and relative to each other (Grice and Segre, 2012). For the vast majority of individuals, a similar ratio of the main types (phyla) of bacteria is typical: Bacteroidetes and Firmicutes (Rajilić-Stojanović et al., 2009). The phylum Bacteroidetes includes Gram-negative bacteria belonging to almost 20 genera; the phylum Firmicutes includes Gram-positive bacteria belonging to more than 200 genera (Claesson et al., 2011). However, the microbiota of each human is individual at the species and especially strain level. The microbial community of the stomach, in which representatives of the genera *Lactobacillus*, *Stomatococcus*, and *Sarcina* are found in the amount of up to 10^2 per 1 g of the content, is the scarcest. In the small intestine (except for distal departments of the ileum), the number of microorganisms does not exceed 10^4–10^5 cells per 1 g of the content. The number of microorganisms in distal departments of the ileum increases significantly, reaching 10^7–10^8 per 1 g of the content. At the same time, mainly Gram-positive aerobic bacteria are found in proximal departments of the small intestine; Gram-negative enterobacteria and anaerobes are found in distal ones. The large intestine microbiota is mainly represented by anaerobic bacteria; their total number reaches enormous values (10^{13} per 1 g of the content) (Sender et al., 2016). With age, the microbial species and generic diversity of human microbiota decreases (Wang et al., 2015; Saraswati and Sitaraman, 2015). In older individuals, the number of Firmicutes decreases to 30–45% of the total microbial composition, while the number of Bacteroidetes increases to 50–70%, while the level of Proteobacteria can reach 23%. By old age (over 75 years), the number of bacteria of the genera *Bacteroides*, *Eubacterium*, *Peptostreptococcus*, and *Clostridium* increases in the intestine with a decrease in the total number of *Lactobacillus*, *Faecalibacterium*, *Parabacteroides*, *Butyricimonas*, *Coprococcus*, *Megamonas*, *Mitsuokella*, *Sutterella*, and *Akkermansia*. Of Firmicutes, bacteria of the genus *Clostridium* are the most numerous. Two more genera of the class Clostridia (*Ficobacteria* and *Ruminococcus*) are important components of the gut microbiota of a healthy person (Claesson et al., 2011). For example, the content of some probiotic species, such as *Desulfovibrio piger*, *Gordonibacter pamelaeae*, and *Odoribacter splanchnicus*, increase with age, which is supposed to contribute to healthy longevity. It can also be promoted by the increased content of *Bacteroides fragilis* in centenarian individuals owing to an increase in the expression of the anti-inflammatory factor IL-10, which decreases the level of chronic age-dependent inflammation (inflammaging) (Claesson et al., 2012; Wang et al., 2022).

Thus, human microbiome undergoes the most noticeable deviations at two critical stages of life (in infancy and old age), when the immunity is in the weakest and most unstable state, which can lead to the development of different pathologies (Nagpal et al., 2018).

MICROBIOME THEORY OF AGING

The role of the microbiome in age-related changes in general and, particularly, in the development of pathologies is significant, which contributed to the emergence of the microbial theory of aging. This theory explains how a microbial imbalance in the intestinal tract (dysbiosis) causes health problems that accelerate aging. Cellular senescence, immunosuppression, and dysbiosis of the intestinal microbiota are considered to be the key modulators of aging (Sharma and Diwan, 2023). The main mechanisms involved include enhanced inflammation, increased level of zonulin (a protein marker of the integrity of tight junctions between epithelial cells of small intestine), destruction of intestinal tight junctions, and intestinal permeability, which allows lipopolysaccharides (LPS) to leak into the systemic circulation. LPS is a powerful endotoxin, which causes chronic inflammation in the entire body, which leads to the development of chronic diseases and accelerated biological aging (Sharma and Diwan, 2023).

Postbiotic metabolites (compounds formed by probiotic bacteria in the large intestine) play an important role in the regulation of the structure and function of the gut microbiome and, accordingly, human health (Pelton, 2023). Modulation of cell antioxidant protection is provided by probiotics that chelate metal ions, and their own antioxidants (superoxide dismutase and catalase enzymes). They also produce antioxidant metabolites (folates and glutathione) and regulate the antioxidant activity of the host. Owing to an increase in the activity of the transcription factor Nrf2 in the host cells, the expression level of antioxidant enzymes increases (Shilovskii and Sorokina, 2020; Jun et al., 2020; Shilovskii et al., 2022). Different molecules exhibit the function of Nrf2 activator, including alkylcatechols: 4-methyl-, 4-vinyl- and 4-ethylcatechol. These compounds arise as a result of biotransformation of plant precursors by lactobacilli (for example, *Lactobacillus plantarum*, *L. brevis*, and *L. collinoides*) expressing phenolic acid decarboxylase. The presence of alkylcatechols (as well as other biotransformable substances, including sulforaphane) in a complete diet contribute to the maintenance of the cell antioxidant protection with age (Senger et al., 2016). Nrf2-activating phenolic compounds can contribute to the growth of probiotics, reduction in the Firmicutes/Bacteroidetes (F/B) ratio, and improvement of microecological imbalance of the intestine (Liu et al., 2024).

CHANGE IN THE COMPOSITION OF MICROBIOTA UNDER THE INFLUENCE OF DIFFERENT FACTORS NORMALLY AND IN PATHOLOGY

The gut microbiota can affect not only the state of the GIT, but also the entire body as a whole, determining the quality and duration of human life (Askarova et al., 2020; Ratanapokasatit et al., 2022; Zhang et al., 2023). The gut microbiota produces more than 10% of metabolites in the blood of mammals. These metabolites can have a systemic effect on the body of the host (Shilovsky et al., 2022). In addition to the enzymatic activity and positive effects of intestinal metabolites on different systems of the human body (nervous, immune, etc.), the microbiota plays a huge role in the protection of the intestine from microbial pathogens and food contaminants (Cheng et al., 2022). The members of the intestinal community cover the intestinal epithelium with a biofilm, preventing the development and attachment of contaminants, occupying the adhesion sites. They also produce the substances with bacteriolytic and/or bacteriostatic effect: bacteriocins and short-chain fatty acids (SCFA) (Rolhion and Chassaing, 2016).

Bacteria included in the microbiota compete with pathogenic microorganisms for the substrates, preventing their development in the large intestine (van der Hee and Wells, 2021). The gut microbiota is able to control the intestinal barrier function, owing to neuroactive substances produced by the microbiota, and SCFA, modulating the immune system (van de Wouw et al., 2017). SCFA act through G-protein-coupled receptors and stimulate the acetylation of histones and non-histone proteins owing to the inhibition of histone deacetylases, as well as through the interaction of these signaling pathways with the pathways of transcription factors NF-κB and Nrf2 (Fock and Parnova, 2023). These main mechanisms of the effect of SCFA on the preservation of the integrity of the blood-brain barrier indirectly affect the disorders of human nutritional behavior and accompanying diseases associated with metabolic disorders (van de Wouw et al., 2017).

As a rule, the approaches to modification of the microbiome are divided into three main groups: purification from microorganisms, their modulation and replacement, and restoration of microbiota. For example, antibiotics are often used for the treatment of conditions caused by nonspecific pathogenic microbiota because of their ability to cleanse efficiently the intestines from bacteria. In addition to age, the composition of human microbiota is affected by such factors such as gender, dietary preferences, socioeconomic status and level of education, and taking antibiotics. Geographical differences associated with the nature of nutrition are also important. Some bacterial taxa (for example, Bacteroidetes) respond quickly to changes in the diet (David et al., 2014). Thus, *Prevotella*, *Clostridium clostridioforme*, and *Faecalibacterium prausnitzii* are dominant bacteria in the microbiota of vegetarians (Graf et al., 2015; Flint et al., 2015). At the same time, the portion of bacteria belonging to Bacteroidetes, Bifidobacteria, and Enterobacteriaceae decreases (Jandhyala et al., 2015). In contrast, the portion of bacteria having proteolytic activity (such as *Bacteroides* spp.) increases with a high-protein diet (Maukonen and Saarela, 2015; Graf et al., 2015). A fat-rich diet leads to the synthesis of large amount of bile acids, contributing to the proliferation of bacteria metabolizing them (such as *Bacteroides*, *Alistipes*, and *Bilophila*) and inhibiting the propagation of other species (Graf et al., 2015, Maukonen and Saarela, 2015).

Microbiota of the large intestine in individuals whose diet is rich in plant fibers and complex carbohydrates is characterized by a diversity of bacterial species (*Prevotella*, *Succinivibrio*, *Treponema*) that ferment polysaccharides and produce SCFA (Graf et al., 2015; Maukonen and Saarela, 2015; Dominianni et al., 2015; Wang et al., 2015; Chung et al., 2016). SCFA are involved in the immune system functioning and in the formation of inflammatory responses. The levels of SCFA in feces (and, to a lesser extent, in blood plasma) are considered to be a reliable practical marker of the state of the gut microbiome (Nogal et al., 2023). SCFA (acetate, butyrate, propionate, hexanoate, valerate, etc.) formed in the process of fermentation of dietary fiber are also key substrates in energy metabolism of colonocytes. They play a crucial role in normal functioning of the intestinal barrier function and modulate the immune system functioning in the host organism (Azad et al., 2013; Greenhill et al., 2015; Greenhalgh et al., 2016; Tanaka and Nakayama, 2017). The possibility of an effect on the composition of microbiota and its metabolic activity by a change in the nature of nutrition (an increase in the portion of vegetables and fruits in the diet, consumption of dietary fibers that contribute to the development of butyrate-producing flora) seems to be a promising direction of practical medicine (Maryam et al., 2016; Suchkov et al., 2024).

The gut microbiome (as well as the oral one) is able to modulate neurochemical and neurometabolic signaling pathways of the brain through the formation of a bidirectional communication axis with the involvement of the endocrine and immune systems, as well as contribute to the development of neuroinflammation and neurodegeneration. For neuropathologies (including Alzheimer's disease (AD) and Parkinson's disease (PD)), a specific pattern of microbiota differs significantly from that in healthy individuals (Harach et al., 2017; Kowalski et al., 2019). Thus, a decrease in the number of Firmicutes and Actinobacteria and an increase in the number of Bacteroidetes is observed in patients with AD. Along with dementia and amyloid deposits, patients have a decrease in the number of *Eubacterium rectal* producing butyrate and an increase in the number of *Escherichia*/*Shigella*, which contribute to the development of inflammation. In addition, there is an association between the number of bacteria and biomarkers of AD (for example, level of Aβ42/Aβ40 in cerebrospinal fluid) (Cattaneo et al., 2017; Vogt et al., 2017). Neuroimmune modulation with microbiota can contribute to the etiopathogenesis or manifestation of the symptoms related to neurobehavioral and neurodegenerative disorders, such as autism spectrum disorder, anxious depression, AD, and PD (Fung et al., 2017). The production of butyrate by the gut microbiota is an important factor in the pathophysiology of PD. Thus, lower content of *Butyricimonas synergistica* (butyrate producer) is associated with worsening of nonmotor symptoms of PD (Nuzum et al., 2023).

PREVENTION AND THERAPY. PROBIOTICS AND PREBIOTICS

It is known that many bacteria use a system of intercellular communication (quorum sensing), which depends on population density. This contributes to the study of microbial activity in vivo and is of a great importance for the development of new drugs and methods of treatment of bacterial pathologies (Abisado et al., 2015; Oleskin et al., 2021). Targeted formation of the gut microbiota using bacteriocins and other antimicrobial drugs has potential as a therapeutic tool for the prevention or treatment of different pathologies such as obesity, type 2 diabetes mellitus, and inflammatory bowel diseases (Walsh et al., 2015).

The preparations used in medicine are divided by the composition or direction of action. Probiotics are nonpathogenic and living microorganisms useful for humans. The very concept of "probiotic," which means "life-extending," was suggested by Mechnikov (1964). All preparations and products of probiotic consortium are a protective component of the intestinal microbial ecosystem, increase the antioxidant activity of superoxide dismutase and glutathione reductase, and have a DNA-protective effect (Saduakhasova et al., 2014). As already mentioned above, these preparations either contain their own antioxidants or induce the expression of the enzymes of the cell antioxidant protection.

LACTIC ACID BACTERIA AND PREPARATIONS BASED ON THEM

Lactic acid bacteria (LAB) isolated from dairy products are of a particular interest as probiotic correctors of normal gut microbiota (*Streptococcus thermophilus*, *Lactococcus lactis*, *Lactobacillus plantarum*, etc.). Mesophilic *L. lactis* ssp. *lactis*, included in the composition of human gut microbiota, have a number of advantages over other LAB owing to their growth rate, absence of pathogenic forms (GRAS status), and ability to suppress the growth of harmful microbes, contributing to normalization of GIT functioning. In addition, most individuals with lactase deficiency are able to tolerate normally fermented milk products owing to the fermentation of lactose into lactic acid by these bacteria (Sorokina et al., 2022). Probiotic preparations containing LAB (lactobacilli, lactococci, and enterococci) are also used in the treatment of different pathologies accompanied by dysbiosis (in irritable bowel syndrome, nonspecific ulcerative colitis, traveler's diarrhea, allergies). Lactobacilli and lactococci easily tolerate the intestinal environment, do not inhibit each other's vital activity, synthesize antimicrobial substances, decrease the process of adhesion of pathogenic microorganisms to the intestinal mucosa, and increase the resistance of the body to the effect of pathogenic and disease-causing bacteria.

In order to decrease any harm from the effect of pathogens in GIT, it is necessary to consume the products containing probiotics, such as yogurt, sauerkraut, and kefir. Kefir is one of the most popular fermented milk products. Microorganisms present in it have a probiotic potential, are resistant to low pH and bile salts in GIT, and are able to adhere to the intestinal mucus. The microbiota present in kefir is capable of producing organic and fatty acids, bacteriocins, etc., suppressing pathogenic microflora, and maintaining normal microflora. The kefir grains inhibit the growth of opportunistic pathogens and, most importantly, of fungi (yeast from the genus *Candida*). As a result, the adhesion of pathogenic microorganisms to the intestinal epithelium is prevented, and the exopolysaccharides contained in kefir promote intestinal health and body health in general (Ding et al., 2022). This achievement allowed us to lay the foundations for the preventive and therapeutic use of kefirs for the treatment of human candidiasis, improvement of digestion, and strengthening of the immune system.

Probiotics. Probiotics on the basis of enterococci and lactobacilli are efficient in multiple sclerosis and *Helicobacter pylori* infections of the stomach. Probiotics with *Escherichia coli* are used in Crohn's disease; those based on *Saccharomyces boulardii* and *Bacillus subtilis* are used in dysbiosis against the background of infectious diseases, for example, enterovirus infections. In older individuals, the use of probiotics is able to cause a modulation of the innate immunity with increased expression of anti-inflammatory cytokines (Eloe-Fadrosh et al., 2015). Foreignness to the microbiome is one of the disadvantages of probiotics. Thus, bacteria grown outside the body in artificial nutrient media can only create the conditions for a restoration of previously suppressed intrinsic microbiota, but are not able to restore the species that disappeared from the microbiocenosis or increase microbial diversity (Nyangale et al., 2015).

Fecal transplantation. Fecal transplantation (a procedure in which the microbiota of a donor is "transplanted" into the body of a patient suffering from dysbiosis) is a possible alternative to probiotics (Choi and Cho, 2016). However, when replacing microbiota of one individual with someone else's, there is a risk of transmitting bacteria or viruses from the donor. It is possible to avoid the undesirable consequences of microbial therapy associated with probiotics or fecal transplantation using the technology of autoprobiotics. It was found that one's own bacteria preserved before the development of dysbiosis can be cultivated and reintroduced into the person with food (Suvorov, 2013). In this case, bacteria are perceived by the immune system not as something foreign, but as a natural part of the body (Gromova et al., 2021; Ermolenko et al., 2023).

CONCLUSIONS

The microbiome has a huge effect on human physiology both in a healthy state and under conditions of pathology. It can affect human health either directly (by secreting biologically active substances such as vitamins, essential amino acids, and lipids) or indirectly (by modulating metabolic processes and the immune system) (Askarova et al., 2020). The prevalence of one of the components (proteins, fats, or carbohydrates) in the diet determines the development of certain species of bacteria in the composition of the gut microbiota (Greenhalgh et al., 2016; Tanaka and Nakayama, 2017). The human microbiome undergoes the most noticeable deviations in infancy and then in old age, when the immunity is at the weakest and most unstable, which can lead to the development of different pathologies such as diabetes, atherosclerosis, and autoimmune and neurodegenerative diseases. With age, individual differences in the microbiome also become more pronounced (Claesson et al., 2011; Odamaki et al., 2016).

The number of the studies and publications on the use of preparations correcting these conditions is steadily growing. Thus, it was demonstrated that probiotic preparations containing lactic acid bacteria (lactobacilli, lactococci, and enterococci) are efficient in the treatment of different pathologies (Sorokina et al., 2022). The aim of probiotics and prebiotics is to activate the growth of "native" beneficial bacteria in the intestine and to inhibit pathogenic ones. All preparations and products of the probiotic consortium are a protective component of the intestinal microbial ecosystem, increase the antioxidant activity of superoxide dismutase and glutathione reductase, and have a DNA-protective effect (Saduakhasova et al., 2014).

Increased interest in probiotics and prebiotics requires the creation of new dosage forms. For example, mobilization of probiotics is one of the important technologies, which has been rapidly developing in the last decade. The advantages of this therapeutic strategy consist in the maintenance of greater cell viability, despite a high acidity of the stomach, and the use of mineral carriers, which allows us to preserve the viability and high probiotic properties of bacteria for a long time (Sorokina et al., 2024). In general, restoring balance along with the fight against dysbiosis is one of the most important conditions for achieving an improved quality of life and healthy longevity of people.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATE

This work does not contain any studies involving human and animal subjects.

CONFLICT OF INTEREST

The authors of this work declare that they have no conflicts of interest.

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