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THE GUT MICROBIOME AND ITS ROLE IN HUMAN HEALTH

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ABSTRACT

Introduction: The human gut microbiome has become the subject of intensive scientific research in recent years due to its significant impact on the body. Disturbances in its composition, called dysbiosis are linked to diseases such as inflammatory bowel disease (IBD), obesity, type 2 diabetes, allergies and neuropsychiatric disorders. This review summarizes current knowledge about the gut microbiome - its composition, functions, research methods, therapeutic options and health impact.
Materials and methods: The review was based on an analysis of scientific literature from the PubMed database. The selected publications concerned the composition and development of the microbiome, its function in the pathogenesis of diseases and diagnostic methods and therapeutic strategies.
Results: The gut microbiome is a complex ecosystem of bacteria, viruses, fungi and archaea. It develops from the perinatal period depending on delivery mode, feeding, diet, antibiotics, and lifestyle. It ferments undigested components into short-chain fatty acids (SCFA), synthesizes vitamins, modulates immunity and protects against pathogens. Dysbiosis is linked to chronic inflammation "leaky gut" and metabolic, autoimmune and neuropsychiatric diseases. Therapies include probiotics, prebiotics, synbiotics, diet changes, fecal microbiota transplantation (FMT) and new methods such as bacteriophages or precise microbiome editing using CRISPR-Cas technology (a biological system that bacteria and archaea use to defend against viruses).
Conclusions: Growing evidence supports the critical role of the gut microbiome in health. Although the links between dysbiosis and disease are clear, direct causality remains uncertain. Future research should identify key microorganisms, develop personalized therapies based on microbiota modulation and ensure the safety of treatments. Properly shaping the microbiome may open new possibilities for preventing and treating chronic diseases.

KEYWORDS

Gut Microbiome, Human Health, Probiotics, Dysbiosis

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1. Introduction

The gut microbiome is a very complex ecosystem of microorganisms that inhabit the human digestive tract. Their number is estimated at about 10^{13}–10^{14} cells, which is comparable to the number of cells in the human body [1]. The gut microbiota performs many important functions in the human body, including supporting digestion, participating in the synthesis of vitamins and short-chain fatty acids (SCFA), shaping the immune system and protecting against pathogens [2]. Disturbances in its composition, referred to as dysbiosis, can cause many diseases, including inflammatory bowel disease, obesity, type 2 diabetes, allergies and neuropsychiatric disorders [3]. With the dynamic development of research on the microbiome, there is a need to organize the vocabulary used. In the scientific literature, terms such as microbiota or microbiome are sometimes used interchangeably or imprecisely, which leads to misunderstandings. In the indicated article, the authors proposed clear definitions of key terms that allow for a better description of the complexity of human microbiological ecosystems. Microbiota refers to the actual community of microorganisms – bacteria, viruses, fungi or archaea – inhabiting a specific environment (e.g. gastrointestinal tract). The microbiome, on the other hand, includes not only these microorganisms but also their genes, metabolic products and environmental context [4].

2. Composition and development of the gut microbiome

The development of the gut microbiome begins already in the perinatal period. Its composition in the first months of life is influenced by the mode of delivery (vaginal birth vs. cesarean section) and the method of infant feeding (breastfeeding vs. formula feeding). Infants delivered vaginally are mainly colonized by bacteria from the mother's birth canal (such as Lactobacillus, Prevotella), whereas those born via cesarean section have a microbiota more similar to the skin microbiota of the mother and medical staff [5]. Feeding method also plays an important role. Breastfeeding promotes the growth of Bifidobacterium and Lactobacillus due to the presence of human milk oligosaccharides (HMOs), which act as prebiotics [6].

In subsequent years, factors such as diet, antibiotics, infections and lifestyle shape a mature gut microbiota profile that remains relatively stable but still susceptible to change. The composition of the microbiota at the genus and species level varies greatly between individuals, and also within the same individual depending on the period of life. In one of the articles, the aim of which was to define the concept of a “healthy” composition of the human gut microbiota and to discuss the factors influencing its variability, the importance of geographical and cultural context was emphasized. Comparative studies show clear differences in the composition of the microbiota between the populations of developed and developing countries, which suggests the influence of a traditional diet (rich in fiber, less processed) on maintaining a favorable microbiota diversity [7].

The predominant bacteria in adults include Firmicutes and Bacteroidetes and to a lesser extent Actinobacteria, Proteobacteria, and Verrucomicrobia. However, dysbiosis, which is an imbalance of microorganisms caused by host inflammation, significantly alters the intestinal environment, promoting the selective growth of bacteria from the Proteobacteria group. They gain a competitive advantage due to the possibility of using alternative respiratory pathways (e.g. nitrates) produced as a result of inflammation. At the same time, the number of Firmicutes and Bacteroidetes bacteria is significantly reduced [8].

In older people, a decrease in microbiota diversity and an increase in the share of potentially pro-inflammatory Proteobacteria are observed. These changes are associated with the aging of the immune system (immunosenescence), chronic, mild inflammation ("inflammaging") and greater susceptibility to infections and chronic diseases, and may also worsen the general health and quality of life. An important factor modulating the gut microbiota remains the diet, the changes of which in old age (e.g. lower fiber intake, less diverse meals) may additionally promote dysbiosis. The authors O'Toole and Jeffery indicate that dietary, probiotic and prebiotic interventions may be promising strategies for supporting gut health and limiting the adverse effects of aging. According to them, it is crucial to conduct further research that will clarify the cause-effect relationships between changes in microbiota and the aging process, which may help in designing personalized interventions to improve the health of older people [9].

The intestinal microbiome is an extremely complex ecosystem, in which, in addition to the dominant bacteria, there are also viruses, fungi (fungal microbiome, mycobiome) and archaea. Although bacteria constitute the majority of microorganisms in the intestines, other groups of microorganisms play important, although still less understood roles in maintaining intestinal homeostasis, functioning of the immune system and affecting human health. Viruses constitute a significant part of the intestinal microbiome and are mainly represented by bacteriophages, i.e. viruses that attack bacteria. Bacteriophages regulate bacterial populations through lysis, which affects the composition and stability of the microbiome. In addition, bacteriophages can transfer genes between bacteria (transduction), which affects the metabolic and immune functions of bacteria and their adaptation to the intestinal environment [8]. Some studies indicate that disturbances in the composition of intestinal viruses may be associated with inflammatory bowel diseases such as Crohn's disease [10].

The gut mycobiome constitutes a small percentage of the total microbiota, but its role is increasingly being appreciated. Fungi such as Candida, Saccharomyces, and Malassezia coexist with bacteria and affect the microbial balance of the gut. The mycobiome can modulate the immune response and support protection against pathogens. However, overgrowth of some species, especially Candida albicans, is associated with dysbiosis and inflammatory bowel disease, as well as allergies and other immune disorders [11].

Archaea are a group of prokaryotic microorganisms that, although similar to bacteria, differ biochemically and genetically. In the human gut, archaea, mainly methanogens such as Methanobrevibacter smithii, play an important role in bacterial fermentation metabolism. Archaea participate in the process of removing excess hydrogen by producing methane, which affects the efficiency of digestion and energy production [12]. Studies suggest that the presence and activity of archaea may affect metabolic diseases, obesity and some inflammatory diseases [13].

3. Functions of the gut microbiome

The gut microbiome plays a significant role in the functioning of the body. Gut bacteria break down food components undigested by human enzymes, fermenting fiber into short-chain fatty acids (SCFA), such as acetate, propionate, and butyrate, which are a source of energy for enterocytes and have anti-inflammatory properties, and also affect glucose and lipid metabolism [3]. The microbiome produces B vitamins (e.g. B12, folates) and vitamin K. Additionally, it produces a number of metabolites (e.g. indoles, biogenic amines), which can act locally or systemically, influencing a number of physiological processes [14]. The microbiota has a key impact on the maturation and regulation of the immune system. It stimulates the maturation of intestinal lymphoid tissue (GALT) and the production of IgA, and also affects the balance of Treg and Th17 lymphocytes. The microbiota participates in the so-called immune tolerance, limiting excessive inflammatory reactions and ensuring a balance between pro- and anti-inflammatory reactions. In this way, it prevents the development of dysbiosis [15]. It also constitutes a protective barrier against the colonization of pathogens through competition for nutrients and adhesion sites on the epithelium, as well as through the production of bacteriocins and antibacterial metabolites [16].

4. Microbiome and health and disease

A few decades ago, microorganisms were mainly associated with pathogenicity. It is now known that their presence in the gastrointestinal tract is essential for maintaining health. It has been proven that patients with Crohn's disease and Ulcerative Colitis have a significantly lower microbiota diversity. A decrease in the number of butyrate-producing bacteria and an increase in the number of pathogenic Proteobacteria have been observed in them. These changes may increase the inflammatory response and cause damage to the intestinal mucosa [17].

It has been shown that obese people have a different microbiome profile (higher ratio of Firmicutes to Bacteroidetes) compared to lean people. Microbiota transplants from obese people to germ-free mice result in an increase in the body weight of the recipients, which suggests an influence of the microbiome on energy metabolism [18]. On the other hand, patients with type 2 diabetes have a reduced diversity and reduced number of bacteria producing short-chain fatty acids (SCFA). Dysbiosis can cause chronic low-grade inflammation, promoting insulin resistance [19]. Studies suggest an association of the microbiome with autoimmune diseases such as rheumatoid arthritis, multiple sclerosis and type 1 diabetes. Changes in the composition of the microbiota may affect the Th17/Treg lymphocyte balance and promote autoimmune reactions [15].

The microbiome influences brain function through the production of neurotransmitters (Gamma-Aminobutyric Acid, serotonin), short-chain fatty acids (SCFA), modulation of the immune system and the vagus nerve. Dysbiosis is a state of imbalance in the gut microbiota. It is characterized by the growth of unfavorable bacteria and a decrease in diversity. It can be caused by: antibiotics, an improper diet (low in fiber, high in saturated fats), infections and chronic stress.

Increasing evidence indicates the existence of the gut-brain axis - a two-way communication between the intestines and the central nervous system [20]. Intestinal dysbiosis has been implicated in anxiety disorders, depression, autism, and Parkinson’s disease. Mechanisms include alterations in neuroactive metabolite production, activation of the HPA axis and chronic inflammation [21].

Dysbiosis results in increased intestinal permeability (so-called "leaky gut"), chronic inflammation of mild intensity and susceptibility to infectious and chronic diseases. Under normal conditions, the intestinal epithelium forms a selective barrier that prevents the entry of microorganisms and toxins into the systemic circulation. However, in a state of dysbiosis, damage to intercellular connections (tight junctions) is observed, which results in the penetration of bacterial components, such as lipopolysaccharide (LPS), into the bloodstream. The presence of lipopolysaccharide (LPS) and other pathogens in the circulation stimulates the immune system, leading to chronic, low-grade inflammation. Such inflammation is considered a significant risk factor in the development of many chronic diseases. The authors of the article discussing the phenomenon of intestinal dysbiosis and the function of intestinal microbiota and its relationship with diseases point out that the inflammation associated with this disorder is not limited only to the gastrointestinal tract, but can be systemic. Additionally, dysbiosis reduces the colonizing resistance of the intestines to pathogens. Normal microbiota plays a protective role by competing with pathogenic microorganisms for nutrients and binding sites in the epithelium. Its perturbations therefore increase host susceptibility to intestinal infections, such as Clostridioides difficile infections. Despite the growing body of research, establishing a causal relationship between dysbiosis and disease remains a challenge, but understanding this correlation seems crucial [22].

5. Microbiome research methods

Microbiome research is currently one of the fastest growing areas of science. Technological advances have enabled increasingly precise determination of the composition, function and dynamics of the microbiota in various ecosystems of the organism. The most commonly used microbiome research methods can be divided into several main categories: DNA sequencing methods, functional analyses and cultural methods. They are mainly based on molecular techniques that allow for the identification and characterization of microorganisms without the need for in vitro cultivation. One of the most popular methods for identifying bacteria and archaea at the genus and often species level is 16S rRNA sequencing. It involves amplifying and sequencing conserved regions of the 16S rRNA gene, which is characteristic of bacteria. This method is fast and relatively cheap, but does not allow for full functional characterization of the microbiome [23].

Shotgun metagenomics is a more advanced method that involves sequencing all DNA isolated from a microbiome sample. It enables more detailed analysis at the species level, as well as the identification of functional genes, which enables the study of the metabolic potential and interactions of microorganisms. Metagenomics requires more computational resources and is more expensive than 16S sequencing, but provides much more data [24].

Metatranscriptomics involves the analysis of the entire RNA (mainly mRNA) of the microbiome, which allows for the assessment of gene activity in real time. This allows for the assessment of the actual function of the microbiota at a given moment by insight into which genes are active and how the microbiome responds to different environmental conditions or changes in the host organism. This is important for understanding the function of the microbiome, not just its composition [25].

Metabolomics is the analysis of metabolites produced by microorganisms, allowing for the understanding of their impact on the host's metabolic economy [26]. Microbiome proteomics, on the other hand, is the study of proteins produced by microorganisms, which also provides information on the functionality and dynamics of the microbiome. Both methods are increasingly used in combination with metagenomics and metatranscriptomics to obtain a more complete picture of the microbiome [27].

Traditional methods of culturing microorganisms are still important, especially in the isolation of specific bacterial strains that can be used, for example, as probiotics or for further functional studies. However, most microorganisms of the gut microbiome are difficult to culture in vitro, which is why sequencing methods have revolutionized microbiome research [28].

6. Modifying the microbiome – prevention and treatment

Probiotics are live microorganisms that, when administered in appropriate amounts, have a beneficial health effect. The most commonly used strains are Lactobacillus and Bifidobacterium. Prebiotics, on the other hand, are dietary components that selectively stimulate the growth of beneficial bacteria. Classic prebiotics are fructooligosaccharides (FOS), galactooligosaccharides (GOS) and inulin. Their consumption increases the production of short-chain fatty acids (SCFA), improves the functioning of the intestinal barrier and can also beneficially modulate the immune response [29]. The best effectiveness of probiotics has been proven in the case of infectious diarrhea and post-antibiotic diarrhea, as well as in the prevention of Clostridioides difficile relapses [30]. The results for other indications, such as irritable bowel syndrome, are also promising but require further research [31]. Synbiotics, on the other hand, are a combination of probiotics and prebiotics, the task of which is to achieve a synergistic effect on the microbiota. The combination of a probiotic strain, i.e. live microorganisms, with an appropriate prebiotic substrate that is not digested is supposed to increase the survival and activity of bacteria in the intestine. The article, which comprehensively discusses the topic of synbiotics, presents evidence for the potential use of these preparations in the prevention and treatment of various diseases – from gastrointestinal diseases (e.g. infectious diarrhea, irritable bowel syndrome), through metabolic diseases (obesity, type 2 diabetes), to allergic and inflammatory diseases [32].

In the article, which presents the results of the European consensus conference on fecal microbiota transplantation (FMT) and its clinical application, experts in gastroenterology, microbiology, infectious diseases and epidemiology developed common guidelines on the efficacy, safety and standardization of this procedure. It involves transferring microbiota from a healthy donor to the gastrointestinal tract of the recipient. The main indication for fecal microbiota transplantation (FMT) is the treatment of recurrent Clostridioides difficile infections, in which the therapy shows high efficacy and is recommended as a standard of care after failure of antibiotic therapy. Research is ongoing on its use in inflammatory bowel disease (IBD), irritable bowel syndrome and metabolic syndromes. Attention was also drawn to the need for strict regulation and

standardization of procedures related to donation, preparation of material and the method of administration (colonoscopy, oral capsules, enemas) [33].

A very important factor in shaping the microbiome is a diet rich in fiber, vegetables, fruits and fermented products that supports the diversity of the microbiota and the production of short-chain fatty acids (SCFA). Unfortunately, the Western diet (rich in saturated fats, simple sugars, poor in fiber) promotes a decrease in the diversity of the microbiota and the growth of pathobionts. The best is a plant-based and Mediterranean diet, as it is associated with a greater richness of the microbiota and a favorable metabolic profile [34].

Currently, novel therapeutic approaches are being developed, such as bacterial consortia (cocktails of well-characterized strains), postbiotics (bacterial products or metabolites), targeted bacteriophages and microbiome editing using CRISPR. Even though many of these methods are at an experimental stage, they may enable precise modulation of the microbiota in the treatment of chronic diseases in the future [35].

Although knowledge about the microbiome is developing very rapidly, many questions still remain unanswered. Future research should focus on: better understanding the relationship between the impact of the microbiome and disease, identifying key bacteria and their functions, personalizing microbiome therapy and standardizing and safety of FMT, as well as developing new forms of probiotics and postbiotics. The combination of metagenomics, metabolomics and clinical data may have a major impact on the development of microbiome medicine in the future [36].

7. Microbiome and pharmacology

The gut microbiome plays a key role in drug metabolism, influencing both efficacy and toxicity. It can activate, deactivate, or transform drugs; for example, some bacteria break down digoxin, while others metabolize anticancer drugs or antibiotics. In a groundbreaking study, Zimmermann and colleagues analyzed the ability of 76 different gut bacteria to metabolize 271 orally administered drugs. The results indicate that many of these drugs are chemically modified by microorganisms. A combination of genetic analyses and mass spectrometry allowed the systematic identification of the gene products of drug-metabolizing microorganisms. Enzymes encoded by the microbiome can directly and significantly affect drug metabolism in mice, which may explain differences in drug metabolism between individuals. This study highlights the importance of the microbiome in individual responses to drug therapy and may have important implications for medical therapies and drug development [37].

Spanogiannopoulos et al. emphasize in their article that gut bacteria act as “microbial pharmacists”, possessing a rich set of enzymes capable of transforming chemical compounds. These enzymes can lead to the activation or inactivation of drugs, affect their bioavailability, and generate metabolites with new, often unpredictable properties. The authors point to anticancer drugs, antibiotics, or anti-inflammatory agents, as an example, whose efficacy and toxicity are modulated by bacterial enzymes such as β-glucuronidases. These enzymes can reactivate drugs previously conjugated in the liver and excreted into the intestines, leading to their reabsorption and potential adverse effects. In addition, this work draws attention to the use of metagenomic tools for systematic mapping of metabolic pathways of the microbiome. Understanding these mechanisms is crucial for the development of personalized medicine, enabling the prediction of drug–microbiome interactions and the design of therapies that take into account the individual profile of the patient’s microbiota [38].

Forslund et al. analyzed the effect of type 2 diabetes (T2D) and metformin treatment on the composition of the human gut microbiota using metagenomics data. The study compared the microbiota of healthy individuals, patients with type 2 diabetes treated with metformin and patients not taking this drug. The results showed that metformin significantly affects the composition of the microbiota – more than the disease itself. Patients taking metformin had an increased presence of Escherichia species, which was associated with gastrointestinal side effects (e.g. diarrhea). Metformin also promoted the growth of bacteria producing short-chain fatty acids (SCFA), which may have beneficial metabolic effects. The study emphasizes the need to separate the effects of treatment from the disease itself when analyzing the microbiota and draws attention to the potential impact of the microbiota on the efficacy and tolerability of drugs [39].

In recent years, it has been discovered that the gut microbiome has a significant impact on the efficacy of cancer therapies, especially immunotherapy with checkpoint inhibitors. Patients with a specific composition of the microbiota are characterized by a better response to treatment, which opens up new therapeutic possibilities, such as modulation of the microbiome to increase the effectiveness of therapy. In the article, which examined the influence of the gut microbiome on the efficacy of anti-PD-1 immunotherapy used in the treatment of epithelial cancers, such as lung and kidney cancer, it was indicated that the composition of the gut

microbiota significantly affects the response of patients to therapy. Patients with a favorable microbiological profile, characterized by the presence of specific bacteria (e.g. Akkermansia muciniphila), show a better response to treatment and longer survival time. Moreover, transplantation of fecal microbiota from positively responding patients to mice improved the efficacy of therapy, confirming a direct relationship between the microbiome and the action of immuno-oncological drugs. The study emphasizes the potential of microbiota modulation as a strategy to increase the efficacy of anti-cancer therapies [40].

Knowledge of the interactions between the microbiome and pharmacology opens the way to so-called pharmacobiomics — a personalized approach to treatment that takes into account the composition of the patient's microbiota. The possibility of modulating the microbiome using probiotics, prebiotics, or even fecal microbiota transplantation can increase the effectiveness and reduce the side effects of therapy. In the future, the microbiome may become an important factor in determining the dose and selection of drugs [37].

8. Summary

The gut microbiome is an incredibly complex and dynamic ecosystem that performs key metabolic, immunological, and protective functions. Its composition is established from birth and is modified throughout life. Disturbances of the microbiome are associated with many chronic diseases, from inflammatory bowel disease to obesity and neuropsychiatric diseases. The composition of the microbiome is influenced by many factors, such as the mode of delivery, infant feeding, diet, antibiotic therapy, age, and lifestyle. Shaping the microbiome – through diet, probiotics, prebiotics, synbiotics, or fecal microbiota transplantation (FMT) – are promising therapeutic and preventive tools. Currently, research is also underway on innovative methods, such as bacterial consortia, targeted bacteriophages, or microbiome editing using CRISPR technology. However, the full potential of the microbiome requires further clinical trials.

The gut microbiota plays a key role in modulating the efficacy and toxicity of anticancer chemotherapy. One of the articles emphasizes that the intestinal microbiome influences the fate of drugs in the body through their direct metabolism – intestinal bacteria can activate or inactivate chemotherapeutics, changing their bioavailability and anticancer efficacy. The microbiota also modulates the host's immune response, which is important in immunomodulatory therapy and in shaping the tumor microenvironment. Modern microbiome studies use advanced molecular techniques that allow for a comprehensive analysis of both the composition and function of the microbiota. The combination of DNA and RNA sequencing methods with the analysis of metabolites and proteins provides a full picture of the microbiome and its role in health and disease. In the future, the development of technologies such as single-cell sequencing or advanced bioinformatic methods will further improve microbiome research.

The intestinal microbiome is an ecosystem of multidirectional interactions not only between bacteria, but also viruses, fungi and archaea. Their cooperation is crucial for maintaining intestinal homeostasis and the health of the entire organism. Microbiome-drug interactions are a rapidly growing area of research that has the potential to revolutionize pharmacotherapy. Understanding these relationships will allow for better tailoring of treatment to individual patient needs, minimizing side effects and developing new therapeutic strategies based on microbiome modulation.

Disclosure

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