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THE ROLE OF THE HUMAN GUT MICROBIOME IN HEALTH AND DISEASE

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Abstract. The gut microbiome is the complex ecological niche of bacteria, archaea, viruses and fungi and their genetic material in the human gut. It plays a role in the metabolism of nutrients, maturation of the immune system, barrier integrity of the gut, colonization resistance, and communication between the gut and remote organs in the body. While there are very large differences in gut microbial composition from one person to the next, there are also many common functions of the gut microbiome that are conserved. Conditions often linked with alteration of this ecosystem (dysbiosis) include inflammatory bowel disease, obesity, type 2 diabetes, cardiovascular disease, colorectal cancer, recurrent infection with Clostridioides difficile, and neurological disorders. However, the dependence of most microbiome--disease associations is two ways and any association should not be taken as a cause. Restoration of microbial function is looked at via dietary modification, using probiotics, prebiotics, fecal microbiota transplantation or using defined microbial therapeutics. The main physiological functions of the gut microbiome, its links to disease, existing microbiome-targeted interventions and key obstacles for implementation in personalized care are summarized in this review.

Keywords: Human Gut Microbiome, Gut Microbiota, Dysbiosis, Microbial Metabolites, Inflammation, Probiotics, Fecal Microbiota Transplantation, Personalized Medicine

Introduction

Gastrointestinal tract is a rich and dynamic microbial community. The microorganisms in gastrointestinal tract are called gut microbiota whereas gut microbiome represents all the gut microorganisms with their genes, metabolites and ecological interactions. Although archaea, bacteriophages, eukaryotic viruses, and fungi are also of great biological importance, the bacteria are the best studied members.

Significant inter-individual differences in the species of microorganisms can be found on a large scale sequencing. The Human Microbiome Project (HMP) revealed that there is a large inter-individual variability in the taxonomic makeup of healthy individuals and yet many common microbial metabolic pathways are observed [1]. More in-depth metagenomic analyses also showed that microbial strains are very unique and can potentially be relatively fixed in the same individual over time [2]. Thus, there is no single, universal, taxonomic profile or even a single bacterium for defining a healthy microbiome.

The microbiome in the gut is constantly in contact with food, the gut epithelial barrier, the immune system, bile acids, hormones and drugs. The interactions enable microorganisms to be a part of digestion and physiological homeostasis. In turn, ecological disruption can lead to a decrease in beneficial microbial activities, inflammation, a decline in colonization resistance or increase in potentially harmful metabolites.

This narrative review analyzes gut microbiome composition and determinants, physiological role of the human gut microbiome, the interrelation of the human gut microbiome and key diseases, and opportunities and limitations of microbiome-targeted therapies.

Methods

This article employed a structured narrative review design to synthesize evidence concerning the composition, determinants, physiological functions, disease associations, and therapeutic modulation of the human gut microbiome. The scope included bacterial, archaeal, viral, and fungal communities in the gastrointestinal tract, with particular attention to microbial mechanisms involved in nutrient metabolism, epithelial-barrier integrity, immune regulation, colonization resistance, and communication between the gut and distant organs.

Relevant literature was identified through PubMed, Scopus, Web of Science, and Google Scholar using combinations of the terms "human gut microbiome," "gut microbiota," "dysbiosis," "short-chain fatty acids," "immune regulation," "inflammatory bowel disease," "obesity," "type 2 diabetes," "cardiovascular disease," "colorectal cancer," "gut-brain axis," "Clostridioides difficile," "probiotics," "prebiotics," and "fecal microbiota transplantation." Priority was given to landmark investigations, multi-omics studies, controlled clinical trials, mechanistic studies, and official regulatory documents that directly addressed the review objectives. Sources with insufficient methodological detail or limited relevance to human health and disease were not emphasized.

The selected evidence was evaluated according to scientific relevance, methodological clarity, and contribution to the principal themes. Findings were synthesized thematically rather than statistically because the studies differed substantially in population characteristics, biological sampling, sequencing platforms, analytical pipelines, clinical outcomes, and intervention designs. The synthesis was organized into microbiome composition and determinants, physiological roles, disease-related dysbiosis, microbiome-targeted interventions, and challenges for clinical translation. No meta-analysis or formal risk-of-bias scoring was performed.

Results and Discussion

The reviewed evidence indicates that the gut microbiome functions as a dynamic metabolic and immunological ecosystem rather than as a fixed taxonomic entity. Despite substantial inter-individual variation, conserved microbial functions repeatedly emerged across studies, particularly dietary fermentation, short-chain fatty-acid production, epithelial-barrier support, immune modulation, colonization resistance, and biotransformation of host and dietary compounds. Disease-associated patterns were most convincing when supported by mechanistic, longitudinal, or interventional evidence; nevertheless, findings for many chronic disorders remained heterogeneous and were strongly influenced by diet, medication, geography, host physiology, and disease severity. The following sections integrate the principal findings with their biological and clinical implications.

Major anaerobic bacterial groups, Bacillota (which was previously known as Firmicutes) and Bacteroidota (also known as Bacteroidetes), are the majority components of the gut microbiome associated with the adult type. Actinomycetota, Pseudomonadota, Verrucomicrobiota, archaea, bacteriophages and fungi are found in smaller but nevertheless significant abundances. The number and type of microbes present in the gastrointestinal tract change along its length as a function of oxygen availability, acidity, bile level, nutrient availability and transit time.

Rapidly changing after birth, the microbiome is affected by labor, feeding, antibiotics, geographical location, pets and other household contacts, and environmental microorganisms. Variation in the microbiome can be accounted for by host genetics but often is driven by the environment and/or lifestyle [3].

One of the most potent modifiable determinants is diet. Changes in microbial community composition and transcriptomic activities have been shown in major dietary changes in a controlled feeding trial to be altered within days [4]. Diets with a variety of plant-based fibers will typically contain substrates for microbial fermentation, while diets with a high proportion of animal-based proteins and fats will typically support microorganisms which are resistant to bile and able to use amino acids in the diet.

The drugs may also alter the microbiome. The most direct disturbance is the antibiotics that

kill susceptible microorganisms, leaving resistant ones to multiply. In a study of healthy adults, the microbiome showed some recovery after the short duration of broad-spectrum antibiotic use, but the recovery was incomplete as several different species were not seen for six months following the antibiotic treatment period [5]. Other routinely used medications such as proton-pump inhibitors, metformin, laxatives, and antibiotics can also disrupt microbial patterns, and thus make it difficult to interpret microbial disease signatures.

Humans do not have enzymes to break down a lot of the complex carbohydrates in the diet. These substrates are fermented by gut microorganisms leading to the production of short-chain fatty acids (mainly acetate, propionate and butyrate). These metabolites may affect the metabolism of glucose and lipids and contribute to the control of appetite and endocrine signals, but they are also responsible for supplying energy to intestinal epithelial cells.

Butyrate is a critical energy source of colonocytes and helps to maintain epithelial barrier function. It also helps in the differentiation of regulatory T cells in the colon, thus creating immune tolerance and reducing excessive inflammation [6]. The microflora are also involved in the transformation or synthesis of vitamins, bile acids, amino acids, polyphenols and other nutrition compounds.

The intestinal barrier is formed by epithelial cells, tight junction proteins, mucous layer, antimicrobial peptides and mucosal immune cells. Commensal microorganisms aid this barrier by facilitating epithelial repair, production of metabolites that help control local immune responses, and production of mucin.

Microbial butyrate also helps to prevent oxygen in the colon and promote obligate anaerobes. Because of the reduction in the numbers of butyrate-producing organisms, the availability of oxygenated epithelia may allow the growth of facultative anaerobes which can be inflammatory, such as some Enterobacteriaceae organisms [7].

Priming by microorganisms enhances maturation and tolerance to innocuous antigens. Microbial products can however also activate inflammatory pathways when the epithelial barrier is disrupted, or when microbes are present in tissues outside of their normal ecological niche.

The way resident microorganisms inhibit the growth of pathogens is through competing for nutritional niches, depriving them of nutrients, producing antimicrobial products, modifying bile acids, and stimulating host immunity. This is called 'colonization resistance' and is of special importance in the prevention of enteric infections.

Microbial metabolites can be in the systemic circulation or activate neural, endocrine and immune pathways. These signals have the ability to communicate along gut–liver, gut–brain, gut–lung, and gut–immune axes. However, the biological role of microbial metabolites is variable: the same metabolite can be beneficial or detrimental in different concentration in different locations and/or in different host situation and/or combined with different host diet.

Table 1. Major physiological functions of the human gut microbiome

Function	Principal microbial mechanisms	Health significance
Dietary fermentation	Conversion of complex carbohydrates into short-chain fatty acids	Energy for colonocytes and regulation of metabolism
Barrier maintenance	Mucus stimulation, tight-junction support, epithelial oxygen regulation	Reduced microbial translocation and inflammation
Immune regulation	Development of regulatory T cells and modulation of cytokine responses	Immune tolerance and controlled inflammation

Function	Principal microbial mechanisms	Health significance
Colonization resistance	Nutrient competition, antimicrobial production, and bile-acid modification	Protection against intestinal pathogens
Biotransformation	Modification of bile acids, vitamins, drugs, and dietary compounds	Influences nutrition and drug response
Inter-organ signaling	Neural, immune, endocrine, and metabolic signaling	Communication with the brain, liver, and other organs

Dysbiosis is commonly a disorder in which the growth of potentially harmful microorganisms is promoted, assessment of ecological stability is decreased, beneficial organisms are lost, or the microbial function is altered. It has multiple diseases and its signs are varied among the diseases. Furthermore, changes in the microbiome can be a direct consequence of disease-related inflammation, medication, diet and ever-changing intestinal transit.

Obesity has been linked with a depletion of a number of obligate anaerobes and a proliferation of facultative anaerobes, as well as modifications of the passage of bile-acids and a decline in the production of bile-acids. Longitudinal multi-omics studies have identified correlated variations in species and microbial gene expression, host inflammatory activity and metabolites at phases of disease activity [8].

Hence, a bidirectional model corresponds to the findings. Host genetics and the dysregulated immune responses give rise to an inflammatory intestinal environment and disturbed microbial functions may instigate the weakened barrier function and maintain intestinal inflammation. Microbial profiles are not consistent across patients and there is no single microbe responsible for each example of inflammatory bowel disease.

The gut microbiome may influence metabolic health by altering the ability to extract energy, its ability to produce short-chain fatty acids, bile-acid signaling pathways, increased intestinal permeability, and inducing systemic inflamation. The energy harvest and the adiposity of recipient mice could be increased by an obesity-associated microbiome in experimental transplantation studies [9]. But, the ratio of major bacterial phyla does not account for the human obesity and early research findings do not always point to the same thing when accounting for different populations.

Moderate dysbiosis and a decrease in the abundance of some of the microbes that had the ability to produce butyrate and increase microbial functions related to oxidative stress were noted in patients with type 2 diabetes [10]. However, dietary habits, obesity, drugs and geographical variation represent major confounder. Thus, the use of microbiome markers is additional to the current conventional metabolic risk assessment.

Choline and carnitine are metabolized in the gut to form trimethylamine by gut microbes that react with trimethylamine to form trimethylamine-N-oxide in the liver. This pathway is linked to the accumulation of cholesterol in macrophage cells, and the risk for atherosclerosis has been associated through experimental and clinical studies [11]. But, the level of circulating trimethylamine-N-oxide also depends on dietary habits, liver metabolism and kidney function. It should thus not be interpreted as a standalone diagnostic marker of a 'microbiome' without taking these into account.

Mechanisms by which the colorectal cancer microbiome could affect carcinogenesis include chronic inflammation, genotoxic compounds, bile-acid metabolism, as well as direct interactions with the tumor cells. Tumor associated microorganisms are known to be sustained during the disease progression since Fusobacterium *nucleatum* has been detected in primary colorectal tumors as well as of the associated metastases [12].

The microbiome can also impact the treatment of cancer. Gut microbial dysbiosis and

alterations in function showed associations with the response to melanoma anti-programmed cell death protein 1 (anti-PD1) therapy [13]. These findings have paved the way for trials that involve changes in the diet, transplanting of microbiota, and use of immune checkpoint inhibitors. However, microbiome signatures are different in various studies, and the ability to make day-to-day clinical predictions using stool composition alone is premature.

The gut has the ability to communicate with the nervous system via microbial metabolites, immune mediators, vagal pathways and neuroendocrine signaling. There are links noted between dysregulated microbiomes and depression, anxiety, autism spectrum disorders, Parkinson's and other neurological disorders.

Transplantation of autistic S. recti to germ-free mice resulted in behavioral and metabolic alterations in the mice [14]. While these studies provide biological plausibility, the studies are not proof that microbiome changes are underlying causes of the complex neurological diseases in humans. Human data are still variable and could be affected by diet, medication, gastrointestinal symptoms and lifestyle of human.

Recurrent *C. difficile* infection provides the strongest clinical example of disease caused partly by loss of microbiome-mediated colonization resistance. Antibiotic exposure reduces microbial diversity and disrupts bile-acid metabolism, enabling *C. difficile* spores to germinate and produce toxins.

Randomized clinical trial efficacy results showed that donors' fecal microbiota infusion was more beneficial in preventing recurrence of the infection than standard vancomycin treatment [15]. This success supporting microbiota restoration as a valid therapeutic principle needs careful donor selection and standardized production in order to reduce the infectious risk.

The most readily available way to impact the gut microbiome is through diet. The intake of diverse types of plant foods and fermentable fibers have the potential to enhance the metabolic activity of microbes and the production of short-chain fatty acids. However, not everyone reacts the same to the same food. One such clinical and microbiome study has shown that with personalized models, accuracy in prediction of postprandial glucose responses was improved, over using identical dietary recommendations, for everyone [16].

Probiotics are living microorganisms that are taken in sufficient amounts and prebiotics are substrates that are selectively utilized and can have a beneficial effect on the host. They have strain-specific and condition-specific effects. Not every probiotic is effective and some commercially available probiotics have limited amounts of evidence. In a single controlled study, it was shown that antibiotic therapy was followed by a slow recovery of the indigenous microbiome when an empiric probiotic mixture was compared to spontaneous recovery or autologous fecal microbiota transplantation [17].

FMT involves transferring microorganisms from screened fecal donors to people. It has the longest history as a preventative for recurrent C. difficile infection following standard antibacterial therapy.

In 2022, REBYOTA, a live rectal fecal microbiota product was approved by the United States Food and Drug Administration [18]. In 2023, it granted approval for the first orally administered fecal microbiota spore (FMS) product called VOWST for recurrence prevention post antibacterial treatment for recurrent infection in adults [19]. The approvals are significant as it marks a transition from the traditional transplantation with donors to standardized products that contain microbiota.

New solutions involve the use of defined consortia of bacteria, the conditioning of bacteria, use of Microbial Enzymes, Microbial Enzymes, Postbiotics, and tailored dietary measures. These techniques might provide greater reproducible and safety than the transfer of donor material that is complex and poorly elucidated.

Recently, a number of methodological issues arise, which restrict clinical translation. The collection, storing, extracting, sequencing, microbiomics pipeline, and statistical analysis of stools influence their microbiome results. Luminal organisms are also more adequately represented in stool than microorganisms attached to the intestinal mucosa.

Patient related confounder is of similar importance. Apparent microbiome–disease relationships can be generated by age, BMI, nutrition, smoking, medications, stool type, geographic location

and severity of the disease. A systematic analysis revealed that if host variables are not controlled sufficiently, there was a possibility of significant errors in the microbial signatures claimed for disease [20].

Future studies should thus focus on longitudinal studies, validation of mechanisms, standardized protocols, the inclusion of different populations, and combining metagenomics with metabolomics, transcriptomics, and integration with the clinical data of the host. Conceptual approaches to clinical intervention need to be on bringing back missing functions, not trying to recreate a single ideal microbial composition.

Conclusion

Gut microbiome plays a crucial role in intestinal, immune and metabolic homeostasis. While many gastrointestinal and systemic disorders have been correlated with dysbiosis, the majority of the interactions are bidirectional. Currently, the best clinical indications for microbiome-directed therapy are the treatment of recurrent C. difficile infection. Applications to metabolic, inflammatory, neurological and malignant disease continue to be promising but there are still unclear causal evidence and standardized interventions. To advance the field of microbiome medicine, integration of microbial, metabolic, dietary and host data likely will be required to attain safe and personalized therapeutic solutions.

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