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The Role of the Microbiome in Human Disease

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ABSTRACT

Since the invention of the microscope, scientists have described microbial communities on living and non-living matter. In terms of human-associated microbes, scientists have documented the beneficial effects of the microbiota for many decades. Prophylactic effects include protection from pathogens, digestion potential, and the production of essential vitamins. However, recent high-throughput methodologies and analytical advances have accelerated microbiome science and our understanding of microbial diversity in living organisms. The microbiome denotes the complex network of all the microorganisms and microbial genes located in specific biotic or abiotic environments. We now realize the enormous diversity and functionality of the microbiota in humans and the endless benefits to health and disease. Dysbiosis facilitates the manufacture of various proinflammatory mediators, biochemical imbalances, and colonization of microbes associated with disease outcomes. Additional work is necessary to determine whether changes in the human microbiome are due to anthropogenic, genetic, or environmental variations. This review will present microbiome research studies focusing on human disease. The findings documented in this article offer optimism on the profound role microorganisms play in supporting human health and how pharmaceutical interactions targeting specific microbes can decrease the incidence of human disease caused by the ecological disturbance of the normal microbiota.

Keywords: Microbiome; Bioinformatics; QIIME; Fecal Microbiota Transplantation

Introduction

The microbiome is the total population of microorganisms (e.g., bacteria, fungi, protozoa, and viruses) in a particular environment [1]. Moreover, as Lederberg and McCray [2] elaborated two decades ago, the term microbiome characterizes human microbial communities based on their type of biological interactions. Microorganisms inhabit different human body parts and may have pathogenic, commensal, or mutualistic properties. Scientists have known for years that distinct populations of human-associated microbiota confer physiological benefits such as providing immunological protection from pathogenic microorganisms, digesting food particles, and synthesizing vitamins and other nutrients that contribute to our overall health and wellness [3]. Currently, microbiome research is under rapid development. In 2007, the National Institutes of Health (NIH) initiated the Human Microbiome Project (HMP) to expand our understanding of the human microbiota, and the intricate role microorganisms play in health and disease [4]. The project's first phase assessed the microbial composition of healthy human subjects. Characterizing commensal microbes was an essential first step in understanding how microbial diversity contributes to homeostasis. Ancillary projects compared the microbiome of healthy and diseased study participants. Intriguing differences in the structure of the microbiome of healthy and diseased subjects gave rise to the next phase of the HMP. The second phase of the project, known as the Integrative Human Microbiome Project, was completed in 2016 and assessed the relationship between variations in the human microbiome for inflammatory bowel disease, preterm birth, and diabetes [5-7]. Additionally, a significant outcome of the Human Microbiome Project was the production of the computational tool QIIME (Quantitative Insights Into Microbial Ecology). QIIME is an open-access bioinformatics application that analyzes microbiome data [8]. This review will highlight selected findings from the Integrative Human Microbiome Project and other studies that implicate the microbiome as a potential factor in the development and progression of human disease

Human Microbiome

Humans are not simply a single species consisting of organs and organ systems but an amalgamation of thousands of species operating as a collaborative ecosystem. Development of the human

microbiome begins at the prenatal stage. The environment, diet, age, familial genetics, childbirth delivery method, antibiotic usage, and other factors affect the human microbiome. Moreover, the formation of a mature microbiota in humans, which occurs between three to five years of life, plays a paramount role in health maintenance and disease reduction throughout an individual's life [7]. Through investigation and technological advances, scientists are now starting to comprehend the importance of the human microbiome, particularly its relevance to human health and disease. Our appreciation for the impact of modifying human microbial communities on health and wellness is constantly evolving. Microbes outnumber human cells, with the largest concentration of microbes residing in the gastrointestinal tract, particularly the distal gastrointestinal region. Moreover, the human body's microbial genome is at least a hundred times greater than the human genome. Humans harbor distinct microbial communities that impact our behavior [9], immunity [10,11], cognition [12], and health [13]. The microbiome regulates human physiology via nutrient modulation mechanisms or by secreting metabolic products that impact human health.

A rapidly growing body of microbiome research studies explores medical and health applications associated with the complex community of human-associated microbes. Human microbiome monitoring currently involves the analysis of stool samples using standard stool sampling methods. A recent report documents the use of a hands-free fecal specimen collection method to improve gastrointestinal monitoring efforts [14]. One medical technique that resulted from our emerging understanding that gut microbiota may have clinical value and serve as a clinical diagnostic marker is the fecal microbiota transplantation (FMT) method. Fecal microbiota transplantation involves reallocating fecal microbes from a healthy individual to an unhealthy patient [15]. It has become clear that inflammation is at the heart of many human diseases. Research findings show that FMT may play a role in Parkinson's disease [16], hypertension [17], and diabetes [18]. This technique's early work primarily focused on treating bacterial infections such as Clostridium difficile. Recent work with young and old mice demonstrated that the FMT method is efficacious in reducing inflammation in older mice [19]. This review presents studies done in animal models (e.g., mice) and human subjects; however, more work needs to be done in humans to develop viable therapeutics and treatments that can benefit humankind.

Obesity and the Human Microbiome

Before the global pandemic caused by SARS-CoV-2, obesity was an emerging public health threat worldwide. One of the earliest experiments that dramatically changed the way scientists viewed the impact of the mammalian microbiome on disease, mainly obesity, was performed by Turnbaugh, et al. [20]. These researchers studied the variability of the microbiota populations in obese and nonobese mice. Transference of microbiota from obese mice was sufficient to shift the phenotype of wildtype lean mice to an obese phenotype. Despite limitations in understanding the relationship between the microbiome and obesity, as reviewed in Marvuda, et al. [21], several studies have presented compelling data to suggest a link. Dysosmobacter welbionis, a novel anaerobic, Gram-negative bacterium believed to be a resident in over half of the human population, was recently isolated. Supplementation of mice with Dysosmobacter welbionis produced anti-obesity and anti-metabolic disorder phenotypes [22]. Future studies with Dysosmobacter welbionis and other novel microbes isolated from humans may lead to subsequent advances in clinical treatments for various metabolic disorders.

Amplicon sequencing of conserved marker genes evaluated the microbiome in human subjects' saliva and fecal samples. Compositional and metabolic differences were shown in obese individuals compared to individuals with a lower body mass index, with the most pronounced differences appearing in the saliva, not fecal samples suggesting that for specific morbidities evaluating saliva may yield more clinically relevant data [23]. Dietary soluble fiber (e.g., pectin) alters the gut microbiome architecture and promotes an anti-obesity microbe-mediated metabolic signature [24]. For instance, the diet of obese rats supplemented with pectin assessed the antagonistic effects on obesity-related indicators (e.g., weight gain, microbial taxa). High-fat diet obese rats displayed a microbiome dominated by Phylum Firmicutes. Pectin consumption led to a reduction in weight and the restoration of a microflora pattern consistent with non-obese rats (e.g., chow-fed rats). Researchers also observed an increase in alkaline phosphatase in rats whose diet contained pectin. Since previous work has shown that obese humans exhibit elevated serum levels of alkaline phosphatase [25], intestinal alkaline phosphatase may serve as a beneficial biomarker to monitor clinical approaches designed to counteract obesity or other intestinal pathologies. More studies involving the functional analysis of microbial metabolites are needed to determine how the microbiome contributes to the pathology of obesity. Mechanistic insight regarding the canonical microbial and human metabolic pathway network remains elusive in the case of obesity and other metabolic disorders.

Cancer and the Human Microbiome

Doocey, et al. [26] recently reviewed the evidence linking cancer tissue-associated microbial communities and their virulence factors with specific human carcinomas. Generally, examination of the microbiota of cancer tissue versus healthy tissue reveals a statistically significant loss of biodiversity and taxonomic richness in the cancer tissue compared to healthy tissue and the occurrence of pathogenic microbes during tumorigenesis. Recent work by Fu, et al. [27] utilized a murine spontaneous breast-tumor model to investigate intratumor microbiota. They found that tumor-localized bacteria promoted metastasis and that by inhibiting bacterial growth, they could suppress metastatic potential. Taxonomically, mounting evidence suggests that Phylum Proteobacteria and Phylum Firmicutes are the most dominant bacterial communities associated with human tumors. The link between bacterial communities and cancer tissue provides potential treatments involving antibiotics and probiotics to target tumor-associated bacteria and restore the physiological microenvironment with beneficial bacteria [28].

Studies in mice point to the therapeutic significance of targeting tumor-associated bacteria to improve clinical outcomes. These research findings are encouraging; however, it is essential to note that the clear and present threat of bacterial antibiotic resistance, as is the case for Helicobacter pylori [29], may render these treatments less effective over time. Researchers have also demonstrated the presence of prokaryotic residents in many other types of cancer, including colorectal [30], renal cell [31], and pancreatic cancer [32] tissues. Regarding renal cell cancer (RCC), 16s rRNA sequencing methods (e.g., V3-V4 amplicon) characterized the cancer-related microbiome. Normal and RCC tissue were examined and evinced a distinct RCC-associated bacteriome. Bioinformatics analysis also produced in silico data predicting functional roles of the bacterial residents linked to RCC maturation. While most of the work explores the relationship between bacteria and cancer, a few studies have examined the role of fungal microbes and cancer development and progression [33]. For example, Yang et al. employed an internal transcribed spacer region 2 (ITS2) sequencing technique to probe the fungal microbiota link with gastric cancer. They demonstrated a mycobiome fingerprint that may serve as a biomarker for gastric cancer.

Neurological Disorders and the Human Microbiome

The connection between the gut microbiome and neurodegenerative diseases (e.g., Alzheimer's and Parkinson's) is unclear. Several studies and reviews have demonstrated that an individual's intestinal microtype (e.g., microbial species distribution) can impact neuroinflammation in the central nervous system and thereby play a role in neurological pathologies [34,35]. Recent animal and human studies have also focused on the connection between microbiota-based metabolites associated with Parkinson's disease. For instance, compared to healthy controls, a metabolic signature encompassing attenuated carbohydrate fermentation and butyrate synthesis was observed in patients with Parkinson's disease [36]. Moreover, Parkinson's patients demonstrated increased phenylacetylglutamine, a biomarker candidate for Parkinson's [37].

Gut microbiota enhances the bioavailability of nutrients, drugs, and other substances. Evidence demonstrates that FLZ, a potential therapeutic for Parkinson's disease, is metabolized by the gut microbiota to facilitate FLZ absorption in the bloodstream [38]. Reductions in crucial operational taxonomic units resulted in a decrease in FLZ absorption efficiency. Using probiotics to reshape the gut microbiota to treat Alzheimer's disease was evaluated using a transgenic mice model and the probiotic Clostridium butyricum. Following a one-month administration of Clostridium butyricum, mice exhibited cognitive improvements, disrupted microglia activation, and blocked the production of cytokines that contribute to neuroinflammation in the brain [39]. Butyrate is the primary microbial metabolite responsible for directing the anti-disease phenotypes observed. Evidence regarding the positive effects of butyrate in Alzheimer's was collected when investigators treated Alzheimer's mouse models with Agathobaculum butyriciproducens, a butyrate-secreting bacterium [40]. Following treatment with Agathobaculum butyriciproducens, mice demonstrated a reduced cognitive decline, immune cell activation, and plaque deposits. Additional human experimentation is necessary to elucidate novel microbial metabolites and canonical pathways that mediate anti-neuroinflammatory effects in the brain in Alzheimer's patients.

Conclusion

The human microbiome refers to all the microorganisms occupying the body's external surfaces and internal organ systems. Since the days of Antonie van Leeuwenhoek and his drawings of «animalcules» from fecal and dental specimens, the world has known that organisms too small to be observed without optical assistance have existed and formed associations with humans [41]. Microorganisms benefit humans by synthesizing biomolecules, contributing to innate immunity, and breaking down contumacious nutrients. Microbial cells and microbial genes outnumber human cells and human genes by a staggering amount. Since microbes and humans share evolutionary history, reciprocal interdependence between microorganisms and humans exists. Technological enhancements in genome sequencing have accelerated our understanding of the myriad microbes associated with biological systems and their components and have provided seminal insights into the functional effects of microbial ecosystems. However, an extensive knowledge gap exists regarding symbiont crosstalk mechanisms and how microbial crosstalk affects human homeostatic processes. Moreover, there is considerable variance in the types of microbes associated with biological ecosystems within the human population; continued human microbiome research efforts in the future may lead to individualized microbiota-based therapies that will revolutionize healthcare. Microbiome restoration techniques and modifying the microbiome using pharmaceutical methods may yield beneficial treatment strategies.

While advances in human microbiome science hold tremendous promise in diagnosing, preventing, and treating disease, robust interdisciplinary research approaches are needed to overcome various research challenges. Specifically, one of the significant problems with microbiome research, in general, is the absence of the standardization of microbial characterization protocols. Abellan-Schneyder, et al. [42] discussed the problems and limitations of 16s rRNA gene profiling. The researchers demonstrated that 16s rRNA gene primer selection, sequence database usage, and the lack of adequate controls could produce differential findings regarding bacterial configurations. The transition from correlation to cause and sequence-based microbial characterizations to functional elucidations is needed. Moreover, understanding the human microbiome's temporal, spatial, and physiological properties is required to accelerate the field.

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Conflicts of Interest

There are no conflicts of interest.

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