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EDITORIAL

# Human Microbiome in Health and Disease: The Good, the Bad, and the Bugly

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## Editors' Introduction

Ask a group of medical professionals and scientists what is the "hottest" area of investigation today, or to suggest a topic for a forum or symposium and the likely answer will be "the microbiome." A quick search of PubMed for the term microbiome yielded 48,504 articles during the past 5 years and 14,817 during the past 12 months. The microbiome has even made it into the popular imagination. The adult cartoon South Park recently aired an episode about fecal transplantation and an attempt to obtain a famous football player's microbiome, ostensibly to create a super athlete (a bit far-fetched, but who knows). This special issue of *Digestive Diseases and Sciences* provides a broad perspective of the role of the human microbiome in health, chronic disease risk, and prevention.

## Methodology, Health, and the Relationship of Human Diet, Nutrition, and the Gut Microbiome

The concept of microbial communities (or microbiota) relevant to health and disease dates at least back to the seventeenth century and the observations that bacteria differ in areas of the body and between healthy and ill individuals. Until recently, however, technology limited our ability to go beyond descriptive correlations and the concept of one pathogen and one disease. New sequencing technologies and the field of metagenomics, which allows for the examination of all genetic materials recovered from the environment and living samples, exploded in the mid-2000s. Current estimates suggest that the human body contains thousands of strains and species of microbes which contribute substantially more genetic material than the human host. The microbiome refers

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to the collective genomes and gene products of the microbiota within a host or environment. Technologies such as gene marker analysis, "shotgun" metagenomics, metabolomics, metaproteomics, and metatranscriptomics (see Galloway-Pena and Hanson) are allowing investigators to address questions related to what constitutes and influences a "normal" microbiome, how dynamic or "plastic" is the microbiome, what are the dynamic interactions between the microbiome and the environment and the human host, what is the role of the microbiome in normal homeostasis, what constitutes the "operational taxonomic unit," and how do alterations in the microbiome influence the human host and subsequently modulate disease states. This complexity will likely require systems biology-based multi-omic approaches and integrative analyses to interrogate the methodological and computational challenges of defining gut-host cross talk (see Ivanov). As part of this effort, the Human Microbiome Project (HMP) and Human Intestinal Tract (MetaHIT) initiatives are large-scale projects aimed at defining the composition and function of the healthy human microbiome.

The human microbiome contains over 30 trillion microorganisms per person (some estimates are up to 100 trillion), but the composition and functional characteristics of the "healthy" microbiome remain to be precisely defined. "The Healthy Human Gastrointestinal Microbiome: Composition and Function After a Decade of Exploration" is the topic of the review by Ruan, Engevik, Spinler, and Versalovic, which explores the relative abundance of different bacteria taxa and the specific metabolic pathways and classes of microbial metabolites contributing to human health and disease prevention. This article stresses that the gastrointestinal microbiome is a dynamic and functional interface between the external environment, e.g., nutrition, and the human body. While shifts in the microbiome are influenced by diet, antibiotics, and even socioeconomic status and geography, one of the features of the healthy microbiome is its resilience and ability to return to an equilibrium state. This article also details how microbial-derived metabolites modulate both intra-kingdom (microbe–microbe) and inter-kingdom (microbe–host) interactions that impact human health. Davis, Dinsmoor, Wang, and Donovan explore the impact of dietary intake and pre- and probiotic interventions on microbiome composition in healthy infants and children from birth to adolescence. This review and the review by Wilson et al. (including a large international group of authors) provide an international perspective on how diet may influence the human gut microbiome. The latter article explores mechanisms that might explain the ability of plant-derived fiber-rich foods to suppress the incidence and mortality from "western" diseases from cancers to cardiovascular and respiratory diseases, diabetes, and obesity. Similarly, Chapkin, Navarro, Hullar, and Lampe discuss how several dietary constituents implicated in colorectal cancer are modified by gut microbial metabolism, and how highly fermentable fiber and n-3 long-chain polyunsaturated fatty acids (PUFAs) may alter critical pathways critical to colorectal cancer prevention. All of these reviews emphasize how a better understanding of the interrelationship between diet and our gut microbial communities may define our nutritional needs, and how diet is linked to human health through the microbiome.

## Inflammation, Inflammatory Bowel Diseases, and the Gut Microbiome

Inflammatory bowel diseases, including ulcerative colitis and Crohn's disease, are chronic relapsing intestinal inflammatory bowel diseases mediated by dysregulated immune responses to resident microbiota. In an in-depth review, Ota and Sartor discuss compelling evidence for how an unbalanced microbiota (dysbiosis) drives immune dysfunction and inflammation in IBD, and the rationale for manipulating the dysbiotic microbiota as therapy. Clinical trials including fecal microbiota transplantation and the use of rationally designed oral biotherapeutic products (LBPs) composed of mixtures of protective commensal bacterial strains are reviewed. Dupont et al. review how fecal microbiota transplantation is being evaluated as a means of reversing dysbiosis and alterations in the diversity of the microbiome in a variety of diseases and disorders including *C. difficile* infection, chronic intestinal disorders including inflammatory bowel diseases (see also Ota and Sartor), irritable bowel syndrome (see also Pimentel and Lembo), functional constipation, obesity, diabetes, immunotherapy-induced colitis (see also Abu-Sbeih and Wang), graft versus host disease, neurodegenerative disorders, nonalcoholic fatty liver disease (see also Shama and Liu and Lechner et al.), and others. Microbial patterns associated with intestinal injury in the neonate including necrotizing enterocolitis are reviewed in an article by Josef Neu. Abu-Sbeih and Wang expand on the role of the gut microbiome in immune checkpoint inhibitor-induced colitis and the potential role of fecal transplantation as therapy or in prevention. Recent studies have postulated that dysbiosis of the gut microbiome in HIV-infected individuals could contribute to chronic immune activation, increased risk of inflammation-related diseases (stroke, cardiovascular disease, cancer, long bone fractures, and renal dysfunction), and therefore increased mortality. Tuddenham and Sears review available data on changes in the structure of the gut microbiome in HIV, including the potential impact of sexual orientation.

## Microbiome and the Gut–Brain Axis

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by persistent deficits in social communication and repetitive behavioral patterns. Among co-occurring medical conditions associated with ASD, gastrointestinal problems (irritable bowel syndrome, recurrent abdominal pain, inflammatory bowel disease) are among the most common. Sauerman, Margolis, and Luna review compelling investigations focusing on the brain–gut–microbiome axis in ASD. Pimental and Lembo review the role of the microbiome in irritable bowel syndrome (IBS), a chronic functional disorder characterized by abdominal pain and altered bowel habits. The effects of diets for IBS on the microbiome and the role of fecal microbiota transplantation as therapy are also reviewed.

## Microbiome and Cancer

The relationship between the microbiome and cancer has been an area of speculation for several decades. In some cases, this seemed biologically plausible such as the association of oncogenic viruses and cancer (e.g., EBV and lymphoma or nasopharyngeal carcinoma). The possible association of colon cancer and colonic bacteria has been studied since at least the 1970s, but the lack of tools beyond simple culture limited studies to correlative data which speculated on the role of bacteria as carcinogens or tumor promoters. The explosion of high-throughput technologies and studies using germ-free mice are now allowing more in-depth analyses which are clarifying how the microbiome may either promote oncogenesis or play a role in prevention of cancer. While many previous studies concentrated on the role of the gut microbiome in inflammation and indirectly cancer development, studies of the impact of the microbiome on the genome and epigenome of epithelial cells and associated pathways are now moving the needle from correlation to causation. How the microbiome influences the immune system and impacts cancer therapy is a growing area of investigation. In this issue, Chapkin Navarro, Hullar, and Lampe describe how diet and gut microbes act coordinately to enhance programmed cell death and potentially reduce colorectal cancer risk. Emlet, Ruffin, and Lamendella characterize the human enteric virome and how it may be related to carcinogenesis in the gut, while Engstand and Graham examine the role of the microbiome and specifically *H pylori* on gastric carcinogenesis. How the gut microbiota may serve as biomarkers for prognosis and predict treatment efficacy and potential adverse effects of chemotherapy (including immune checkpoint inhibitor therapy) is reviewed in articles by Ervin, Ramanan and Bhat, by Khan, Arora and Wargo, and by Abu-Sbeih and Wang. These articles include examination of the bidirectional interactions between the gut microbiome and the immune system.

## Microbiome and Hepatobiliary Diseases

Chronic liver disease is a growing cause of morbidity and mortality worldwide. Lechner, Yee, Limketkai, and Pham examine the role of the microbiome in mediating the development and progression of chronic liver diseases, while Sham and Liu describe how the reciprocal interactions between the gut microbiota and omega-3 PUFA may influence nonalcoholic fatty liver disease (NAFLD).

## What Next?

Advances in high-throughput technologies and systems biology-based modeling have greatly accelerated our ability to investigate microbial communities and their dynamic interactions with each other and the human host. This will assist in moving our knowledge from descriptive classification to a critical understanding of the function of the microbiome in health and disease. These tools will enhance our understanding of what constitutes temporal variation in an individual's microbiome, differences between individuals, and the dynamic interactions between human microbes and the environment. Perhaps we may even see the creation of "synthetic" human microbiomes which move the field beyond probiotics and fecal replacement therapy as treatment for a myriad of diseases. Early nutrition or the lack thereof (e.g., malnutrition) plays a critical role in terms of the development, trajectory, and resilience of the gut microbiome. A better understanding of the nature of microbial–host interactions, and the ability to manipulate these interactions, will undoubtedly lead to improvements in human nutrition and health.

## Final Comments

We sincerely hope that you will find this Special Issue of *Digestive Diseases and Sciences* comprehensive, informative, and thought-provoking. We are grateful to all of the authors who have generously contributed their time and expertise to this issue. We would also like to thank Meghan Keeffe, the Managing Editor of DDS, for assistance with the innumerable organizational details required for a project of this magnitude.

Bob and Robb