# Physiology in Health and Disease

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Jun Sun • Pradeep K. Dudeja
Editors

# Mechanisms Underlying Host-Microbiome Interactions in Pathophysiology of Human Diseases

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*Editors*
Jun Sun
Division of Gastroenterology
and Hepatology, Department of Medicine
University of Illinois at Chicago
Chicago, IL, USA

Pradeep K. Dudeja
Division of Gastroenterology
and Hepatology, Department of Medicine
University of Illinois at Chicago
Chicago, IL, USA

Jesse Brown VA Medical Center
Medical Research Service (600/151)
Chicago, IL, USA

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*I dedicate this book to my family: my father Zong-Xiang Sun, mother Xiao-Yun Fu, husband Yinglin Xia, and sons Yuxuan and Jason. I want to thank them for their love, understanding, and support. —Jun Sun*

*谨以此书献给我的父亲孙宗祥母亲付小云。—孙俊*

*I dedicate this book to my late parents, Mr. Lachman Dass Dudeja and Mrs. Ved Rani Dudeja, for their constant love and support throughout my life. I also dedicate this book to my wife Renu and my son Amish and daughter Akanksha for their constant love and support. —Pradeep Dudeja*

# Preface

Only recently has the biomedical community begun to appreciate the roles of microbiome in health and diseases. Some scientists are still skeptical about the link between the gut microbiome and various diseases pertaining to other organs beyond the intestine. In April 2016, we organized a symposium entitled "Mechanisms Underlying Host–Microbial Interactions in the Pathophysiology of Diseases" for the Experimental Biology meeting. The symposium was well attended, even when it was scheduled to start at 8:00 in the morning on the last day of the meeting. We were very encouraged by the scientific content presented by speakers, the active Q&A section, and the enthusiasm of the audience standing at the back of the conference room when we ran out of seats. The American Physiological Society (APS) noted this enthusiasm of the audience with great interest in this symposium on the gut microbiome. Dr. Sun was contacted by Dr. Dee Silverthorn, Chair of the APS Book Committee. She thought that expanding our topic into an APS e-book would be an effective way of reaching more scientists around the world than just those who attended the meeting. Right after the EB, we submitted a book proposal to the APS and started to consider the possibility of creating an e-book of our symposium. We were so glad that the book proposal was supported by the committee members and well-received by the peer review. They were pleased to see something on the emerging subject, and believed that "the microbiome book is very timely, important and of wide interest and the table of contents appeared to be well thought out and should attract a broader community of readers."

In the summer of 2016, we started to invite authors to contribute to the book. The original theme of the EB Symposium focused on the gut microbiome and intestinal diseases. Over the past year, we were able to further develop the chosen topics in the book. In the current book, we have not only included chapters on the role of intestinal bacterial communities in various diseases, but have also included the microbiome from some other organs, such as the oral and lung microbiomes. As the

concept of the microbiome includes viruses and fungi, we have, therefore, included chapters covering progress on commensal fungi and virus.

Chicago, IL Jun Sun
Chicago, IL Pradeep K. Dudeja

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# Introduction

The microbiome is the collection of microbes or microorganisms that inhabit an environment, creating a sort of "mini-ecosystem." Our human microbiome is made up of communities of commensal, symbiotic, and pathogenic bacteria, fungi, and viruses. We can consider the human microbiome a newly discovered organ that interacts with other organs and influences the development of diseases. This so-called "microbiome organ" weighs over 1 kg, equivalent to the weight of the human heart or liver. Although it has no distinct structure, the organized system of cells is more akin to the immune system than the liver. The human gut microbiome is dominated by four large groups of bacteria or phyla: Firmicutes, Bacteroidetes, Proteobacteria, and Actinobacteria. Firmicutes and Bacteroidetes are generally the most abundant in the gut microbiota, followed by Proteobacteria and Actinobacteria. The basic functions of the microbiome, the invisible organ, include (1) gleaning indigestible ingredients and synthesizing nutritional factors (e.g., vitamins); (2) producing anti-microbial products that negatively affect pathogenic bacteria through the development of colonization resistance; (3) developing a systemic and intestinal immune system; (4) providing signals for epithelial renewal and maintaining barrier functions; and (5) detoxifying xenobiotics and affecting the host metabotypes.

The complex microbial communities that inhabit most external human surfaces play a critical role in health and diseases. Perturbations of host–microbe interactions can lead to altered host responses that increase the risk of pathogenic processes and promote disorders. It is only recently that we have begun to appreciate the role of the microbiome in health and diseases. Environmental factors and a change of life style, including diet, significantly shape the human microbiome, which in turn appears to modify gut barrier function, affecting nutrient, electrolyte and fluid absorption and triggering inflammation. The functions of the microbiome are vital, because in the absence of the microbiota or in the event of its ablation with long-term broad-spectrum antibiotics, there can be significant consequences, e.g., improper development of the immune system, barrier integrity, metabolic disturbances, and the development of *C. difficile* antibiotics-associated colitis.

Dysbiosis is an imbalance in the structural and/or functional properties of the gut microbiota. Dysbiosis can disrupt host–microbe homeostasis and be involved in various human diseases beyond the digestive system. Three notable areas are: (1) obesity, diabetes, and metabolic syndrome; (2) cardiovascular and renal diseases; and (3) stress/anxiety (gut–brain axis) including irritable bowel syndrome (IBS), autism, and Parkinson's disease. Approaches that can reverse the dysbiosis are represented as reasonable and novel strategies for restoring the balance between host and microbes.

In the current book, we offer a summary and discussion of the advances in our understanding of the pathophysiological mechanisms of microbial–host interactions in human diseases, including necrotizing enterocolitis (NEC), viral infectious diseases, diarrheal diseases, obesity, inflammatory bowel diseases (IBDs), Irritable bowel syndrome (IBS), allergic disorders, and cancers. We discuss not only bacterial community, but also viruses and fungi. In addition to the intestinal microbiome, we have chapters on the microbiome in other organs. For example, a review of the oral microbiome and its potential link to systemic diseases and cancer is included, in addition to a chapter on the lung microbiome.

Microbial colonization plays a significant role in the normal postnatal development of the intestine and other organs. Early-life exposure to microbes decreases the risk of developing allergic disease. Also, exposure to a protected modern lifestyle environment may lead to decreased allergen exposure, potentially creating an immune system that is intolerant to allergens. In particular, Humphrey and Claud focus on the topic of the role of microbiome in intestinal development and outline ways in which poor clinical outcomes in the preterm infant, such as NEC, are related to gut dysbiosis. The benefits of the microbiome are not seen in preterm infants, who experience delayed and altered microbial community colonization after birth. In combination with the reduced intestinal functions in the preterm, dysbiosis can further damage existing intestinal functions and exacerbate the hyperreactive inflammatory state. Perkins and Finn summarize the roles of microbiome from the intestine, skin, and lung in the development of allergic diseases of childhood. They review four of these: food allergy, atopic dermatitis, asthma, and allergic rhinitis. The allergic diseases are related to each other in that having one of these diseases early in life increases the risk of acquiring another allergic disease at a later age.

A growing number of scientists are investigating the role of the microbiome in the development of and protection from disease. One area of particular interest is recovery from infection and injury. Lei et al. outline the pathogenesis, immunity, and role of microbiome/probiotics in enteric virus infections. Liu and Sun update the current understanding of pathogenic *Salmonella* infection, inflammatory response of the host, and anti-inflammatory and apoptotic death mechanisms in infection and cancer. The established experimental models (e.g., organoids, the chronic infected mouse model, and the infected colon cancer model) can be applied to the investigation of other bacteria and their interactions with hosts. Kumar et al. present an overview of the evidence-based effects of probiotics in diarrheal diseases, in addition to a detailed overview of the mechanisms of action of probiotics.

Multiple anti-inflammatory activities can be mediated via various pathways in mammalian cells. This is exemplified by the probiotics story. Thus, probiotics may serve as the paradigm for the multiplicity of the sometimes seemingly contradictory activities of this group of anti-inflammatory agents. Taken together, insights into the anti-inflammatory mechanisms of the bacterial proteins and probiotics should provide promising opportunities for therapeutic intervention.

Healthy microbial–host interactions enhance motility, digestion, and absorption. They also strengthen barrier function and immune homeostasis. The chapter by Raja et al. summarizes the critical roles played by the microbiota in gastrointestinal (GI) motility. They describe the influence of the microbiota in shaping the enteric nervous system. Next, they discuss how microbial metabolites can regulate intestinal motility. Finally, they demonstrate how dysbiosis can lead to motility disorders (e.g., IBS and colonic pseudo-obstruction). Yeoh and Vijay-Kumar discuss altered microbiotas and their metabolism in host metabolic diseases. This chapter examines several key concepts and potential mechanisms that underscore the link between the gut microbiome and metabolic diseases, and provide examples of the extent to which specific bacteria and/or their metabolites affect host metabolism.

It is clear that microbes in the colon, and perhaps in the small intestine, are significant players in the development of colon cancer. Kordahi and DePaolo review the influence of the microbiota on the etiology of colorectal cancer (CRC). They explore the conceptual frameworks through which certain members of the microbiota are believed to cause CRC, and toll-like receptors (TLRs). They discuss the various strategies aimed at manipulating the microbiota and targeting the TLRs in developing new treatment approaches.

Dysbiosis can disrupt host–microbe homeostasis and be involved in various human diseases beyond the digestive system. Vasquez et al. discuss the roles of the oral microbiome, especially the potential link to systemic diseases including cancer. Perkins and Finn focus on the microbiome at different body sites (gut, skin, and lung) that promote resilience or susceptibility to allergic diseases and describe the potential in the inflammatory process of allergic disorders.

Because the human microbiome is made up of communities of bacteria, fungi and viruses, Chen and Huang outline the research progress of fungi *Candida albicans* commensalism and human diseases. They evaluate the roles of *Candida albicans* in specific host niches, including the oral cavity, reproductive tract, and GI tract.

Microbiome studies are likely to facilitate diagnosis, functional studies, drug development, and personalized medicine. It requires a multi-disciplinary team effort, involving basic, translational, and clinical investigators. Further, we discuss the current knowledge and future directions of probiotics and fetal microbiome transplantation (FMT) in various diseases. The chapter by Chis et al. takes us through the key aspects of FMT, including methodology, physician and patient attitudes, safety and regulation, and its therapeutic potential for the treatment of *Clostridium difficile* infection and other GI conditions, including IBD, obesity, IBS, and CRC.

The next phase of research investigation of the gut microbiome should be guided by specific biological questions relevant to the clinical aspects and natural history of the disease, utilizing the full spectrum of "omic" technologies, bioinformatic analysis, and experimental models. To emphasize the significant roles of bioinformatic and biostatistical methods in gut microbiome studies, we also include a chapter by Xia and Sun focusing on statistical models and analysis of microbiome data.

Taken together, our book highlights the microbiome in the context of health and disease, focusing on mechanistic concepts that underlie the complex relationships between host and microbes.

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Chicago, IL Pradeep Dudeja

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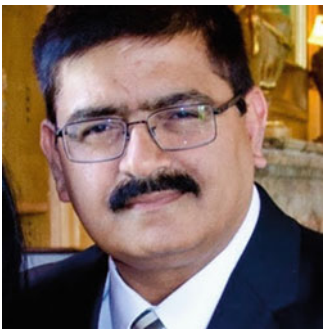
# About the Editors

**Jun Sun** is a tenured Associate Professor at the University of Illinois at Chicago, Chicago, USA. She is a Fellow of the American Gastroenterological Association. Her research interests are host–microbiome interactions in inflammation and cancer, and her key achievements include: (1) characterization of the role of vitamin D receptor in the regulation of the gut microbiome in intestinal homeostasis and inflammation; (2) identification of dysbiosis and gut dysfunction in amyotrophic lateral sclerosis (ALS); (3) identification of the role of gut bacteria in regulating intestinal stem cells, and (4) identification and characterization of the *Salmonella* effector protein AvrA in host–bacterial interactions in infection and cancer. Dr. Sun has published over 140 scientific articles in peer-reviewed journals, including *Cell Stem Cells*, *Nature Genetics*, *Gut*, *JBC*, *American Journal of Pathology*, and *American Journal of Physiology-GI*. She is on the editorial board of more than 10 peer-reviewed, international scientific journals. She serves on the National Institutes of Health (NIH), the American Cancer Society, and other national and international research foundations. Her research is supported by the NIH, the Department of Defense (DOD), and other industry-sponsored awards. Using several models, including transgenic mice, germ-free animals, and human samples, her laboratory is currently pursuing the following research topics: (1) novel roles of the gut microbiome in colon cancer, inflammatory bowel diseases (IBDs), infectious diseases, obesity, ALS, and other human diseases; (2) bacterial regulation of vitamin D/vitamin D receptor in inflammation and cancer; and (3) bacterial regulation of intestinal stem cells.



**Pradeep K. Dudeja** is a Professor of Physiology in Medicine at the University of Illinois at Chicago and a Senior Research Career Scientist at the Jesse Brown VA Medical Center, Chicago, IL, USA. His research primarily focuses on an understanding of the pathophysiology of diarrheal diseases and on developing better therapeutic interventions. His focus has been on host–microbe interactions with regard to the mechanisms underlying infectious diarrhea as it relates to infections by a food-borne pathogen enteropathogenic *E. coli* and diarrhea elicited by *C. difficile* infection. He is also investigating the mechanisms underlying the antidiarrheal role of probiotics. Another focus of his group has been to understand the mechanisms of the absorption of key bacterial metabolites: short chain fatty acids and their role in intestinal health in general and the implications for gut fluid absorption and gut inflammation. Dr. Dudeja has published over 200 original peer-reviewed articles in journals including *Gastroenterology*, *Journal of Clinical Investigation*, *Journal of Inflammatory Bowel Diseases* and *American Journal of Physiology*. He serves as an Editor for *Comprehensive Physiology* and on the editorial board of many journals including *Gastroenterology*, *AJP-GI-Liver*, *Digestive Diseases & Sciences*, and *Physiological Reports*. He has been serving on many grant review committees, including the NIH and the Department of Veterans Affairs.