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Editorial

Gut Microbiome: The Cornerstone of Life and Health

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After the completion of the Human Genome Project in April 2003, scientists realize that decoding human genome is not enough to understand human biology because there are tremendous microorganisms living in and on the human body throughout the full life cycle, and they are critically affecting human life. Currently, the Human Microbiome Project, conceived as a "second human genome project," has become the research spotlight of the scientific community of the whole world [1]. The human microbiome, known as the "forgotten organ," has been elevated to an unprecedented importance in a wide array of host processes such as growth, development, physiology, immunity, nutrition, and diseases in the last decade. Trillions of microorganisms such as bacteria, archaea, viruses, parasites, and fungi symbiotically inhabit inside and outside the mammal body. That is why humans are regarded as "superorganisms." The in-depth exploration of human microbiome by fast renovation of sequencing technologies, complemented by analysis of transcriptomes, proteomes, metabolomes, and immunomes, and by mechanistic experiments in model systems, has dramatically reshaped our understanding of the correlations between human health and microbiomes.

Among all the organs of the mammalian body, the microbiome in the gut has attracted the most attention in biomedical research. The gut microbiome, a collection of microbiota and their genetic contents from gut, exerts an extensive consortium of immune modulation and metabolic activities [2]. Researchers from all over the world have investigated the dynamic gut microbiome-host-environment cross-talks extensively to decipher its roles and mechanisms in health and disease. Through concerted efforts over the last two decades, we now have better understanding of the identity and functionality of the gut microbiome. This is mainly attributed to the state-of-the-art methodological advances. Recent culture-independent multiomics techniques, including genomics, transcriptomics, proteomics, metabolomics, and culturomics, combined with modern sequencing technologies, have revealed that the compositions, functions, and homeostasis of gut microbiome, and its interactions with the host can have an immense influence in both the maintenance of health and the pathogenesis of diseases. Moreover, the cutting-edge researches have identified that the gut microbiome contributes to not only the health and diseases of the gut itself but also to those remote extraenteric organs such as the liver, brain, skin, heart, muscle, and bone *via* bidirectional signaling process. These findings provide new clues to comprehend the pathogenesis of those extraenteric diseases and will also subvert our previous knowledge.

The gut microbiome has recently been implicated a host of chronic diseases ranging from gastrointestinal inflammatory and metabolic diseases to neurological, cardiovascular, respiratory illnesses, and even cancers. However, most of the current gut microbiome cross-sectional studies exhibit significant heterogeneity influenced by host and environmental factors [3]. Large-scale, cross-regional, longitudinal disease progression follow-up studies with well-phenotyped

subjects will be more conducive to clarifying and verifying the correlations between the gut microbiome and the different stages of diseases, which will shed light on the novel diagnostic and therapeutic strategies in the basis of the gut microbiome.

Increasing health and diseases are found to be intricately reliant on the gut microbiome and influence the pathophysiological functions which we are beginning to understand. In fact, the findings from most current microbiome observational studies, even in large-scale longitudinal observations, are limited to identifying the associations and correlations instead of causations.

Although it is critical to be wary of correlations without mechanistic insights, transmuting observational findings from correlation to causation has obvious difficulties. Given innumerable distinct exogenous and endogenous factors involved in host-microbiota interaction over a lifetime, the host-microbiota impact each other reciprocally, and the microbiota interact in many modes among themselves, and the decipher of causality between the gut microbiome and a specific disease becomes a formidable challenge.

Now, human microbiome investigations have reached a critical inflection point. Scientists are trying to figure out the mechanism that the gut microbiome affects host health and diseases in the second wave of microbiome studies, elucidating the particular molecular mechanisms by which the microbiome impacts on host physiology and pathology [4]. Apparently, it is ethically impossible to inoculate human experimental subjects with aetiological agents to fully understand the roles and mechanisms of the gut microbiome in health and diseases, while the animal models can be considered as an important alternative. The germ-free animal models have emerged as one of the valuable experimental tools for host-microbiome interactions research. Moreover, genetically modified germ-free animals can be used to investigate interactions between specific genes and the gut microbiome. Monocolonized germ-free animals can be used to investigate how specific gut microbes affect host health and diseases, and humanized microbiota-associated animals have been commonly used for addressing causal relationships between altered microbiomes and host pathology [5]. In addition, these animal models can also be used to evaluate the roles of diet, nutrients, functional foods, bioactive compounds, and live organisms on treating host diseases by targeted to the gut microbiome. New animal models (especially larger mammalian models) can provide valuable insights into the role of the microbiome. However, the gut microbiome is significantly impacted by host genes and other environmental factors, including (but not limited to) food, bedding, caging, and temperature. Thus, more rigorously controlled animal experimental designs should be highlighted to ensure high rates of experimental repeatability and reproducibility. Meanwhile, such studies pave an essential first step toward the development of microbiome-based diagnostic and therapeutic strategies for diseases.

With the rapid development of gut microbiome research and fast growing of knowledge update and accumulation, monitoring of the human microbiome has become an emerging area of diagnostics for personalized medicine.

The microbiome-disease associations or correlations and the cause-consequence effects of the specific gut microbiome signatures make it possible to develop novel diagnostic, prognostic, and most importantly, therapeutic strategies based on microbiome manipulation. Noninvasive sampling for gut microbiota research can also facilitate large-scale public health applications, including early diagnosis and risk assessment in various diseases. Before microbiome-based diagnostics and therapies are translated to clinical medicine, it should be defined what is healthy or normal microbiome [6]. However, universal healthy microbiome is so far undefined, since gut microbiome varies with aging, sex, race/ethnicity, dietary habit, life styles (e.g., alcohol, smoking, and physical activity), geographic location, and medicine taken [7, 8]. Besides, the gut microbiome is dynamic, referred as "a necessary and ever-changing organ." Many larger-scale microbiome studies have only recognize the healthy gut microbiome from those healthy subjects in their eyes, which cannot be considered as the universal healthy microbiome. Other studies simply regarded populations of specific microbes as the healthy gut microbiome. Therefore, although it is important for developing microbiome-based diagnostic applications to characterize disease-associated changes in the microbiome before and after disease onset in individuals, a global criterion of healthy or normal gut microbiome is still an unmet challenge for researchers and waiting to be established. Apparently, the field is just getting started and warrants further work. We may expect to see the implementation of microbiome diagnostics in routine medical practice in the next decade.

Gut microbiome has also been considered as a novel target for precise and personalized medicine, as the fact of contributing to gut epithelial construction and function maintenance, food digestion and metabolism, and immune system development [2]. The gut microbiome has the characteristics of resilience and can be reshaped by perturbations. We cannot really change our genome, but we can easily change our gut microbiome through our life. Gut microbiome researches have made it become possible to read out our microbiome, as well as to find and modify the predispositions. Microbiome-targeted therapies aim to rehabilitate perturbed microbial ecosystems into healthy or normal status, which can restore health or prevent diseases [9]. Many microbiome-targeted therapies such as dietary intervention, nutritional supplement, antibiotics, probiotics, prebiotics, synbiotics, postbiotics, psychobiotics, bacteriophage, and fecal microbiota transplantation have been used to regulate the human microbiome [10, 11]. So far, great progress has been achieved in treating metabolic diseases, cardiovascular disorders, and cancer.

As mentioned above, the cause-and-effect relationships between the gut microbiome and diseases suggest that the function of the gut microbiome may be more relevant targets than its altered taxonomic abundances. Thus, the microbiome-targeted therapies should focus on the modulation of the microbiome functions instead of simply changing the taxonomic abundances. Deeper mechanistic understanding of the function of the gut microbiome or specific microbes are required to develop precise therapeutics and

treatments. Scientists have realized this need and has started to studying the functional aspects of the microbiome. Although strong momentum in this field, few microbiome-based therapeutic products have been applied in clinic as pharmaceuticals. The development of microbiome-targeted therapy is still in its early stages and faces great challenges: (i) the standardized microbiome sampling, sequencing, and analyzing; (ii) the individual dynamic variations of the gut microbiome; (iii) the safety, tolerability, efficacy, and of the microbiome-targeted therapies; (iv) the pharmacokinetics and pharmacodynamics of the microbiome-targeted therapies; (v) the side effects of the microbiome-targeted therapies; (vi) a healthy microbiome definition. Anyway, the microbiome-targeted therapies tantalize us with the promise of novel therapeutic strategies for a range of intractable diseases. We believe that the advances in our understanding of gut microbiome will profoundly transform our way of life in the next decade.

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Conflicts of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Authors' Contributions

Zongxin Ling, Hang Xiao, and Wei Chen conceived and designed this editorial. Zongxin Ling wrote the first version of the manuscript. Hang Xiao and Wei Chen revised and finalized the manuscript. All authors read and approved the final version of the manuscript.

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