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COMMENTARY

A microbiome war in our gut

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Received: October 20, 2024; Accepted: December 9, 2024; Published Online: December 17, 2024; https://doi.org/10.59717/j.xinn-life.2024.100111

Citation: Wang W., Qu M., Zhang T., et al. (2025). A microbiome war in our gut. *The Innovation Life* **3**:100111.

The advancement of high-throughput sequencing technology has led to a greater understanding of the significant relationship between gut microbiota and human health. Intestinal microflora refers to the collective presence of all the microbes in the animal's intestinal tract, which resides in the host's intestines and assists the host in performing various physiological and biochemical functions. Numerous studies have indicated that alterations in the gut microbiota's composition are linked to a range of human diseases, such as cancer, type 2 diabetes (T2D), neurodegenerative disorders, and inflammatory bowel diseases (IBD).[1,2] Additionally, the clinical practice of fecal microbiota transplantation from healthy individuals to patients to alleviate disease symptoms has been proven to be quite effective,[3] reinforcing the strong connection between the gut microbiota and human health. Researchers widely agree that there is a core microbiome that maintains human health, but a clear definition of this core microbiome has yet to be

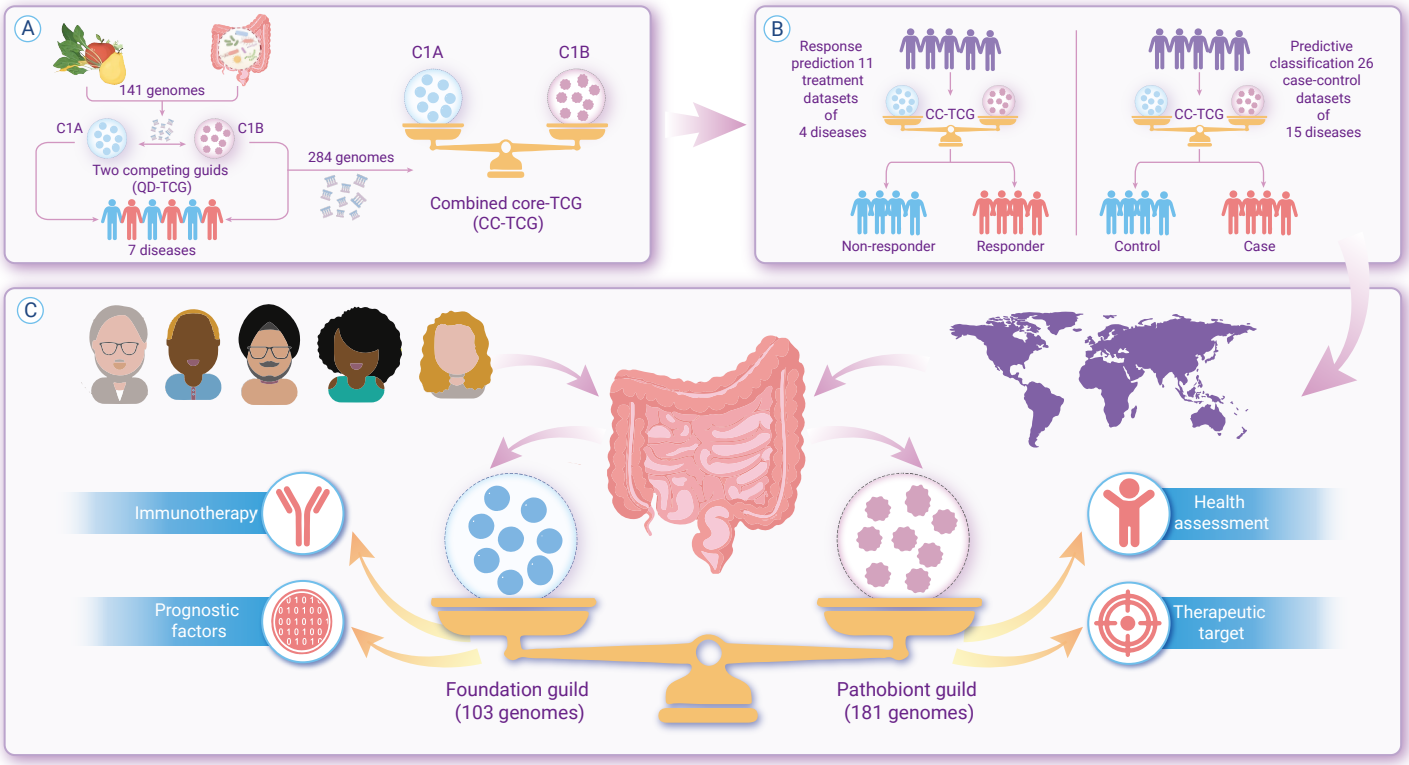

Figure 1. A comprehensive collection of essential gut bacteria that supports human health (A) Stable functional microbial community under dietary disturbance. (B) Stable functional microbiota under disease perturbation. (C) The universal "seesaw" model is applicable across different regions, races, and diseases, offering wide-ranging potential for use.

determined. A recent study conducted by Zhao et al.,[4] which utilized high-quality metagenome-assembled genomes (HQMAGs),[5] has identified two competing groups that function in a cooperative manner, leading to the development of the two competing guilds (TCGs) model. This significant discovery has identified a core microbiome that maintains host health regardless of geographical location, ethnicity, and disease types.

First, the researchers conducted a trial of a dietary intervention targeting the gut microbiota, called QD, involving patients with T2D. Using shotgun metagenomic sequencing technology, 1,845 non-redundant HQMAGs were reconstructed from stool samples collected at different time points. Gut microbiota composition was significantly changed in the high-fiber diet group and returned to the pre-intervention levels at 1-year follow-up, indicating the resilience of gut microbiota composition. Some changes associated with inhibition of microbiota structure are observed in host metabolic characteristics, such as hemoglobin A1c (HbA1c) levels. The significant changes in the gut microbiota structure of patients in the high-fiber interventional group provided a reference for the identification of stable related genomes as potential health related microbial members.

The researchers conducted a network analysis on fecal samples collected, focusing on 184 HQMAGs that exhibited significantly similar correlations across different time points. Among these, cluster C1 was further subdivided into two sub-clusters, C1A and C1B, both of which demonstrated strong correlations with the primary outcome, hemoglobin A1c. Additionally, the researchers discovered that there is a consistent cooperative relationship among these two functional clusters, whereas a stable competitive relationship is noted between C1A and C1B, creating a "seesaw" network interaction framework, with C1A likely benefiting health and C1B possibly harming it. Subsequently, the researchers analyzed the associations between these two

functional clusters and 43 host biological clinical parameters employing a linear mixed-effects model. Furthermore, the "seesaw" model demonstrates the robustness of the model across different samples and its effectiveness in distinguishing T2D patients from healthy controls. The accuracy of "seesaw" model in classifying samples from other case-control studies was evaluated. These two functional clusters were found in nearly all gut samples from patients and healthy controls, and preserved the "seesaw" structure of the two competing functional groups.

Moreover, the researchers identified a major cluster across various diseases, including T2D, colorectal cancer (CRC), and IBD, to investigate the potential identification of TCGs in relation to disease disturbances. Subsequently, following a read recruitment analysis of TCGs from all other metagenomic datasets in the case-control dataset collection I (CCDC-I), 788 non-redundant HQMAGs were identified, called combined TCG (C-TCG). In the CCDC-I, the classifier trained on the top 302 HQMAGs showed the best classification performance, resulting in 284 HQMAGs that were consistently assigned to TCGs, called the combined core set of the TCGs (CC-TCG). An additional 15 independent metagenomic datasets (CCDC-II) from 10 different diseases were compiled and CC-TCG showed moderate to excellent diagnostic performance in 10 of the 15 datasets. Then, all 26 datasets from CCDC-I and CCDC-II and randomly assigned samples were used for training (80%) and testing (20%) CC-TCG based random forest classifier. It could distinguish CC-TCG from controls using a generic model, suggesting that changes in CC-TCG can serve as a universal indicator of human health. In addition, the researchers compiled 11 pre-treatment metagenomic datasets associated with four diseases, and performed read recruitment analysis on the TDC metagenomic dataset using 284 HQMAGs from CC-TCG as the reference genomes. The results highlight the potential of using CC-TCG to predict the therapeutic effects of various diseases and therapies.

The breakthrough in robust identification of core gut microbiota can be attributed to improvements in both technology and research methodology. Technically, the newly developed HQMAGs technology has improved resolution down to the strain level without relying on existing databases. For strains that were previously uncharacterized and could not be analyzed, HQMAGs can trace their genome sequence to examine their ecological behavior. It incorporates machine learning methods for accurate data analysis and predictions at both the strain and gene levels. In terms of research methodology, the researchers view the gut microbiota as a complex adaptive system and thus adopt a community framework focusing on genome-specific analysis, database independence, and microbial interactions. Additionally, inspired by systems biology, the researchers propose that the core microbiome remains stable even after environmental perturbations. As a result, they concentrate on the microbiota that maintains stable cooperative or competitive interactions following dietary interventions.

In summary, the researchers propose the TCG model, identifying a foundation guild primarily composed of short-chain fatty acid-producing bacteria associated with disease alleviation, and a pathobiont guild mainly composed of opportunistic pathogens associated with disease exacerbation. Among them, the foundation guild carried more fiber degrading genes, but no resistance or virulence genes. And the pathobiont guild is rich in various resistance genes and virulence factors. These two types of microbiota are interdependent and mutually restricted to maintain the balance of gut flora. The foundation guild's prevalence keeps the pathobiont guilds in check, fostering stability in the intestinal microecosystem. On the other hand, if the pathobiont guilds gain the upper hand, they can trigger inflammatory reactions and result in different health issues. It's akin to a battle between these two microbiota types, with the victor influencing our well-being. Consequently, the suggested TCG model allows for the evaluation of gut flora balance by measuring the ratio of core flora, enabling predictions about health risks and trends. This approach is anticipated to be significant for future health management and disease prevention. And the beneficial strains in the foundation guild contribute to the development of live biotherapeutic products. In addition, targeted nutritional interventions can decrease the presence of harmful pathobionts in patients' intestines, leading to better health outcomes. Meanwhile, efforts to strengthen the foundation guild provide guidance for the research and development of probiotics and prebiotics. Simultaneously, the TCG model has emerged as a possible theoretical foundation for diagnosing traditional Chinese medicine and herbal remedies. The TCG model has successfully quantified microecosystems and advanced the understanding of microecological theory towards the dynamic analysis of core microbial community functions, representing a significant advancement in the field. The relationship between gut microbiota and human health involves complex biological processes that have not been fully elucidated in this study. Further bioinformatics analysis and experimental research are needed to fill these gaps in the future.

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FUNDING AND ACKNOWLEDGMENTS

This work was funded by the National Key R&D Program of China (2021YFC2102700), National Natural Science Foundation of China (No. 32272269). The funders had no role in study design, data collection and analysis, decision to publish or preparation of the manuscript.

AUTHOR CONTRIBUTIONS

Wenqian Wang wrote the manuscript and designed the figures. Mingqin Qu, Tong Zhang, Yang Wang and Ceping Zheng wrote the manuscript. Fuping Lu reviewed the manuscript. Xiangming Wang and Fufeng Liu conceived the original idea and provided critical revisions.

DECLARATION OF INTERESTS

The authors declare no competing interests.