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SPECIAL TOPIC: Gut microbiome and metabolism

EDITORIAL

Progress in gut microbiota-host interaction

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Recently, the gut microbiota has been recognized as a novel endocrine organ in the human body. It produces various bioactive metabolites and participates in metabolic processes. In addition, the gut microbiota is involved in the metabolism of drugs and natural components, which in turn influences the effects of various oral medications. With the rapid advancement of multiomics technologies, including transcriptomics, proteomics, and metagenomics, metabolic disease-related cohorts have been established. These cohorts analyze the composition of the gut microbiota and the abundance of its bioactive metabolites, thereby clarifying the correlation between gut microecology and diseases. To address the vital role of gut microbiota-derived metabolites in host health, we organized a special topic, "Gut Microbiome and Metabolism". In this topic, we included three articles and two reviews that offered deeper insight of gut microbiota-host interaction. Zeng et al. (2023) found that the disruption of the gut barrier caused by a high-fat diet (HFD) is linked to extracellular ROS produced by the gut microbiota. Yao et al. (2023) reexamined the relationship between the changes in the relative abundance of the microbial signatures linked to the development of type 2 diabetes (T2D) in a cohort of Chinese athletic undergraduates stratified by body fat and physical fitness. Zhu et al. (2023) discovered that PvrA binds to multiple pseudo-palindromic sites simultaneously for effective transcription activation. Chen et al. (2024) summarized how the various components of tobacco use impact the composition and function of the gut microbiota. Jia et al. (2023) summarized far-reaching effects of bile acid-mediated metabolic and immune control throughout the body.

Lifestyles influence gut microbiota

The gut microbiota, acting as a bridge between the host and the external environment, is influenced by various factors such as diet and exercise and maintaining a dynamic balance. An imbalance in the interaction between the gut microbiota and the host has been identified as the primary cause of several diseases (Cani et al., 2019).

According to Sharkey et al. (2018), the gut barrier is the most crucial barrier in humans. It comprises intestinal epithelial cells, immune cells, tight junctions, a mucus layer, and gut microbiota, all of which are exposed to and sensitive to external nutrients, such as fats and carbohydrates (Sharkey et al., 2018). For instance, fat increases the production of bile acid, which dissolves the mucosal barrier (Gasaly et al., 2021), alters the distribution of epithelial tight junctions (Cani et al., 2008), exacerbates intestinal inflammation (Zou et al., 2018), changes the characteristics of intestinal mucus, and induces dysbiosis of the gut microbiota. Although the underlying mechanisms are still being understood, disruption of the gut barrier is associated with an imbalance of the gut microbiota. In this context, Zeng et al. found that the disruption of the gut barrier caused by a HFD is linked to extracellular ROS produced by the gut microbiota. This finding suggests a potential therapeutic target for disorders associated with HFDs.

T2D has long been managed and prevented through exercise (Luan et al., 2019). A growing body of research suggests that the reciprocal relationships between exercise and gut microbiota contribute to these metabolic benefits (Evans et al., 2014; Luan et al., 2019). Exercise performance may be enhanced by acetate and propionate (Scheiman et al., 2019), two prevalent short-chain fatty acids produced by the microbial fermentation of dietary fibers (Koh et al., 2016). Experiments using fecal microbiota transplantation provided additional evidence that exercise-induced gut microbial adaptations improved glucose metabolism in obese mice (Liu et al., 2020). However, whether some of the microbial changes associated with prediabetes and diabetes could be attributed to physical fitness remains unclear. In this context, Yao et al. reexamined the relationship between the changes in the relative abundance of the microbial signatures linked to the development of T2D (Wu et al., 2020) in a cohort of Chinese athletic undergraduates stratified by body fat and physical fitness. This study suggested that the gut microbiota plays a role in mediating the protective effects of exercise against type 2 diabetes, at least in part.

Gut microbiota adapts to external factors

The gut microbiota has co-evolved in symbiosis with humans, adapting to the host gut environment and external disturbances. Antibiotic treatment, although being the primary defense against pathogenic bacteria, often leads to drug resistance owing to chronic misuse. Tetracycline repressor (TetR), a broad class of transcriptional regulators, controls the genes that confer tetracycline resistance (Ramos et al., 2005). In *Pseudomonas aeruginosa*, a common cause of hospital acquired infection (Longo et al., 2013), over 38 genes encode TetR-type proteins. Pseudomonas virulence regula-

tor A (PvrA), encoded by the gene *PA2957*, is a new TetR activator in *P. aeruginosa*. Recent findings reveal that PvrA directly upregulates genes involved in phosphatidylcholine consumption during *P. aeruginosa* infection (Pan et al., 2020). Previous work demonstrated that PvrA directly binds to specific DNA locations within promoter regions to regulate the production of genes governing fatty acid breakdown (Pan et al., 2020). However, the specific structural information underlying PvrA's activation process remains unknown, limiting our understanding of PvrA's critical functional role in *P. aeruginosa*. Zhu et al. discovered that PvrA binds to multiple pseudo-palindromic sites simultaneously for effective transcription activation. Their findings illuminate the unique mechanism through which PvrA controls virulence and global stress in *P. aeruginosa*, advancing our knowledge of the relationship between TetR family structure and function and providing new insights into the mechanism governing *P. aeruginosa* virulence.

Globally, tobacco smoking is a prevalent and harmful habit that increases the risk of several diseases, including cancer, heart disease, liver disease, and chronic obstructive pulmonary disease. While the detrimental health impacts of tobacco use have been extensively studied, recent research indicates that gut microbial dysbiosis may be a significant factor in these results (Fluhr et al., 2021). Many components of tobacco smoke, including nicotine, are present in the gastrointestinal system and interact with the gut microbiota, causing long-term effects on host health and disease (Chen et al., 2022). Chen et al. summarized how the various components of tobacco use impact the composition and function of the gut microbiota. They provided an overview of recent developments in our understanding of the effects of tobacco smoking-induced dysbiosis of the gut microbiota on host health, as well as a new perspective on how changes in the gut microbiota after quitting smoking may be associated with withdrawal symptoms and improvements in smokers' health.

Bioactive microbial metabolites regulate host metabolism

Recent years have seen a growing recognition of the profound impact of gut microbiota and metabolites on human health, thanks to the advanced techniques of multiomics analysis such as metabolomics and metagenomics. The interaction between the host intestinal epithelial tissue and gut microbiota leads to the production of various bioactive metabolites, including trimethylamine N-oxide, branched-chain amino acids, bile acids, and short-chain fatty acids, all of which play significant roles in numerous metabolic diseases (Qu et al., 2023). Understanding the intricate dynamics between the gut microbiota and the host intestinal epithelium holds promise for identifying novel molecular targets for treating metabolic disorders. Bile acids, synthesized from cholesterol in the liver and secreted into the intestine with bile, undergo further modifications by the gut microbiota, enhancing their diversity. Bile acids are pivotal in nutrient absorption and serve as key regulators of lipid and glucose metabolism, as well as immune homeostasis (Cai et al., 2022). They primarily participate in host metabolism by binding to specific receptors, including membrane receptors like TGR5 and nuclear receptors like FXR (Sun et al., 2021). In their article, Jia et al. explore the far-reaching effects of bile acid-mediated metabolic and immune control throughout the body, spanning the liver, intestines, eyes, brain, skin, adipose tissue, and muscles. They advocate for a focus on receptor signaling and bile acid production as a promising avenue for developing cutting-edge treatments for various systemic illnesses.

Remark

The significant progress in basic research on gut microbiota can be largely attributed to the advent of technologies. However, the practical application of gut microbiota-based clinical therapies is currently progressing at a slower pace. Holistic interventions such as fecal bacteria transplantation carry risks, and prolonged antibiotic treatment could lead to the emergence of drug-resistant bacteria. There is an urgent need for more comprehensive research to identify the critical metabolites and functional molecules that the gut microbiota contributes to host metabolism. This would support the development of targeted clinical intervention strategies and potentially revolutionize the treatment of a range of conditions.

Compliance and ethics

The author(s) declare that they have no conflict of interest.

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Prof. Changtao Jiang, vice dean of the School of Basic Medical Sciences of Peking University, chairman of the Department of Immunology. He proposed a new theory of "Intestinal microbial enzymes regulate host homeostasis across kingdoms." He presented for the first time the concept of gut Microbial-Host isozymes (MHIs), identified the bacterial-derived isozyme dipeptidyl peptidase 4 (DPP4) and highlighted its important role in metabolic diseases. He identified an endogenous nicotine-degrading gut microbiota and proposed a novel intervention strategy for gut bacteria to alleviate metabolic diseases through the nicotine-degrading enzyme NicX. He revealed the role of various bile acid metabolizing enzymes in the regulation of metabolic diseases. In the past 5 years, Prof. Changtao Jiang has published more than 20 SCI papers in *Science*, *Nature*, *Nature Medicine* (3 articles), *Cell Metabolism* (3 articles) and other journals as the corresponding author. Among these, four articles were selected as highly cited papers, one article received an F1000 Prime recommendation with the highest rating score, and eight articles gained recommendations from internationally renowned scholars and contemporaneous reviews. He received the Xplorer Prize, China's top 10 advances in life sciences in 2023, the China Youth Science and Technology Award, the Shulan Medical Young Scientist Award, the Chinese-American Diabetes Association (CADA) Young Investigator Award, the Mao Yisheng Beijing Youth Science and Technology Award and other awards. He is in charge of the projects supported by the Key Program of the National Natural Science Foundation of China, the Major Research Plan of the National Natural Science Foundation of China and the National Key Research and Development Program of China. He is the principal investigator for a project supported by the Science Fund for Creative Research Groups of the National Natural Science Foundation of China.