Editorial

Age-specific microbiota in altering host inflammatory and metabolic signaling and metabolome based on sex

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We read the recent study, "*Age-specific microbiota in altering host inflammatory and metabolic signaling as well as metabolome based on the sex*", published in *Hepatobiliary Surgery and Nutrition* about the effects of sex-dependent changes in gut microbiota on age-related metabolic disease (1). The authors examined the relationships between fecal microbiota and age-dependent metabolic phenotypes in both sexes and demonstrated the efficacy of fecal microbiota transplantation (FMT) in altering insulin sensitivity depending on the sex of the recipients.

Aging is considered a state of low-grade inflammation without clear etiological factors, and is accompanied by many age-associated pathologies, including both gastrointestinal and non-gastrointestinal pathological diseases, such as metabolic issues (2). In the study, the authors observed that aging increased the expression of inflammatory signaling and reduced the expression of metabolic signaling and insulin sensitivity in both sexes. Age-associated inflammation is an important risk factor for overall mortality in older adults. Individuals with higher than age-average levels of inflammatory markers are more likely to have a variety of diseases (3). Despite the clinical importance of age-related inflammation, the etiology responsible for its development has not yet been identified.

The human gut microbiota is a complex ecosystem harboring trillions of microbiota whose number is somewhere between 10^{13} and 10^{14} (4). Microbes are established from birth and become more diverse and variable with advancing chronological age (5). Many studies have shown that the gut microbiota is not only involved in human physiology but also affects host immune regulation and metabolism and regulates local or systemic inflammation (6,7). It has been reported that aging and age-related metabolism in humans is associated with the composition and diversity of intestinal microbiota (8). Cross-sectional studies of fecal samples from individuals in different age groups suggest that gut microbiota in adults is highly individual and specific (9). With advancing chronological age, overall richness decreases, and a certain group of the gut microbiome has been identified in the elderly populations associated with frailty increases. This change may be related to the deterioration of the intestinal mucosal barrier and chronic low-grade inflammation in the elderly.

Growing data showed that the age-related changes in the microbiota led to increased permeability in the colon and caused inflammatory response, further affecting metabolic diseases (10,11). In Drosophila intestinal epithelial cells, a dysregulated proliferation of intestinal stem cells increases with aging with the loss of the selectively permeable intestinal barrier, leading to increased infection and mortality (12). Transferring gut microbiota from aged mice to young germ-free mice triggers innate immune and inflammatory responses similar to "inflammation" (13). Age-related inflammation and dysbiosis of the microbiota drive gut permeability and increase levels of inflammatory mediators in circulation (14). In the article, the authors observed that aging reduces glucose and lipid metabolism regulators, such as sterol-regulatory element binding protein-1C, fatty acid synthase, and *Cyp4a10*, which suggested abnormal glucose and lipid metabolism. The mitochondrial biogenesis-related genes, such as silent

mating type information regulation 2 homolog, cytochrome oxidase subunit IV, citrate synthase (Cs), and estrogen-related receptor α, exhibited metabolic abnormalities. It has been suggested that changes in gut microbiota may contribute to aging and age-related diseases; however, the causal relationship between aging and changes in gut microbiota remains controversial.

Additionally, the authors observed that aged male mice were the most insulin-resistant group, while young female mice were the most insulin-sensitive group. When aged FMT (AFMT) was performed using aged male feces, aging was found to shift fecal microbiota composition, and alterations in microbial function with aging were found to be sex specific. AFMT only induced insulin resistance in female mice, and the sex difference in terms of insulin sensitivity was narrowed. Notably, Gao *et al.* found that gender differences in gut microbiota and glucose metabolism did not appear before sexual maturity, and only appeared in adulthood, indicating that sex hormones may be an initiating factor (15).

A previous study showed that the prevalence of diabetes in adult males is significantly higher than that in females, especially before the age of 55, which suggests that there may be gender differences in the occurrence and development of diabetes (16). The results of animal experiments have also shown that the glucose metabolism of male mice is worse than that of females, but the exact reason for this is unclear (15). A metagenomics study of Chinese diabetic patients published in *Nature* in 2012 found that changes in gut microbiota are associated with type 2 diabetes (T2D), and genes related to butyrate synthesis are lacking in the intestinal bacteria of T2D patients (17). Targeting age- and sex-specific microbiota community structure may be an effective approach to preventing and treating metabolic diseases.

The treatment of different kinds of diseases via interference with the host microbiota has begun to attract more attention. Currently, a wide variety of FMT is used to normalize the composition and gain a therapeutic benefit. The first records of FMT have been traced back to the Dong-Jin dynasty in China, where human fecal material, called yellow soup, was used for patients with severe diarrhea (18). Later, a similar therapy was used in the treatment of gastrointestinal or non-gastrointestinal diseases, including age-related metabolic conditions (19). In 2012, the United States Food and Drug Administration classified FMT as a new investigational therapeutic option in the treatment of particular diseases. Several cohort studies have sought to apply FMT to multiple fields of gastrointestinal and extra-gastrointestinal disorders (20). Aging-related metabolic diseases, such as insulin resistance, are the early and most common field in FMT. Further, it has been shown that transferring microbiota via fecal transplantation evoked alterations in insulin sensitivity in both rodents and humans (21). However, response rates of FMT are not satisfactory and a great majority of FMTs have only been applied in animal experiments, and clinical research is lacking.

Several factors may continuously alter microbiota diversity and function. First, in addition to gut microbial composition, the genetic composition of microbial genomes also changes dynamically over time. Microbial genome changes due to species evolution and strain substitution, such as single-nucleotide mutations and the gain or loss of genomic regions, have been implicated in the development of human disease. However, studies on changes in microbial genetic composition over time are still lacking. Second, while cross-sectional association analyses have reported associations between many microbiome features and host health and disease, they often lack longitudinal (i.e., temporal) validation over long periods. Third, given the widespread use of antibiotics in recent decades, other bacterial derivatives, including antibiotic resistance and virulence factors, have become a major concern. However, the time-dependent trends of related microbial derivatives have not been clearly revealed, hindering the effective control of bacterial infections.

In summary, research on gut microbiota is in its infancy, and many questions remain, such as: Which bacterial traits are both individually specific and temporally stable? Is it possible to use these features as "fingerprints" to distinguish samples from the same person? Which bacterial signatures exhibit large temporal changes? Could their temporal changes be linked to changes in the host's clinical phenotype and lifestyle? Long-term prospective studies need to be conducted to determine the role of the gut microbiota in the development of chronic human diseases. Currently, FMT is the best-validated model for determining the causal relationship between microbiome alterations and disease pathogenesis.

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