Editorial Commentary

Gut microbiome evolution impacts the clinical outcomes of diseases

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The human digestive tract is home to trillions of microbes, and owing to the advent of next-generation sequencing at the turn of the century and the development of bioinformatics technology, researchers have been able to unravel the picture of the gut microbiome (1). The role of gut microbes in diseases is a hot topic. Among the topic-oriented answers, species abundance and richness are the most widely discussed. However, in many cases, before changes in composition and abundance appear, notable gut microbiome evolution has already occurred, which significantly affects disease outcomes.

The core of the standard evolutionary theory lies in the stable inheritance of genetic variation through DNA. Common forms of genetic variation include single-nucleotide substitutions [single nucleotide polymorphism (SNP)/single nucleotide variant (SNV)], short insertions/deletions, structural variants (SV), copy number variation, and simple sequence repeats (2). Mutations may occur at any time, especially when there are certain stimuli. For example, perturbation of endocrine function might accelerate the accumulation of somatic cell mutations, inducing a wide range of malignancies (3). These mutations occur not only in humans but can also be seen in various creatures, subtly influencing people's health. For example, severe acute respiratory syndrome coronavirus 2, the causative agent of the global pandemic, possesses various spike protein mutations, enabling greater immune-evasion capabilities over time, thus resulting in recurrent peaks of infection (4). There are numerous similar examples. Contributing to shotgun metagenomics, the identification of these mutations has become a new norm in bioinformatics research.

In 2019, Garud *et al.* reported the paradigm of gut bacterial evolution. They quantified the evolutionary dynamics within individual hosts and across the larger population and successfully proved the existence of both short-term and long-term evolution (5). In the corresponding period, Zeevi *et al.* detected 7,479 SVs in 56 species from 887 human gut microbiome samples and elucidated the distinct genetic functions as a result of these mutations (6). Zhao *et al.* demonstrated that the stable acquisition of *Bacteroides fragilis* point mutations produces beneficial biological effects in healthy people owing to within-host adaptation (7). Their discoveries ascertained gut microbiome mutations, highlighted the adaptive evolution of gut microbes, and paved the way for a new dimension of the relationship between gut microbiomes and health.

The evolution of the gut microbiome has been spotted in many diseases. In type 2 diabetes patients, while the abundance of *Bacteroides coprocola* shows few significant differences from healthy controls, a striking enrichment of SNPs is observed (8). In inflammatory bowel disease (IBD) patients, a G>A SNV of *Escherichia coli* leads to Blc G84 conversion and potentially contributes to *E. coli* enrichment in the feces (9). The scope of this matter goes far beyond what has been presented here.

Many underlying mechanisms remain unknown. Given

the high mutation rate observed, a considerable amount of research is required to elucidate the precise role of microbiome evolution in disease.

The complicated causality between the gut microbiome and various diseases is currently being investigated. Several theories seem convincing. According to Van Valen's "Red Queen Hypothesis", the adaptation of a species is accompanied by counteracting adaptations of other interacting species. Microevolutionary dynamics arise from biotic conflicts, and biotic drivers promote macroevolution (10); this is also true for gut microbiomes. As gut ecology changes, microbial populations undergo co-evolution, leading to the development or reversal of diseases. Huang *et al.* confirmed the effect of gut selection pressure on the genetic stability of *Lactiplantibacillus plantarum* in humans. Non-synonymous mutations in its gene related to glycosidase emerged over time. Simultaneously, its ecological competitors, such as *Bacteroides* spp. and *Bifidobacterium* spp., accumulated adaptive mutations, characterizing the co-evolution of the resident microbiome. Improved carbohydrate utilization and acid tolerance can be observed during this process, possibly reducing the production of proinflammatory factors while activating anti-inflammatory cytokines in IBD (11,12). This study suggests that the organic linkage between microbes and the gut environment is a non-negligible part of health and diseases. The manifestation of a disease phenotype may be attributed to complex trans-kingdom networks underlying its pathogenesis. The macrocosm of the network is mirrored in the subliminal changes in microbes, metabolites, and immune factors, inducing immense chain reactions in disease onset, progression, and remission.

Deeper insights into the association between gut microbiome evolution and disease may revolutionize disease prediction, diagnosis, and treatment. Ma *et al.* built a colorectal cancer predictive model based on 22 SNVs belonging to four species after analyzing sequencing data of Japanese, Australian, and Italian individuals, the accuracy of which has been proven (13). Yang *et al.* identified the within-host evolution of *Enterococcus gallinarum*. Lineages in different digestive tract segments develop distinct functions; some tend to evade immune detection and elimination, and some are able to translocate across the epithelium into lymph nodes and the liver, possibly prompting gut and liver inflammation (14). These vivid examples strongly imply the tremendous potential of identifying genetic mutations in clinical medicine. Compared with invasive diagnostic techniques such as biopsy, fecal samples are more accessible, which can prevent secondary infection and many other side effects of invasive auxiliary examinations. Novel diagnostic models can be constructed if sensitivity and specificity are guaranteed, allowing definite diagnosis and outcome prediction from the genetic perspective. The mutation information of gut microbiomes can also be used in treatment. As a measure of disease prevention, specially designed diets can be adopted to acclimate microbes to advantageous gut ecology. The elimination of specific microbes before liver transplantation and other operations may enhance disease outcomes. Fecal microbiome transplantation (FMT) still has many side effects and yields unsatisfactory results despite its application in the treatment of various diseases, such as neurological and psychiatric disorders, gastrointestinal diseases, metabolic disorders, and cancers (15). If certain strains are chosen based on individuals' gut microbiome evolution patterns in FMT, desirable metabolic or immunologic effects might be realized, thus boosting therapeutic efficacy and reducing side effects.

In summary, tracing gut microbiome evolution would be revolutionary in the era of precision medicine. Therefore, it is important to add the dimension of evolution to gut microbiome studies, not only for fulfilling the picture of the gut microbiome kingdom but also for individualized disease prediction, prevention, and treatment. In the near future, the utilization of genetic variations of microbiomes might be part of people's daily health care.

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Footnote

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aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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