Editorial

Targeting the gut microbiome for non-communicable diseases: present and future

Subhashree Shivani[1], Amrita Chattopadhyay[2], Eric Y. Chuang[1,2,3]

[1]Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei; [2]Bioinformatics and Biostatistics Core, Centre of Genomic and Precision Medicine, National Taiwan University, Taipei; [3]Biomedical Technology and Device Research Laboratories, Industrial Technology Research Institute, Hsinchu

Correspondence to: Eric Y. Chuang. Department of Electrical Engineering, Graduate Institute of Biomedical Electronics and Bioinformatics, National Taiwan University, Taipei 10617. Email: chuangey@ntu.edu.tw.

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In the 19th century, Dr. William Coley (the father of immunotherapy) mixed streptococcal bacteria with medicine and successfully treated a patient with inoperable sarcoma (1). The idea was to stimulate an immune response due to the bacterial infection, which presumably helped in treating the cancer. Although chemotherapy and radiotherapy eclipsed this field of research, their adverse effects have rekindled research into bacterial therapy. The human body is inhabited by trillions of symbiotic bacteria and microbes that coevolved with human beings. Bacterial metabolites and bacteria-host interactions shape the biological well-being of the host by actively impacting multiple host functions. One of the important consequential abodes of bacteria is the gut. Thanks to the rapidly growing sequencing industry, scientists are extensively studying the composition of gut microbiota in relation to various demographic and clinical characteristics such as geography (2), sex (3), age (4), dietary habits (5), and body mass index (6).

Many studies have revealed the susceptibility of gut microbiota to a host's diseases (7,8). Some studies have also shown the role of gut microbiota in modulating host response to immune checkpoint inhibitor cancer immunotherapy (9). Determination of healthy gut microbiota baselines is beneficial in tracking dysbiosis in many chronic non-communicable diseases such as Alzheimer's (10), kidney disease (11) and schizophrenia (12). As the microbiome plays an integral part in the metabolism of its host, recognizing the effect of a dysbiotic microbiome in diseases could help in providing alternate therapy. Gut microbiota can directly modulate coronary artery disease by producing bile acids, coprostanol, short chain fatty acids, and trimethylamine-N-oxide, or indirectly by manipulating the immune system (13). In cardiovascular disease (CVD), heart failure has been associated with specific gut microbial species like *Escherchia coli*, *Klebsiella pneumoniae* and *Streptococcus viridian* (14). In another study, author showed altered gut microbiota in patients with symptomatic strokes and transient ischemic attack with increased abundance of *Enterobacter*, *Megasphaera*, *Oscillibacter* and *Desulfovibrio* (15). In the case of chronic kidney disease, a dysbiotic gut microbiome produces excess uremic toxins such as phenols and indoles, which can't be completely removed during dialysis and lead to further complications (16). Wilkins *et al.* identified *Bacteroides*, *Corynebacterium*, *Anaerococcus*, *Prevotella*, *Rothia*, *Sutterella*, *Eubacterium*, *Fusobacterium*, *Leptotrichia*, *Parabacteroides*, *Peptoniphilus*, *Porphyromonas*, and *Veillonella* bacteria as the major genera associated with kidney diseases (17). Shen *et al.* compared the gut microbiota of 64 schizophrenic patients with 53 healthy individuals, aiming to identify potential biomarkers for schizophrenia (18). They identified changes in Gammaproteobacteria (class-level), Enterobacteriales (order-level) and *Bacteroides fragilis* (species-level) with potential association with schizophrenia. Zheng *et al.* demonstrated that germ-free mice receiving a fecal microbiome transplant from a schizophrenia patient exhibited lower glutamate and higher glutamine and GABA in the hippocampus and displayed schizophrenia-like behavior (19). They also identified a panel of *Aerococcaceae*, *Bifidobacteriaceae*, *Brucellaceae*, *Pasteurellaceae*, and *Rikenellaceae* bacteria with the capability to distinguish

schizophrenia patients from healthy controls. Alzheimer's disease involves deposition of amyloid beta (Aβ) in the brain followed by formation of plaques and neurofibrillary tangles composed of hyperphosphorylated tau protein (20). These amyloid deposits are responsible for neuroinflammation leading to synapse loss and neuronal death (21). Gut *Escherichia coli* is a source of curli, a bacterial amyloid (22), and it has been shown that rats exposed to curli-producing *E. coli* displayed increased neuronal alpha-synuclein deposition in both the gut and brain, and enhanced microgliosis and astrogliosis compared to rats exposed to bacteria unable to produce curli (23).

Identifying the gut microbiota through 16srRNA sequencing is the first step in microbial therapy. Considering the role of gut microbiota in pathways pertaining to multiple diseases, researchers are targeting the involved gut microbiota for potential therapy. Wang *et al.* showed how a gut microbiota imbalance facilitates infiltration of the brain by peripheral immune cells, contributing to cognitive impairment by enhancing microglial activation (24). GV-971, a sodium oligomannate that has shown cognitive improvement in phase 3 trials in China, reverses cognitive impairment by suppressing gut dysbiosis and associated phenylalanine/isoleucine accumulation.

In another study, targeting the gut microbiome for kidney diseases, Devlin *et al.* described a novel approach to reduce the production of indoxyl sulfate (25). Using computational methods, the authors identified a tryptophanase gene present in some bacteria species colonizing the gut. Tryptophanase helps produce indole, a precursor to indoxyl sulfate, using tryptophan. Upon colonizing germ-free mice with mutant bacteria harboring the deleted tryptophanase gene, authors observed no detectable serum or urinary indoxyl sulfate in the germ-free mice, in contrast to mice with wild-type bacteria. To determine if dietary intervention could alter the relative abundance of indole-producing species, the authors colonized mice with both indole producer (wild-type *Bacteroides theta*) and non-indole producer (wild-type *B. caccae*) bacteria. A diet rich in fructo-oligosaccharides (favors growth of *B. caccae*) shifted the bacterial community structure and decreased urinary indoxyl sulfate levels.

Gut microbiota have emerged as a powerful alternative for therapy for complex diseases. Modulating the gut microbiota has efficiently suppressed disease complications in mouse models. Although this field is gaining momentum rapidly, this field of research is still in its infancy. The major challenge is confirming the dysbiosis of the gut microbiome as a cause or consequence of the disease. Also, along with gut microbiota, other host factors such as genetics and geography might play an important role in the efficacy of microbial therapy. Understanding the interactions between different bacteria in the gut and in the diseased sites is also important to optimize therapeutic conditions. In conclusion, understanding the complex interactions of targeted bacteria with their surroundings and the host is required to optimize the overall impact of bacterial therapy in the host and minimize side effects. Whole genome sequencing and a multi-omics approach is needed to unveil bacterial structure and mechanisms and broaden our understanding of host-bacteria interactions. Resolving these challenges will bring the use of bacterial therapy to its maximum potential and possibly initiate a new era of truly personalized medicines.

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