VIEWPOINT

SCIENTIFIC DISCOVERY AND THE FUTURE OF MEDICINE

Manipulating the Human Microbiome to Manage Disease

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More than a decade after the launch of the Human Microbiome Project, research in this field has grown exponentially, with studies associating microbial states or species with disorders including novel infectious etiologies and complex human disease. Scientists are searching for the potential utility of the microbiome (the community of bacteria, fungi, and viruses in an environment), with particular focus on manipulating microbial communities as novel therapeutic modalities. This Viewpoint highlights current applications of microbiome science to human health and examines successes and remaining challenges.

Fecal microbiome transplantation (FMT) has demonstrated the potential for normal human-associated microbes to ameliorate or even cure disease. In 2013, van Nood et al[1] reported the results of a single-center trial that used duodenal infusion of donor feces to manage recurrent *Clostridioides difficile* infection (CDI; formerly known as *Clostridium difficile*). Forty-three patients were randomized to receive FMT, oral vancomycin, or vancomycin plus bowel lavage. The trial was terminated early when FMT was deemed more effective than antibiotic therapy, with 13 recipients (81%) cured by a single infusion. In total, 15 participants (94%) who received FMT had resolution of CDI compared with 4 (31%) who received antibiotics alone and 3 (23%) who received antibiotics plus lavage. Additional studies have shown that FMT can be used to treat CDI. However, questions about the how and why of the clinical effectiveness of FMT remain unanswered. For instance, do donor strains stably colonize the gut? Are complex communities of fecal microbes required for success? Mechanistic studies are required to understand the differential responses in FMT recipients as well as safe therapeutic and experimental implementation, given the potential for FMT-related transmission of serious viral infections or multidrug-resistant bacteria.

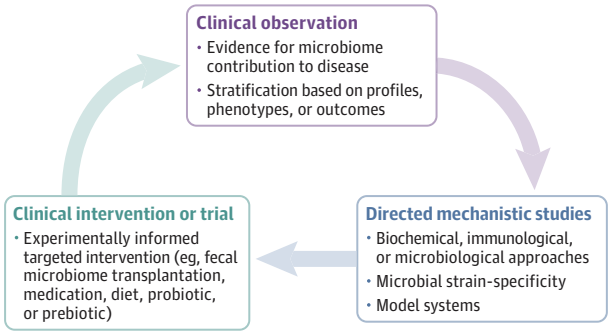
The promising results with CDI have prompted researchers to investigate FMT as a treatment for individuals with inflammatory bowel diseases, generating some modest and mixed results. A multicenter trial randomized 73 patients with ulcerative colitis with mild to moderate disease to receive either donor or autologous FMT.[2] Twelve donor FMT recipients (32%) achieved the primary end point of steroid-free remission at 8 weeks compared with 3 autologous FMT recipients (9%). While donor FMT may represent a new therapeutic modality for managing ulcerative colitis, patient outcomes with donor FMT and standard systemic immunosuppression have generally been equivalent. The lack of understanding of how the microbiome contributes to inflammatory bowel disease pathogenesis and the limited results with FMT suggest that manipulation of complex microbiome communities in inflammatory disease will be challenging. Development of effective interventions will require deeper understanding of disease pathophysiology, including stratifying disease groups based on microbial profiles to interpret outcomes.

The complexity of microbial communities, in terms of the number and percentage of different species in an environment, could be a critical factor in identifying a tractable intervention to alter microbiomes. For example, a disease with low microbiome complexity, whether inherent or antibiotic-induced, may be easier to return to health. The vaginal microbiome exemplifies a less complex microbiome than the gut. Bacterial vaginosis is characterized by anaerobic species predominance over typical lactobacilli. This prevalent disorder is associated with high recurrence and antibiotic treatment failure rates. In a preliminary study of vaginal microbiome transplant in patients with chronic bacterial vaginosis, long-term remission occurred in 4 of 5 patients and lasted up to 21 months.[3] Three patients required repeat transplant for remission, 1 of whom needed an alternate donor. This study suggests that alteration of even chronically imbalanced microbiomes is possible. Similar to FMT studies, greater insight is needed to elucidate the biological variables involving both host and donor that influence therapeutic success.

Microbial intervention of a single bacterial strain was demonstrated to be effective in altering disease risk in the low-complexity microbiome of the newborn gut. In 2017, Panigrahi et al[4] reported findings from a randomized, double-blind, placebo-controlled trial of 4556 infants that evaluated the effect of probiotics on neonatal sepsis in rural India. For 1 week perinatally, infants received daily oral supplementation of a probiotic bacterium (*Lactobacillus plantarum*) combined with a prebiotic (fructo-oligosaccharide) to augment Lactobacillus growth or placebo. Probiotic plus prebiotic therapy led to a 40% reduction in combined outcomes of neonatal sepsis and death (absolute rate of 5.4% vs 9.0% with placebo), and an interim analysis conducted midway through the trial resulted in termination of the study for benefit. The final number needed to treat to prevent 1 instance of sepsis was 27. Extensive prior investigations to select the specific probiotic strain with the ability to colonize guts of infants in the same population were critical to the study's success. Other interconnected factors contributed to the positive outcomes of the study, including geographical location, nutrition, socio-economic status, and high prevailing neonatal sepsis rates in the region. Thus, the finding that probiotics are beneficial cannot be generalized to all newborns.

There is also substantial interest in how diet influences the microbiome and development of diseases, such as obesity and type 2 diabetes. A study by Zeevi et al[5] demonstrated that postprandial glycemic response to diet

Figure. Translating Microbiome Science Into Clinical Practice



in 800 participants were specific to individuals, determined by combinatorial effects of biochemical, clinical, and microbiome attributes. The individuality of postprandial glycemic response could subsequently be predicted by a machine learning algorithm, which was applied to develop individualized diets for sustained normalization of glycemic response. More generalizable microbiome features were demonstrated when Gehrig et al[6] examined 343 Bangladeshi children with severe acute malnutrition. With standard nutritional supplementation, children with severe acute malnutrition converted to chronic moderate acute malnutrition, but without improvement in long-term developmental sequelae. Serial blood metabolite and gut microbiome profiling in this cohort of children treated for severe acute malnutrition demonstrated correlation between specific intestinal bacterial species and biomarkers of growth.[6] Findings from animal models informed the randomized trial of dietary supplements in 63 children with moderate acute malnutrition, in which 1 combination produced proteome profiles that more closely resembled the profiles of healthy children.[6] These studies demonstrate the potential of beneficial dietary manipulation on the microbiome and illuminate the need to study the complex nature of these diet-microbe-host interactions.

High-profile studies have correlated different clinical outcomes with microbiome-drug interactions. For instance, response to immune checkpoint therapy in patients with melanoma has been linked to distinct gut bacterial profiles.[7] However, these human studies have not yet demonstrated that this is a modifiable factor for disease outcome. In individuals with Parkinson disease, peripheral metabolism of levodopa to dopamine in the gut is well known and problematic. Despite coadministration of decarboxylase inhibitors to inhibit this metabolism, response to levodopa remains variable among patients with Parkinson disease. Maini Rekdal et al[8] identified specific enteric bacterial species, *Enterococcus faecalis* and *Eggerthela lenta*, which contribute to clinical heterogeneity through Levodopa decarboxylation. The investigators determined that variants of bacterial decarboxylase enzymes, present within only specific strains, influenced gut dopamine metabolism and demonstrated the ability to inhibit *Enterococcus faecalis* and *Eggerthella* decarboxylation of levodopa with an alternate decarboxylase inhibitor.

Based on the clinical insight that bacterial vaginosis is associated with higher rates of HIV acquisition, Klatt et al[9] studied the potential influence of vaginal microbiome on effectiveness of topical prophylaxis with tenofovir in in South African women. Women with bacterial vaginosis had a 3-fold reduction in the efficacy of tenofovir in reducing HIV incidence compared with women with normal *Lactobacillus* dominant vaginal profiles, with HIV incidence rates of 14 of 219 women vs 9 of 331. In vitro testing revealed that *Gardnerella vaginalis* metabolized tenofovir and rendered the drug inactive, explaining the reduced efficacy, which was independent of medication adherence. Studies such as these exemplify how hypotheses generated from clinical observations can be integrated with microbiome research to provide molecular insights with translational application.

Some common themes have emerged from microbiome studies that have demonstrated clinical utility. First, complexity matters. Successful examples of transplant have involved low-complexity biomes, either in an infectious state dominated by a single pathogen or in vaginal or infant microbiomes. Second, bacterial strain level resolution is important. Bacterial strain selectivity potentially underlies why microbiome transplant frequently necessitates repeat application from alternate donors. Third, disease state is crucial. Before adopting microbiome intervention for management of conditions such as inflammatory or chronic diseases, researchers need a better understanding of the roles microbiota have in initiation, maintenance, and progression of disease (**Figure**). Only through basic mechanistic research informed by fundamental clinical questions will the field progress to the large clinical trials needed to understand the translation of microbiome science, achieving the ultimate goal of precision medicine.

ARTICLE INFORMATION

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