The Microbiome Hype
Integrative analyses of metagenomics, metatranscriptomics, metaproteomics, and metabolomics have provided unprecedented insight into the physiologic role of the human microbiome in health and disease. Studies using genome-scale metabolic networks and metagenome-assembled genomes reveal that several metabolic pathways in humans are the result of the combined activities of the human genome and microbiome. A recent study showed that gut microbiota associate with 38 self-reported common diseases and 51 medications (1). Changes in the gut microbiota could promote CKD progression through alterations in immune response, BP regulation, and metabolic changes. In this Perspective, we focus on the recent advances in the field of microbiome that are relevant to kidney disease.

Dysbiosis in CKD
The concepts of “niche partitioning” and “functional redundancy” are highly relevant to the shaping of microbiome in CKD. The former refers to the process by which competing species use the environment differently, permitting them to coexist. Functional redundancy is a mechanism by which many phylogenetically unrelated taxa carry similar genes and perform similar functions. It is possible that CKD milieu results in loss of “key taxa,” shifting the community structure. The resulting dysbiosis drives CKD progression through a generation of a multitude of uremic toxins. Impaired protein digestion in CKD results in delivery of undigested protein to the colon, which fosters the preferential proliferation of bacteria with urease and uricase enzymes and taxa involved in indole and phenol metabolism. Concomitant reduction in saccharolytic bacteria leads to reduced generation of short-chain fatty acids (2), which are involved in energy homeostasis, maintaining gut barrier, BP control, and immune regulation.

Dysmetabolism in CKD
Protein catabolism by gut microbiota is generally viewed as detrimental because it results in production of toxins, such as ammonia, amines, phenols, indoles, and sulfurous compounds, which accumulate in CKD. Gut microbiota convert tryptophan to indole and indole derivatives, such as indoxyl sulfate. Bacterial fermentation of the aromatic amino acids tyrosine and phenylalanine generates phenolic compounds, such as p-cresol sulfate. Dietary choline can be metabolized to trimethylamine by the microbiota, which is oxidized in the liver to trimethylamine N-oxide. Several studies have shown that trimethylamine N-oxide alters cholesterol transport, promotes formation of foam cells, and exacerbates atherosclerosis.

Members of Lactobacilli, Bifidobacteria, and Clostridia genera can deconjugate bile acids and convert them to secondary bile acids, including deoxycholic acid and lithocholic acid. Deoxycholic acid is elevated in CKD and is directly toxic to vascular smooth muscle cells. Mechanistic studies have shown that microbiome-derived indoles, phenols, and amines could mediate CKD progression through glomerular and interstitial fibrosis.

It is becoming evident that elevated plasma levels of microbiome-derived uremic retention solutes in
CKD cannot be fully explained by differences in bacterial generation rates alone (5). Retention of these solutes due to decreased tubular secretion and, to a smaller extent, reduced glomerular filtration contribute to accumulation of these molecules in CKD (5).

**Microbiome Therapeutics**

With the expanding knowledge of the microbiome, recent efforts have sought to harness the power of microbiome for health benefit (Figure 1). These therapies could be broadly classified as (1) supplementing the host microbiota with fecal transplantation, specific strains of microbiota, or a consortium of natural or engineered micro-organisms; (2) elimination of specific deleterious members of the microbiota using nonspecific or targeted antimicrobials, such as bacteriocins and bacteriophages; (3) modulation of host microbiota by administration of agents, such as prebiotics; and (4) postbiotics that target downstream signaling pathways of the microbiome. Advances in orthogonal niche engineering in which uncommon/unused nutrients are employed has enabled engraftment of therapeutic bacteria.

For a probiotic to be effective, the bacteria should be able to colonize, proliferate, and be metabolically active in that environment. Furthermore, microbes are interdependent on each other for nutrients and signaling molecules, so the effective probiotic needs a supportive microbiome as well. These phenomena explain the mixed results seen with prebiotic and probiotic-based interventions in patients with CKD.

Cardiovascular disease contributes to CKD progression and remains the leading cause of death in patients with CKD. Researchers have explored several avenues to reduce trimethylamine N-oxide and stall the atherosclerotic process. Methanogenic archaea can use methylated amines, such as trimethylamine, as growth substrates. Colonization of ApoE−/− mice with *Methanobrevibacter smithii* resulted in a sustained reduction in plasma trimethylamine N-oxide concentrations and a tendency for reduction in atherosclerosis (6). 3,3-Dimethyl-1-butanol is a structural analogue of choline that inhibits trimethylamine lyases (7). 3,3-Dimethyl-1-butanol inhibits choline-induced endogenous macrophage foam cell formation and atherosclerotic lesion development in ApoE−/− mice (7). Flavin-containing mono-oxygenase 3 is the rate-limiting enzyme in the conversion of trimethylamine to trimethylamine N-oxide. Knockdown of flavin-containing mono-oxygenase 3 mice has been shown to attenuate atherosclerosis. Iodomethylcholine is a suicide substrate inhibitor, which selectively accumulates within gut microbes, reducing production of trimethylamine by inhibiting trimethylamine-lyase. In animal models, iodomethylcholine reduces kidney fibrosis and preserves kidney function (8).

**Figure 1.** Microbiome-based therapeutics and their site of action. Fecal transplants could be least specific with large-scale changes in microbial community, whereas engineered bacteria are specific. Recent advances in our understanding of the molecular basis for disease have enabled us to alter the function rather than change the microbiome profile. CVD, cardiovascular disease; DMB, 3,3-dimethyl-1-butanol; FMO3, flavin-containing mono-oxygenase 3; FMO3 KO, FMO3 knockout; SCFA, short-chain fatty acid; Th17, T helper 17 cell; TMA, trimethylamine; TMAO, trimethylamine N-oxide; Treg, T regulatory cell.
Knowledge about the biochemical pathways in disease and the microbiome has led to novel therapies. In the intestine, bacterial urease converts host-derived urea to ammonia and carbon dioxide, contributing to hyperammonemia. A consortium of eight bacteria, with minimal urease gene content, resulted in sustained reduction in ammonia production in antibiotic-treated mice (9). Tryptophanase, involved in the conversion of tryptophan to indole, is expressed by gut commensal Bacteroides. Delvin et al. (10) showed that indole production could be inhibited by deleting the tryptophanases or eliminating the bacteria carrying the enzyme. Bacterial catabolism of the sulfur-containing amino acids produces hydrogen sulfide, which could function as an endogenous signaling molecule and a substrate for mitochondrial energization. A high sulfur amino acid–containing diet resulted in post-translationally modified microbial tryptophanase activity and preservation of kidney function in a mouse model of CKD (11).

Advances in DNA technologies for the manipulation of microbial genome have permitted scientists to engineer smart bacteria that could deliver therapeutic molecules and reprogram host cells by delivering transcription factors. However, safety and biocontainment remain major concerns that have not yet been fully addressed. In our quest for microbiome therapeutics, we need to be mindful of the undesired propagation of genetically modified bacteria or genetic material into the ecosystem.

**Concluding Remarks**

The lack of large-scale metagenomic data has greatly impeded progress in understanding the role of the microbiome in CKD. Existing evidence indicate that dysbiosis drives the production of many uremic retention solutes. The field of microbiome therapeutics is transitioning from probiotic and prebiotic to postbiotics. The use of bacteria as engineered therapeutics is a rapidly evolving field that is poised to transform the management of many chronic diseases, including CKD. As we strive to decipher the language of microbiome, healthy skepticism is good, but we should be open to embrace true scientific discoveries and be prepared for future microbiome-based therapies.

**Disclosures**

D.S. Raj reports having other interests in or relationships with the American Association of Kidney Patients; serving in an advisory or leadership role for National Heart, Lung, and Blood Institute, National Institute of Diabetes and Digestive and Kidney Diseases, and Novo Nordisk; receiving research funding from the National Institutes of Health (NIH); and having consultancy agreements with, and receiving honoraria from, Novo Nordisk. The remaining author has nothing to disclose.

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**Author Contributions**

D.S. Raj was responsible for funding acquisition; and D.S. Raj and D. Shankaranarayanan conceptualized the study, wrote the original draft, reviewed and edited the manuscript, and were responsible for visualization.

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