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Integrated Metagenomics and Metabolomics Analysis in CKD

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Advanced renal failure alters the biochemical milieu of the gastrointestinal tract leading to leak gut. The leak gut leads to bacterial translocation causing micro-inflammation, abnormal immunity and production of noxious metabolites aggravating uremic toxicity. Several studies and our previous works, mainly by 16S rRNA gene sequencing, have indicated intestinal bacterial overgrowth with alterations in the gut microbiota diversity and composition in CKD patients. Increases of *Firmicutes* (mainly *Clostridia)*, *Actinobacteria* and *Proteobacteria* were noted in hemodialysis patients and decreases of *Bifidobacterium* and *lactobacillus* in peritoneal patients. Furthermore, shotgun metagenomics study also unveils changes in several gut microbes along with the progression of CKD. These findings explain the possibility of the gut microbiome as candidate biomarker for CKD and also a possible target for therapeutic intervention. Although 16S pyrosequencing studies of gut microbiota in CKD patients provided important strides in clinical microbiology at phylum or genus-level base; however, deep shotgun sequencing and metagenome-wide association studies have enabled more in-depth characterization and insights into the function of human microbiomes than 16S pyrosequencing with more detailed functional repertoire. Here we will discuss the alteration of intestinal dysbiosis associated with CKD and the current advances in the research of gut microbiota.

Fermentation of nutrients can derive noxious compounds from microbiome-host interaction: p-cresyl sulfate (pCS, from tyrosine), indoxyl sulfate (IS, from tryptophan), trimethylamine N-oxide (TMAO), from L-carnitine), short-chain fatty acid (SCFA, from starch), dimethylglycine (from choline), glutarate (from lysine) among others. In patients with CKD; however, gut dysbiosis along with multiple dietary restrictions and diminished renal excretion, display metabolite imbalance with possible biological function to health. These metabolites play critical roles in anti-tumorigenesis, anti-lipogenesis, anti-inflammation and endothelial vasodilatation. The possible roles of these metabolites on renal outcomes will be presented in this talk.

The dysbiosis of CKD gut not only alters the production of metabolites but also impairs intestinal epithelial barrier function leading to the translocation of endotoxin and impaired host immunity. *Bacteroides* and *Clostridium* can induce regulatory T cells and *Prevotella* can induce the production of Th17 Cells in the murine colon, elevating Th17-related cytokine levels in the serum of mice. Intestinal bacteria, through the breakdown of dietary fibers into SFCA, can active G protein-coupled receptors (GPCRs, expressed on hematopoietic stromal cells and intestinal epithelial cells) leading to induction of Treg cells, and can reinforce tight junctions to promote barrier function. This presentation will discuss the complex intersection between gut dysbiosis and metabolomic alteration in CKD patients.