# Preface to the human microbiome in urologic health and disease

We are very pleased to present this special issue of the *Annals of Translational Medicine*, "The Human Microbiome in Urologic Health and Disease." This issue developed from the Basic Science Symposium of the same name sponsored by the American Urological Association (AUA) Office of Research at the Annual meeting of the AUA on May 6, 2016. Speakers who presented at that symposium comprise the invited authors for this issue.

This issue provides a both a primer and advanced reflection of the many roles of the microbiome, both bacterial and fungal, in the function and dysfunction of the lower urinary tract. As discussed in this issue, the microbiome is ubiquitous, and is found even in the once-considered-sterile urinary system. Moreover, this bacterial and fungal 'occupation' of the urinary tract is multi-faceted, playing protective roles by outcompeting pathogens for necessary nutrients, producing antimicrobial substances, stimulating the immune and neuronal systems, and maintaining homeostasis of the mucosal environment, as well as playing the known deleterious roles associated with pathological infection.

As briefly summarized below, several articles spanning a wide range of microbiome-related topics are presented in this special issue.

Arora *et al.* explore the composition and roles of the gut and urinary microbiomes in chronic prostatitis/chronic pelvic pain syndrome (CP/CPPS). Although the absence of any identifiable bacterial infection is a hallmark of CP/CPPS, recent studies have detected bacterial ribosomal RNA in both chronic bacterial prostatitis and chronic non-bacterial prostatitis, and have correlated microbiome dysbiosis with symptom scores, disease severity, and disease sub-type. These findings present potential new diagnostic and therapeutic targets in CP/CPPS patients.

Schwanderer and Wolfe examine the association between bacteria and urinary stone disease (USD). The high rate of urinary tract infection (UTI) in urinary stone patients and multiple case series of culture-positive urinary stones, including stones composed of CaOx or CaPhos, associate microbes with stone formation. They also discuss whether these bacteria are causal, disease modifying or passively present remains to be determined. However, evidence that bacteria aggregate selectively to crystals, that their presence is associated with increased clumping of crystals, and that they stimulate incorporation of proteins into the stone matrix suggest a mechanistic rather than merely passive role for bacteria in stone formation.

Urinary stones is also the topic of a review by John Lieske and studies the utility of probiotics for prevention of urinary stones. In this review, Dr. Lieske discusses data showing that the intestines of animals on a high oxalate diet contain diverse communities of microorganisms that can function together to degrade and detoxify a large oxalate load. This suggests that the intestinal microbiome likely modifies gastrointestinal absorption of lithogenic substances and influences urinary stone risk. The challenge remains to determine whether probiotics or pharmaceuticals can be developed that induce risk-reducing microbiome dysbiosis.

The USD theme is extended by Marguerite Hatch, who presents a perspective on how the gut microbiota can impact urinary oxalate excretion in the context of hyperoxaluria, a major risk factor in kidney stone disease. This perspective delineates mouse model data suggesting that oxalate degrading bacterial, particularly *Oxalobacter*, play key roles in regulating urinary oxalate concentrations. Unfortunately very little is known about any of the factors that foster or repress the persistence of *Oxalobacter* colonization in humans or in experimental animals other than the sensitivity to certain antibiotics. Nevertheless, strategies to increase the number and activity of oxalate-degrading bacteria, particularly *Oxalobacter*, in patients prone to hyperoxaluria and kidney stones are clearly warranted and could have great clinical utility in patients prone to kidney stone disease.

The female urinary microbiome is the subject of a review by Brubaker and Wolfe, who consider the associations between female urinary microbiota (FUM), urinary health, and common urinary disorders. Though research on The FUM just began 5 years ago, it is becoming clear that that microbial dysbiosis is a useful concept for the consideration of human urinary disorders, including asymptomatic bacteriuria (ASB), UTI and certain forms of urinary incontinence (UI). Utilization of the enhanced quantitative urine culture (EQUC) protocol is encouraged to increase urinary bacterial detection of both known and suspected uropathogens. This review also queries whether the urinary microbiota may be clinically modified to prevent lower urinary tract disorders.

Challenges associated with studying the microbiome are presented by Bao *et al.* These challenges arise primarily from the sensitivity of the methodologies employed and the large potential for contamination when working with low abundance microbiomes. In particular, they relate that surgical instruments utilized to isolate urine may harbor nucleic acids that are not destroyed during sterilization; that *16S rRNA* gene sequencing does not distinguish between DNA originating from live or dead cells, and that many commercially available DNA purification kits are not designed to isolate the small quantities of microbial DNA that may comprise just 1/billionth of total DNA in human tissue. Strategies to address these challenges are also presented.

The 'flip' side of the bladder-microbiome equation is examined by Wu *et al*., who described the diverse antibacterial activities of bladder epithelial cells (BECs), particularly in response to challenges from the gut microflora that promote UTIs. As detailed in the review, BECs do not passively permit microbial infection; rather, extracellular and intracellular actions are activated by TLR4 and other pattern recognition receptors (PRRs) in BECs that provoke the immune system to combat bacterial invasion and expulse invading bacteria back into the bladder lumen following infection. Thus, although, they are the primary targets of microbial attack, BECs appear to be equipped with a diverse repertoire of defense schemes to fend off many of these microbial challenges. Moreover, these defense mechanisms may be amenable to pharmaceutical augmentation.

The fungal microbiome, or mycobiome, is the subject of a review by Ackerman and Underhill. They examine the composition and functions of fungi, rather than bacteria, in the human urinary tract. They demonstrate that the mycobiome is an important but understudied component of the human microbial ecosystem. Culture-independent approaches, such as next-generation sequencing methods, have discovered specific, characteristic commensal fungal populations present in different body sites. Early evidence suggests the urinary mycobiome is a diverse community with high intra-individual variability. However, methodological and technological barriers to studying the mycobiome, such as protocols for optimal cellular disruption/lysis and subsequent DNA extraction, sequencing, and sequencing analysis for fungal samples have not been clearly defined. Moreover, there is no evidence that the urinary mycobiome reflects the bladder mycobiome, and both may be subject to temporal fluctuations. However, it is likely that knowledge about the role of fungi in urinary tract disease will lead to novel potential therapeutic approaches, such as fungus-specific vaccinations, fungal probiotics, or targeted antifungal drugs.

Lastly, this issue also presents an intriguing Editorial from Schreiber *et al.* entitled "One size doesn't fit all: unraveling the diversity of factors and interactions that drive E. coli urovirulence." This Editorial focuses on the critical gaps in our understanding of the pathogenic and non-pathogenic colonization of uropathogenic *Escherichia coli* (UPEC) in different habitats in the host, and describes a new perspective on UTI susceptibility that better reflects the complexity of this disease. In particular, the concept that putative urovirulence factors (PUFs), that differ between branches of the *E. coli* phylogenetic tree, correlate with pathogenicity, is explored. A novel "Key and Lock" model posits that the outcome of an encounter between a specific host and potential UPEC isolate is dependent upon the combination of the particular fitness state of the UPEC isolate (the "key") matched with the particular host environment and susceptibility (the "lock"). This novel paradigm promises to yield new insight into the conserved and targetable mechanisms of virulence, critical for the development of novel therapeutic strategies that are increasingly needed to face the rising tide of antibiotic resistance.

We hope that you enjoy this special issue and that it answers questions, provokes new avenues of research, and recruits new investigators into the study of the microbiome of the urinary tract. Happy Reading!

 


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