The human microbiome and genitourinary malignancies

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Abstract: The human microbiome contains a vast network of understudied organisms that have an intimate role in our health and wellness. These microbiomes differ greatly between individuals, creating what may be thought of as a unique and dynamic microbial signature. Microbes have been shown to have various roles in metabolism, local and systemic inflammation, as well as immunity. Recent findings have confirmed the importance of both the gut and urinary microbiomes in genitourinary malignancies. Numerous studies have identified differences in microbial signatures between healthy patients and those with urologic malignancies. The microbiomes have been shown to contain microbes that may contribute to the etiology of disease state as well as yield information in regard to a person's health and their responsiveness to certain drugs such as immune checkpoint inhibitors (ICIs) and tyrosine kinase inhibitors (TKIs). Less well understood are the effects of antibiotics on oncologic outcomes in such treatment courses. This review will explore our current understanding and advancements in the field of microbiome research and discuss its intimate association with genitourinary diseases including bladder cancer, prostate cancer, and kidney cancer. With a better understanding of the association between the microbiome and genitourinary malignancy, further investigation may produce reliable predictors of disease, prognostic indicators as well as therapeutic targets.

Keywords: Genitourinary; microbiome; genitourinary malignancy

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Introduction

The close interactions between humans and bacteria have been studied for quite some time. Although bacteria are often thought of as pathogenic to their human hosts, we now know that they exist within nearly every organ system of the body in both commensal and mutualistic relationships (1,2). Not surprisingly, these organisms can have profound effects on both normal physiology and disease states (1).

The total assembly of microorganisms within a given community is collectively referred to as a microbiome. In many ways, the idea that microbiota is associated with our health is actually quite familiar to the general population. An estimated one in five Americans take probiotics, which seek to supplement the “normal” bacterial flora in our digestive systems to improve digestive health (3). In 2008, the National Institute of Health (NIH) sought to characterize our microbiome in order to better understand its role in human health and disease by establishing the Human Microbiome Project (HMP), which generated the largest microbial genome databases for different body sites including nares, oral cavity, skin, GI tract, breast, and urogenital (GU) tract (4). Recently, it was shown that the urinary microbiome in women may be influenced by age, menopausal status, and sexual activity (5). With advances in high-throughput sequencing, transcriptomics, and metabolomics this endeavor has led to multiple reports intimately linking the human microbiome to various
The role of the microbiome in the development and treatment of GU malignancies is just starting to be appreciated. This review explores our current understanding of the human microbiota in relation to GU malignancies and discusses advancements in its manipulation for disease benefit.

**The microbiome**

Our body’s microbiome has been linked to a variety of health conditions, likely through its effect on metabolism, tissue development, inflammation, and immunity (10,11). It has been demonstrated that microbial flora of the gut and intestinal tract can promote various malignancies such as colorectal, liver, and pancreatic cancers (12). Additionally, key work in the murine model has shown the powerful role of gut microbiota in influencing the response of tumors to both chemo- and immunotherapeutic agents via a modulation of the tumor microenvironment (10,13). Thus, manipulation of the microbiome is a potential mechanism by which the course of disease can be altered. Initially, the HMP predominantly focused on characterizing the gut flora, but later was expanded to include the GU tract, mouth, vagina, skin, and nasal cavity (14). The bladder was notably left out of these early endeavors as urine was widely considered to be sterile. However, this dogma was challenged when more sophisticated detection techniques were employed to examine urine specimens. Various investigators were able to use 16s rRNA sequencing to identify urinary organisms in both men and women who had negative urine cultures based on standard laboratory testing (15-17). Furthermore, Hilt et al. used an expanded quantitative urine culture protocol to show that many of these species identified were in fact culturable (18). As detection of these different bacteria has challenged the dogma of “sterile” urine, it has also brought to light the role the genitourinary microbiome may play in GU health.

**The microbiome and bladder cancer**

One of the earliest links between GU microbiome and malignancy was with our understanding of Schistosoma haematobium infections. S. haematobium is a species of parasitic blood flukes that can infect the urinary tract causing schistosomiasis and has been associated with the development of squamous cell carcinoma (SCC) of the bladder (19,20). Prior to the availability of effective treatments for schistosomiasis, endemic areas such as in the Middle East and Africa had a much higher incidence of bladder cancer than the rest of the world. In the 1970s, nearly one in three solid malignancies in Egypt was bladder cancer (21). As with other causes of bladder SCC, it appears that inflammatory changes precipitated by S. haematobium organisms are the culprit. In a leading hypothesis, it is proposed that the inflammatory responses occur following the implantation of the parasite’s eggs into the bladder wall. Byproducts of these reactions may include nitrosamine formation and other carcinogenic free radicals, which mediate malignant transformation (22-24). Interestingly, there is evidence that the urinary microbiome could mediate some of these reactions. Adebayo et al. found that distinct GU microbiota existed within the urine samples from patients who were healthy, those who had schistosomal infections but no resultant pathology, and those with schistosomal induced bladder pathology (25). Some of organisms differentially found in patients with schistosomal induced bladder pathology, including Fusobacterium, Sphingobacterium, Bacteroides, and Enterococcus, are known mediators of inflammatory and immunogenic processes, suggesting their presence may influence schistosomiasis disease progression. Nevertheless, further research is needed to understand the exact mechanism by which the microbiota within the bladder promote malignant transformation following schistosomal infections.

Comparative analysis of the GU microbiome between patients with and without bladder cancer has also provided important insight into how distinct bacterial species may be related to disease progression and recurrence (**Table 1**).

Wu et al. collected and compared urine samples from 31 patients with urothelial carcinoma of the bladder and 18 healthy controls. Interestingly, there was a larger bacterial diversity in the bladder cancer cohort and various bacterial species were differentially observed in this cohort (28). Similar results were seen in an analysis by Bučević Popović et al. in which the genus Fusobacterium was overrepresented in the bladder cancer cohort (27). Although no clear microbial signature has been developed that can serve as a “microbial biomarker” of malignancy, comparing the urinary microbiome in patients with and without various
GU malignancies is shaping our understanding of how the microbiome may be involved in the disease process. While the GU microbiome has a possible role in bladder cancer progression, it may also play a role in treatment resistance. Intravesical administration of Bacillus Calmette-Guerin (BCG), a live-attenuated strain of Mycobacterium bovis, after transurethral resection of bladder tumor (TURBT) is the standard first-line therapy for high grade non-muscle invasive bladder cancer (NMIBC) (29). However, approximately 20–40% of patients are unresponsive to BCG therapy and up to 20% progress to muscle invasive disease (30,31). Although there is no agreement on how resistance to BCG develops, some investigators have postulated that the GU microbiome may play a role in modulating the response to BCG therapy by competitively binding cellular components, such as fibronectin and α5β1 integrins, required for BCG activity (32). McMillan et al. showed that Lactobacillus iners, which is found in the GU microbiome, binds fibronectin with higher affinity than any other species (33). Characterization of the GU microbiome for patients with NMIBC treated with BCG highlighted that Proteobacteria were enriched in patients with recurrent disease whereas there was an enrichment of Lactobacillales in patients without recurrence. This may suggest that Lactobacillus synergizes with BCG to amplify the elicited response to treatment; however, further work needs to be done to determine the exact mechanism by which the GU microbiome affects BCG therapy. Additionally, the role of the microbiome in modulating systemic immunotherapeutic agents will need to be evaluated given the recent approval of the PD-1/PD-L1 inhibitors for advanced urothelial carcinoma (UC) of the bladder, including those who are BCG-unresponsive (34-38). Later in this review we discuss the work of Routy and colleagues who examined the effect of antibiotics on treatment outcomes for a small cohort of patients with advanced UC treated with PD-1 inhibitors (Table 2) (39). To date, most studies looking at the interaction between the microbiome and immunotherapy have focused on the gut microbiome. Future work should explore the role of the urinary microbiome in greater detail.

### The microbiome and prostate cancer

Emerging data from several recent studies has provided interesting insight about the microbiome related to prostate cancer (PCa). It has been proposed that proinflammatory bacteria in the urinary microbiome may contribute to carcinogenesis (43). Comparative analysis of urine samples taken from men with biopsy proven prostate cancer and men with negative biopsies did not demonstrate any clear clustering of bacterial species but did identify a cluster of pro-inflammatory bacteria that was enriched within the PCa cohort (44) (Table 3).

Recent work from Banerjee et al. used next-generation sequencing to compare the microbiome within prostate tissue samples from PCa to benign prostate hyperplasia and found three different microbial signatures that could

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**Table 1** Selection of studies evaluating compositional differences of bacteria in urine samples of patients with urothelial carcinoma

| Study            | Patient population                                      | Higher abundance in bladder cancer | Higher abundance in healthy control |
|------------------|---------------------------------------------------------|-----------------------------------|-----------------------------------|
| Xu et al. (26)   | Patients with urothelial carcinoma                      | Streptococcus, Pseudomonas, Anaerococcus | Not evaluated                      |
| Bucević et al.   | Male patients with non-muscle invasive UC of the bladder | Fusobacterium, Actinobaculum, Facklamia, Campylobacter | Veillonella, Streptococcus, Corynebacterium |
| Wu et al. (28)   | Male patients with UC of the bladder                    | Acinetobacter, Anaerococcus, Rubrobacter, Sphingobacterium, Atopostipes, Geobacillus | Serratia, Proteus, Roseomonas, Ruminiclostridium-6, and Eubacterium-xylanoph |

UC, urothelial carcinoma.
| Study           | Patient population (n)                                                                 | Systemic treatment                   | Outcome                                                                 |
|-----------------|----------------------------------------------------------------------------------------|--------------------------------------|-------------------------------------------------------------------------|
| Routy et al.    | Advanced RCC (n=67); UC (n=42)                                                         | PD-1/PD-L1 inhibition                | PFS: 7.4 months (no abx) vs. 4.3 months (abx), P=0.012; HR 2.12 (1.11–4.05), P=0.026; OS: 27.9 months vs. 23.4 months, P=0.154 |
|                 |                                                                                        |                                      | PFS: 4.3 months (no abx) vs. 1.8 months (abx), P=0.049; HR 1.96 (0.91–4.23), P=0.094; OS: not reached vs. 11.5 months, P=0.098 |
| Hahn et al.     | Metastatic RCC                                                                         | VEGF-TKI                             | PFS: 18.0 months (abx with Bacteroides coverage) vs. 8 months (without abx); HR 0.52, 95% CI: 0.24–1.00; P=0.052 |
| Derosa et al.   | Advanced RCC (n=121)                                                                   | PD-1/PD-L1, CTLA-4                   | PFS: 7.4 months (no abx) vs. 1.9 months (abx), HR 3.1 (1.4–6.9), P<0.01 |
|                 |                                                                                        |                                      | OS: 30.6 months (no abx) vs. 17.3 months (abx); HR 3.5, (1.1–10.8), P=0.03 |
| Lalani et al.   | Metastatic RCC: institutional cohort (n=146); trial-database (n=4,144)                 | PD-1/PD-L1, interferon-alpha, mTOR inhibitor, VEGF-TKI | PFS–8.1 months (no abx) vs. 2.6 months (abx), HR 1.96 (1.20–3.20), P=0.007; OS: 79 months (no abx) vs. 65 months (abx), HR 1.44 (0.75–2.77), P=0.27 |
|                 |                                                                                        |                                      | PFS: 7.0 months (no abx) vs. 5.2 months (abx), HR 1.17 (1.04–1.30), P=0.008; OS: 19.5 months (no abx) vs. 14.5 months (abx), HR 1.25 (1.10–1.41), P<0.001 |

GU, genitourinary; HR, hazard ratio; mTOR, mechanistic target of rapamycin; OS, overall survival; PD-1/PD-L1, programmed cell death-1/programmed cell death ligand-1; PFS, progression-free survival; RCC, renal cell carcinoma; UC, urothelial carcinoma; VEGF-TKI, vascular endothelial growth factor tyrosine kinase inhibitor.

| Study           | Type of sample                                                                 | Higher abundance in prostate cancer | Higher abundance in healthy controls |
|-----------------|--------------------------------------------------------------------------------|-------------------------------------|--------------------------------------|
| Shrestha et al. | Urine from men prior to prostate biopsy                                         | Propionibacterium lymphophilum, Anaerococcus murochil, Auritidiibacter ignavus, Corynebacterium coyleae, Ureaplasma urealyticum, Ureaplasma parvum | Enterozobacteriaeae, Corynebacterium genitalium, Haemophilus haemolyticus |
| Liss et al.     | Rectal swabs from men undergoing prostate biopsy                                | Bacteroides, Streptococcus          | Not reported                          |
| Golombos et al. | Stool sample from men undergoing prostate biopsy                                | Bacteroides massiliensis            | Faecalibacterium prausnitzii, Eubacterium rectale |
| Sfanos et al.   | Rectal swabs from men with different clinical states of prostate cancer         | Higher in men taking androgen axis target therapy: Akkermansia muciniphila, Ruminococcaceae spp., Lachnospiraceae spp. Lower in men on ADT: (family) Brevibacteriaceae, Erysipelrichaceae, Streptococcaceae | Not reported |
| Feng et al.     | Prostate tissue from men with prostate cancer and benign tissue                  | No significant difference in cancer and benign samples | No significant difference in cancer and benign samples |
| Alanee et al.   | Voided urine after prostatic massage                                             | Increased: Veillonella, Streptococcus, Bacteroides; Lower: faecalibacterium, lactobaccili, Actinobacter | Not reported |
|                 | Rectal swab                                                                     | Increased Bacteroides               | Not reported                          |

ADT, androgen deprivation therapy; spp, species.
be correlated to the stage, grade, and Gleason score of the PCa. Furthermore, they found that the microbiome was not limited to bacterial species, but had a diversity of viruses, fungi, and parasites that were differentially identified (50). This is in contrast to Feng and colleagues who failed to find any significant differences in the abundance of bacterial taxa in prostate tissue samples between a cohort of patients with and without prostate cancer (48). Clearly a significant amount of heterogeneity in the microbiome exists among patients, making validation of any microbial signatures difficult.

Composition of the intestinal microbiome has also been linked to prostate cancer. Liss et al. performed rectal swabs on men prior to prostate biopsies and then correlated the microbiome to the cancer status (45). Among patients with prostate cancer, Bacteroides and Streptococcal species were enriched, as well as pathways linked to folate and arginine metabolism. Similarly, comparison of GI microbiome from men with prostate cancer to BPH in a separate analysis demonstrated enrichment of Bacteroides in prostate cancer and Faecalibacterium and Eubacterium in BPH (46). Interestingly, Bacteroides has been shown to be increased in both urine samples and stool samples among men with prostate cancer compared to healthy controls in other studies as well, highlighting its potential role as an underlying factor in prostate cancer development (49) (Table 3).

In a similar study, Sfanos and colleagues collected rectal swabs from 21 patients with prostate cancer and found significant compositional diversity compared to healthy controls (47). Furthermore, they showed that Ruminococcaceae and Akkermansia muciniphila were significantly more prevalent in men taking oral androgen receptor axis-targeted therapies. The authors did not investigate a cause-effect relationship, or whether they had consequences for treatment response and patient survival. However, they did hypothesize that their findings represent a possible explanation for why PD-1 inhibition elicited a response in patients with metastatic prostate cancer who progressed on enzalutamide therapy as prior reports have shown that the same types of bacteria were associated with a positive response to anti-PD-1 immunotherapy (39,51-53).

Radiotherapy is one of the mainstay therapies to treat prostate cancer. However, radiation-induced side effects such as radiation enteropathy can limit the amount of radiation dosing. Reis Ferreira et al. examined three cohorts of patients with acute enteropathy, late enteropathy, and a cohort who underwent colonoscopies in the Microbiota-and Radiotherapy-Induced Gastrointestinal Side-Effects (MARS) study (54). Interestingly, decreased bacterial diversity was observed in patients who experienced radiation enteropathy, with increased counts of Clostridium IV, Roseburia, and Phascolarctobacterium in these patients as well. The role of an altered microbiota on developing radiation enteropathy due to the pelvic radiation has significant implications for possible therapies for assessing and treating these side-effects.

The microbiome and kidney cancer

Epidemiologic evidence has also supported a role of the urinary microbiome in GU malignancies. For example, a population-based analysis of the Iowa Cancer Registry found that a history of a urinary tract infection (UTI) conferred a higher risk of having renal cell carcinoma (RCC) (OR 1.9; 95% CI: 1.5–2.5) after controlling for known modifiable risk factors such as BMI, smoking, hypertension, and alcohol consumption (55). Nevertheless, in this study men that were smokers with history of UTI had the highest risks of RCC suggesting that other modifiable factors can also be critical for developing RCC.

Recent data also suggests that the GI microbiome may play an important role in the development side effects from the systemic therapies for metastatic RCC. Systemic targeted therapy and immunotherapy are important tools in the treatment of GU malignancies. For RCC, tyrosine kinase inhibitors (TKI) that target the vascular endothelial growth factor receptor (VEGF) are first-line treatment options for patients with stage IV disease (56). Unfortunately, these treatments are sometimes associated with harsh toxicity profiles including cardiotoxicity, hypertension, thrombosis, thyroid dysfunction, skin toxicity, and diarrhea (57). One of the most common side effects, diarrhea, has been reported in up to 51% of patients undergoing VEGF TKI therapy, with 10% of patients having grade 3–4 diarrhea (58-60). Those affected by this may be required to have dose reductions, which can alter treatment efficacy, or the discontinuation of the drug altogether. To date, the exact etiology of this side effect is not known and no definitive methods for preventing or managing it exists. Some have suggested that these drugs directly damage the colonic mucosa, with the gut microbiome potentially mediating this interaction (61).

Recently, Pal et al., prospectively enrolled 20 patients with metastatic RCC who would receive VEGF-TKI therapy (61). These patients had no prior history of bowel disease, of which 12 patients did report symptomatic
diarrhea during treatment while 8 were without this symptom. The patients gave a single stool sample during their treatment and 16s rRNA sequences from the stool were gathered to quantify the relative abundance of microbiota in each group. They found that higher levels of Bacteroides and lower levels of Prevotella were in patients with diarrhea, with the opposite present in those without diarrhea. These findings are consistent with preclinical studies in mice revealing that an increase in Bacteroides spp. is associated with an increase in chemotherapy-induced diarrhea (62,63). Hahn and colleagues attempted to evaluate these findings in a clinical context by analyzing the effect of antibiotic therapy on patients who underwent VEGF-TKI treatment for metastatic RCC (40). They retrospectively analyzed 145 patients who during their treatment either received (I) no antibiotics, (II) antibiotics with Bacteroides spp. coverage, or (III) antibiotics without Bacteroides spp. coverage. Based on the aforementioned studies, it was hypothesized that targeting Bacteroides with antibiotics would result in less diarrhea and improved tolerance of VEGF-TKIs. While no difference in dose reductions were seen between the groups, there was an improved progression-free survival (PFS) for patients who took antibiotics directed against Bacteroides. It is likely that any effect antibiotics may have on oncologic outcomes is more complex than just their influence on the severity of diarrhea and should be further investigated. Regardless, these studies provided preliminary evidence that microbiome alterations can modulate the effect of therapeutic agents.

Our current understanding of the immunogenic nature of genitourinary malignancies and the development of therapies that target the immune response has shifted the paradigm in the treatment of advanced disease states. Immune checkpoint blockade via the PD-1/PD-L1 and CTLA-4 pathways has demonstrated durable responses, with various FDA approved agents now available for both urothelial and kidney cancers (34,38,64-68). Nevertheless, resistance is seen in a subset of patients and the microbiome has been implicated in mediating this response (10,69) (Table 2). Routy et al. looked at patients who were enrolled in clinical trials evaluating nivolumab [NIVOREN (70) and Checkmate 025 (67)] and atezolizumab [PCD4989g (71)] for advanced RCC and durvalumab for patients with advanced urothelial carcinoma of the bladder (UC) [MEDI47361108 (37)] (39). This cohort consisted of 67 patients with RCC and 42 with bladder UC. Oncologic outcomes of these patients were compared for those who were prescribed antibiotics for any reason within two months before or after starting immune checkpoint blockade therapy. Interestingly, antibiotic therapy significantly decreased PFS in both the RCC (7.4 vs. 4.3 months, P=0.012) and UC (4.3 vs. 1.8 months, P=0.049) cohorts. OS was significantly shortened in antibiotic treated groups as well when all patients of study were considered (20.6 vs. 11.5 months, P<0.001). These findings support the claim that antibiotic effects on oncologic outcomes are complex and must be further investigated. The authors also performed metagenomic profiling of 40 patients with RCC who underwent PD-1 therapy to quantify the composition of the microbiome. They found an overrepresentation of various bacterial species such as Akkermansia muciniphila in patients with longer PFS suggesting an enrichment of this species might help mediate the treatment effect.

An analysis from a single institution’s database showed similar results (41). This study examined 121 patients with advanced RCC treated, 16 of whom took antibiotics within 60 days of starting immune checkpoint inhibitor (ICI) treatment. Antibiotic therapy was associated with a significantly increased risk of progressive disease and shorter PFS and OS. In a larger analysis, Lalani and colleagues analyzed 146 patients from an institutional cohort with metastatic RCC who received PD-1/PD-L1, as well as 4,144 patients from a clinical trial participant database (42). The cohort included 709 patients that received antibiotics immediately prior to or after initiating an ICI. Those who had antibiotics had a significant lower objective response rate (ORR 19.3% vs. 24.2%, P=0.005), shorter PFS (adjusted HR 1.15, 95% CI: 1.04–1.30, P=0.008), and worse OS (adjusted HR 1.25, 95% CI: 1.10–1.41, P<0.001). Similar findings were found in the institutional cohort, where 31 patients had antibiotic treatment, which was associated with a significantly lower objective response rate, PFS, and a trend towards a lower OS. Taken together, these studies suggest antibiotic therapy may be associated with worse outcomes in patients receiving immunotherapy. This appears to contrast with the work showing improved survival when Bacteroides spp. is targeted with antibiotics in patients undergoing VEGF-TKI treatment. The mechanisms driving these findings are not known, though differences in how the systemic agents interact with the microbiome may play a role. Additionally, available studies are retrospective in nature and thus subject to inherent biases. Findings should therefore encourage future prospective evaluations.

Collectively, the results of these clinical studies suggest
a biologic relationship between gut microbiome and immunotherapy efficacy, though the exact mechanism is unknown. It is possible that there are innate immunogenic bacteria required for the activation of these drugs, and antibiotic therapy results in their elimination (41). Fecal microbiota transplantation has been looked at as a way to reconstitute the responsiveness to immune checkpoint inhibition in mice. In one such study, stool samples from human subjects with RCC who did or did not respond to PD-1 blockade were collected and transplanted into mice (39). These mice were then orthotopically injected with an RCC cell line resistant to PD-1 therapy and then given a CTLA-4 and PD-1 blocker. Imaging analyses determined stool transplantation from patients who had responded to PD-1 therapy conferred a higher antitumor activity than mice receiving stool from non-responders (39), further suggesting an intimate role between the GI microbiota and ICI efficacy.

Conclusions

Recent evidence strongly suggests that the human microbiome plays various roles in the pathogenesis and management of GU malignancies. Though these interactions are complex and not completely defined, preclinical and clinical data show that microbial organisms are intricately related to these disease processes. With further work both the gut, and the recently described urinary microbiome, may soon be used as reliable predictors of disease occurrence and prognostic indicators. Although there are numerous published studies on the urinary microbiome’s role in bladder, kidney and prostate cancer, there is a lack of published research on the urinary microbiome’s role in other GU malignancies such as penile cancer and testicular cancer. This warrants investigation in future studies. Additionally, the manipulation of the microbiome by means such as antibiotic or probiotic use might one day be employed for therapeutic purposes. Well-designed prospective trials will aid in incubating these ideas and bringing them closer to routine clinical use. Nascent efforts to understand the role of the microbiome and GU malignancy have predominantly examined the role of bacterial abundance in disease processes. The role of viral, fungal, bacterial interplay in promoting disease progression and treatment response remains to be understood and may be an important avenue for identifying patients at high risk for progression or treatment failure.

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