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PROSTATE CANCER (S PRASAD, SECTION EDITOR)

The Microbiome and Prostate Cancer Risk

Karen M. Wheeler[1] · Michael A. Liss[1]

Abstract

Purpose of the Review There is an abundance of evidence that the human microbiome plays an important and nuanced role in controlling human metabolism, immunity, and cancer. Herein we aim to review the most current research looking at prostate cancer and its link with the gut and genitourinary microbiome.

Recent Findings Summary There is now a host of evidence for a unique genitourinary (GU) microbiome. The prostate microbiota, to include viral, bacterial, fungal, and parasitic contributions, as assessed from formalin-fixed tissue is described nicely in the study by Banerjee et al. Further hierarchical analysis by this group found a unique microbiome signature for higher Gleason score cancers and validation PCR studies noted a marked number of viral genomic insertions into host DNA. Shretha et al. also recently established unique GU microbiomes in patients with prostate cancer or benign prostate pathology based on urine samples. The gut microbiome likely also has an indirect but significant role in prostate cancer development and treatment. Liss et al. and Golombos et al. found significant associations between specific gut microbiota and prostate cancer. Interestingly, the balance of inflammatory and anti-inflammatory bacterial lipopolysaccharides, production of bile salts, and metabolism of dietary fiber to short chain fatty acids all likely play important roles in creating systemic pro- or anti-carcinogenic states. In terms of prostate cancer treatment effects, Sfanos et al. noted a unique microbial signature in patients undergoing oral androgen deprivation therapy (ADT) as compared with prostate cancer patients not on ADT. Patients undergoing ADT also had enrichment of bacterial metabolic pathways promoting androgen synthesis. Together, these studies have identified a unique GU microbiome and linked both the GU microbiome and unique gut microbial signatures with prostate cancer and prostate cancer treatments. Whether this information can be used in cancer prevention, treatment, or diagnosis are areas of ongoing and active research.

Keywords Prostate cancer · Microbiota · Gut microbiome · Genitourinary microbiome

Introduction

The human body is estimated to harbor well over 10^{12} microorganisms whose genetic material greatly outnumbers our own [1]. The term "microbiota" refers to the particular set of microorganisms inhabiting a specific environment (i.e., skin, gut, hair) [2]. The microorganisms in question can include bacteria, archaea, fungi, and protozoa and are often unique to different epithelial surfaces or solid organs [3, 4]. The microbiome, which is often used interchangeably with microbiota, is the bioinformation that results from processing microbial DNA for the purposes of analyzing groups of bacteria and interactions with disease [2]. The microbiota and subsequent microbiome have formed a large symbiotic network within the human body and generate a large portion of the metabolites derived from diet [3, 5]. Some have even hypothesized that microbiota are heritable as a polygenic trait [6] with the subsequent symbiotic relationship governing host defense, metabolism, and even reproduction [7, 8].

Alterations in microbiota can occur with recurrent or concurrent stressors including age, diet, medications, smoking, diseases, exercise, and other environmental factors [9–13]. These alterations in microbiota, often referred to as dysbiosis, have been associated with diseases such as obesity, heart disease, diabetes, cancer, rheumatoid arthritis, and inflammatory bowel disease [2, 14]. Indeed, chronic infection and/or chronic

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✉ Michael A. Liss
liss@uthscsa.edu

Karen M. Wheeler
wheelerk1@uthscsa.edu

[1] Department of Urology, University of Texas Health Science Center, 7703 Floyd Curl Drive, San Antonio, TX 78229, USA

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inflammation has been shown to contribute to carcinogenesis in a number of cancers as postulated by Virchow nearly 150 years ago [15]. The link between disturbances in normal microbiota and cancer has become more clinically apparent recently—affecting both cancer pathogenesis as well as response to treatment (for example *H. pylori* and gastric cancer) [16].

Regarding prostate cancer, bacteria have long been thought to be a source of chronic, low-grade inflammation which may induce prostate cancer. In order to study the microbiome associations and prostate cancer, there are two approaches: direct and indirect. Direct measurements include analysis of prostate tissue directly or testing of urine as a surrogate for the intra-prostatic environment due to the prostate's inherent access to the urinary tract. Indirect measurements largely assess the fecal microbiome as it likely has systemic defects that may impact the development and progression of prostate cancer. Herein we aim to review the most current research looking at prostate cancer and its link with the gut and genitourinary microbiome.

Microbiome in Prostate Cancer

In murine models using germ-free and gnobiotic mice, microbiota appear to have tumor-promoting effects in models of breast, colon, liver, lung, and skin cancer [17, 18]. However, studies in humans have shown that using antibiotics to target specific bacteria can be therapeutic to some cancers [19]. Given the large number of microbiota present and the nuanced interactions that exist between the microbiota themselves and with the host, it is likely not an all-or-none effect in promoting or treating tumors, but rather an imbalance, or dysbiosis, in healthy microbiota that may have cancer-promoting effects. A well-studied example is *H. pylori*, which increases the risk of peptic ulcer disease and gastric cancer, but is associated with decreased risk of reflux esophagitis, esophageal cancer, and childhood asthma [2, 20].

The GU Microbiome (Direct) Although it is a common teaching that urine is sterile, several studies have established the presence of a unique microbiome within the urinary tract [21]. Older studies looking for microbiota suffered from insensitive detection platforms like bacterial culture and high background contamination from skin, vaginal, and rectal sources. Even more current studies may suffer from contamination based on specimen source [22], degradation of genetic material from formalin fixation, and bacterial contamination from prostate biopsy. More contemporary studies do, however, use more sensitive and higher-throughput analysis tools like 16S rDNA and rRNA sequencing and shotgun metagenomics techniques, allowing for better understanding of microbiota present in the GU system.

Prostate Tissue Microenvironment (Direct)

Bacteria One of the first manuscripts of the microbiome in the prostate cancer tissue was produced by Cavarretta and colleagues. Cavarretta et al. noted that *Propionibacterium* species were the most abundant overall and that *Staphylococcus* species were more represented in the tumor and peri-tumor tissue ($p < 0.05$) [23]. Feng et al. were the first to use integrated metagenomic and metatranscriptomic analysis to identify microbiota in frozen radical prostate specimens from tumor and adjacent benign tissue from 65 Chinese patients [24]. They identified over 40 unique bacterial genera with *Pseudomonas*, *Escherichia*, *Acinetobacter*, and *Propionibacterium* being some of the more abundant. They did not detect STI-related microbes, nor did they detect viruses. In addition, there was no difference between tumors and benign tissue in terms of overall (alpha) bacterial diversity or group (beta) diversity, regardless of Gleason grade, although tissue from the same patient preferentially clustered on beta-diversity analysis.

One of more comprehensive papers specifically addressing microbiome within prostate cancer tissue was published by Banerjee et al. in 2019 [25]. Using microarray metagenomic analysis (PathoChip, Agilent Tech.) of formalin-fixed tissue from 50 prostate cancer patients and 15 patients with BPH, viral, bacterial, and fungal DNA signatures were identified. The bacteria isolated were mostly gram-negative with the following phyla in descending magnitude: Proteobacteria, Firmicutes, Actinobacteria, and Bacteroidetes. A hierarchical analysis performed found unique clusters of microbiota signatures that correlated with prostate cancer grade. However, studies characterizing non-tumor and tumor tissue from formalin-fixed tissue of prostate cancer patients found no difference in microbiota signatures between the tissue types [23, 24].

Mycoplasma genitalium has long been associated with prostate cancer and can induce oncogenic transformation in in vitro and murine studies [26]. Miyake et al. screened 45 prostate cancer and 33 BPH patient specimens for various sexually transmitted infectious agents. Only mycoplasma genitalium was independently associated with prostate cancer and with higher stage cancers [27]. *Propionibacterium acnes* has also been implicated in the development of prostate cancer and found in specimens using immunofluorescence [28] and RNA-seq [29]. Javurek et al. suggested *P. acnes* to be part of the unique GU microbiome after identifying it in untreated seminal vesical fluid in mice [30].

An emerging new field is the pro-carcinogenic role of bacterially derived products. For instance, in breast cancer, bacterially derived quorum–sensing peptides have been implicated in tumor cell invasion and angiogenesis [31]. As the bacterial microbiome in the prostate becomes better understood, this could be a new avenue of exploration.

Viruses As with cervical and head and neck cancers, viral etiologies, such as the polyoma BK virus and the herpesvirus human cytomegalovirus, have been proposed for prostate cancer for several years [32, 33]. Other studies have not found evidence of viral DNA in prostate tissue [29]. Banerjee et al. utilized pathochip technology to investigate viruses within the prostate tissue. Among the viruses isolated, 41% were known tumorigenic viruses, including high-risk human papilloma virus (HPV) strains 16 and 18 (present in > 80% of samples) as well as human cytomegalovirus (HCMV) [25]. On hierarchical analysis, HPV18, KSHV, and Polyomaviridae were found to be associated with lower Gleason scores. Integration of HPV18, KSHV, HPV2, and HPV18 viral DNA into host DNA was found on PCR confirmation of pathochip results, and many of these insertions involved potentially tumorigenic genes.

Viruses are known to prevent clearance from their host through creation of immune tolerance, with one mechanism being downregulation of the STING (stimulator of interferon genes) pathway. Whether this mechanism plays a role in prostate cancer pathogenesis remains unstudied. However, viral infections by polyomaviruses, human papillomaviruses (HPVs), and human cytomegalovirus (HCMV) have all been implicated in infecting human prostate tissue and have higher prevalence in prostate cancer [32, 34]. Typically, cells will recognize when foreign material (DNA) is in the cell, triggering the "alert system" and production of molecules that attract the immune system to destroy that cell. The "alert system" is known as the STING pathway and can detect viral DNA, bacterial DNA, and tumor DNA. Similar to some viruses, cancer can turn off the STING pathway to prevent the immune system from destroying the cell. We hypothesize that viruses could provide this mechanism to turn off the immune system to infected tumor cells. The inhibition of STING pathway activation by the virome may represent a mechanism of immune evasion during carcinogenesis and could allow "foreign" bacteria to colonize within the prostate tumor, but not necessarily be attributed to an "infection".

Urine-Based Profiling (Direct) Shrestha et al. performed an extensive review of urine samples from patients with benign ($n = 65$) and cancerous ($n = 65$) prostate pathologies using 16S rDNA profiling [35]. Analysis of beta-clustering did not separate benign disease from cancer. However, *Streptococcus*, *Anaerococcus*, *Actinobaculum*, *Varibaculum*, and *Propionimicrobium* were more prevalent in urine samples from prostate cancer patients. Yu et al. performed 16S rRNA sequencing in prostatic secretions from Chinese patients with prostate cancer or BPH and identified bacteria unique to the prostate cancer (*Propionicimonas*, *Phingomonas*, *Ochrobactrum*, *Alphaproteobacteria*, *Firmicutes*, *Lachnospiraceae*) and BPH groups (*Eubacterium* and *Defluviicoccus*). However, these studies cannot rule out contamination or alterations in microbiota from urinary obstruction and/or instrumentation of the urinary tract from the given pathology.

The Gut Microbiome (Indirect) In addition to a unique GU microbiome, the most studied and largest source of commensal microbiota is the gut. The gut itself has a dynamic and complex role in production of various hormones that can interact with the central nervous system, stress responses, and various other bodily systems [36–38]. In turn, the microbes within the gut can both sense and react to hormones produced by the body as well as secrete their own molecules [36]. Thus, changes in the composition of the gut microbiome and/or dysbiosis can have whole-body implications. Indeed, variations in gut microbiota have been associated with obesity, differential metabolism of drugs, energy usage, direct effects on the immune system, etc. [38, 39]. One of the first demonstrations of the influence of whole gut microbiota on cancer growth was performed by Sivan and Gajewski and colleagues. Identical mice from different labs grew melanoma at different rates, but transferring gut microbiota, through co-housing or fecal transplant, caused tumors to grow at similar rates, favoring a slower-growing tumor [40]. Ultimately, this group found *Bifidobacterium* to be the causative microbe for slowed tumor growth. Susan Erdman's lab had shown prior to this that, in pathogen-free–housed mice prone to cancer development due to mutations in the adenomatosis polyposis coli gene ($Apc^{Min/+}$), intestinal infection with *Helicobacter hepaticus* could induce a TNFα-dependent cytokine response leading to mammary carcinogenesis [41]. Later work by this group found that bulk transfer of mesenteric lymph nodes cells from *H. hepaticus*–infected $Apc^{Min/+}$ could transfer prostate cancer into wild-type mice in a TNFα-dependent manner [42]. These studies indicate that dysbiosis of the gut microbiota may cause aberrant inflammatory signals that have systemic effects. One such inflammatory signal may be lipopolysaccharide (LPS).

Lipopolysaccharide Hypothesis LPS is a compound in the bacterial cell wall, usually identified by the immune system as a "danger-signal," causing immune-cell activation to help rid the body of the offending microbe. Bacterial LPS has been identified as a triggering factor for the development of diabetes and related to both obesity and prostate cancer [43]. In a study of a high-fat versus a regular diet mice fed, there was an increase in LPS-containing bacteria in the gut of mice on a high-fat diet; a continuous infusion of LPS could recapitulate the elevated plasma glucose levels, and weight gain was seen in high-fat diet fed mice [44]. This LPS-induced metabolic syndrome was dependent on CD14 [44], the main soluble transport molecule necessary for LPS binding to its primary receptor, toll-like receptor 4 (TLR4) [43]. TLR4 is expressed by human prostate cancer and laboratory models of prostate cancer have been used to show that TLR4 activation by LPS

promotes survival in serum-starvation conditions as well as inducing production of VEGF and CCL2 [45]. LPS signaling through the TLR4 receptor activates NF-κB, which mediates transcription of a variety of stress-related compounds and has been shown to be upregulated in aggressive prostate cancer [46]. Interestingly, another murine model found an increase in prostatic NF-κB signal in mice fed a high-fat diet [47]. These results are all consistent with the hypothesis that dysbiosis increases obesity and metabolic syndrome through an LPS-induced inflammatory mechanism that can have significant effects on prostate and other cancers.

Not all LPS are created equal; however, LPS from *E.coli* has more inflammatory effects than LPS in other bacteria [48], such as *Bacteroidales* species, which produce an antagonistic form of LPS that silences pro-inflammatory LPS signaling [49]. Ultimately, the total LPS load from the healthy gut is thus immunoinhibitory [49]. The predominating type of bacteria is only one component affecting levels of LPS level in the blood. In addition, the guts' propensity to allow for bacterial translocation or hormonal diffusion (aka "leakiness" of the gut) can be determined by a variety of dietary, disease, and host related factors [50]. We could potentially investigate human small nucleotide polymorphism profiles and LPS levels to correlate the genetic components of gastro-intestinal barrier to LPS levels while controlling for the gut microbiome; however, the sample size would require thousands.

Immune System Modifications The gut microbiome is present from and changes significantly after birth [51] and is necessary for the normal development of the immune system [4, 52]. The types of microbes and their proportions can also directly affect the adaptive immune system by driving differentiation of T cells into regulatory cells or varying types of T helper populations (Th1, Th2, Th17) [4, 53–55]. Regulatory T cells (Treg) help to maintain normal immune tolerance, with their dysfunction leading to autoimmune disease. In cancer, however, Treg are generally thought to be tumor-promoting through silencing immune clearance of tumor cells. Fewer Treg have been found in mice with limited gut bacterial diversity, whereas *Mucispirillum* spp., *Bifidobacteria infantis*, and *Faecalibacterium prausnitzii* have been shown to induce Treg in the gut [56–58]. Whether this could have subsequent systemic effects on cancer immune surveillance is currently not well studied. Moreover, the proportion and functionality of different T helper populations, driven by gut microbiota, can have tumor promoting or quieting effects. Thus, dysbiosis likely creates a systemic environment that is more tumor-friendly, metastasis-friendly, or more likely to see and clear cancers. The nuances of the interactions between the immune system, microbiome, and cancer, are active areas of research (Fig. 1).

Microbial Metabolism In an analysis of rectal swabs from 104 patients obtained prior to undergoing prostate biopsy, Liss et al. found significant compositional associations (beta clustering) between patients with and without cancer on subsequent biopsy [59]. *Bacteroidetes* and *Streptococcal* species were enriched in prostate cancer patients as were pathways involved with folate and arginine metabolism. Golombos et al. similarly found an enrichment in Bacteroidetes in stool specimens from 12 prostate cancer patients compared with *Faecalibacterium* and *Eubacterium* in 8 men with BPH [60]. The study also found enrichment of metabolically active pathways in the patients with benign disease over those with cancer. Most recently Alanee and colleagues compared 16S rRNA sequencing of rectal swabs and prostatic massage on 30 patients 2 weeks before and 2 weeks after prostate biopsy [61]. The results showed significant microbiome clustering close to rectal microbiota post-biopsy, indicating there may a significant amount of contamination in prostate specimens after biopsy; how long this contamination remains is unknown. There are several implications of this study that impact microbiome collection techniques and timing to prostate biopsy. Clear collection techniques and time from antibiotics are necessary if research is being conducted on men prior to prostatectomy. We are unsure of the changes in the stool or urine microbiome after antibiotic prophylaxis or the urine if the biopsy was performed using the transrectal technique. A control group would be required to identify how long after prostate biopsy could an intervention take place if either urine or stool microbiome is an outcome.

Bile Salts Bile salts represent a large pool of host-derived metabolites with anti-bacterial properties. Dietary fat content can upregulate bile acid production and have subsequent effects on the microbiota content of the gut [62]. In 2011, Islam et al. described that feeding mice cholic acid increased the Firmicutes:Bacteroidetes ratio and increased the serum levels of adiponectin; findings that are consistent with mice given a high-fat diet [63]. In 2017, Zheng et al. extensively analyzed the gut microbial and metabolite changes in mice fed a high-fat or regular diet [62]. After only 12 h on a high-fat diet, mice had increased levels of bile acids (cholic acids specifically), which were positively associated with the presence of Firmicutes, Proteobacteria, and Actinobacteria. Moreover, feeding mice cholic acids recapitulated the change in gut microbiota as well as an obesity phenotype, whereas inhibition of bile acid synthesis using a farnesoid X receptor agonist decreased the significance of these changes. Ma and colleagues found that mice that normally develop spontaneous hepatocellular carcinomas had smaller tumors when treated with antibiotics [64]. This effect was due to a reduction in bacterial metabolism of primary to secondary bile acids largely by *Clostridium* species, leading to more tumor-surveying natural-killer T (NKT) cells in the liver. In humans, a meta-analysis of studies that used shot-gun metagenomics in

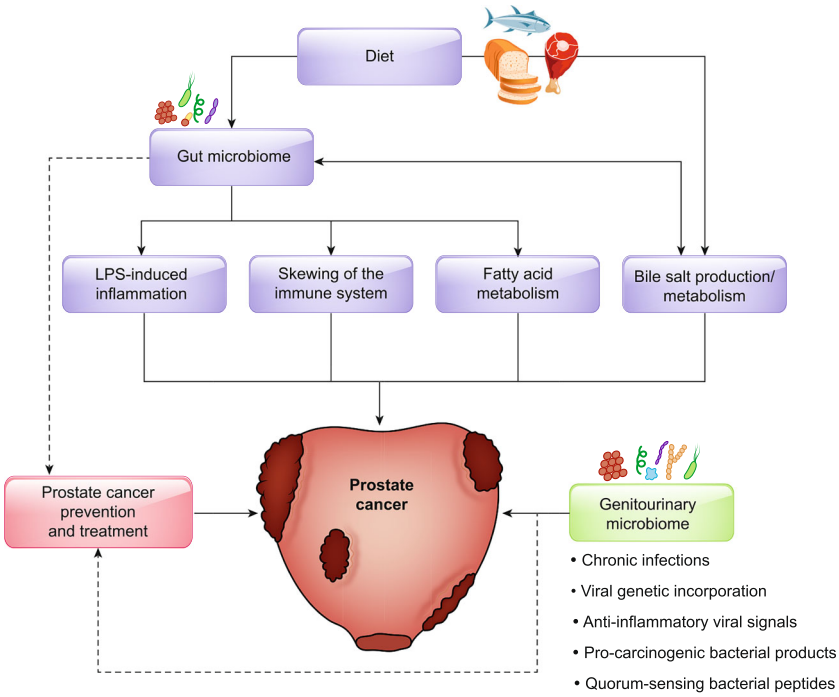

Fig. 1 Interactions between gut and genitourinary microbiome and prostate cancer. Potential mechanisms of action and interactions of each microbiome are highlighted

patients with colorectal cancer found an increase in bacterial genes associated with bile acid degradation in cancer patients [65]. A high-fat or Western diet may change the body's production of bile acids, with subsequent effects on gut microbial content. This in turn affects bile acid metabolism and all aspects of this pathway may affect immune surveillance of cancer.

Short Chain Fatty Acids Gut microbiota can produce short chain fatty acids (SCFAs) during fermentation of dietary fiber, which have a chemical structure similar to hormones [66]. On analysis of murine gut microbiota and metabolites, SCFAs were positively associated with bacteria from the phyla Bacteroidetes [62]. SFCAs propionate (produced by the genus *Propionibacteria*) and butyrate have been shown to induce apoptosis of colon cancer and lymphoma cell lines in vitro [67], mechanistically inhibiting histone deacetylase in cancer cells [68]. Additionally, SFCAs appear to increase regulatory T cell frequency in the gut, aiding in the maintenance of a healthy gut-immune axis [69]. Taken together, the data on increased dietary fiber intake and subsequent SFCA production supports the idea that SFCA promote an improved body composition, reduced weight, and improved insulin sensitivity [66, 70].

Microbiome in Treatment Effect of Cancers

As important as understanding whether the microbiome plays a pathogenic role in prostate cancer, is to understand if the microbiome can specifically affect treatment of prostate cancer. Knowing microbes can create dramatic systemic inflammatory responses that can affect cancer is not a new concept. The first immunotherapy for cancer was Coley's toxin; heat inactivated Streptococci that was used in bone and soft tissue sarcomas in 1891 [71]. In addition, attenuated mycobacterium is a standard treatment for non-invasive bladder cancer. These microbes induce a significant inflammatory response to treat cancer. Not surprisingly, the human microbiome can exert significant effects on various cancer treatment modalities. Conversely, cancer therapies may significantly affect the normal microbiota, potentiating or ameliorating their effects.

Natural Products Natural interventions to alter the microbiota may also help prostate cancer therapy. Murine studies have shown decreased prostate tumor xenograft growth after treatment with indole-3-carbanole (a compound derived from cruciferous vegetables), as well as subsequent alterations in microbial interactions and networks [72]. Gnobiotic mouse work has shown that changing from a low fat/plant-rich diet to a high-fat diet alters the gut microbiome within a day and beta-diversity significantly changes after a week [73]. Further, Newton et al. describe an ongoing trial testing exercise as an intervention to promote "healthy gut bacteria" in prostate cancer patients undergoing ADT [74]. Alterations in diet may be simple and easy ways to affect cancer development, progression, and/or treatment response.

Hormonal Effects/Androgen Deprivation The mainstay of medical treatment for prostate cancer is androgen deprivation therapy. There is certainly a link between androgens and the

microbiome. Wistar rats treated with testosterone and/or estrogen therapy develop chronic prostate inflammation with increased bacterial diversity within the prostate based on 16S rRNA sequencing [9]. In 2016, Harada et al. showed that castration of mice on a high-fat diet increased their feeding efficiency, leading to obesity and an increase in the Firmicutes:Bacteroidetes ratio [75]. The effect of castration, however, was negated by antibiotic use. Conversely, Liu et al. found that a high-fat diet promoted prostate cancer in a transgenic mouse model but found a decreased Firmicutes:Bacteroidetes ratio [76].

Sfanos et al. were the first group to look at the microbiome in human prostate cancer patients who have undergone ADT [77]. A total of 30 patients underwent 16S rDNA profiling of rectal swab samples and consisted of patients who had prostate cancer and were undergoing ADT, who had prostate cancer and were not undergoing ADT, or who had benign disease. They found higher overall bacterial diversity in patients with benign disease and significant taxonomic clustering differences in prostate cancer patients on ADT or not. The most significant differences were seen in patients taking oral ADT given the direct effects oral ADT will have on gut microbiota. This group had high percentages of *Akkermansia muciniphila*, which is positively correlated to anti-PD1 immunotherapy response [78], as well as species in the Verrucomicrobiaceae family. Many bacteria also appeared to have enzymatic machinery necessary to generate steroids. In all, this paper highlights the many changes that may occur during treatment for prostate cancer, as well as the possibility of using gut microbiota as a marker for treatment effect or response.

Immunotherapy As immunotherapy has emerged as a treatment for many cancers, including prostate, there has been a growing body of literature on the impact of host microbiota to treatment outcomes. Murine studies found that anti-CTLA-4 therapy does not work in antibiotic or germ-free mice and therapy is potentiated by *Bacteroides fragilis* [79]. Work by Sivan et al. that found mice with different commensal microbes responded differently to anti-PDL1 and improved response could be transferred through oral gavage of fecal material [40]. Ultimately *Bifidobacterium* species were found to be the therapy-sensitizing bacteria. These relationships were confirmed in melanoma patients; those that respond well to anti-PD-1/PD-L1 or anti-CTLA-4 therapies have different microbiomes than non-responders [80–82]. Gopalakrishnan and colleagues found increased microbial diversity and enrichment of *Faecalibacterium* spp. in responders and *Bacteroidales* spp. in non-responders [80]. Similarly, Matson et al. found *Bifidobacteriaceae* to be associated with responders. In prostate cancer, immunotherapy in the form of autologous cell activation (Sipuleucel-T) or those targeting the PD-1/PDL-1 axis are not currently first-line treatment strategies. However, understanding of how the genitourinary and/or gut microbiome may potentiate response to these therapies may allow for earlier and more efficient use in disease treatment.

Conclusion

Understanding the role that microbiota play in the pathogenesis and treatment of prostate cancer remains largely underexplored. We have reviewed data indicating a unique urinary tract microbiome that may correlate with prostate cancer. Whether specific microbiota are causative in prostate cancer, and if so, how, remains to be determined. Additionally, the role that gut microbiota have on prostate cancer pathogenesis and treatment response remains an area of active investigation. Whether the urinary or gut microbiomes play more important roles in prostate cancer compared with gut microbiota may be ultimately difficult to determine, as microbial epidemiology is fraught with nuanced and often unknown interactions [83]. If microbiota play direct roles in cancer pathogenesis, altering the microbiome may be indicated for cancer prevention. If microbiota decrease or increase treatment responses, alterations may be used to augment cancer treatment. All together the nuanced relationship between microbiota and host likely does affect prostate cancer and understanding these associations is worth continued investigation.

Compliance with Ethical Standards

Conflict of Interest Karen M. Wheeler and Michael A. Liss each declare no potential conflicts of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- • Of importance
- •• Of major importance

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