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The human gastrointestinal microbiota and prostate cancer development and treatment

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The human gastrointestinal microbiome contains commensal bacteria and other microbiota that have been gaining increasing attention in the context of cancer development and response to treatment. Microbiota play a role in the maintenance of host barrier surfaces that contribute to both local inflammation and other systemic metabolic functions. In the context of prostate cancer, the gastrointestinal microbiome may play a role through metabolism of estrogen, an increase of which has been linked to the induction of prostatic neoplasia. Specific microbiota such as *Bacteroides*, *Streptococcus*, *Bacteroides massiliensis*, *Faecalibacterium prausnitzii*, *Eubacterium rectalie*, and *Mycoplasma genitalium* have been associated with differing risks of prostate cancer development or extensiveness of prostate cancer disease. In this Review, we discuss gastrointestinal microbiota's effects on prostate cancer development, the ability of the microbiome to regulate chemotherapy for prostate cancer treatment, and the importance of using Next Generation Sequencing to further discern the microbiome's systemic influence on prostate cancer.

Keywords: Microbiota; Prostatic neoplasms

INTRODUCTION

The human microbiome describes the bacteria, archaea, fungi, and protozoa that reside in the epithelial surfaces of the body [1]. The microbiome affects many physiologic functions, such as cognitive abilities, hematopoiesis, inflammation, and metabolism [2]. There are five main bacterial phyla in the gastrointestinal (GI) mucosa: *Bacteroides*, *Proteobacteria*, *Actinobacteria*, *Verrucomicrobia*, and *Firmicutes*; the most common anaerobes are *Bacteroides*, *Eubacteria*, *Bifidobacteria*, *Peptostreptococci*, *Clostridia*, and *Ruminococci* [3-5].

The host and the GI microbiota share a complex balanced relationship that is symbiotic. The intestinal microbiota has 10^{13} to 10^{14} microorganisms that have a large role in the metabolism of glycans, amino acids, and xenobiotics [6]. The composition of intestinal microbiota are dependent on various host factors such as colonization at birth, diet, smoking, drinking, and presence of disease [7-9]. This is a bidirectional relationship, as evidenced by the microbiome in turn affecting host: gut microorganisms are responsible for educating the immune system and promoting differentiation of regulatory T-cells, which are involved in anti-inflammatory processes [10].

Germ-free rodents that were fed vitamins that are normally supplied by commensal intestinal microbiota lived significantly longer than their conventionally-raised coun-

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terpart rodents [11]. Studies with axenic (germ-free) rodents and those colonized with specific microbiota show that commensal microorganisms are required for a fully functioning immune system, and has local and systemic effects. When studying a similar hypothesis in humans, antibiotics were found to be associated with decreased progression-free survival in melanoma patients [12]. When environmental changes occur, the microbiome can be thrown into a state of dysbiosis which can lead to the promotion of inflammatory diseases and cancer through infiltration of the epithelial barrier [13].

There has been increasing interest in the microbiome's role in cancer development and progression, and studies show that distinct microbiota can both promote and inhibit tumor development [14-20]. The microbiome can influence the development of cancer as well as response to therapies, and this could be through both direct promotion of cancer as well as indirect mechanisms involving immune modulation, metabolic changes, and epithelial damage [21]. Therefore, understanding the gut microbiome's effects on cancer is critical to potentially manipulating it therapeutically for cancer treatment.

There is still a limited pool of knowledge about prostate cancer and GI microbiome. In this review, we will explore the relationship between proposed etiologies of how the gastrointestinal microbiome affects prostate cancer development, specific bacteria implicated in pathogenesis, and the microbiome's impact on prostate cancer treatments.

MICROBIOME AND PROSTATE CANCER RELATIONSHIP

Prostate cancer is the second leading cause of death in the United States and accounts for 1 in 5 new diagnoses in the male population [22]. The lifetime risk for prostate cancer is about 16%, with 276,000 new cases in 2018 [23]. Typical treatments for prostate cancer include androgen-based therapies; however, this does not take into account other risk factors for prostate cancer, such as bacterial infections, environmental stimuli, or inflammatory markers. Despite prostate cancer's high prevalence, these alternate risk factors have not been fully explored [24].

The composition of GI microbiome may influence the metabolism of certain compounds that may be associated with increased prostate risk [25]. Intake of calcium in dairy products [26], red meat [27], and fat [28] have been linked to increase prostate cancer risk or progression. This may relate to the microbiome's role in phytochemical digestion [29], dairy product digestion [30], and the generation of inflammatory molecules [31-33], which can influence neoplastic development.

Antibiotics select for certain resistant bacterial survival by increasing susceptibility of pathogenic bacterial proliferation. A reduced diversity profile can lead to an overgrowth of bacteria that promote inflammation and neoplasia. Studies have shown that antibiotic usage increases likelihood of bacterial infections from *Clostridium difficile* and methicillin-resistant *Staphylococcus aureus* [34]. These bacterial species are typically present in the GI microbiome, but are able to proliferate under conditions of microbial disruption. The association between prostate cancer risk has been investigated in the context of antibiotic exposure. Tulstrup et al. [8] described that antibiotic-induced changes in microbiota form changes in intestinal permeability, introducing risk of neoplastic changes. Boursi et al. [35] hypothesized that an antibiotic would cause a change in the bacterial diversity of the GI and induce chronic inflammation. He found that the risk of prostate cancer increased moderately with the use of penicillins, quinolones, sulphonamides, and tetracyclines.

When describing how the microbiome affects distant carcinogenesis from the GI, as in the case of prostate cancer, Plottel and Blaser [36] postulated a functional estrobiome, or enteric bacterial genes that are able to metabolize estrogen. β-Glucuronidases and β-glucuronides are particularly important in the metabolism of estrogen by conjugation and deconjugation. Estrogen has been reported to be elevated in patients with prostate cancer compared to healthy controls [37]. Estrogen promotes carcinogenesis by activating polycyclic aromatic hydrocarbons (PAHs) which involve the formation of carcinogenic metabolites, diol epoxides and radical cations. Diol epoxides and radical cations react with DNA that can lead to cancer-promoting mutations. This estrogen mechanism is linked to Plottel's hypothesis of the estrobiome, or estrogen-metabolizing bacteria, and therefore when disturbed would cause an increase in serum estrogen.

In addition to the estrogen-driven carcinogenesis hypothesis, chronic inflammation has been proposed to create dysbiosis and subsequently increase cancer risk. Several studies have shown that there is an increased risk of prostate cancer in men with a history of prostatitis [38-42]. Poutahidis et al. [43] confirmed *in vivo* that GI tract bacterial infection is sufficient to enhance prostate intraepithelial neoplasia (PIN) and microinvasive carcinoma. Induction of neoplasia was abrogated by the prior neutralization of inflammatory molecules such as tumor necrosis factor α, suggesting that GI microbial-based inflammation plays a large role in tumor formation and progression. Liss et al. [44] collected rectal swabs from men and sequenced their rectal microbi-

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ome profiles prior to transrectal prostate biopsy. There were significant increases in proinflammatory *Bacteroides* and *Streptococcus* species in those diagnosed with prostate cancer. Inflammation may be related to neoplasia by inflicting cellular and genomic damage, triggering a cascade of cell repair, angiogenesis, and tissue repair on a larger level [45]. Furthermore, it has been hypothesized that reactive oxygen species and reactive nitrogen species are released through immune cells during times of inflammation, directly damaging cells and DNA [46]. This oxidative damage and cellular death is the cause of proliferative inflammatory atrophy, which is identified as a precursor to prostatic neoplasia, PIN and potentially adenocarcinoma [47].

Probiotics are a potential adjuvant for cancer treatment given more knowledge of the gut microbiome. *Lactobacillus rhamnosus GG* (LGG) is often administered as a complement to traditional colorectal cancer treatment to promote symbiosis of the GI microbiome [18]. LGG has been observed to be anti-inflammatory and result in increased tumor regression in animal models [18]. Probiotic administration after cancer therapy has been shown in multiple trials to alleviate GI-related stress and re-populate the commensal microbiota [48]. This probiotic has not yet been investigated in the context of prostate cancer.

There are certain microbes that have shown to increase the risk of prostate cancer *in vivo*. *Campylobacter jejuni* was found to induce cell cycle arrest, chromatin fragmentation, and cell death from its toxin termed cytolethal distending toxin [17]. *Clostridium* was found to convert glucocorticoids in the gut to androgens by side-chain cleavage, which could contribute to prostate cancer development [49]. *Escherichia coli* is common in the human gut and is typically in symbiosis with the host; however, Cuevas-Ramos et al. [50] noted that *in vivo* infection of *E. coli* induced DNA damage response with signs of incomplete DNA repair. In addition, *E. coli* has been found to be associated with prostate inflammation. Elkahwaji et al. [51] infected mice with *E. coli* bacteria or a control buffer. Each of the *E. coli*-infected mice developed bacterial prostatitis and many developed dysplastic changes; zero of the control mice developed prostate infections or inflammation.

Liss et al. [44] further hypothesized that bacteria related to carbohydrate metabolic pathways had a higher relative abundance in those diagnosed with prostate cancer compared to healthy controls. However, research in folate and prostate cancer has shown inconsistent results; Figueiredo et al. [52] found that men randomized to folic acid supplementation had a 2.6 times risk of being diagnosed with prostate cancer compared to their placebo counterparts. However, high dietary folate intake was associated with a decreased risk of prostate cancer. Liss et al. [44] noted microbiota involved in folate production were increased in men without prostate cancer; therefore, there seems to be a difference between endogenous folate production and folate supplementation. This could have implications for preventative medicine by encouraging men to use probiotics for natural folate production and discourage use of folate supplements. The complexity of the folate pathway, microbiota, and prostate cancer reveal that larger metatranscriptomic studies are needed to further understand their relationship with each other.

SPECIFIC MICROBIAL BACTERIA AND PROSTATE CANCER

With an increasing understanding of microbial effects on carcinogenesis, studies have been conducted exploring specific GI microbes and prostate cancer outcomes.

As mentioned previously, Liss et al. [44] found enrichments of *Bacteroides* and *Streptococcus* in prostate cancer cases as compared to the healthy controls. However, the fecal microbiome of the cohort of men undergoing prostate biopsy did not have significant differences between prostate and non-prostate cancer groups.

Alanee et al. [53] conducted a prospective study to determine the association between fecal microbiota and prostate cancer diagnosis and found that patients with prostate cancer had a higher relative abundance of *Bacteroides*; however, fecal clustering patterns were not significantly associated with Gleason score staging of those with prostate cancer.

Golombos et al. [54] found a higher relative abundance of *Bacteroides massiliensis* in prostate cancer cases compared to healthy controls; *Faecalibacterium prausnitzii* and *Eubacterium rectalie* were in higher relative abundance in controls. *F. prausnitzii* had shown to be protective in numerous studies, having anti-inflammatory and symbiotic properties [55,56]. *F. prausnitzii* functions to metabolize acetate into butyrate, which is a primary source of energy for colonocytes, and is an anti-inflammatory compound [57]. *F. prausnitzii* demonstrated other mechanisms of anti-inflammation unrelated to butyrate in Crohn disease patients. *E. rectalie*, the other bacteria elevated in controls compared to prostate cancer patients, also produces anti-inflammatory butyrate [58].

Miyake et al. [59] found that the rate of extensive prostate disease was higher in those with *Mycoplasma genitalium* infection compared to those who did not have *M. genitalium* infection. *M. genitalium* is a clinically important sexually transmitted pathogen, which causes diseases that

induce inflammation such as chronic prostatitis and urethritis. This inflammation can translate to neoplastic changes in the prostate.

Sfanos et al. [60] reported a greater alpha diversity in those without prostate cancer compared to those with prostate cancer. Alpha diversity refers to how divergent the species within the microbiome are in a specific landscape. A decrease in gut microbiota diversity has been established as a risk factor in certain other diseases [61]. This warrants further exploration of microbial diversity and risk factor for prostate cancer.

The studies exploring the specific microorganism and prostate cancer risk discussed above are summarized in Table 1 [44,53,54,59,60].

PROSTATE CANCER TREATMENT

It is well established that the GI microbiota influence both the local and systemic immune [14]. Paulos et al. [14] found that microbial translocation to the GI increases the function of CD8+ T cells via TLR4 signaling. This microbial translocation operates under the notion that particular bacteria and their products can activate the innate immune system which can trigger tumor regression. Since Paulos' findings, there has been increasing interest in further exploring the microbiome's relationship with prostate cancer treatment.

Growing evidence has shown that gut microbiota modulates how the host responds to chemotherapy drugs in a systemic fashion, such as in prostate cancer [62-64]. These studies have shown that gut microbiota have an intimate relationship with certain chemotherapies such as methotrexate, 5-fluorouracil, cyclophosphamide, irinotecan, anti-programmed death-ligand 1 and anti-cytotoxic T-lymphocyte-associated protein 4. Alexander et al. [65] proposes three main clinical outcomes from microbial influence: 1) facilitation of drug efficacy, abrogation of anticancer effects, and mediation of toxicity. From others' data, Alexander et al. [65] proposed a framework for how gut microbiota mechanistically influence chemotherapeutic pharmacologic effects: "TIMER," which stands for Translocation, Immunomodulation, Metabolism, Enzymatic degradation, and Reduced diversity. For translocation, Viaud et al. [62] discussed how a chemotherapy drug cyclophosphamide can cause a shortening of the villi in the gut intestinal wall, which allows microbes to cross and enter secondary lymphoid organs such as lymph nodes, tonsils, and the spleen. Viaud et al. [62] therefore hypothesized that cyclophosphamide's efficacy is due in part to their ability to stimulate antitumor immune responses of gut microbiota from lymphoid organ infiltration. For immunomodulation, intestinal microbiota facilitate immunomodulation of chemotherapeutic drugs [65]. For metabolism and enzymatic degradation, bacteria in the GI engage in metabolic processes such as reduction, hydrolysis, dihydroxylation, and dealkylation, which can be taken into consideration when thinking about chemotherapeutics. For reduced diversity, chemotherapy can cause changes to the microbiome which can lead to adverse outcomes such as colitis or diarrhea from proliferation of pathogenic mirobiota [65]. Montassier et al. [66] found that fecal samples collected after chemotherapy contained a decreased abundance of Firmicutes, Actinobacteria, and increases in Proteobacteria compared to the patients' samples prior to chemotherapy.

It has also been reported that *Mycoplasma hyorhinis* can metabolize the prostate cancer drug Gemcitabine into an inactive metabolite, therefore decreasing the efficacy of the drug [67]. This may be important in the personalizing of treatment for those who have an increased relative abundance of *M. hyorhinis*.

The microbial composition of the GI is changed by an-

Table 1. Studies discussed about specific gastrointestinal microbiota and prostate cancer

Study	Results	Bacteria involved
Liss et al. [44] (2018)	Rectal swabs were taken and found an increase in *Bacteroides* and *Streptococcus* in those with prostate cancer compared to controls.	*Bacteroides, Streptococcus*
Alanee et al. [53] (2019)	*Bacteroides* from fecal samples was highly associated with prostate cancer diagnosis.	*Bacteroides*
Golombos et al. [54] (2018)	*Bacteroides massiliensis* was in higher relative abundance in prostate cancer cases, while *Faecalibacterium prausnitzii* and *Eubacterium rectalie* was in higher relative abundance in controls.	*B. massiliensis, F. prausnitzii, E. rectalie*
Miyake et al. [59] (2019)	Men with more extensive prostate cancer disease (T2c-3b) had a higher rate of *Mycoplasma genitalium* infection compared to those who had benign prostate hyperplasia.	*M. genitalium*
Sfanos et al. [60] (2018)	Alpha diversity of the microbiome was greater in those without prostate cancer as compared to those with prostate cancer.	NA

NA, not applicable.

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drogen receptor axis-targeted therapies (ATT), the most common line of prostate cancer treatment [13]. Cimadamore et al. [13] showed that *Ruminococcaceae* spp. and *Akkermansia muciniphila*, which are both involved in steroid hormone biosynthesis, were linked to a more favorable response to anti–programmed death-1 (PD-1) immunotherapy. In patients who had *Ruminococcaceae* spp., antibiotic therapy was correlated with an increased risk of progressive disease. Sfanos found similar results, with a distinct difference in the GI microbiota of those on ATT compared to those without prostate cancer. In prostate cancer patients taking ATT, there was a higher relative abundance of *A. muciniphila* and *Ruminococcaceae* spp., which Cimadamore et al. [13] had described to be more favorable for anti-PD-1 immunotherapy [60]. Oral hormonal therapy for prostate cancer may influence GI micriobiota and have an effect on clinical responses and the antitumor effects of immunotherapy.

NEXT GENERATION SEQUENCING

In the past decade, we have seen a revolution of sequencing technology that has already enabled us to understand many concepts in genetics and genome biology [68]. Historically, genomic sequencing has been used primarily in the context of the tumor DNA to determine mutations such as BRCA or other somatic mutations [69]. To supplement this, Next Generation Sequencing (NGS) has been demonstrated in different phase I and II trials to extend our knowledge of the GI microbiome. This profile report by NGS contains information about the commensal and pathogenic GI bacteria detected, bacterial load, and resistance to different antibiotics detected.

This may allow for personalized treatments depending on their patient's unique microbial profile [70]. On a larger level, genomic data may shed light on the heterogeneity of microbial change of the cancer process to ultimately generate evidence between neoplasia and microbiota [71]. This can elucidate prostate cancer tumor genesis pathways and alterations of these pathways by individually distinct microbiome signatures. In addition, the implementation of NGS will lead to a decreased consumption of antibiotics by discerning microbiomes that are resistant. This will have implications for patient side-effects and a preventing growing resistance.

CONCLUSIONS

The relationship between the GI microbiome and prostate cancer is a small but growing body of knowledge. Currently, the exact relationship and mechanism of the microbiome's influence on prostate cancer is not known. Based on current literature, it seems that those who have prostate cancer and those who do not have distinct microbial profiles and different relative abundances of certain bacteria.

The proportion of directionality of the relationship between prostate cancer and GI microbiome is unclear: on one hand, the cancer changes the microbiome and leads to dysbiosis, and on the other hand, the dysbiosis itself induces neoplastic changes. The bacteria that live in the epithelial lining of the GI may influence inflammation and neoplastic events both as a local and systemic level. The local microorganism change has been implicated in GI-diseases such as inflammatory bowel disease and colitis.

The estrobiome has been postulated in describing the gut microbiome's role in systemic prostate carcinogenesis. Estrogen may promote neoplasia by activating PAHs which form carcinogenic metabolites and free radical cations.

There are certain microorganisms that are associated with increased risk of prostate cancer or more extensive prostate cancer disease. Microbes such as *Bacteroides*, *Streptococcus*, *B. massiliensis*, and *M. genitalium* were associated with greater risk, whereas *F. prausnitzii* and *E. rectalie* were higher in control groups. These particular GI bacteria should be further explored through NGS in the context of prostate cancer.

The studies presented in this review show that the GI microbiome plays a role in the pathogenesis of prostate cancer through systemic mechanisms. Understanding the specifics of gut microbiota in the context of prostate cancer is needed for the development of personalized treatments. It is critical to further explore and understand the relationships between bacteria and prostate cancer pathogenesis, development, and progression.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

AUTHORS' CONTRIBUTIONS

Research conception and design: Sybil Sha and Vladimir Mouraviev. Data acquisition: Sybil Sha. Statistical analysis: Liqiang Ni and Sybil Sha. Data analysis and interpretation: Liqiang Ni and Sybil Sha. Drafting of the manuscript: Sybil Sha, Matthew Dixon, and Maria Stefil. Critical revision of the manuscript: Sybil Sha and Vladimir Mouraviev. Obtaining funding: Vladimir Mouraviev. Administrative, technical, or material support: Vladimir Mouoraviev. Supervision: Vladimir Mouraviev. Approval of the final manuscript:

Sybil Sha and Vladimir Mouraviev.

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