The human microbiome links to prostate cancer risk and treatment (Review)

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Abstract. Prostate cancer (Pca) is the second most common cancer type worldwide. Microorganisms colonized in different body parts may affect the development/progression and treatment of Pca through direct or indirect interactions. The composition of microorganisms in different colonization sites and their effects on Pca may differ. In recent years, several studies have focused on the differences in the microbiota of patients with Pca, and dysbiosis may affect the inflammatory status, hormone levels and microbial metabolites leading to Pca progression. However, little is known about the interaction between Pca treatment and microorganisms; for example, how androgen deprivation therapy and androgen receptor axis-targeting therapeutics for Pca affect microbiota composition and metabolism, and how the microbiota affects treatment response in patients with Pca remain to be understood. The present review explored the current studies on the relevance of microbiota to Pca progression and treatment to provide direction for future microbiome-Pca research. Due to the complexity of the potential interconnections between Pca and the microbiota, further investigation is critical.

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Abbreviations: ADT, androgen deprivation therapy; AR, androgen receptor; ATT, androgen receptor axis-targeting therapeutics; BPH, benign prostatic hyperplasia; CRPC, castration-resistant prostate cancer; DHEA, dehydroepiandrosterone; FMT, fecal microbiota transplantation; HSPC, hormone-sensitive prostate cancer; ICI, immune checkpoint inhibitor; IGF-1, insulin-like growth factor-1; NGS, next-generation sequencing; Pca, prostate cancer; SCFAs, short-chain fatty acids

Key words: prostate cancer, microbiota, gut microbiome, urinary microbiome

Contents

1. Introduction

The human body contains microbiota, which plays a vital role in health and disease; the number of microorganisms is estimated to be ~10^{13}, and constitutes 1-3% of the body mass (1). Microbiota is in a symbiotic equilibrium with the host. Environmental factors including age, diet, disease and drug metabolism can lead to microbial imbalance, which can induce inflammatory responses or lead to drug resistance (2,3). Disruption of this equilibrium also has an impact on cancer; the microbiota can influence every stage of cancer as well as the therapeutic process through direct and indirect actions, the main mechanisms of which may be associated with the metabolites produced by microorganisms and the inflammatory state they cause (4,5). There are also beneficial effects of microbiota on cancer treatment, as confirmed by recent clinical trials on fecal microbiota transplantation (FMT) in combination with immunotherapy for cancer treatment, potentially opening up new targets for cancer treatment (6).

Prostate cancer (Pca) is the second most common cancer type globally, with nearly 1.4 million new cases and ~0.4 million Pca-associated mortalities worldwide in 2020 (7). Radical surgery and radiotherapy continue to be the options for treating localized diseases. Androgen deprivation therapy (ADT), hormone therapy and chemotherapy are also effective in male patients with Pca (8). However, certain patients progress to castration-resistant prostate cancer (CRPC) within 2-3 years after starting ADT treatment, resulting in a poor prognosis (9). However, there is still a lack of effective tests to distinguish between indolent and resistant Pca at an early stage. Thus, there is an urgent need for improved risk stratification tools to avoid overtreatment and under-treatment of aggressive Pca (10).

Next-generation sequencing (NGS) and metagenomics are expected further to establish the link between microbiota and

Pca, opening up new areas of Pca research (11). Microbiota may not only be a stratification factor to predict risk, but may also provide new options for treating Pca by clarifying the interaction between cancer and microbiota (12). Therefore, understanding the link between the microbiome and Pca is critical.

It has been proposed that the microbiota may have a direct or indirect effect on Pca tumorigenesis and progression. However, further research is needed to provide definitive evidence in this area (13). In the present review, focus was addressed on the effect of prostate cancer treatment on the microbiome and the scope of the microbiome was expanded to include the entire body, not just the intestinal microbiome. The present review provides a detailed overview of the current research on the role of human microorganisms in the risk, progression and treatment of Pca from the aspects of direct and indirect mechanisms.

2. Microbiota and Pca

Since 2015, studies on Pca and microbiota have mainly focused on the association between prostate microbiota and Pca. As gut microbiota research has further developed, studies focusing on the indirect effects of microbiota and Pca have increased in the last 5 years, which have explored the effects of gastrointestinal microbiota and urinary microbiota on Pca, and evaluated the association of prostatic fluid or semen with Pca.

As shown in Tables I-III, the present study systematically searched for studies related to the microbiome and Pca based on PubMed and Web of Science databases. The search included articles published up to March 11, 2023 in English language. Search keywords included 'prostate cancer OR prostatic carcinoma OR prostatic tumor' AND 'microbiome OR microbiota'. After excluding review articles (n=21), original studies related to Pca and prostate tissue, urine, semen, prostatic fluid and gut microbiota analysis were selected (n=36).

Pca and prostate microbiome (direct): Alteration of prostate microbiota in patients with Pca. Several studies have confirmed the existence of pathogens related to the risk of disease in cancerous prostate tissue, including bacteria, viruses or fungi. However, direct evidence that microorganisms contribute to the development of Pca and how microorganisms influence the progression of Pca is still lacking. In 2005, using bacterial cultures of prostate tissue, Cohen *et al* (14) found that *Propionibacterium acnes spp*. was the predominant microorganism detected in 35% of the Pca samples. In 2008, Sfanos *et al* (15) analyzed prostate tissue from 30 post-operative patients with Pca for bacterial culture and 16S ribosomal RNA (rRNA) gene sequencing. The majority of individual bacterial cultures were negative, while 16S rRNA gene sequencing showed the presence of 83 distinct microorganisms, and the authors suggested that the species present in the prostate may be 'unculturable'.

Certain studies using 16S rRNA have found that *Propionibacterium acnes* may be associated with the occurrence and progression of Pca (16-18). Cavarretta *et al* (18) assessed microbiome profiles in prostate tumors, peri-tumor and non-tumor tissues. It was found that *Propionibacterium spp*. was the predominant genera in tumor tissues, but no significant differences were found in peri-tumor and non-tumor tissues. However, considering that *Propionibacterium acnes* is one of the common sequencing contaminants and should be treated with skepticism, further studies are still needed to clarify the role of *Propionibacterium acnes* in Pca (19,20).

Geographical and ethnic diversity exists in all parts of the human microbiome (21). Feng *et al* (22) used metagenomic analysis of microbial content within prostate tumor tissue from different regions. A significant increase was identified in α-diversity from the African sample compared with the European-derived sample (P=0.004), and high-risk Pca tissues in Africa contained an abundance of anaerobic bacteria. In another study, Feng *et al* (23) analyzed the microbial content of postoperative prostate tissue from 65 Chinese patients with Pca, and it was revealed that *Escherichia*, *Propionibacterium*, *Acinetobacter* and *Pseudomonas* were the most abundant microbiome, which forms the core of the prostate tissue, which was also consistent with previous studies (16-18). Such study may be the first to investigate the association between Pca and prostatic microbiota in a Chinese population (23).

Pca and prostate microbiome (direct): Resulting chronic inflammation produced by prostate microbiota. Several studies identified viruses or infection factors from Pca tissues such as *Human papillomaviruses* and *Mycoplasma genitalium* (24,25). However, these studies were limited by the factor of sample size, and lacked supporting evidence. Another study utilized large-scale RNA-sequencing data along with matched clinical data from 242 patients with Pca from The Cancer Genome Atlas, and found that the microbiome from prostate tissue played a major anticancer role in Pca by recruiting immune cells, which were negatively correlated with Pca Gleason score, Tumor-Node-Metastasis stage, prostate-specific antigen level, and androgen receptor (AR) expression (26). Further *in vitro* and *in vivo* experiments are necessary to validate these results. A recent study compared the microbiota profile from 94 patients with Pca with tumor and benign tissue sequencing by meta-transcriptomic analysis (27). It was demonstrated that *Shewanella* was enriched in malignant prostate tissues, while *Staphylococcus saprophyticus* and *Vibrio parahaemolyticus* were decreased in malignant prostate tissues. In addition, the researchers also observed that *Microbacterium* was significantly enriched in pathologically advanced T3 (P<0.01) (27).

These studies suggested that Pca tissue contained different microbial species, which may be related to prostatic inflammation and carcinogenesis (24-27). It is generally accepted that healthy prostate tissue appears unlikely to have commensal microbiota, prostatic fluid containing high levels of zinc and antimicrobial immune proteins or prostatic epithelial cells expressing pathogen pattern recognition receptors such as Toll-like receptor 4, which block the entry and colonization of the microbiota in prostate tissue (28,29). In the pathological state, the prostate epithelial cell barrier is disrupted, and the reduction of antibacterial components in the prostatic fluid may lead to microbial infiltration and the development/progression of Pca (30). Future research is needed to investigate further the reasons for colonization of the prostate by the microbiota and the direct mechanisms of their interaction. However, ethical concerns make it difficult to truly analyze the prostate tissue of healthy individuals. The emerging organoid method may help to clarify the mechanism of prostate microbiota and Pca (31).

Table I. Selected studies up to 2023 investigating on the prostate microbiome and Pca.

Reference	Tissue	Samples	Main findings
Cohen *et al*, 2005 (14)	Fresh tissue	34 patients with Pca	*Propionibacterium acnes* was the predominant microbiome in Pca tissue and positive association with prostatic inflammation
Sfanos *et al*, 2008 (15)	Fresh Prostatectomy tissues	30 patients with Pca	Pca tissue presence of 83 distinct microorganisms, there was no significant association between the presence of particular species of bacteria and histologic evidence of acute or chronic inflammation
Alexeyev *et al*, 2006 (16)	Formalin-fixed and embedded in paraffin	352 patients with BPH of which 171 progressed to Pca	*Propionibacterium acnes* was the most common bacterium in BPH and associated with Pca development
Yow *et al*, 2017 (17)	Fresh-frozen tissue	10 patients with Pca	*Enterobacteriaceae* and *Propionibacterium acnes* was the most common species
Cavarretta *et al*, 2017 (18)	Formalin-fixed and embedded in paraffin	Tumor, Peri-tumor, and non-tumor tissues in 16 patients with Pca	*Propionibacterium spp*. was the most abundant in all regions of the tumor, *Staphylococcus spp*. were more represented in the tumor/peri-tumor tissue
Feng *et al*, 2019 (22)	Fresh-frozen tissue	6 African and 16 Australian with Pca	*Proteobacteria* was the predominance bacterial genera. Compared with Australian and Chinese, African samples had significantly increased bacterial abundance
Feng *et al*, 2019 (23)	Fresh-frozen tissue	65 patients with Pca	*Escherichia*, *Propionibacterium*, *Acinetobacter* and *Pseudomonas* were most abundant in the prostate and constituting the core of the prostate microbiome
Banerjee *et al*, 2019 (24)	Formalin-fixed and embedded in paraffin	50 patients with Pca	Some viral genomic sequences were inserted into the host Pca sample
Miyake *et al*, 2019 (25)	Formalin-fixed and embedded in paraffin	45 patients with Pca and 33 BPH	*Mycoplasma genitalium* infection was significantly different and associated with Pca and with high Gleason scores
Ma *et al*, 2020 (26)	Fresh-frozen tissue	242 Pca sequencing data from The Cancer Genome Atlas	*Listeria monocytogenes*, *Methylobacterium radiotolerans JCM 2831*, *Xanthomonas albilineans GPE PC73*, and *Bradyrhizobium japonicum* were overrepresented in tumor samples
Salachan *et al*, 2022 (27)	Fresh-frozen tissue	23 benign and 83 malignant	Under-representation of *Staphylococcus saprophyticus* and *Vibrio parahaemolyticus*, over-abundance of *Shewanella* in Pca tissue

Pca, prostate cancer; BPH, benign prostate hyperplasia.

Pca and urinary microbiome (indirect): Differences in urethral microbiota between patients with Pca and healthy individuals are inconclusive. Compared with prostate microbiota, urinary microbiota samples are easy to obtain, non-invasive and have the potential to be used as screening biomarkers that can improve prediction of Pca risk (32). Previous studies have suggested that healthy urine is sterile, while thanks to the advancement of NGS methods, recent studies have revealed that urine microbiota has unique structures that are different from gut microbiota and show diversity in different sex, ages and disease states (33-35). Urinary microbiota was associated with various female urinary diseases, including emergency urinary incontinence and overactive bladder (33). There are differences in the abundance of urinary microbiota between males and females (34). However, few studies have investigated the association between urinary microbiota and Pca.

Shrestha *et al* (36) collected urine samples from 135 patients assessed by 16S rRNA sequencing analysis and found that the abundance of *Propionibacterium lymphophilum* was significantly increased in patients with Pca; however,

Table II. Selected studies up to 2023 investigating on the urinary microbiome and Pca.

Reference	Tissue	Samples	Main findings
Shrestha *et al*, 2018 (36)	Fresh urine samples handled using sterile technique	63 benign and 66 with Pca	No significant difference in alpha/beta-diversity of urine microbiome between benign/tumor patients
Ma *et al*, 2019 (37)	Fresh-frozen prostatic fluid	32 Pca and 27 non-Pca	The diversity of microbiota in prostatic fluid of Pca patients is reduced, the abundance of *Alkaliphilus*, *Enterobacter*, *Lactococcus*, *Cronobacter*, *Carnobacterium*, and *Streptococcus* were significantly different
Yu *et al*, 2015 (38)	Urinary, EPS and seminal fluid samples without contamination	13 patients with Pca and 21 BPH	*Escherichia coli* was decrease in urine sample and *Escherichia coli* was increase in EPS and seminal fluid, *Enterococci* increased in semen in the Pca group
Alanee *et al*, 2019 (39)	First voided urine samples	16 benign and 14 with Pca	Increased abundance of *clostridium XVIII & IV*, *lachnospira*, *acetanaerobacterium*, and *faecalibacterium* in Pca patients
Tsai *et al*, 2022 (40)	Fresh-frozen urine samples	62 BPH and 62 Pca and benign	Compared with the control group, *Faecalibacterium*, *Staphylococcus*, *Ruminococcaceae_UCG_002*, *Neisseria*, and *Agathobacter* had significant abundance differences in the Pca group

Pca, prostate cancer; BPH, benign prostate hyperplasia; EPS, expressed prostatic secretions.

there was no significant difference in diversity. In the study by Guest *et al* (32), there was no significant difference in the microbiota diversity in urine samples from patients with Pca compared with controls. Previous studies have demonstrated differences in certain urinary microbiota in patients with Pca; however, the exact role of these microorganisms in Pca tumorigenesis and progression remains unclear. Further research is needed to establish a concrete connection between urinary microbiota and Pca.

The microbiota in semen and prostatic fluid appears to be more associated with prostate tissue than urine. Few studies have evaluated the association between seminal and prostatic fluid microbiota and Pca. In a study by Ma *et al* (37), 16S rRNA sequencing was used to analyze the prostatic fluid microbiota of patients with Pca. It was identified that the diversity of prostatic fluid microbiota in patients with Pca was reduced compared with the non-cancer group. No specific microbial species existed in the Pca or non-cancer groups. It was suggested that the prostatic fluid microbiome may contribute to maintaining the stability of the prostatic microenvironment.

In another Chinese cohort study, prostate/seminal fluid and urine samples from patients with Pca/benign prostatic hyperplasia (BPH) were collected for analysis. In seminal fluid, the abundance of *Enterococcus* was decreased in the Pca group, but there was little change in prostatic fluid and urine (38). Notably, in the study of prostate microbiota, several studies found that *Enterobacteriaceae* was one of the most abundant microbiotas in prostate tissue (17,27). The limitations of the study were the small sample size and the control of contamination during sampling of the urinary microbiome, which remains a problem to be solved.

In 2019, Alanee *et al* (39) found that patients with Pca had similar bacterial communities within their urinary microbiome profile, and increased abundance of *Veillonella*, *Streptococcus* and *Bacteroides*, as well as decreased abundance of *Faecalibacterium*, *Lactobaccili* and *Acinetobacter* in patients with Pca compared with patients with BPH. The researchers also collected the fecal microbiota of the patients for analysis, and no clustering was found in the fecal microbiota with benign or malignant tumor. In a similar study, researchers also found significant differences in the abundance of *Faecalibacterium* in the urine flora of the Pca group (40). The articles did not investigate whether the gut microbiome affected the urinary microbiome, although some studies have found that gut microbiota was associated with recurrent urinary tract infections (41), and FMT could reduce urinary tract infections (42). The association between gut and urine microbiota needs to be further explored.

Pca and gut microbiome (indirect): Differences in the composition of gut microbiota in patients with Pca. Although all body sites were colonized, the highest microbial counts were found in the colon (43). Gut microbiota can regulate numerous functions of the tumor-bearing organism, and thus influence tumor development and treatment (43,44). The known mechanisms include modulating the intestinal epithelial barrier, regulating the functional activity of lymphoid organs, regulating the tumor microenvironment and influencing the function of anticancer drugs (44). certain studies have been conducted to investigate

Table III. Selected studies up to 2023 investigating on the gut microbiome and Pca.

Reference	Tissue	Samples	Main findings
Zhong *et al*, 2022 (47)	Frozen fecal samples	15 patients with Pca and 20 BPH	Antibiotic exposure leads to elevated relative abundance of *Proteobacteria* and increased LPS affects Pca progression through the NF-κB-IL6-STAT3 axis in mice
Amirian *et al*, 2013 (48)	N/A	N/A	There may be significant differences in the composition of the gut microbiome among individuals at higher risk of Pca
Liss *et al*, 2018 (49)	Frozen rectal swab samples	64 with Pca and 41 without cancer	The abundant of *Bacteroides* and *Streptococcus* was significantly increased in Pca, with no significant differences in microbiome diversity
Golombos *et al*, 2018 (50)	Frozen fecal samples	8 benign and 12 with Pca	Higher relative abundance of *Bacteriodes massiliensis* was in Pca patients
Matsushita *et al*, 2021 (51)	Frozen fecal samples	96 with Pca and 56 without cancer	High-risk Pca patients had an increased relative abundance of SCFAs-producing bacteria, including *Rikenellaceae, Alistipes* and *Lachnospira*
Liu *et al*, 2019 (54)	Frozen fecal samples	N/A	11 phylotypes were decreased in abundance in HFD-fed Pca-mcie, including equol-producing bacterium *Adlercreutzia*
Liu *et al*, 2019 (55)	Frozen fecal samples	N/A	Higher abundance of *Lachonospiraceae*, *Roseburia* and *Amycolatopsis*, increased serum L-methionine decreased α-linolenic acid in combined maternal and post-weaning HFD-fed Pca mice
Matsushita *et al*, 2021 (57)	Frozen fecal samples	N/A	Gut microbiome affects IGF-1 levels in serum and prostate tissue via SCFAs, which promote Pca cell proliferation
Matsushita *et al*, 2022 (57)	Frozen fecal samples	N/A	Dysbiosis of gut microbiota leads to elevated LPS and promotes Pca progression through histamine H1 receptor signaling in HFD-fed mice
Sato *et al*, 2022 (59)	Fresh-frozen tissue	203 Pca, 150 Pca and 50 Pca sequencing data from GEO	LD-fed Pca mice abundance of *Clostridiales* and *Lactobacillales*. The proportion of the order *Lactobacillales* was negatively related with PCa progression.
Liu *et al*, 2020 (66)	Frozen fecal samples	21 matched patients with HSPC and CRPC	The abundance of *Phascolarctobacterium* and *Ruminococcus* increased in CRPC, and there was no significant difference in microbiota diversity
Li *et al*, 2021 (67)	Frozen fecal samples	56 patients on ADT and 30 patients underwent RRP	There are significant differences in the diversity of the microbiota, *Ruminococcus Gnavus* and *Bacteroides spp*. were enriched in the ADT group
Kure *et al*, 2022 (68)	Frozen fecal samples	23 Pca patients under going ADT	The abundance of *Proteobacteria* changed significantly after ADT and was positively correlated with lactate concentration
Pernigoni *et al*, 2021 (69)	Frozen fecal samples	19 patients with HSPC and 55 patients with CRPC	The gut microbiota of CRPC patients or castrated mice, including *Ruminococcus gnavus*, can convert androgen precursors into active androgens
Liu *et al*, 2021 (70)	Frozen fecal samples	5 patients with Pca	FMT from CRPC patients to prostate mice increased the abundant of *Ruminococcus*, resulting in Pca growth
Huang *et al*, 2021 (71)	Frozen fecal samples	N/A	*Akkermansiaceae* was elevated in the first three weeks of the cancer-bearing Pca mice
Sfanos *et al*, 2018 (75)	Frozen fecal samples	6 control, 3 benign and 21 Pca patients	The relative abundance was high in Pca patients taking ATT, *Akkermansia muciniphila* and *Ruminococcaceae spp*.

Table III. Continued.

Reference	Tissue	Samples	Main findings
Daisley *et al*, 2020 (76)	Frozen fecal samples	33 Pca patients without treatment, 21 with ADT alone and 14 with ADT + AA	Compared with patients without treatment, *Corynebacterium spp*. abundance was reduced in patients with ADT or ADT+AA, and *Akkermansia muciniphila* abundance was increased in patients receiving oral AA
Terrisse *et al*, 2022 (79)	Frozen fecal samples	10 patients with HSPC and 32 patients with CRPC	PC reduced the relative abundance of *Akkermansia muciniphila*, ADT reversed the effects of Pca on thymic cortical areas and increased circulating recent thymic emigrant cells
Peiffer *et al*, 2022 (80)	Frozen fecal and oral swish samples	23 with mCRPC of which 12 patients classified as responder	Decrease the abundance of *Akkermansia muciniphila* in the responded to ITT treatment samples

Pca, prostate cancer; BPH, benign prostate hyperplasia; LPS, lipopolysaccharide; SCFAs, short-chain fatty acid; HFD, high-fat diet; LD, lard diet; IGF-1, insulin-like growth factor-1; ADT, androgen deprivation therapy; HSPC, hormone-sensitive prostate cancer; CRPC, castration-resistant prostate cancer; FMT, fecal microbiota transplantation; ATT, androgen receptor axis-targeting therapeutics; AA, Abiraterone acetate; N/A, not available.

if the composition of gut microbiota may be involved in the progression of Pca, particularly CRPC. However, numerous mechanisms by which gut microbiota affects Pca remain unclear, and further research is needed to support the translation of these current results into clinical practice.

Antibiotics not only act on the bacteria that cause infections but also affect the microbiome in the body. Treatment with antibiotics affected the abundance of 1/3 of the gut microbiota and there were individual differences in recovery time (45). The use of penicillin, quinolones and sulfonamides increased the risk of Pca, which the investigators hypothesized may be associated with the human microbiota (46). In a study by Mao *et al* (47) in 2022, it was found that disruption of the intestinal barrier and dysbiosis of the gut microbiota due to antibiotic exposure exacerbated the progression of Pca. Previous studies have also found that antibiotic-induced gut microbiota disturbances affect the efficacy of docetaxel in Pca (47).

Amirian *et al* (48) hypothesized in 2013 that the composition of the gastrointestinal microbiome may be significantly different in individuals with a higher risk of Pca. This hypothesis was completed in 2018 by Liss *et al* (49), who developed a microbiome-derived risk factor to predict the future risk of Pca. The aforementioned study assessed the gut microbiota composition, and found that *Bacteroides* and *Streptococcus* were enriched in the Pca group. A previous study also illustrated an increased relative abundance of *Bacteroides* in the gut microbiome of patients with Pca compared with patients with BPH (50). Similarly, Matsushita *et al* (51) identified that patients with high-risk Pca had an increased relative abundance of short-chain fatty acids (SCFAs)-producing bacteria. These studies have suggested a correlation between gut microbiota composition and Pca risk, potentially due to microbiota metabolites, which has implications for identifying high-risk patients and may provide additional insights into the development of Pca.

Pca and gut microbiome (indirect): Lifestyle habits affect Pca through the gut microbiome. Lifestyle, particularly dietary patterns, also have a significant impact on the occurrence and development of Pca (8). Previous studies have shown that obesity due to a high-fat diet (HFD) induces chronic systemic inflammation and participates in the progression of Pca, and one of the possible mechanisms involved may be the gut microbiota (52,53). One study found that the abundance of 21 bacterial phylotypes in the gut microbiota of HFD-fed mice with Pca was increased, and the abundance of equol-producing bacteria *Adlercreutzia* was decreased compared with the control group, and the serum equol of HFD-mice was significantly decreased (54). Another study by the same group found that post-weaning HFD significantly promoted Pca in the offspring, yet combined maternal HFD and post-weaning HFD decreased Pca progression in the offspring (55). The gut microbiota compositions are predominantly of vertical inheritance (56), and additional studies may be needed to clarify the correlation between vertically transmitted microbiota profile and Pca.

To investigate the effect of HFD on Pca progression, Matsushita *et al* (57) found that, in HFD-fed Pca mice, oral administration of an antibiotic mixture significantly altered the abundance of gut microbiota, inhibited the proliferation of Pca cells, and reduced circulating insulin-like growth factor-1 (IGF-1) levels and prostate IGF-1 expression. The results suggested the existence of a gut microbiota-IGF-1-prostate axis. The authors found that the gut microbiota may be associated with tumor progression through the generation of SCFAs, leading to elevated IGF-1 levels (57). In another study, HFD-fed mice prostate tissue expression of Hdc and gene levels of histamine receptors were upregulated. Fexofenadine, a histamine H1 receptor antagonist, significantly reduced the proliferation of Pca cells in HFD-fed mice by suppressing the IL6/STAT3 signaling pathway (58). There were also differences in the

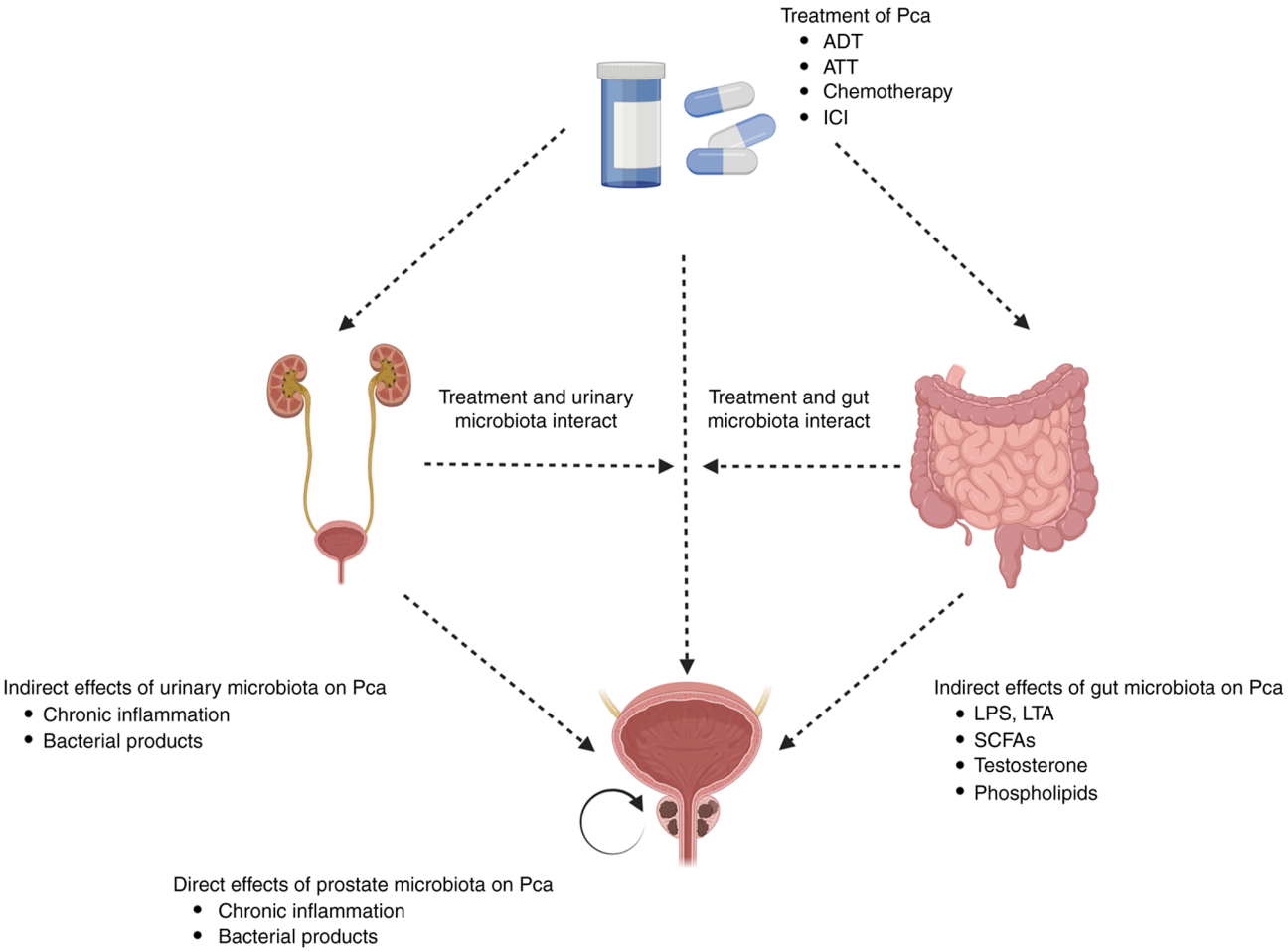

Figure 1. The direct/indirect connection of microbiota in Pca progression and treatment. Studies have indicated that prostate, urethral, and intestinal microbiota may be directly or indirectly involved in the progression of Pca, potentially through the induction of chronic tissue inflammation or the stimulation of microbiota products. There is a close relationship between the microbiota and Pca treatment, as the administration of treatment can alter the microbiota structure of patients, and microbiota may also affect the efficacy of Pca treatment. Pca, prostate cancer; ADT, androgen deprivation therapy; ATT, androgen receptor axis-targeting therapeutics; ICI, immune checkpoint inhibitor; LPS, lipopolysaccharide; SCFAs, short-chain fatty acid; LTA, lymphotoxin alpha.

composition and diversity of gut microbiota in mice fed with different components of HFD, such as lard and fish oil diets, and it was revealed that a diet rich in saturated fatty acids could lead to the progression of Pca and change the abundance of gut microbiota (59). The gut microbiota dysbiosis caused by HFD leads to Pca progression through multiple pathways, which further supports the existence of the gut microbiota-prostate axis. Modifying dietary patterns and intervention of gut microbiota may reduce the risk of Pca development (52-55,57-59).

Microbiota and Pca therapy: Interaction of microbiota with Pca treatment. As shown in Fig. 1, antitumor treatment could potentially result in changes in the microbiota profile, and the microbiota could also affect the efficacy of the treatment or the absorption and metabolism of the drug (44,60). The mechanisms linking the human gut microbiome with treatment could be an important basis for a new generation of therapies. In 2018, Routy *et al* (61) found that patients treated with antibiotics developed resistance to anti-PD-1 immunotherapy drugs. By comparing the gut microbiome of patients with cancer who responded to this immunotherapy with that of patients with cancer who did not respond, it was found that the relative abundance of *Akkermansia muciniphila* correlated with clinical response to this immunotherapy in patients with cancer. It has also been found that patients with high levels of *Bifidobacterium longum*, *Collinsella aerofaciens* and *Enterococcus faecium* have a higher propensity to respond to anti-PD-L1 therapy, and FMT from responding patients to germ-free mice may improve the efficacy of anti-PD-L1 therapy (62). Patients treated with chemotherapy/radiotherapy also showed significant changes in the composition of the microbiota. A recent study revealed significant differences in gut microbiota abundance at the end of chemo-radiation therapy for rectal cancer, and these changes were associated with ethnic or regional factors (63). Individual differences in microbiota resulted by regional, ethnic, dietary and genetic factors affect the efficacy of oncology treatment, and treatment also changes the composition of the microbiota. The interaction between cancer management and microbiota may be one of the key factors contributing to the individualized differences in oncology treatment (64).

For Pca, radiotherapy/chemotherapy as well as ADT treatment have the potential to influence the gut/urine/prostate microbiota composition; however, few studies have precisely elucidated the effect of specific microbial species or microbial profiles on the efficacy or toxicity of Pca treatment. FMT can

alter the composition of the intestinal microbiota. A clinical trial (trial registration number NCT03341143) in 2021 found that treatment of PD-1-refractory melanoma with FMT in combination with anti-PD-1 drugs was effective in enhancing the efficacy of PD-1 drugs, and the results of the study showed that the use of FMT could alter the gut microbiome of patients and affect the tumor microenvironment to overcome anti-PD-1 therapy resistance in patients with melanoma (6). In addition, certain probiotics have been found to be effective in promoting cancer cell apoptosis and combating oxidative stress, and probiotic supplementation has also been shown to reduce the adverse effects of chemotherapy/radiotherapy and immunotherapy (60). In summary, recent studies have shown that microbiota composition is crucial to the efficacy of oncology treatment. On one hand, knowing the microbiota composition of a patient before treatment can assist physicians in determining the most appropriate treatment protocol for the patient; on the other hand, targeting therapy to the microbiota can also enhance the patient's response to other oncological treatments (62). It is necessary to gain an improved understanding of the correlation between different profiles of microbiota and treatment in Pca, so that the role of microbiota in the treatment of Pca can be comprehensively appreciated.

ADT remains the primary treatment for patients with advanced Pca. Although nearly all patients respond to ADT, which is termed hormone-sensitive prostate cancer (HSPC), the duration of ADT treatment sensitivity varies from months to years, and patients often develop resistance to ADT, which is termed CRPC (65). Several studies have hypothesized that intestinal microbiota may play a role in the resistance of Pca to ADT. Liu and Jiang (66) used 16S rRNA to compare the microbiota of patients with Pca (n=21) before and after ADT treatment, and 12 microbial phylotypes including *Phascolarctobacterium* and *Ruminococcus* were found to have increased abundance in the gut microbiota of patients with CRPC after ADT treatment. Another study similarly found significant differences in microbiota diversity among patients with Pca treated with ADT (n=56), with an increased abundance of the pro-inflammatory bacteria *Ruminococcus gnavus* and *Bacteroides spp*. (67). It was identified that the gut microbiota changed over time not only before and after ADT, but also after ADT. Kure *et al* (68) revealed that microbiota diversity decreased significantly at 24 weeks after ADT, and the abundance of *Proteobacteria* changed significantly after ADT, and was positively correlated with lactate concentration. Previous studies have found that ADT can lead to significant changes in the microbiota of patients with CRPC. These findings suggest a possible link between ADT and alterations in the microbiota, but there is a lack of evidence on how gut microbiota affects Pca progression after ADT.

In 2021, Pernigoni *et al* (69) showed that the expansion of androgen-synthesizing gut microbiota may mediate resistance to ADT. The study used two mouse models of Pca that initially showed tumor shrinkage after surgical castration and subsequent progression to CRPC, and *Ruminococcus gnavus* was significantly enriched in CRPC mice. In patients with CRPC, *Ruminococcus* was also shown to be significantly enriched and associated with phospholipid metabolism (70). Next, the investigators performed FMT from CRPC mice and healthy mice on recipient mice in the castration-sensitive phase. The results revealed that FMT from healthy mice inhibited tumor growth, while FMT from CRPC mice led to tumor progress. Metabolomic analysis showed that the dehydroepiandrosterone (DHEA) and testosterone levels were significantly elevated in FMT-CRPC mice. Similarly, functional analysis in a previous study showed an increase in the taxa of bacteria with steroid biosynthesis functions in Pca mice (71). *In vivo* and *in vitro*, Pernigoni *et al* (69) demonstrated the ability of *Ruminococcus gnavus* to convert pregnenolone into active DHEA and testosterone. The aforementioned studies observed increased abundance of certain gut microbiota, including *Ruminococcus* (66,69,70), *Bacteroides* (67,69) and *Phascolarctobacterium* (66), which act as antagonists to ADT, potentially due to the additional androgens provided by specific genus. While most studies have primarily focused on increasing the fraction of microbiota after ADT treatment, few have investigated which microbiota exhibit decreased in abundance post-treatment, which may be a potential target for probiotic supplementation in CRPC. For instance, *Prevotella* enrichment in HSPC has been found to inhibit Pca progression in mice (69).

There is an interactive association between gut microbiota and drug therapy. On one hand, it has been shown that gut microbiota impacts drug absorption, disposal, metabolism, pharmacology or toxicity. On the other hand, drug treatment can also lead to changes in gut microbiota and affect the host (47,72). However, few studies have clarified the effect of specific microbial species on the efficacy/toxicity of drug therapy for Pca.

In patients with CRPC, there were still small concentrations of extragonadal androgens present even after the end of ADT treatment, part of which was synthesized by the gut microbiota (69), and systemic upregulation of androgen synthesis could also activate the AR pathway in Pca cells (73). Based on these observations, oral AR axis-targeting therapeutics (ATT) have become one of the prominent treatment options for patients with advanced CRPC, including abiraterone acetate and enzalutamide (74). Sfanos *et al* (75) found that the abundance of *Akkermansia muciniphila* and *Ruminococcaceae spp*. was higher in patients with Pca receiving ATT (including bicalutamide, enzalutamide and abiraterone acetate), and functional enrichment analysis suggested a significant enrichment in the oral ATT group for functions involved in steroid/hormone biosynthesis. A previous study has shown a correlation between the relative abundance of *Akkermansia muciniphila* and clinical responses to immune checkpoint inhibitors (ICIs), and it was observed that oral supplementation with *Akkermansia muciniphila* restored the efficacy of PD-1 blockers (61). Following treatment with ATT in patients with Pca, a study found that treatment with abiraterone acetate resulted in enrichment in *Akkermansia muciniphila*, which, through a specific interaction with abiraterone acetate, increased the ability to synthesize vitamin K2 and influenced treatment response in patients with Pca (76). These current results suggested that the role of gut microbiota in ATT treatment was inconsistent. Part of genera may attenuate the effect of ATT treatment by synthesizing extra-tumoral androgens, while part of genera may play a synergistic role with ATT through other pathways, and different genera could play different roles.

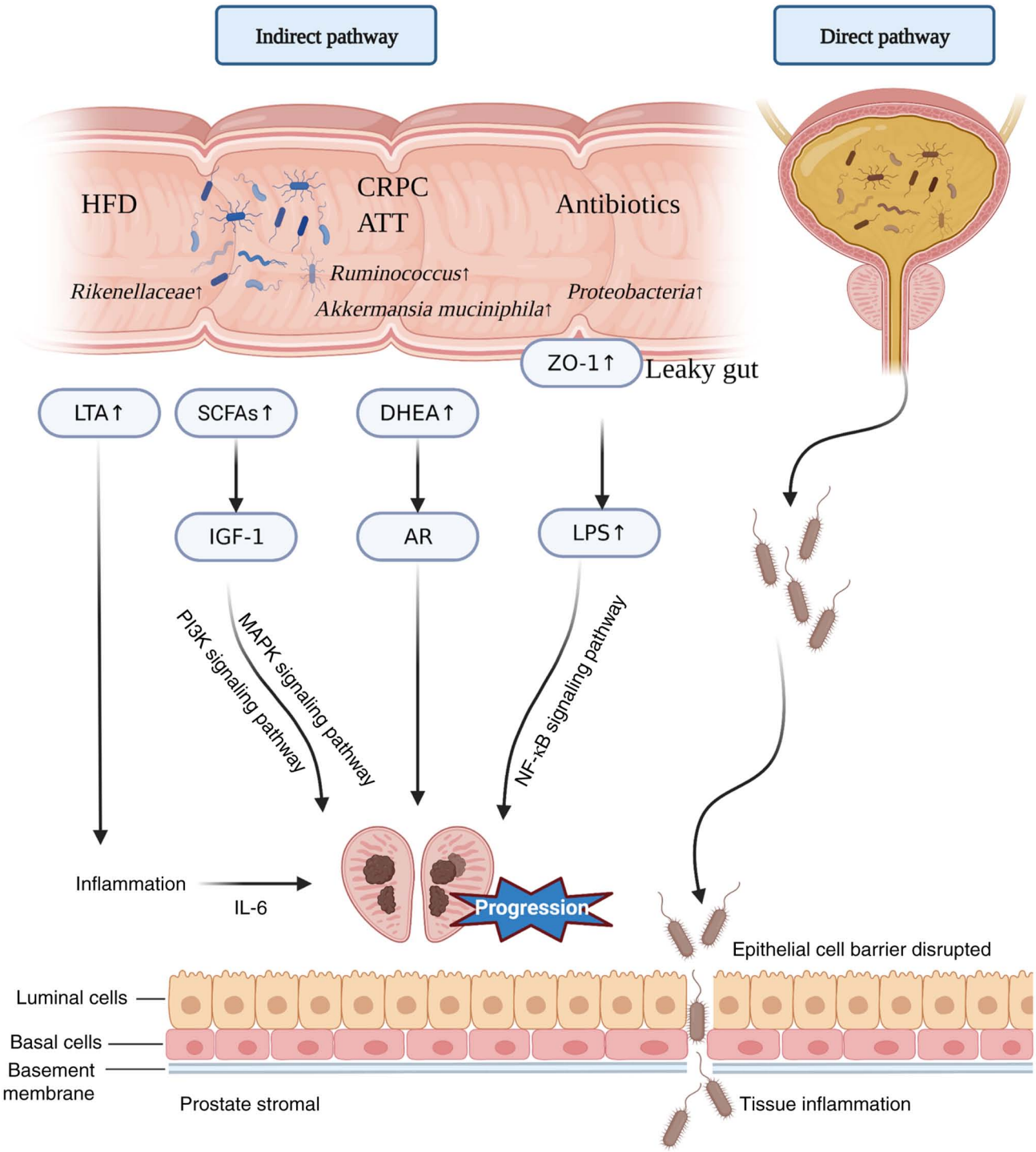

Figure 2. Mechanisms of impact of gut and urinary microbiota on Pca. Antibiotic use leads to increased intestinal permeability and infiltration of the bacterial component LPS into the body circulation, promoting Pca progression. HFDs promote Pca progression by upregulating IL-6 and promoting local inflammation in the prostate. SCFAs have been found to play an important role in the promotion of Pca growth. The ATT or CRPC cause an increase of *Ruminococcus* in the gut, and the production of DHEA promotes Pca growth. Disruption of the prostate epithelial cell barrier in pathological states may contribute to microbial infiltration and the progression of Pca. Pca, prostate cancer; LPS, lipopolysaccharide; HFD, high-fat diet; SCFA, short-chain fatty acid; ATT, androgen receptor axis-targeting therapeutics; CRPC, castration-resistant prostate cancer; DHEA, dehydroepiandrosterone; IGF-1, insulin-like growth factor-1; AR, androgen receptor; LTA, lymphotoxin alpha; ZO-1, zonula occludens-1.

Significant variability in the response of ICIs such as anti-CTLA-4 and anti-PD-L1 in different individuals and tumor types could also be attributed to the effect of gut microbiota (61,77). The gut microbiota composition was found to predict response to anti-PD-1 therapy (78), and FMT from immunotherapy-responsive patients into tumor xenograft mouse models enhanced antitumor immunity (61,77). Terrisse *et al* (79) found that the immune system and gut microbiota determined the efficacy of ADT in Pca, and that ADT reversed the effects of Pca on thymic cortical areas and increased circulating thymic emigrant cells. However, treatment with ICI in patients with Pca did not enhance the efficacy of ADT.

To investigate whether different gut microbiota composition affects the efficacy of ITT therapy in Pca, Peiffer *et al* (80) performed 16S rRNA gene sequencing of the profile of gut microbiota of patients with CRPC before and after anti-PD-1 treatment, and inconsistent with previous results from other oncology studies (61), the study found a decrease in the relative abundance of *Akkermansia muciniphila* in the responding samples. Shaikh *et al* (78) combined sequencing data from multiple ICI-related microbiome studies to develop an integrated microbiome prediction index to identify whether or not there was a response to ICI therapy. However, the study found no significant difference in the index results between responders and non-responders (80). In the area of Pca, the interactive effect of microbiota and ICI needs further investigation.

3. Conclusions and future directions

The present review aimed to clarify the direction of subsequent research by providing the current state of research in Pca and microbiota research. An increasing number of studies have been conducted to analyze the correlation between microbiota and Pca. Microbiota is recognized as one of the potentially critical factors influencing Pca development/progression. However, there is still a lack of adequate understanding of the mechanisms of microbiota at different locations in the development/progression and treatment of Pca. Recent studies have demonstrated that, compared with healthy individuals, there may be differences in the abundance of microbiota in patients with Pca, whether in the urethra, prostate tissue or intestine. Nevertheless, the research provided in the present review often presents conflicting information, emphasizing the need for further study in this area using a standardized approach.

Research on the association between urinary and prostate microbiota and Pca has progressed slowly. Previous studies suggest that epithelial structural disruption and inflammatory states leading to colonization may be potential mechanisms for Pca progression. However, this mechanism is not yet understood. Gut microbiota may act indirectly through different microbiota metabolites and sex hormone levels, and influence Pca progression and treatment (Fig. 2). Understanding how gut microbiota affects Pca will help to stratify in an improved manner the risk of Pca progression and develop new treatments. The impact of the microbiome on cancer (including Pca) treatment is bilateral. On one hand, the microbiome can significantly influence the treatment of cancer, while cancer treatment can in turn shape the composition of the microbiome. As therapeutic tools continue to evolve, particularly ATT treatment for Pca, it is critical to explore and understand the complex underlying links between Pca and the microbiome.

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Competing interests

The authors declare that they have no competing interests.

References

1. Sender R, Fuchs S and Milo R: Revised estimates for the number of human and bacteria cells in the body. PLoS Biol 14: e1002533, 2016.
2. Lynch SV and Pedersen O: The human intestinal microbiome in health and disease. N Engl J Med 375: 2369-2379, 2016.
3. Marchesi JR, Adams DH, Fava F, Hermes GD, Hirschfield GM, Hold G, Quraishi MN, Kinross J, Smidt H, Tuohy KM, *et al*: The gut microbiota and host health: A new clinical frontier. Gut 65: 330-339, 2016.
4. Xavier JB, Young VB, Skufca J, Ginty F, Testerman T, Pearson AT, Macklin P, Mitchell A, Shmulevich I, Xie L, *et al*: The cancer microbiome: Distinguishing direct and indirect effects requires a systemic view. Trends Cancer 6: 192-204, 2020.
5. Whisner CM and Aktipis CA: The role of the microbiome in cancer initiation and progression: how microbes and cancer cells utilize excess energy and promote one another's growth. Curr Nutr Rep 8: 42-51, 2019.
6. Davar D, Dzutsev AK, McCulloch JA, Rodrigues RR, Chauvin JM, Morrison RM, Deblasio RN, Menna C, Ding Q, Pagliano O, *et al*: Fecal microbiota transplant overcomes resistance to anti-PD-1 therapy in melanoma patients. Science 371: 595-602, 2021.
7. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A and Bray F: Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin 71: 209-249, 2021.
8. Litwin MS and Tan HJ: The diagnosis and treatment of prostate cancer: A review. JAMA 317: 2532-2542, 2017.
9. Chandrasekar T, Yang JC, Gao AC and Evans CP: Mechanisms of resistance in castration-resistant prostate cancer (CRPC). Transl Androl Urol 4: 365-380, 2015.
10. Bratt O, Folkvaljon Y, Eriksson MH, Akre O, Carlsson S, Drevin L, Lissbrant IF, Makarov D, Loeb S and Stattin P: Undertreatment of men in their seventies with high-risk nonmetastatic prostate cancer. Eur Urol 68: 53-58, 2015.
11. Salachan PV and Sørensen KD: Dysbiotic microbes and how to find them: A review of microbiome profiling in prostate cancer. J Exp Clin Cancer Res 41: 31, 2022.
12. Alexander JL, Wilson ID, Teare J, Marchesi JR, Nicholson JK and Kinross JM: Gut microbiota modulation of chemotherapy efficacy and toxicity. Nat Rev Gastroenterol Hepatol 14: 356-365, 2017.
13. Katongole P, Sande OJ, Joloba M, Reynolds SJ and Niyonzima N: The human microbiome and its link in prostate cancer risk and pathogenesis. Infect Agent Cancer 15: 53, 2020.

14. Cohen RJ, Shannon BA, McNeal JE, Shannon T and Garrett KL: Propionibacterium acnes associated with inflammation in radical prostatectomy specimens: A possible link to cancer evolution? J Urol 173: 1969-1974, 2005.
15. Sfanos KS, Sauvageot J, Fedor HL, Dick JD, De Marzo AM and Isaacs WB: A molecular analysis of prokaryotic and viral DNA sequences in prostate tissue from patients with prostate cancer indicates the presence of multiple and diverse microorganisms. Prostate 68: 306-320, 2008.
16. Alexeyev O, Bergh J, Marklund I, Thellenberg-Karlsson C, Wiklund F, Grönberg H, Bergh A and Elgh F: Association between the presence of bacterial 16S RNA in prostate specimens taken during transurethral resection of prostate and subsequent risk of prostate cancer (Sweden). Cancer Causes Control 17: 1127-1133, 2006.
17. Yow MA, Tabrizi SN, Severi G, Bolton DM, Pedersen J, Giles GG and Southey MC: Australian prostate cancer bioresource: Characterisation of microbial communities within aggressive prostate cancer tissues. Infect Agent Cancer 12: 4, 2017.
18. Cavarretta I, Ferrarese R, Cazzaniga W, Saita D, Lucianò R, Ceresola ER, Locatelli I, Visconti L, Lavorgna G, Briganti A, *et al*: The microbiome of the prostate tumor microenvironment. Eur Urol 72: 625-631, 2017.
19. Eisenhofer R, Minich JJ, Marotz C, Cooper A, Knight R and Weyrich LS: Contamination in low microbial biomass microbiome studies: Issues and recommendations. Trends Microbiol 27: 105-117, 2019.
20. Achermann Y, Goldstein EJ, Coenye T and Shirtliff ME: Propionibacterium acnes: From commensal to opportunistic biofilm-associated implant pathogen. Clin Microbiol Rev 27: 419-440, 2014.
21. Lloyd-Price J, Abu-Ali G and Huttenhower C: The healthy human microbiome. Genome Med 8: 51, 2016.
22. Feng Y, Jaratlerdsiri W, Patrick SM, Lyons RJ, Haynes AM, Collins CC, Stricker PD, Bornman MSR and Hayes VM: Metagenomic analysis reveals a rich bacterial content in high-risk prostate tumors from African men. Prostate 79: 1731-1738, 2019.
23. Feng Y, Ramnarine VR, Bell R, Volik S, Davicioni E, Hayes VM, Ren S and Collins CC: Metagenomic and metatranscriptomic analysis of human prostate microbiota from patients with prostate cancer. BMC Genomics 20: 146, 2019.
24. Banerjee S, Alwine JC, Wei Z, Tian T, Shih N, Sperling C, Guzzo T, Feldman MD and Robertson ES: Microbiome signatures in prostate cancer. Carcinogenesis 40: 749-764, 2019.
25. Miyake M, Ohnishi K, Hori S, Nakano A, Nakano R, Yano H, Ohnishi S, Owari T, Morizawa Y, Itami Y, *et al*: Mycoplasma genitalium infection and chronic inflammation in human prostate cancer: Detection using prostatectomy and needle biopsy specimens. Cells 8: 212, 2019.
26. Ma J, Gnanasekar A, Lee A, Li WT, Haas M, Wang-Rodriguez J, Chang EY, Rajasekaran M and Ongkeko WM: Influence of intratumor microbiome on clinical outcome and immune processes in prostate cancer. Cancers (Basel) 12: 2524, 2020.
27. Salachan PV, Rasmussen M, Fredsøe J, Ulhøi B, Borre M and Sørensen KD: Microbiota of the prostate tumor environment investigated by whole-transcriptome profiling. Genome Med 14: 9, 2022.
28. Stamey TA, Fair WR, Timothy MM and Chung HK: Antibacterial nature of prostatic fluid. Nature 218: 444-447, 1968.
29. Gatti G, Quintar AA, Andreani V, Nicola JP, Maldonado CA, Masini-Repiso AM, Rivero VE and Maccioni M: Expression of toll-like receptor 4 in the prostate gland and its association with the severity of prostate cancer. Prostate 69: 1387-1397, 2009.
30. Sfanos KS, Yegnasubramanian S, Nelson WG and De Marzo AM: The inflammatory microenvironment and microbiome in prostate cancer development. Nat Rev Urol 15: 11-24, 2018.
31. Weeber F, Ooft SN, Dijkstra KK and Voest EE: Tumor organoids as a pre-clinical cancer model for drug discovery. Cell Chem Biol 24: 1092-1100, 2017.
32. Guest C, Harris R, Sfanos KS, Shrestha E, Partin AW, Trock B, Mangold L, Bader R, Kozak A, Mclean S, *et al*: Feasibility of integrating canine olfaction with chemical and microbial profiling of urine to detect lethal prostate cancer. PLoS One 16: e0245530, 2021.
33. Hilt EE, Putonti C, Thomas-White K, Lewis AL, Visick KL, Gilbert NM and Wolfe AJ: Aerococcus urinae isolated from women with lower urinary tract symptoms: In Vitro aggregation and genome analysis. J Bacteriol 202: e00170-e20, 2020.
34. Lewis DA, Brown R, Williams J, White P, Jacobson SK, Marchesi JR and Drake MJ: The human urinary microbiome; bacterial DNA in voided urine of asymptomatic adults. Front Cell Infect Microbiol 3: 41, 2013.
35. Adebayo AS, Ackermann G, Bowyer RCE, Wells PM, Humphreys G, Knight R, Spector TD and Steves CJ: The urinary tract microbiome in older women exhibits host genetic and environmental influences. Cell Host Microbe 28: 298-305.e3, 2020.
36. Shrestha E, White JR, Yu SH, Kulac I, Ertunc O, De Marzo AM, Yegnasubramanian S, Mangold LA, Partin AW and Sfanos KS: Profiling the urinary microbiome in men with positive versus negative biopsies for prostate cancer. J Urol 199: 161-171, 2018.
37. Ma X, Chi C, Fan L, Dong B, Shao X, Xie S, Li M and Xue W: The microbiome of prostate fluid is associated with prostate cancer. Front Microbiol 10: 1664, 2019.
38. Yu H, Meng H, Zhou F, Ni X, Shen S and Das UN: Urinary microbiota in patients with prostate cancer and benign prostatic hyperplasia. Arch Med Sci 11: 385-394, 2015.
39. Alanee S, El-Zawahry A, Dynda D, Dabaja A, McVary K, Karr M and Braundmeier-Fleming A: A prospective study to examine the association of the urinary and fecal microbiota with prostate cancer diagnosis after transrectal biopsy of the prostate using 16S RNA gene analysis. Prostate 79: 81-87, 2019.
40. Tsai KY, Wu DC, Wu WJ, Wang JW, Juan YS, Li CC, Liu CJ and Lee HY: Exploring the association between gut and urine microbiota and prostatic disease including benign prostatic hyperplasia and prostate cancer using 16S rRNA sequencing. Biomedicines 10: 2676, 2022.
41. Worby CJ, Schreiber HL IV, Straub TJ, van Dijk LR, Bronson RA, Olson BS, Pinkner JS, Obernuefemann CLP, Muñoz VL, Paharik AE, *et al*: Longitudinal multi-omics analyses link gut microbiome dysbiosis with recurrent urinary tract infections in women. Nat Microbiol 7: 630-639, 2022.
42. Jeney SES, Lane F, Oliver A, Whiteson K and Dutta S: Fecal microbiota transplantation for the treatment of refractory recurrent urinary tract infection. Obstet Gynecol 136: 771-773, 2020.
43. de Vos WM, Tilg H, Van Hul M and Cani PD: Gut microbiome and health: Mechanistic insights. Gut 71: 1020-1032, 2022.
44. Sepich-Poore GD, Zitvogel L, Straussman R, Hasty J, Wargo JA and Knight R: The microbiome and human cancer. Science 371: eabc4552, 2021.
45. Dethlefsen L, Huse S, Sogin ML and Relman DA: The pervasive effects of an antibiotic on the human gut microbiota, as revealed by deep 16S rRNA sequencing. PLoS Biol 6: e280, 2008.
46. Boursi B, Mamtani R, Haynes K and Yang YX: Recurrent antibiotic exposure may promote cancer formation-another step in understanding the role of the human microbiota? Eur J Cancer 51: 2655-2664, 2015.
47. Zhong W, Wu K, Long Z, Zhou X, Zhong C, Wang S, Lai H, Guo Y, Lv D, Lu J and Mao X: Gut dysbiosis promotes prostate cancer progression and docetaxel resistance via activating NF-κB-IL6-STAT3 axis. Microbiome 10: 94, 2022.
48. Amirian ES, Petrosino JF, Ajami NJ, Liu Y, Mims MP and Scheurer ME: Potential role of gastrointestinal microbiota composition in prostate cancer risk. Infect Agent Cancer 8: 42, 2013.
49. Liss MA, White JR, Goros M, Gelfond J, Leach R, Johnson-Pais T, Lai Z, Rourke E, Basler J, Ankerst D and Shah DP: Metabolic biosynthesis pathways identified from fecal microbiome associated with prostate cancer. Eur Urol 74: 575-582, 2018.
50. Golombos DM, Ayangbesan A, O'Malley P, Lewicki P, Barlow L, Barbieri CE, Chan C, DuLong C, Abu-Ali G, Huttenhower C and Scherr DS: The role of gut microbiome in the pathogenesis of prostate cancer: A prospective, pilot study. Urology 111: 122-128, 2018.
51. Matsushita M, Fujita K, Motooka D, Hatano K, Fukae S, Kawamura N, Tomiyama E, Hayashi Y, Banno E, Takao T, *et al*: The gut microbiota associated with high-Gleason prostate cancer. Cancer Sci 112: 3125-3135, 2021.
52. Hayashi T, Fujita K, Nojima S, Hayashi Y, Nakano K, Ishizuya Y, Wang C, Yamamoto Y, Kinouchi T, Matsuzaki K, *et al*: High-fat diet-induced inflammation accelerates prostate cancer growth via IL6 signaling. Clin Cancer Res 24: 4309-4318, 2018.
53. Smith KS, Frugé AD, van der Pol W, Caston NE, Morrow CD, Demark-Wahnefried W and Carson TL: Gut microbial differences in breast and prostate cancer cases from two randomised controlled trials compared to matched cancer-free controls. Benef Microbes 12: 239-248, 2021.
54. Liu Y, Wu X and Jiang H: High dietary fat intake lowers serum equol concentration and promotes prostate carcinogenesis in a transgenic mouse prostate model. Nutr Metab (Lond) 16: 24, 2019.
55. Liu Y, Wu X and Jiang H: Combined maternal and post-weaning high fat diet inhibits male offspring's prostate cancer tumorigenesis in transgenic adenocarcinoma of mouse prostate model. Prostate 79: 544-553, 2019.

56. Moeller AH, Suzuki TA, Phifer-Rixey M and Nachman MW: Transmission modes of the mammalian gut microbiota. Science 362: 453-457, 2018.
57. Matsushita M, Fujita K, Hayashi T, Kayama H, Motooka D, Hase H, Jingushi K, Yamamichi G, Yumiba S, Tomiyama E, *et al*: Gut microbiota-derived short-chain fatty acids promote prostate cancer growth via IGF1 signaling. Cancer Res 81: 4014-4026, 2021.
58. Matsushita M, Fujita K, Hatano K, Hayashi T, Kayama H, Motooka D, Hase H, Yamamoto A, Uemura T, Yamamichi G, *et al*: High-fat diet promotes prostate cancer growth through histamine signaling. Int J Cancer 151: 623-636, 2022.
59. Sato H, Narita S, Ishida M, Takahashi Y, Mingguo H, Kashima S, Yamamoto R, Koizumi A, Nara T, Numakura K, *et al*: Specific gut microbial environment in lard diet-induced prostate cancer development and progression. Int J Mol Sci 23: 2214, 2022.
60. Badgeley A, Anwar H, Modi K, Murphy P and Lakshmikuttyamma A: Effect of probiotics and gut microbiota on anti-cancer drugs: Mechanistic perspectives. Biochim Biophys Acta Rev Cancer 1875: 188494, 2021.
61. Routy B, Le Chatelier E, Derosa L, Duong CPM, Alou MT, Daillère R, Fluckiger A, Messaoudene M, Rauber C, Roberti MP, *et al*: Gut microbiome influences efficacy of PD-1-based immunotherapy against epithelial tumors. Science 359: 91-97, 2018.
62. Matson V, Fessler J, Bao R, Chongsuwat T, Zha Y, Alegre ML, Luke JJ and Gajewski TF: The commensal microbiome is associated with anti-PD-1 efficacy in metastatic melanoma patients. Science 359: 104-108, 2018.
63. González- Mercado VJ, Lim J, Berk L, Esele M, Rodríguez CS and Colón-Otero G: Gut microbiota differences in Island Hispanic Puerto Ricans and mainland non-Hispanic whites during chemoradiation for rectal cancer: A pilot study. Curr Probl Cancer 44: 100551, 2020.
64. Dai Z, Fu J, Peng X, Tang D and Song J: Intestinal microbiota: The driving force behind advances in cancer immunotherapy. Cancers (Basel) 14: 4796, 2022.
65. Watson PA, Arora VK and Sawyers CL: Emerging mechanisms of resistance to androgen receptor inhibitors in prostate cancer. Nat Rev Cancer 15: 701-711, 2015.
66. Liu Y and Jiang H: Compositional differences of gut microbiome in matched hormone-sensitive and castration-resistant prostate cancer. Transl Androl Urol 9: 1937-1944, 2020.
67. Li JKM, Wang LL, Wong CYP, Chiu PKF, Teoh JYC, Kwok HSW, Leung SCH, Wong SH, Tsui SKW and Ng CF: A cross-sectional study on gut microbiota in prostate cancer patients with prostatectomy or androgen deprivation therapy. Prostate Cancer Prostatic Dis 24: 1063-1072, 2021.
68. Kure A, Tsukimi T, Ishii C, Aw W, Obana N, Nakato G, Hirayama A, Kawano H, China T, Shimizu F, *et al*: Gut environment changes due to androgen deprivation therapy in patients with prostate cancer. Prostate Cancer Prostatic Dis 13: 10.1038/s41391-022-00536-3, 2022.
69. Pernigoni N, Zagato E, Calcinotto A, Troiani M, Mestre RP, Calì B, Attanasio G, Troisi J, Minini M, Mosole S, *et al*: Commensal bacteria promote endocrine resistance in prostate cancer through androgen biosynthesis. Science 374: 216-224, 2021.
70. Liu Y, Yang C, Zhang Z and Jiang H: Gut microbiota dysbiosis accelerates prostate cancer progression through increased LPCAT1 expression and enhanced DNA repair pathways. Front Oncol 11: 679712, 2021.
71. Huang PY, Yang YC, Wang CI, Hsiao PW, Chiang HI and Chen TW: Increase in Akkermansiaceae in gut microbiota of prostate cancer-bearing mice. Int J Mol Sci 22: 9626, 2021.
72. Wilson ID and Nicholson JK: Gut microbiome interactions with drug metabolism, efficacy, and toxicity. Transl Res 179: 204-222, 2017.
73. Mohler JL, Gregory CW, Ford OH III, Kim D, Weaver CM, Petrusz P, Wilson EM and French FS: The androgen axis in recurrent prostate cancer. Clin Cancer Res 10: 440-448, 2004.
74. Buttigliero C, Tucci M, Bertaglia V, Vignani F, Bironzo P, Di Maio M and Scagliotti GV: Understanding and overcoming the mechanisms of primary and acquired resistance to abiraterone and enzalutamide in castration resistant prostate cancer. Cancer Treat Rev 41: 884-892, 2015.
75. Sfanos KS, Markowski MC, Peiffer LB, Ernst SE, White JR, Pienta KJ, Antonarakis ES and Ross AE: Compositional differences in gastrointestinal microbiota in prostate cancer patients treated with androgen axis-targeted therapies. Prostate Cancer Prostatic Dis 21: 539-548, 2018.
76. Daisley BA, Chanyi RM, Abdur-Rashid K, Al KF, Gibbons S, Chmiel JA, Wilcox H, Reid G, Anderson A, Dewar M, *et al*: Abiraterone acetate preferentially enriches for the gut commensal Akkermansia muciniphila in castrate-resistant prostate cancer patients. Nat Commun 11: 4822, 2020.
77. Vétizou M, Pitt JM, Daillère R, Lepage P, Waldschmitt N, Flament C, Rusakiewicz S, Routy B, Roberti MP, Duong CP, *et al*: Anticancer immunotherapy by CTLA-4 blockade relies on the gut microbiota. Science 350: 1079-1084, 2015.
78. Shaikh FY, White JR, Gills JJ, Hakozaki T, Richard C, Routy B, Okuma Y, Usyk M, Pandey A, Weber JS, *et al*: A uniform computational approach improved on existing pipelines to reveal microbiome biomarkers of nonresponse to immune checkpoint inhibitors. Clin Cancer Res 27: 2571-2583, 2021.
79. Terrisse S, Goubet AG, Ueda K, Thomas AM, Quiniou V, Thelemaque C, Dunsmore G, Clave E, Gamat-Huber M, Yonekura S, *et al*: Immune system and intestinal microbiota determine efficacy of androgen deprivation therapy against prostate cancer. J Immunother Cancer 10: e004191, 2022.
80. Peiffer LB, White JR, Jones CB, Slottke RE, Ernst SE, Moran AE, Graff JN and Sfanos KS: Composition of gastrointestinal microbiota in association with treatment response in individuals with metastatic castrate resistant prostate cancer progressing on enzalutamide and initiating treatment with anti-PD-1 (pembrolizumab). Neoplasia 32: 100822, 2022.