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Role of microbiome and its metabolite, short chain fatty acid in prostate cancer

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The microbiome which is an assembly of all microbes living inside our bodies performs a major role in maintaining human health and wellness. It has been found that the imbalance of the microbiome can cause various diseases in humans. Similarly, there is growing evidence that the microbiome largely affects a person's chance of contracting certain cancers and how the disease develops and progresses. Studies have shown that about 15% to 20% of all cancers are caused by microbial pathogens. The prevalence of prostate cancer, which is increasing rapidly in Korea, is related to lifestyle including diet. These diets can alter the gut microbial composition, and the effect of the microbiome on prostate cancer development can be estimated. However, the microbiome associated with prostate cancer has been reported differently according to race. This means that the metabolite rather than the specific microbiome will be important. Short chain fatty acids, metabolites of the microbiome, plays an important role in the action mechanism of the microbiome. Short chain fatty acids play roles such as immunomodulation and inhibition of histone deacetylase. Here, we examined the most up-to-date literature featuring the effects of the microbiome on the risk and pathogenesis of prostate cancer.

Keywords: Microbiome; Prostate cancer; Short chain fatty acid

INTRODUCTION

The microbiome which is an assembly of all microbes living inside our bodies performs a major role in maintaining human health and wellness. It also plays in important role in the development and progression of human diseases [1]. Since the launch of the Human Microbiome Project in 2007 by the United States National Institutes of Health, human understanding on the role of microbiota in people's health and illness has grown in leaps and bounds. There is growing evidence that the microbiome largely affects a person's chance of contracting certain cancers and how the disease develops and progresses [2]. Previous studies have shown that about 15% to 20% of all cancers are caused by microbial pathogens [2]. Researchers have been vigorously pursuing studies concerning the role of the microbiota, particularly the role of gut microbiota in the body's responses to certain treatments such as chemotherapy, immunotherapy and radiotherapy. One of such studies has focused on the link between human urinary microbiome and genitourinary malignancies such as prostate cancer.

Prostate cancer has been identified as the second most common cancer among men in the world after lung cancer [3]. As such, it is vital to understand factors and mechanisms

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related to prostate cancer, especially its causes, development, and progression. Several studies have shown that microbiota can directly or indirectly affect tumorigenesis of the prostate [4,5]. Under direct mechanisms, prostate cancer is linked to long term inflammatory urinary tract conditions such as chronic prostatitis and benign prostatic hypertrophy (BPH) [6]. On the other hand, the gut microbiota can affect metabolic processes and cause systemic inflammation that activates prostate tumorigenesis through indirect mechanisms [7].

Early studies investigated differences in microbiome composition between prostate cancer and BPH [8-10]. Liu et al. [11,12] have compared gut microbial compositions of patients who have castration-resistant prostate cancer (CRPC) to those who have hormone-sensitive prostate cancer (HSPC) and found that CRPC patients display abnormal gut microbial compositions showing an increased abundance of short chain fatty acids (SCFAs)-producing bacteria such as *Ruminococcus*, *Alistipes*, *Phascolactobacterium* and others. SCFAs are produced by bacterial fermentation of fibers in the colon [11]. CRPC patients likewise also show a corresponding high rate of SCFAs, particularly acetate and butyrate. However, how the microbiome affects people's risk of developing prostate cancer and how prostate cancer develops remains unclear [7,9]. When reviewing the current literature concerning the correlation between microbiome and prostate cancer, we put the spotlight on the function of SCFAs in this particular relationship. Metabolites of the microbiome, SCFAs, have roles such as immunomodulation and inhibition of histone deacetylases (HDACs). In this paper, we examined and summarized the current literature covering the relationship between the microbiome and prostate cancer with a particular emphasis on the role of SCFAs.

MICROBIOME

The microbiome is considered the second human genome. It encodes 150 times more genes than humans [13]. Although the microbiome changes with aging, it remains relatively stable after adulthood. Thus person's unique microbiome is sometimes thought of as a "fingerprint" of an individual [14]. Since most microorganisms in intestinal in microbiota are anaerobic, it is difficult to identify them using traditional culture technique or analyze their functions before the advent of metagenomics. Recent studies have shown that the microbiome is involved in the regulation of gene expression, health, development, homeostasis, and the occurrence of numerous diseases through interaction with the human host. The role of the microbiome is to protect the host from pathogenic microorganisms and regulate metabolic processes. Most importantly, the microbiome plays a role in the development of innate and adaptive immune systems and maintenance of homeostasis [15].

The imbalance between pathogenic microbes and microbes of protective dynamics is called dysbiosis. Intestinal microbial dysbiosis has been reported to be associated with inflammatory bowel disease [16], obesity [17], diabetes [18], colorectal cancer [19], cardiovascular disease [20], and neurological disease [21]. Recently, a relationship between intestinal microbiota and several urinary tumors has also been identified [22]. In general, cancer is caused by interactions between environmental factors and host genetic factors. In addition to genetic factors, microorganisms might also play an important role in cancer biology [23]. Oncogenic microorganisms might have functions such as acting on the development of tumors, promoting progression, and so on. In the case of prostate cancer, an increase in the abundance of *Bacteroides massiliensis* and *Enterobacteriaceae* species has been observed [9,24].

Although many studies have been conducted about the association between cancer development and microbiota, the exact mechanism of their interaction is still unknown. Perhaps intestinal dysbiosis is transmitted to distant sites through immune regulation and intrinsic signaling pathways in the microbiome, and these transmissions are mediated by some substances such as postbiotics, enzymes, vitamins, and SCFAs [25]. Postbiotics include all substances released by microorganisms that have beneficial effects on the host or are produced through metabolic activities of microorganisms. Since postbiotics do not contain live microorganisms, risks associated with ingestion could be minimized. Thus, they are attracting attention as an important substance to mediate the microbiome activity.

PROSTATE CANCER

Prostate cancer is the fourth most common cancer among men in Korea [26] and most common type of cancer among men in the United States [27]. Similar to its high frequency in the United States, its incidence in Korea is also very rapidly increasing. Thus, it is important to elucidate the mechanism of progression of prostate cancer. It is known that lifestyle including diet is related to the development of prostate cancer. In particular, excessive consumption of animal fat and obesity are recognized as risk factors for prostate cancer [28]. Chronic inflammation is associated with the development of prostate cancer [29]. The gut microbiome plays an important role in these infections [30]. The gut mi-

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crobiota is also strongly influenced by dietary habit and affects the host's inflammatory and immune responses [31].

To study the association between prostate cancer and the microbiome, studies have been performed using urine, feces, and prostate cancer tissues of prostate cancer patients (Table 1, Fig. 1). Yu et al. [8] have conducted a study using urine and found that abundances of *Bacteroidetes*, *Alphaproteobacteria*, *Firmicutes*, *Lachnospiraceae*, *Propionicimonas*, *Sphingomonas*, and *Ochrobactrum* are significantly increased while as those of *Eubacterium* and *Defluviicoccus* are significantly decreased in the prostate cancer group than in the BPH group. Shrestha et al. [32] have found that abundances of *Streptococcus anginosus*, *Anaerococcus lactolyticus*, *Anaerococcus obesiensis*, *Actinobaculum schaalii*, *Varibaculum cambriense*, and *Propionimicrobium lymphophilum* are increased in prostate cancer patients (Table 1).

An early study regarding the association between prostate cancer and the microbiome using feces was done by Golombos et al. [9]. They performed a prospective case-controlled study in patients with BPH or localized prostate cancer and found that the abundances of *Bacteroides* was increased in fecal samples of prostate cancer patients, whereas abundances of *Faecalibacterium* and *Eubacterium* were more abundant in the BPH group [9]. Their results were similar to those of other studies. Liss et al. [33] have used a sample with a cotton swab inserted into the rectum and confirmed the abundance of *Bacteroides* and *Streptococcus* species in prostate cancer patients. However, in a Japanese study [34], the relative abundance of *Rikenellaceae*, *Alistipes*, and *Lachnospira* was observed in high-grade prostate cancer, suggesting that the association between prostate cancer and the intestinal microbiome might differ according to race. As for phylogenetic diversity (PD), which estimates the abundance of bacterial flora in alpha diversity, a study in the United States reported that PD was significantly higher in patients without prostate cancer, whereas a study in Japan showed no difference [34,35]. Another study conducted in the United States did not show a difference in alpha diversity between patients with and without prostate cancer [33]. Thus, solid evidence for the association between the diversity of gut microbiota and prostate cancer is still lacking (Table 1).

Cavarretta et al. [10] have conducted a study regarding the association between prostate cancer and the microbiome using prostate cancer tissues and analyzed microbiome profiles for 16 radical prostatectomy specimens by ultradeep pyrosequencing. Although the number of samples was limited, *Propionibacterium* spp. was the most abundant one at the genera level. This is a similar result to the earlier study conducted by Cohen et al. [36]. Banerjee et al. [37] have performed metagenome analysis using formalin-fixed paraffin-embedded (FFPE) prostate adenocarcinoma samples from 50 prostate cancer patients and FFPE from 15 patients with BPH. Most bacteria identified were Gram-negative, including *Firmicutes*, *Proteobacteria*, *Bacteroidetes*, and *Actinobacteria*. Through hierarchical cluster analysis, it was possible to divide the microbiome into three groups. The correlation between a specific cluster and the Gleason score of prostate cancer was also confirmed [37]. Another study showed that *Propionibacterium* was involved in the progression of prostate cancer [38]. Miyake et al. [39] reported a significant increase of *Mycoplasma genitalium* in prostate cancer tissue, but a study conducted by Feng et al. [40] did not confirm the specific microorganism associated with prostate cancer tissue. Metabolites of microbiota also important. In fact, Matsushita et al. [34] have confirmed that the number of SCFA-producing strains is increased in high-grade prostate cancer (Table 1). Therefore, a thorough study of prostate bacterial metabolites is necessary.

Some studies have focused on how the makeup of the gut microbiome controls the metabolism of compounds linked to an increased risk of prostate cancer, while others have concentrated on the composition of the microbiota found in prostate cancer patients versus the control group. Several studies have found no significant difference in composition of the microbiota between prostate cancer patients and non-cancer patients. Alanee et al. [41] have examined the gut microbiota of 30 men undergoing transrectal prostate biopsy and found a higher abundance of *Bacteroides* spp. in prostate cancer patients compared to the control group. However, they concluded that there was no significant correlation between microbiota clustering patterns and Gleason scores among prostate cancer patients.

Sfanos et al. [35] have performed a cross-section study of men comprising 30 healthy male volunteers and those with various clinical states of prostate cancer. They created profiles of men's fecal microbiota using 16S rDNA amplicon sequencing and found a greater alpha diversity in those who did not have cancer than those who did have.

SHORT CHAIN FATTY ACID

1. Role of SCFA

SCFA is a type of waste produced by intestinal microorganisms, which are produced by decomposing indigestible dietary substrates. Acetate, propionate, and butyrate are main SCFAs [42]. SCFAs are produced by two major groups of bacteria. Propionate and acetate are produced by *Bacteroidetes*

Table 1. Studies on the association between prostate cancer and microbiome reported to date

Author	Year	Population (n)	Stage	Sample	Method	Main result
Alanee et al. [41]	2019	PCa (14) Control (16)	GS >7	Urine Stool	16s RNA	PCa exhibited an increased abundance of the bacterial species *Veillonella*, *Streptococcus*, and *Bacteroides*, while they had a decreased abundance of *Faecalibacterium*, *Lactobaccilli*, and *Actinetobacter*. No difference.
Banerjee et al. [37]	2019	PCa (50) BPH (15)	T2bN0 (1) T2cN0 (14) T2N0 (10) T3aN0 (19) T3bN0 (5) T3bN1 (1)	Tissue	PCR and targeted NGS	In PCa tissue, *Proteobacteria* were the most predominant phylum detected, comprising 55% of the total bacterial genera detections in the prostate tumors. The next most abundant phyla detected in the prostate tumor samples were *Firmicutes* (19%), followed by *Actinobacteria* (11%) and *Bacteroides* (7%).
Cavarretta et al. [10]	2017	PCa (16) Control	pT2c (1) pT3a (11) pT3b (4)	Tissue	16s rRNA	Prostate microbiome is enriched by Actinobacteria, as the dominant phylum in all types of samples, followed by *Firmicutes* and *Proteobacteria*. In genus level, *Staphylococcus* is abundance in prostate cancer and *Streptococcus* is abundance in non-tumor tissue.
Cohen et al. [36]	2005	PCa (34)		Tissue	16s rRNA	*Propionibacterium acnes* positively associated with prostatic inflammation.
Feng et al. [40]	2019	PCa (65) Control (65)		Tissue	Shotgun-based integrated metagenomic and metatran-scriptomic analysis	Neither the total bacterial load nor any specific genus showed significant differential distribution between the tumour and benign specimens.
Golombos et al. [9]	2018	PCa (12) BPH (8)	GS≥7 (4+3) cN0M0	Stool	Shotgun	In prostate cancer, species: *Bacteroides massiliensis*. In normal prostate, species: *Faecalibacterium prausnitzii*, *Eubacterium rectale*.
Liss et al. [33]	2018	PCa (64) Control (41)	GS≥6 (3+3)	Rectal swab	16s rRNA	In prostate cancer, species: *Bacteroides*, *Streptococcus*.
Miyake et al. [39]	2019	PCa (45) BPH (33)	pT2a (15) pT2b (4) pT2c (12) pT3a (10) pT3b (4)	Tissue	PCR	The positive rate of *Mycoplasma genitalium* was significantly different between the PCa cohort (18/45, 40%) and the BPH cohort (6/33, 18%).
Shrestha et al. [32]	2018	PCa (61) Control		Urine	16s rRNA	More abundant in cancer, *Propionimicrobium lymphophilum*, *Anaerococcus murdochii*, *Auritidibacter ignavus*/*Corynebacteium coeleae*, *Ureaplasma urealiticum*, *Ureplasma parvum*.
Yow et al. [24]	2017	PCa (10)		Tissue	16s rRNA	*Enterobacteriaceae* was dominant taxon (55.4%), followed by *Escherichia* (20.9%). The most common organisms identified in these studies were members of the family *Enterobacteriaceae* and specifically species related to *Escherichia coli*.
Yu et al. [8]	2015	PCa (13) BPH (21)		Urine	16s rRNA	In PCa, species: *Bacteroidetes bacteria*, *Alphaproteobacteria*, *Firmicutes bacteria*, *Lachnospiraceae*, *Propionicimonas*, *Sphingomonas*, *Ochrobactrum*. In BPH, species: *Eubacterium*, *Defluviicoccus*.

PCa, prostate cancer; GS, Gleason score; BPH, benign prostate hyperplasia; PCR, polymerase chain reaction.

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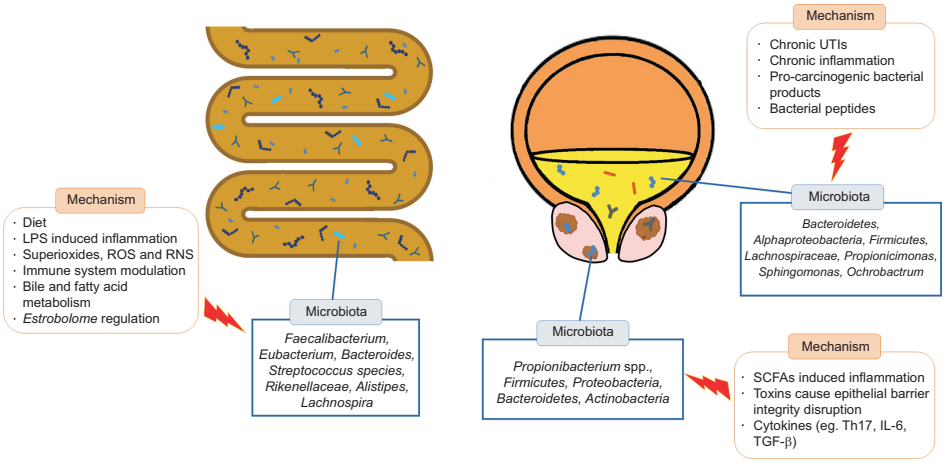

Fig. 1. Potential mechanisms of action of how gut, urinary, and prostate tissue microbiome interacts with prostate cancer. LPS, lipopolysaccharide; ROS, reactive oxygen species; RNS, reactive nitrogen species; UTI, urinary tract infection; SCFA, short chain fatty acid; IL, interleukin; TGF, tumor growth factor.

and butyrate is produced by *Firmicutes* [43]. The fact that SCFAs are produced from digestion of dietary fiber means that changes in the host's diet can cause significant changes in the composition of gut microbiota and lead to changes in the production of microbial metabolites [44]. In fact, it has been demonstrated that a continuous low-fiber diet can inhibit SCFA production and that a high-fiber diet can increase microbial SCFA production, leading to rapid changes in serum SCFA [44]. Although acetate is generally the most abundant SCFA, the ratio of acetate:butyrate:propionate varies widely according to studies reported [45,46].

SCFAs play an important role in the interaction between the host and the gut microbiota. Recent studies have indicated that SCFA may influence the progression of various diseases, such as inflammatory bowel disease, diabetes, atherosclerosis, and colorectal cancer [47-49]. The microbiome is expected to affect these diseases. A study on SCFA has confirmed that the concentration of SCFA in feces is significantly lower in those with an inflammatory bowel disease than in the control group [48]. When enema is performed with a mixture of SCFA, it is effective in improving clinical symptoms of ulcerative colitis patients [50]. It has been confirmed that SCFA levels show negative correlations with the risk of obesity, insulin resistance, and type 2 DM [51]. A role for SCFA on cancer has been reported in colorectal cancer, gastric cancer, and breast cancer [52-55]. Increases of inflammatory disorders and cancer have been demonstrated when SCFA poor diet is continued or when the amount of SCFA in feces is reduced [52]. SCFA can induce apoptosis, reduce carcinogenesis, and prevent gastric and lung cancers [52,56]. A high-fiber diet is associated with a lower cancer risk than red meat intake [57]. The role of SCFA in several urological diseases has also been recently reported [58]. When SCFA is administered in acute renal injury model rats, the degree of renal injury is decreased and the concentration of butyrate in SCFA is decreased significantly with increasing grade of chronic renal failure [58]. Microbiota is important in the development of urolithiasis. Several studies have reported the effect of microbiota in preventing urinary stone through its metabolites, SCFAs [59].

2. Mechanism of SCFA

SCFAs play an important role in the immune system. SCFAs have regulatory effects on various immune cells such as regulatory T (Treg) cells, macrophages, antigen presenting cells, type 3 innate lymphocytes and B cells [60,61]. SCFAs can support defense responses of systemic tissues such as the spleen and lymph nodes. SCFAs can also modulate cytokines in immune cells [62].

SCFA might also inhibit HDAC. SCFA receptors belong to G-protein coupled receptors (GPCRs). Among various GPCRs, GPR43, GPR41, and GPR109A have been identified as SCFA receptors [63]. SCFA-induced activation of GPR43 (FFAR2) can promote the secretion of glucagon-like peptide-1 (GLP-1), which has the ability to lower blood glucose levels by increasing insulin secretion [63]. Conversely, GPR43-deficient mice show reduced SCFA-induced GLP-1 secretion and improved insulin resistance. GPR43 is also abundantly expressed in adipocytes. GPR43-deficient mice exhibit obesity, whereas fat-specific GPR43-overexpressing mice exhibit lean body shapes under normal conditions [64]. SCFA can protect GFR43-dependent colitis in mice by regulating Treg cells [60]. GPR41 (FFAR3) is mainly activated by propionate and butyrate [65]. Similar to GPR43, GPR41 is also involved in energy homeostasis [66]. Activation of GPR43 can induce the release of noradrenaline from the sympathetic nerve, which regulates body energy homeostasis through sympathetic control. GPR41 might be involved in beneficial effects of SCFAs by modulating immune responses [63]. GPR109A, known as a receptor for niacin, is a receptor for SCFA. However, it

is not activated by acetate or propionate [67]. GPR109A is present on the surface of adipocytes, colonocytes, and macrophages [68]. The expression of GPR109A is suppressed in human colon cancer. Activation of GPR109A by butyrate can induce differentiation of Treg cells and IL10-producing T cells, thereby suppressing colonic inflammation and carcinogenesis [69].

After cell entry, butyrate can inhibit HDAC activity, consequently regulating gene expression [70]. This enzyme is involved in cell cycle regulation, proliferation, and programmed cell death. Butyrate can reduce the incidence of colitis by inducing the differentiation of Treg in the colon as a result [71].

3. SCFA and prostate cancer

As mentioned earlier, the composition of microbiome according to race might be different in prostate cancer patients. However, Matsushita et al. [34] have confirmed that, prostate cancer is associated with an increase in starch and sucrose metabolism in high-grade prostate cancer, in addition to the composition of the microbiome. Although a study on microbiome composition conducted in the US was different from the Japanese study, both studies showed a common thing: an increase in microbiota was related to starch and sucrose metabolism [33,34]. This suggests that bacterial metabolites rather than specific microbiota are involved in prostate cancer development. One such metabolite is SCFA.

SCFAs produced by the gut microbiota contribute to the regulation of HDACs. This might be very important for cell homeostasis as affecting cell adhesion, immune cell migration, cytokine production, chemotaxis, and programmed cell death [53]. Therefore, manipulation of SCFA levels in the intestinal tract by altering the microbiota might be considered as a possible strategy for the treatment and prevention of cancer. In particular, it has been demonstrated that breast cancer and gastric cancer are mediated in subjects on a diet low in SCFAs or in subjects with reduced amounts of SCFA in feces [52]. SCFA can inhibit cell growth, migration, HDAC and induce apoptosis, thereby reducing the incidence of cancer [53]. Before being recognized as a metabolite of the microbiome, SCFA has been studied as an antiproliferative or differentiation agent for the treatment of solid tumors such as prostate and breast cancers [72].

A study on effects of acetate on prostate cancer was initiated by Samid et al. [73] in the early 1990s. When LnCap (a HSPC cell line), PC3 and DU145 (hormone-refractory prostate cancer cell line) cells were treated with phenylacetate (PA), dose-dependent inhibition of cell proliferation was confirmed in all cell lines. Also, when PA-treated PC3 cells were transplanted into nude mice, tumors did not occur, indicating the antitumor effect of acetate. In another study, the effect of butyrate was studied [74]. It was found that growth inhibitory and apoptotic effects of butyrate were superior to those of acetate in prostate cancer cell lines. Although clinical studies of acetate and butyrate were small, phase 1 studies, they were insufficient to prove their effectiveness because only a very small number of patients were treated [75,76].

However, recent studies have reported that SCFA is associated with the progression of prostate cancer. Matsushita et al. [77] have studied changes after intake of animal fat in prostate-specific *Pten* knockout mice. Prostate cancer cell proliferation was confirmed after feeding a high-fat diet containing a large amount of lard. However prostate cancer cell proliferation was inhibited after oral administration of an antibiotic mixture. It was confirmed that compositions of intestinal microorganisms such as *Rikenellaceae* and *Clostridiales* were significantly reduced. Decrease of fecal SCFA was also confirmed. In addition, expression levels of *Igf1* and circulating insulin like growth factor-1 (IGF1) in the prostate were decreased. However, SCFA supplementation increased IGF1 and growth of prostate cancer cells [77]. It was estimated that intestinal bacteria such as *Rikenellaceae* and *Clostridiales* increased IGF1 through SCFA production and influenced the growth of prostate cancer.

Another study reported an increase in the relative abundance of SCFA-producing strains *Rikenellaceae*, *Alistipes*, and *Lachnospira* in high-grade prostate cancer [34]. In addition, an increase in *Subdoligranulum*, *Lachnobacterium*, and *Christensenellaceae* was confirmed in high-grade prostate cancer, they are strains of SCFA producer as like *Lachnospira*. These results suggest that SCFA may play an important role in the progression of prostate cancer.

Recently, Liu et al. [78] have observed the effect after transplantation of a fecal suspension from a patient with castration refractory prostate cancer (CRPC) into a transgenic TRAMP mouse model (unpublished). Fecal material transplantation from CRPC patients accelerated cancer progression in TRAMP mice. SCFA enhanced migration and invasion of prostate cancer cells *in vitro*.

CONCLUSIONS

Microbiome can positively or negatively influence tumor development and progression. Certain microbiota may inhibit or treat cancer by enhancing anti-tumor immunity. However, microbiota can also produce tumor-inducing components that can induce immune-suppressive or inflamma-

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tory responses to promote tumor development. Microbiome can influence local and systemic immune responses using several metabolites such as SCFA. Although the effect of SCFA on prostate cancer is still unclear, recent studies suggest that it has an adverse effect on prostate cancer progression. Further studies of these associations could improve our knowledge of the diagnosis and treatment of prostate cancer.

CONFLICTS OF INTEREST

The authors have nothing to disclose.

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AUTHORS' CONTRIBUTIONS

Research conception and design: all authors. Data acquisition: Hee Jo Yang. Data analysis and interpretation: Hee Jo Yang. Drafting of the manuscript: all authors. Critical revision of the manuscript: Jae Heon Kim. Obtaining funding: Jae Heon Kim. Supervision: Jae Heon Kim. Approval of the final manuscript: all authors.

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