Research Highlight

Microbiota and urinary tumor immunity: Mechanisms, therapeutic implications, and future perspectives

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Introduction

Newborns typically acquire microbiota from both their mothers and the surrounding environment, which can eventually reach around 500 g in adulthood (1). Microbiota serves as a historical record of an individual's life and may also hold a predictive value for their future health (2). Human microbiota is involved in disease occurrence and progression (3,4). Recent microbiota research has unveiled intricate connections between the microbiota and cancer, offering new insights into the pathogenesis of urological malignancies (5,6). Urological tumors, mainly including renal, bladder and prostate cancers, represent a significant global healthcare concern (7-10). Microbiota composition plays a pivotal role in urological carcinogenesis by influencing immune responses (11-13). Notably, the interplay between microbiota and immunity also contributes to the progression of renal (14), bladder (15) and prostate (16) cancers. Furthermore, microbiota has demonstrated its capacity to synergize with existing clinical treatments for the management of urologic tumors by modulating immune responses (17). Several microbiota species have been identified with anti-tumor function, with some already involved in clinical practice, effectively controlling urological malignancies (16,18). For example, Bacillus Calmette-Guerin (BCG) has significantly reduced recurrence rates in middle- and high-risk non-muscle-invasive bladder cancer (NMIBC) and is recommended as the standard therapy for these cases (19,20). BCG exerts its inhibitory effects on bladder cancer (BC) cells by enhancing immune responses, although the precise underlying mechanism remains to be fully elucidated (21).

The advent of new techniques, such as single-cell sequencing (22), biomedical materials (23) and artificial intelligence (24), holds the promise of providing comprehensive insights into the intricate interplay between microbiota and immunity in urological tumors. Moreover, microbiota can be categorized by location, such as intestinal microbiota (25), urine microbiota (26), intratumoral microbiota (27) and oral microbiota (28). These subtypes differ in composition and function. For example, the predominant microbiota varied between bladder cancer tissues and urine samples (26). Additionally, variations in intestinal microbiota composition and function were significantly associated with differing gastrointestinal toxicity risks in prostate cancer (PCa) patients undergoing radiotherapy (29). Consequently, it is essential to consider the composition of various microbiota types in urological cancers. In this study, our primary objective is to understand the interactions between microbiota and immune regulation within urological tumors and their potential impacts on tumor development and treatment through the following aspects: 1) How does the microbiota impact urological carcinogenesis? 2) What role does the microbiota play in regulating cancer progression? 3) How does the microbiota influence the effectiveness of other drugs? 4) What strategies can be employed to enhance the prognosis of patients with urological malignancies through microbiota interventions? and 5) How many clinical trials of microbiota-combined therapy for urologic tumors are in progress?

How does microbiota impact urological carcinogenesis?

Emerging studies have highlighted the significance of the gut, urine, and intratumoral microbiota in urological carcinogenesis, prompting questions about whether microbiota functions as a guardian or an invader in this context. Current research primarily focuses on discerning microbiota differences between individuals with normal urological conditions and those with primary tumors (30). The initiation of urological tumors is substantially influenced by the intricate interplay between the immunological microenvironment and microbiota. For instance, in renal cell cancer (RCC), Yang *et al.* (12) reported that alterations in the gut microbiota led to increased immune cell numbers and upregulation of genes associated with macrophages (such as GABBR1, TLR2, and so on), ultimately contributing to renal carcinogenesis. Specifically, *Lactobacillus* was identified as a protective bacterium, while *Desulfovibrionaceae* was associated with pro-tumorigenesis effects. In terms of BC, Schistosoma haematobium and its products within the urological tract have been implicated in promoting bladder carcinogenesis by modulating inflammation-induced immune activity (31). However, these studies merely reported a potential relationship between microbiota and urological carcinogenesis, lacking mechanistic insights or direct functional outcomes. Additionally, different BC studies have found inconsistent microbial species differences between normal and cancerous tissues (32-34). This phenomenon is not unique to BC but also extends to RCC (14,35,36) and PCa (37,38). Several factors may account for the inconsistent results. Firstly, sample collection methods can significantly influence study outcomes. For instance, some studies utilized clean midstream urine samples (34,39), while others obtained urine through catheterization (40). Additionally, one study extracted urine from the upper urinary tract (41). These variations in collective methods and locations may introduce data bias (5). Furthermore, sex and age could serve as potential sources of bias, as studies have already reported differences in microbiota between male and female urine samples and BC tissue comparisons (42,43). Moreover, contamination of samples during surgical collection and laboratory testing may occur, leading to biased results (44). Thus, standardizing sample collection procedures (including collective methods, locations, sex and age) is essential for future research. Secondly, microbiota sequencing is primarily conducted using two techniques: 16S ribosomal RNA (rRNA) sequencing and whole-shotgun metagenomics sequencing (WMS). However, these techniques possess varying detection capabilities. WMS can analyze genera that are less abundant and may be missed by 16S rRNA sequencing (45). This discrepancy can introduce biases in the results, potentially affecting studies focused on cancer initiation, progression, and treatment outcomes. In the process of data analysis, inconsistent results appeared between initial analysis and re-analysis (46). Moreover, low microbial biomass samples may generate false positive results without a proven sequencing and data analysis procedure (47). This potential bias should be significantly noticed in intratumoral study due to the low microbial biomass feature of tumor tissue (48). Additionally, the limited availability of data on gut and urological microbiota from healthy donors, along with the establishment of comprehensive microbiota banks, has complicated the

analysis process and may lead to errors in analysis. Fortunately, Sergaki *et al.* (WHO REFERENCE NUMBER: WHO/BS/2021.2403) have proposed a WHO collaborative study aimed at standardizing reagents for gut microbiome analysis. This initiative holds the potential to greatly enhance the reproducibility and comparability of future research endeavors in this field. Furthermore, there are other techniques that could also be applied to urological conditions, such as metatranscriptome and metaproteomics. Considering these factors, we can conclude that the interplay between microbiota and immunity may contribute to urological carcinogenesis. Nevertheless, further investigation is required to delineate and characterize the anti-tumor and pro-tumor microbial species involved in urological tumorigenesis.

What role does microbiota play in regulating cancer progression?

Microbes constitute the largest organic group in the human body and they can influence the development of tumors by interacting with tumor cells and the host immune system in a variety of ways (49,50). In terms of urological tumors, microbiota has been identified to affect cancer progression through the modulation of immune response. In RCC, Liss *et al.* (51) proved that RCC tissues had more diverse microbiomes compared with normal adjacent tissues. Interestingly, they also found that three common oral commensal microbial subjects were enriched in RCC tissues with overexpressed programmed cell death ligand 1 (PD-L1), compared to adjacent non-cancerous tissues. In another RCC study, the bacterial burden in RCC tissue was significantly lower than that in normal adjacent tissue. In further analysis, authors found that bacterial burden in cancer tissue was negatively correlated with the infiltration of PU.1+ macrophages and CD66b+ neutrophils (14). The infiltrated immune cells were positively associated with a good prognosis, suggesting that intratumoral microbiota affected the development of RCC by regulating the immune cell infiltration. *Cutibacterium acnes (C. acnes)* is a bacterium found in the normal skin microbiota that can survive intracellularly in macrophages and is substantially more frequent in PCa tissue than in normal prostate tissue (52). Davidsson *et al.* (53) found that stimulated with *C. acnes* significantly increased their expression and protein of immunosuppressive genes [PD-L1, C-C motif chemokine ligand (CCL)17, and CCL18] and infiltration of regulatory T (Treg) cells in tumor stroma and tumor epithelia. Moreover, Treg cell infiltration was positively associated with the presence of *C. acnes* in the cohort consisting of 137 PCa patients. Furthermore, some studies have compared gut, urological, oral, and intratumoral microbiota (51,54), but the relationship between intratumoral microbiota and microbiota at other locations (such as gut, oral, and urological microbiota) remains unclear. In another PCa research, gut microbiota-secreted short-chain fatty acids could facilitate cancer cell autophagy and M2 macrophage polarization in tumor microenvironment (TME), enhancing the invasion and metastasis potential of castration-resistant PCa (16). Immune cells' development and activity can be altered by microbiota, which can also change where they are distributed and how they work within tumors (55). This study identified that some microorganisms may release poisonous compounds affecting the development of tumors. These above results indicated that the microbiota might potentiate tumor immune evasion by promoting an immune suppressive TME and thereby regulating the progression of urological tumors, where complement system and cytokines especially for chemokines may play a key role in the process. The complement system is involved in both innate and adaptive immunity, and dysregulation of complement activation can alter tissue pathology (56). The latest research by Dr. Wu *et al.* (57) suggested the gut has an independent complement system synthesized by intestinal cells where luminal C3 is induced by the microbiota and varies between individuals in both mice and human. Moreover, C3 is mainly originated from stromal cells located in intestinal lymphoid follicles and plays an important role in combating pathogens and maintaining gut bacterial homeostasis. Except for complement system, retinoic acid related orphan receptor γt (RORγt) is a nuclear hormone receptor and attracts a great amount of attention as a critical regulator of anti-microbial immunity and a major target in the fight against inflammatory pathologies (58). Circadian rhythm significantly affects immune modulation (59). RORγt is also an intriguing molecule that is regulated by the circadian rhythm and includes cholesterol metabolites as ligands which thus links anti-microbial immunity with circadian rhythms and steroids (58). The regulation of intestinal immune homeostasis and inflammatory response, particularly the establishment of immunological tolerance to intestinal bacteria, is significantly influenced by RORγt+ immune cells including group 3 innate lymphoid cells, T helper (Th) 17 cells, Treg cells, invariant NKT cells, Tγδ cells and

extrathymic aire-expressing cells (58,60,61). In addition, patients with rectal cancer and inflammatory bowel disease can be seen to have different RORγt+ immune cell compositions and dysfunctions (62-64). Dr. Hepworth *et al.* (65,66) found that lymphoid tissue inducer-like ILC3s could present microbial antigens through major histocompatibility complex class II (MHCII) to screen and inhibit intestinal microbiota-specific Th17 cells, thereby maintaining intestinal homeostasis. Similarly, Dr. Lyu *et al.* (67) proved that ILC3s themselves could effectively promote the differentiation of antigen-specific T cells into RORγt+ Tregs, inhibit their differentiation into Th17 cells, and establish normal microbial immune tolerance in the gut. This process was induced by ILC3-mediated antigen presentation, αV integrin and competition for interleukin-2. Parallel findings were reported by other researchers (68,69). They proposed another novel pathway and challenged the traditional concept that dendritic cells are mainly responsible for the induction and promotion of Treg cell differentiation. Therefore, the above results demonstrate the tight relationship between microbiota and immune and the vital role of complement system and RORγt+ immune cells in regulating gut microbiota homeostasis and immune tolerance. However, whether these factors have an influence on peripheral Treg cells, effector Treg cells, other immune and non-immune cells and intratumoral microbiota and how to execute their functions are not clear now.

In addition, human microbiota may influence cancer development and therapeutic efficacy through the following mechanisms (55,70). Firstly, gut microbiota can affect host cell function through its metabolites, such as short-chain fatty acids. These metabolites act as histone deacetylase inhibitors, blocking the cell cycle and inducing apoptosis, which promotes intestinal homeostasis (71,72). Moreover, Dr. Pernigoni *et al.* (73) found that species with the ability to transform androgen precursors into active androgens were more prevalent in the intestinal microbial community in mice and patients with castration-resistant PCa and antibiotic-induced ablation of the gut microbiota could postpone the emergence of castration resistance even in immune-deficient mice. Secondly, changes in the microbiota can also affect the integrity of the intestinal mucosal barrier. Damage to this barrier allows bacteria to enter the bloodstream, triggering systemic or local inflammatory responses in the host immune system and contributing to the development of tumors (74). Apart from the host's gut microbiota, the bacteria found within tumors are also of significant importance. Goto *et al.* (75) have identified bacteria with anti-cancer effects from solid tumors. When these bacteria were used to treat mice, it was observed that intratumoral bacteria and their microbial combinations can stimulate systemic anti-tumor immunity, effectively killing primary tumors. Additionally, a recent study revealed that intratumoral oncolytic bacteria exhibit potent immunogenic anticancer effects, leading to the recruitment of immune cells and the cultivation of an anti-tumor immune microenvironment in breast, lung, and colorectal cancers (75). The above findings indicated that both gut microbiota and intratumoral microbiota might play an important role in the progression and therapeutic effect of cancer. *Figure 1* shows the correlation between human microbiota and urological tumors.

How does microbiota influence effectiveness of common clinical anti-tumor drugs?

Many drugs are susceptible to biotransformation or bioaccumulation, which can interact with gut microbiota and potentially impact their anti-tumor efficacy (73,76). For example, exposure to antibiotics can lead to an enrichment of *Proteobacteria* in patients with metastatic PCa. This enrichment results in increased gut permeability and higher levels of intratumoral lipopolysaccharide, further promoting PCa progression and docetaxel resistance through the activation of the NF-κB/IL6/STAT3 axis in mouse models (77). Thus, many new therapies are created to treat PCa (78,79). Of these, a key task is still to elucidate the contributions of microbiota components to cancer, fostering the advancement of novel drugs and personalized therapeutic strategies. The native microbiota or microbiota influenced by treatments play a pivotal role in therapy resistance. Consequently, researchers are exploring methods such as fecal microbial transplantation (FMT) to cultivate anti-tumor microbiota, potentially restoring sensitivity to resistant therapies. In a BC research, Miyake *et al.* (80) discovered that a probiotic mixture of *Lactobacillus casei Shirota* and *Bifidobacterium breve* could effectively inhibit tumor growth in mice undergoing gemcitabine and cisplatin (GC) therapy. Specifically, GC could induce the depletion of *Pseudoclostridium* and promote the enrichment of *Robinsoniella, Merdimonas*, and *Phocea* in the gut of tumor-bearing mice. Meanwhile, the GC-induced TME led to a decreased recruitment of cancer-associated fibroblasts and Treg cells, while promoting the activation of CD8+ T cells

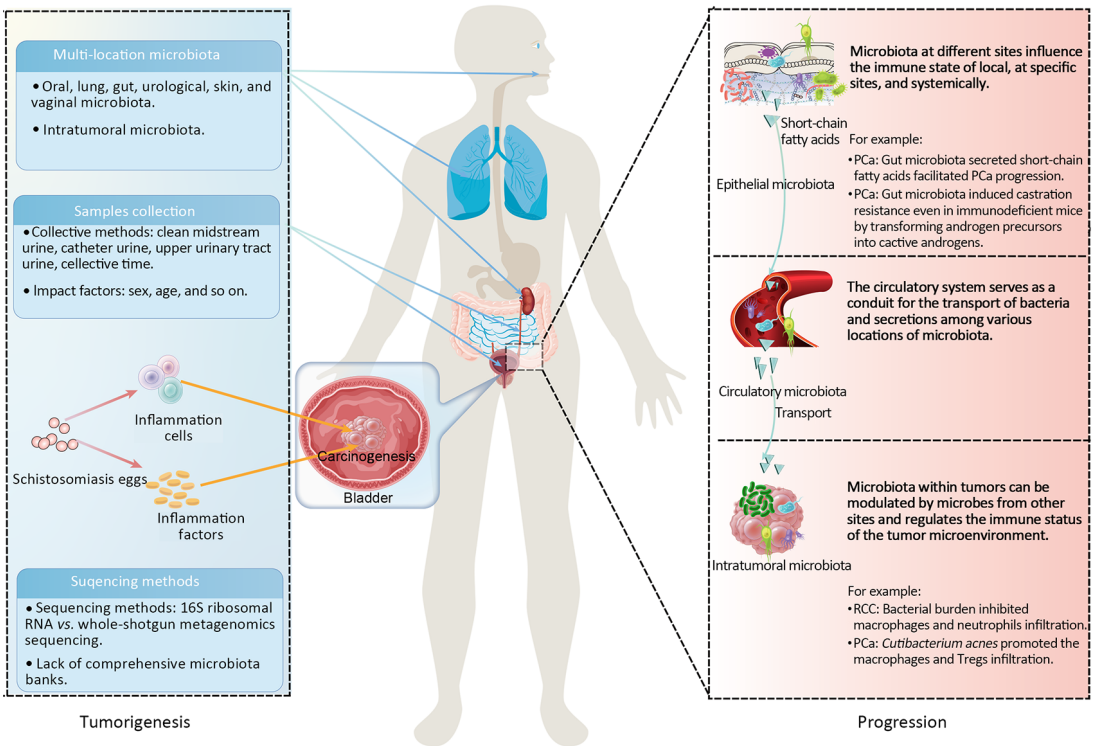

Figure 1 Research findings on correlation between human microbiota and urological tumors: Results, potential mechanisms, and existing issues. RCC, renal cell cancer; PCa, prostate cancer. Females do not have a prostate or develop prostate cancer. Completed by Figdraw (www.figdraw.com).

and dendritic cells, ultimately contributing to chemoresistance. Their further findings revealed that the probiotic supplementation reversed the transformation of TME, enhancing the efficiency of GC. The efficiency of FMT was also identified in another chemotherapy study. PCa could attenuate the relative abundance of *Akkermansia muciniphila* in the gut, while the bacterial could be recovered by receiving androgen deprivation therapy (ADT) (17). Oral administration of *Akkermansia* FMT was found to restore acquired immune defects in immunodeficient mice by upregulating circulating recent thymic emigrant cells, thereby enhancing the efficiency of ADT. The above findings suggest that medication can modulate gut microbiota, hence influencing the efficacy of drugs. The results from FMT highlight that manipulating gut microbiota could be a crucial approach to overcome therapy resistance.

In addition to chemoresistance, FMT also involves in the regulation of immunotherapy resistance. For example, *Blautia coccoides*, enriched in the gut microbiota, could promote CD8+ T cell infiltration in the BC TME by secreting trigonelline (81). Specifically, *Bautia coccoides* secreted trigonelline into the bloodstream, which reached the TME and inhibited β-catenin expression. Reduced β-catenin levels suppressed PD-L1 expression, alleviating PD-L1-mediated inhibition of IFN-γ and Granzyme B expression while reducing IL-1β and TNF-α levels. This ultimately induced CD8+ T cell infiltration and activation, enhancing the efficiency of anti-PD-L1 therapy. Similarly, Wang *et al.* (82) found that gut *Parabacteroides* blocked the infiltration of CD4+ T and CD8+ T cells into the BC TME, attenuating anti-PD-L1 therapy efficacy. The recolonization of gut *E. clostridioformis* species induced by antibiotic exposure would decrease mucosal addressin cell adhesion molecule 1 (MAdCAM1) expression through the modulation of bile acid metabolism in BC and RCC, enhancing the infiltration of Treg17 cells in the TMEs of tumor-draining lymph nodes and tumor tissue and thereby suppressed the antitumor function of immune checkpoints inhibitors (ICIs) *in vivo*. The infiltration would be attenuated by feeding with FMT, restoring the efficiency of ICIs. Furthermore, the further result indicated that low-serum-soluble MAdCAM1 could predict the survival benefits of patients with BC or RCC and was deemed as a strong predictor (83). Similarly, another study also reported that antibiotics depressed the anti-tumor function of ICIs

through the disruption of gut microbiota composition (84). There was a positive correlation between ICIs efficiency and the enrichment of *Akkermansia muciniphila* in gut. In terms of mechanisms, oral administration of *Akkermansia muciniphila* and FMT with non-responder feces in RCC mice significantly increased the recruitment of CCR9+CXCR3+CD4+ T lymphocytes into the TME, thus restoring the efficacy of ICIs. The above result indicates that the composition of gut microbiota significantly affects the efficiency of current treatments via immune regulation in the TME. Another significant attention is the antibiotics. Based on the results, antibiotic exposure appears to promote chemoresistance and immunotherapy resistance. However, it's important to recognize the intricate interactions between various antibiotics and different cancer treatments. We can only suggest that antibiotic exposure plays a role in regulating therapy efficiency by modulating gut microbiota. Several issues still require investigation, such as the potential impact of antibiotics on urine microbiota, the differences between liver-metabolized antibiotics and renal-metabolized antibiotics in cancer treatment, and the potential influence of antibiotics on intratumoral microbiota.

In intratumoral microbiota, certain species can also influence the efficacy of current therapies against cancer. For instance, CP1, a specific microbe in the TME of PCa with MYC and PTEN mutation, could activate CD8+ T cells, Th17 T cells, mature dendritic cells, M1 macrophages, and NK cells, while inhibit Treg cells and VEGF in TME (85). The regulation induced an anti-tumor immune microenvironment. Furthermore, the combination of CP1 with ICIs significantly inhibited PCa proliferation and prolonged survival *in vivo*, demonstrating an anti-tumor effect within the TME without observable toxicity. This study suggested an alternative approach to overcoming therapy resistance by targeting the intratumoral microbiota. It is important to note that the effectiveness and safety of FMT depend significantly on the quality of the samples used. However, these samples are typically obtained from healthy volunteers without a standardized procedure, leading to heterogeneity in FMT preparations (86). This variability not only limits the widespread clinical application of FMT but also raises safety concerns for patients. Additionally, microbiota composition is influenced by various factors, including tumor cell-inherent interactions (such as microbiome-derived tumor-associated antigens and molecular mimetic antigen), biochemical and physical properties of TME [immune cell components and phenotype, biochemistry-physical properties and composition of extracellular matrix (ECM)-like mechanical stresses, vascular formation and integrity, and status of energy metabolism], patient features (such as age, gender, pregnancy and disease status), therapeutic interventions (surgery, radiotherapy, and drug treatment) and environmental factors (such as diet, physical exercise, stress, circadian rhythm and geographical location) (87-89). Among these factors, we hereby specify three factors which are relatively less mentioned by other researchers. Currently, it is a common concept that specific antigen-induced T cell clone and differentiation mediate the anti-tumor immunity. The advancement of immunotherapy and T cell antigen identification help us characterize tumor-presented T cell antigens including tumor-specific antigen, tumor-related antigen and those sources of cancer antigens which are not widely accepted like microbiome-derived tumor-associated antigens (89). These antigens could be human endogenous retrovirus or the remnants of pathogens which are not eliminated and in turn mediate malignant transformation like *Helicobacter pylori*, human papillomavirus, and hepatitis B and C viruses (89,90). They might also trigger the cross-reacted response with other tumor-related antigens in the form of molecular mimicry like prophage in lung cancer and renal cancer (89,91). ECM of TME is a highly dynamic entity, which uses the interaction network of protein and proteoglycan to form cellular support structures, and to stockpile and insulate bioactive molecules in the form of concentration gradient, like receptors (especially integrin), growth factors and cytokines temporally or spatially (92). It provides physical barriers, anchoring points, or trajectories of motion for cellular movement through its physical properties including hardness, density, porosity, insolubility, and topography (spatial alignment and orientation). In addition, it could adjust the biological behaviors of cells through the array of signal transduction pathways mediated by ECM components like adhesion proteins such as fibronectin, integrin, and non-integrin receptors, as well as growth factors and related signaling molecules. Moreover, changes in the mechanical properties of TME are caused by remodeling of the ECM by tumor cells or activated stromal cells. These stromal cells normally secrete transforming growth factor β (TGF-β), leading to excessive deposition and cross-linking of ECM components such as collagen, fibronectin, and hyaluronic acid. Increased ECM deposition and crosslinking together lead to elevated ECM stiffness, which affects tumor cell

phenotype (93). Elena Cambria *et al.* (93) indicated that heterogeneous primary tumor cell populations induced by genetic instability and unregulated proliferation are selected by microenvironment barriers like immune surveillance, hypoxia, or mechanical stress. During this process, mechanical memory is formed and reserved through mechanotransduction and persistent epigenetic changes to keep biophysical adaptation of cells to mechanical stress and enable tumor cell extravasation, survival, and colonization in the distant organ (93). We speculated that introtumoral microbiome might also involve in remodeling the ECM and in turn was affected by ECM just as other cells in the TME.

In addition, several studies indicate that objective stressors (such as negative life events like the death of a spouse, divorce, or illness) and subjective stress (such as surgery-related stress, depression, or anxiety) might increase cancer susceptibility and progression in humans and mice (94-97). Horowitz *et al.* (97) summarize that in animal models, stress-induced glucocorticoids and catecholamines can directly govern cell death while also increasing tumor cell proliferation, treatment resistance, stemness characteristics, and dissemination. Furthermore, these substances can remodel the tumor matrix by stimulating angiogenesis, lymphogenesis, axonogenesis, and ECM development (98). For example, norepinephrine also confers anti-apoptotic effects on human prostate and breast cancer cells by inactivating the apoptotic promoter BAD (99). Glucocorticoid-induced and catecholamine-induced metabolic reprogramming also favors tumor growth and metastasis, which is dependent on transcriptional regulation of genes involved in glycolysis and oxidative phosphorylation (100,101). Moreover, stress-induced proinflammatory cytokines and neuroendocrine factors such as catecholamines, histamine, 5-hydroxytryptamine, and corticotropin-releasing hormone could result in gut leakage and ultimately imbalance of microbiota and derivate metabolites, thereby leading to immune dysregulation (88). Thus, it is worth investigating the intricate network of stress, microbiota and immune system in cancers including urinary tumors. Moreover, in urological tumors, it was discovered that arsenic exposure interfered with the composition of urine microbiota and the related metabolism of rats, leading to the development of bladder epithelial lesions (102). The high-fat diet promotes PCa progression by altering the proportion of intestinal microorganisms and causing overexpression of lipogenic genes (103). These differences and mutability necessitate that FMT should be produced with reference to different conditions. Another limitation is the occurrence of side effects, such as diarrhea and gastroenteritis (104). Therefore, some researchers are exploring the use of specific bacteria or microbiota-derived products to overcome treatment resistance, which still requires extensive experimental data. *Figure 2* shows the correlation between the human microbiota and the treatment of urological tumors.

What strategies can be employed to enhance prognosis of urological malignancies through microbiota interventions?

Many studies are trying to control disease using human microbiota-related treatment (105). Some of these studies focused on cancer management, particularly in the context of emerging findings in urological tumors (106,107). Notably, the use of dendritic cell vaccines presents a promising approach for cancer control (108,109). In RCC, Ding *et al*. (18) developed an oncolytic adenovirus to augment the efficacy of a dendritic cell vaccine for anti-tumor purposes. This oncolytic adenovirus improved the antigen-targeting capacity of the adenovirus-assembled dendritic cell vaccine, potentially impacting the microbiota within the TME. As a result, the combination of the oncolytic adenovirus and dendritic cell vaccine activated cytotoxic T lymphocytes to eliminate cancer cells and induced memory CD8+ T cells to maintain a long-lasting anti-tumor immune TME. This study not only proposes an effective therapy for RCC but also underscores the potential role of viruses in cancer management. In a bacteria study, a gene edited *E. coli* strain MG1655 was injected to the tumor or intravenous of mice with RCC or PCa (110). The *E. coli* consistently produced TNFα, attracting immune cell infiltration and suppressing tumor growth without causing toxicity in mice. These living bacteria could thrive and replicate in the TME, resulting in a sustained anti-tumor immune TME. This approach may offer an effective and convenient option for patients compared to current treatments. It cultivated an anti-tumor immune microenvironment by secreting immune factors after receiving gene editing. We still should notice the potential weakness of this approach. Firstly, genetic editing of many microbiomes presents significant challenges, limiting their widespread use. Furthermore, safety concerns must be addressed, as they may arise during the editing process. Additionally, utilizing intratumoral bacteria to control tumors raised some concerns about the presence of

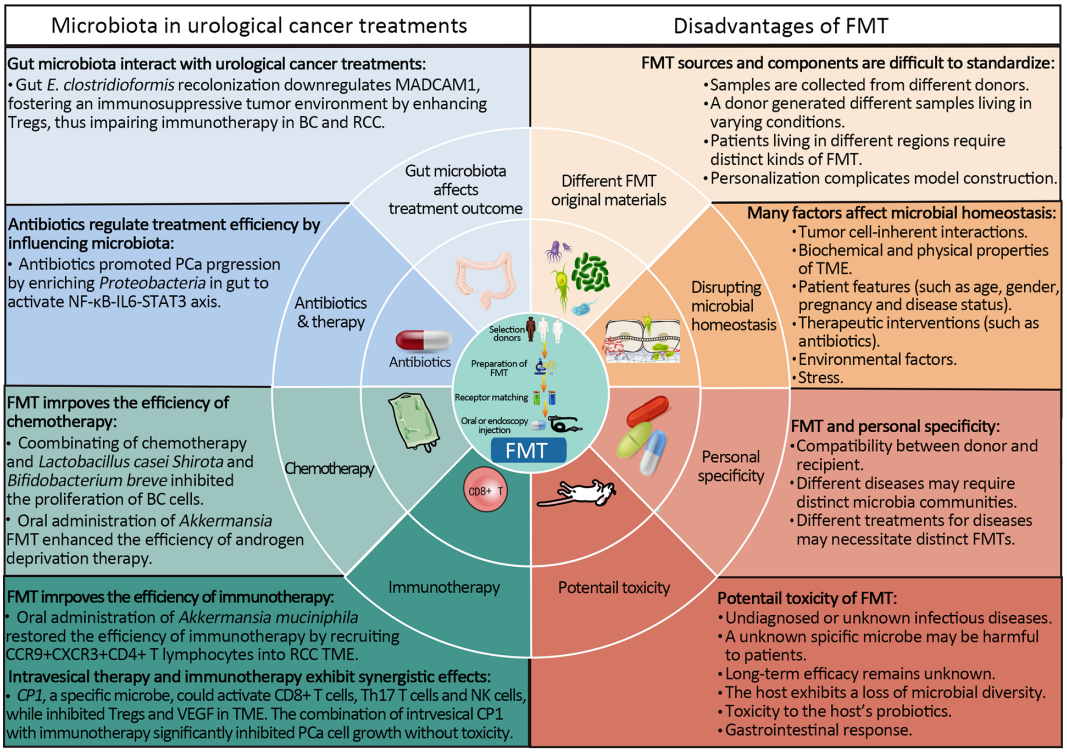

Figure 2 Function of microbiota in treatment of urological tumors. Advantages and disadvantages of FMT. FMT, fecal microbial transplantation; TME, tumor microenvironment; RCC, renal cell cancer; PCa, prostate cancer; BC, bladder cancer; VEGF, vascular endothelial growth factor. Completed by Figdraw (www.figdraw.com).

resistant microbial communities or species within the drug-resistant tissues, potentially contributing to treatment failure, or the regulation of microbiota in other sites may lead to drug resistance in tumor tissues. As we mentioned above (75), intratumoral oncolytic bacteria established an anti-tumor immune microenvironment through their inherent immunogenicity in cancer tissue. The bacteria preferentially colonize the targeted tumor tissues, indicating the superiority of intratumoral delivery in tissue specificity and minimizing side effects. Leveraging this tissue selectivity, Ling *et al.* (111) successfully developed a novel bionic drug delivery system using *Escherichia coli* shells as carriers for the chemotherapeutic drug paclitaxel liposomes, encapsulated within a cancer cell membrane homologous to metastatic lung cancer cells. This innovative bionic drug-carrying bacterial formulation not only achieved significant tumor suppression but also substantially reduced the absorption and damage to normal tissues caused by chemotherapeutic drugs. Furthermore, this treatment significantly reduced the immunogenicity of *Escherichia coli*, preventing inflammatory storms. This study presents an alternative approach to utilizing intratumoral bacteria for cancer therapy, effectively controlling immune responses in microenvironment. However, it has a notable limitation: the need for multiple injections discourages long-term efficacy. These novel anticancer pathways demonstrate considerable potential of intratumoral bacteria in tumor control, necessitating rapid establishment of standardized databases for normal and tumor microbiota as a foundation for further drug development.

In terms of BC, BCG has been utilized in BC management for decades (112). Intravesical BCG inhibits the BC cells by inducing an anti-tumor immune TME (21). Interestingly, a recent study found differences in urinary microbiota before and after BCG treatment (113). This alteration in composition underscores the interplay between BCG and urinary microbiota. However, there were still around 30% of patients failing to response to BCG (114). A few studies tried to find new microbiota component to manage these patients (15). For instance, heat-killed *Lactobacillus casei, Shirota strain* (LC9018) exhibited significant anti-tumor function for BC *in vivo* (115). Specifically, intravesical LC9018 promoted the infiltration of neutrophils and macrophages in the TME, resulting in the depression of tumor growth. While BCG has been utilized in clinical practice for decades, the precise

anti-tumor mechanism of BCG remains unclear. Historically, the urological tract was considered sterile, but recent studies have confirmed the existence of normal urine microbiota (34). Furthermore, natural products may improve BC treatment efficacy through the microbiota and immune regulation (116,117). For instance, Psyllium plus inulin significantly depressed BC proliferation by recruiting CD8+ T cell infiltration (118). Similarly, the combination of icariin and curcumol could affect gut microbiota composition and function by regulating the metabolism of short-chain fatty acids and recruiting CD8+ T cell infiltration, blockading PCa progression (119). Current understanding of gut microbiota is more advanced than that of urine microbiota, and may provide a roadmap for developing studies that investigate urine microbiota interactions with host microbiota and tumors, thus offering a promising avenue for the development of biomarkers, risk classification and treatment advancements of such patients. *Figure 3* shows new drugs based on human microbiota for urological tumors. *Table 1* provides key references of this review.

How many clinical trials of microbiota-combined therapy for urologic tumors are in progress?

We conducted a search on the Chinese Clinical Trial Registry (https://www.chictr.org.cn/), ClinicalTrials (https://clinicaltrials.gov/), and the International Clinical Trials Registry Platform (https://trialsearch.who.int/). We identified and selected a total of 13 clinical trials which focused on the efficiency and safety of microbiota-combined therapy for urologic tumors. Five trials are designed to assess the potential of microbiota-combined therapy for RCC, all of which are in either phase I or phase II. There are seven trials assessing the safety and efficacy of microbiota-based therapy in BC, and one trial investigates female microbiota changes after receiving instillation therapy. Among these, both nocardia rubra cell wall skeleton and pseudomonas aeruginosa are registered in China and are in phase IV trials. As for PCa, three trials are dedicated to assessing the safety and efficacy of microbiota-based therapy. Additionally, one trial (NCT06126731) aims

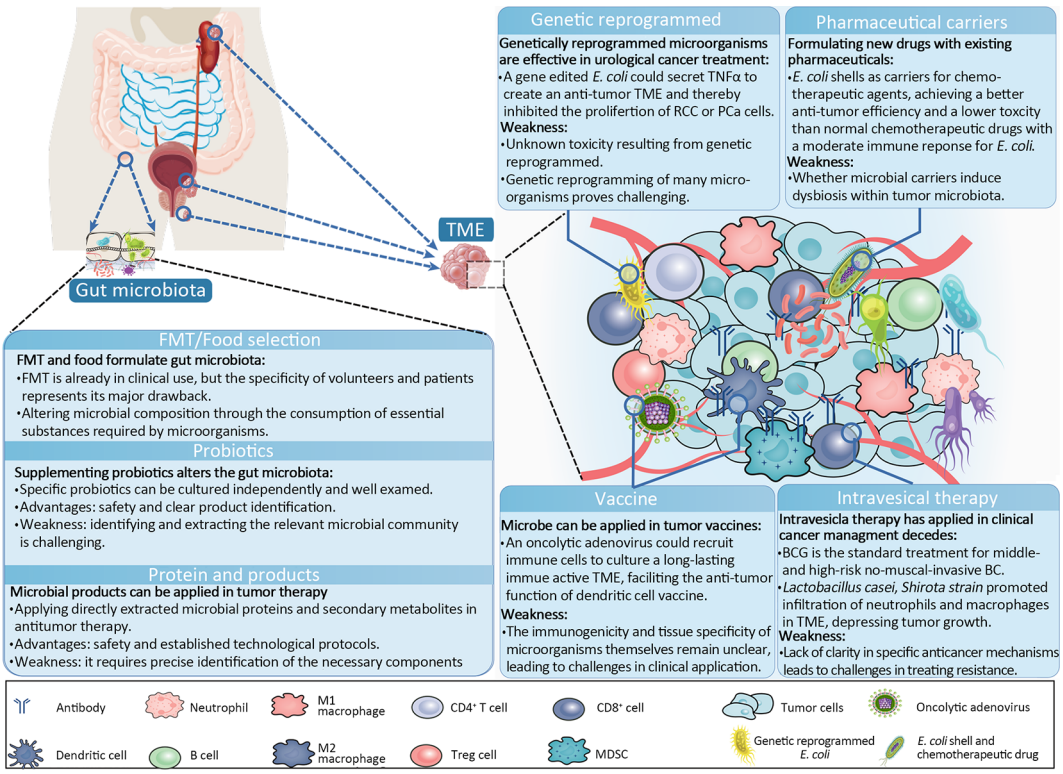

Figure 3 New drugs based on microbiome are categorized into: Drugs targeting gut microbiota and drugs targeting intratumoral microbiota. FMT, fecal microbial transplantation; TME, tumor microenvironment; RCC, renal cell cancer; PCa, prostate cancer; BC, bladder cancer; BCG, Bacillus Calmette-Guerin. Females do not have a prostate or develop prostate cancer. Completed by Figdraw (www.figdraw.com).

Table 1 Key references

Ref.	Year	Cancer	Types	Results
(12)	2023	RCC	Gut microbiota	*Lactobacillus* was identified as a protective bacterium, while *Desulfovibrionaceae* was associated with pro-tumorigenesis effects.
(84)	2018	RCC	Gut microbiota	Oral supplementation with *A. muciniphila* after FMT with nonresponder feces restored the efficacy of PD-1 blockade in an interleukin-12-dependent manner by increasing the recruitment of CCR9+CXCR3+CD4+ T lymphocytes into mouse tumor beds.
(51)	2020	RCC	Oral/Intratum oral microbiota	Renal tumors have more diverse microbiomes than normal adjacent tissues. Identification of resident oral microbiome profiles in clear-cell renal cancer with tumor thrombus provides a potential biomarker for thrombus response to PD-L1 inhibition.
(14)	2022	RCC	Intratumoral microbiota	For the first time, we demonstrated a significant correlation between bacterial burden and the content of PU.1+ macrophages and CD66b+ neutrophils in kidney tumors.
(18)	2023	RCC	Virus	OAV-IL-12 potentiated DCs-CD137L/CAIX treatment generated a long-lasting protective effect against tumors by inducing memory CD8+ T cell immune responses.
(83)	2023	RCC/BC	Gut microbiota	The MAdCAM-1-α4β7 axis constitutes an actionable gut immune checkpoint in cancer immunosurveillance.
(113)	2023	BC	Urine microbiota	BC patients with no recurrence and/or progression exhibited a different urinary microbiome profile compared to those with tumors.
(15)	2021	BC	Salmonella	IL-2, TRAIL and their MIX proteins in MB49 cells have cytotoxic potential and that this is associated with oxidative stress and apoptosis pathways.
(80)	2023	BC	Gut microbiota	The positive effects of a probiotic mixture of *Lactobacillus* and *Bifidobacterium* in enhancing anti-tumor effects through the gut-tumor immune response axis.
(115)	2001	BC	Shirota strain (LC9018)	LC9018 is potentially more potent and safer as a therapeutic agent than BCG for superficial bladder tumors.
(110)	2017	RCC/PCa	*E. coli* strain MG1655	Therapeutic efficacy and safety of TNFα expressing bacteria *in vivo,* highlighting the potential of non-pathogenic bacteria as a platform for restricting the activity of highly potent cancer agents to tumors.
(85)	2018	PCa	CP1	CP1 is an immunotherapeutic tool demonstrating how a tissue-specific microbe can increase tumor immunogenicity and sensitize an otherwise resistant cancer type to immunotherapy.
(16)	2023	PCa	Gut microbiota	Intervention of SCFAs-producing microbiotas may be a useful strategy in manipulation of CRPC.
(17)	2022	PCa	Gut microbiota	The potential clinical utility of reversing intestinal dysbiosis and repairing acquired immune defects in PC patients.
(53)	2021	PCa	Cutibacterium acnes	Cutibacterium acnes may contribute to an immunosuppressive tumor environment that is vital for PCa progression.
(81)	2024	BC	Gut microbiota	Blautia coccoides and its metabolic product, trigonelline, could serve as a synergistic treatment method with PD-1 inhibitors in clinical applications.

RCC, renal cell cancer; BC, bladder cancer; PCa, prostate cancer; PD-1, programmed cell death 1; PD-L1, programmed cell death ligand 1; CRPC, castration-resistant prostate cancer; BCG, Bacillus Calmette-Guerin.

to investigate the role of antibiotics in patients receiving enzalutamide, which is a significant topic in PCa treatment. The details of these trails are presented in *Table 2*.

Conclusions and perspectives

There is no doubt that microbiota research is an emerging field with great potential which is used to decode tumorigenesis and interactions between tumor cells and immune cells and therefore formulate the therapeutic strategies for urinary tumors. In-depth investigation into these interactions and their impacts on tumor growth and therapy can shed light on the pathophysiological underpinnings of these cancers and result in more potent therapeutic approaches. This work issues a strong warning to researchers to change the way they conduct human urological cancer research. Researchers must acknowledge the key role that the microbiota play in oncogenesis,

Table 2 Clinical trials of microbiota-combined therapy for urologic tumors

Title	Cancer types	ID	Year	Status	No. of patients	Stage
MRx0518 in patients with solid tumors waiting surgical removal of the tumor (MICROBIOME)	RCC, PCa, BC	NCT03934827	2019-05-02	Active, not recruiting	120	Phase 1
The female microbiome in patients undergoing bladder instillation therapy	BC	NCT05414305	2023-10-11	Active, not recruiting	29	Phase 2
Role of gut microbiome and fecal transplant on medication-induced GI complications in patients with cancer	RCC, PCa, BC	NCT03819296	2019-01-28	Recruiting	800	Phase 1/2
A FIH combination treatment study with a single dose level of BMC128	RCC	NCT05354102	2022-04-29	Recruiting	12	Phase 1
Preventing toxicity in renal cancer patients treated with immunotherapy using fecal microbiota transplantation (PERFORM)	RCC	NCT04163289	2019-11-14	Recruiting	20	Phase 1
CBM588 in combination with Nivolumab and Cabozantinib for the treatment of advanced or metastatic kidney cancer	RCC	NCT05122546	2021-11-16	Recruiting	30	Phase 1
Combination study of Antibiotics with Enzalutamide (PROMIZE)	PCa	NCT06126731	2023-11-02	Recruiting	39	Phase 1/2
OH2 oncolytic viral therapy in advanced BC	BC	NCT05248789	2022-05-25	Recruiting	45	Phase 2
OH2 oncolytic viral therapy in non-muscle-invasive BC	BC	NCT05232136	2022-07-11	Recruiting	30	Phase 1/2
Oncolytic adenovirus combined with PD-1 inhibitor in patients with non-muscle-invasive BC	BC	NCT05564897	2022-08-26	Recruiting	25	Phase 2
HB-302/HB-301 therapy in participants with metastatic castration-resistant PCa	PCa	NCT05553639	2023-05-23	Recruiting	70	Phase 1/2
An exploratory clinical study of Nocardia rubra cell wall skeleton (N-CWS) for injection compared with BCG vaccine for medium- and high-risk non-muscularly invasive BC TURBT postoperative irrigation	BC	ChiCTR2100042774	2021-01-28	Prospective registration	30	Phase 4
The randomized controlled study for intravesical instillation of pseudomonas aeruginosa and gemcitabine in the prevention of postoperative recurrence of non-muscle invasive BC	BC	ChiCTR1900026643	2019-10-17	Prospective registration	40	Phase 4

GI, gastrointestinal; FIH, first-in-human; PD-1, programmed cell death 1; BCG, Bacillus Calmette-Guerin; TURBT, transurethral resection of bladder tumor; RCC, renal cell cancer; PCa, prostate cancer; BC, bladder cancer.

progression, and response to existing treatments and therefore not overlook metagenomic and other microbial methodologies in their experimental planning. With 99% of cells in the human body being bacteria, and with growing evidence showing us that these bacteria play a considerable role in cancer, we consider it no longer advisable to exclusively include human genes in large scale omics experiments. We suggest that this "human only" approach is now outdated, given the evidence presented herein. Our growing understanding of the field gives us the exciting opportunity to develop cutting-edge methods of diagnosis, therapy, and individualized care, ultimately enhancing the quality of lives of such patients. However, we must acknowledge that numerous issues remain to be resolved from preclinical discoveries to clinical implementations.

As mentioned above, microbiota from different locations vary in composition and function. For example, intratumoral *Lachnoclostridium* and *Sutterella* promote BC progression by regulating immune infiltration (120), while another study found that gut *Blautia coccoides* enrichment exhibited a key role in inhibiting BC progression (81). These studies highlight the distinct tumor-promoting or tumor-suppressing microbiota species in different locations, warranting further exploration and comparison. Furthermore, different kinds of studies have reported varying results. For instance, in a prospective multi-center clinical trial, researchers compared the gut microbiota of

men with and without PCa using 16S rRNA sequencing (121). The results showed that *Prevotella 9* was highly enriched in the gut microbiota of PCa patients. However, a Mendelian randomization study indicated that PCa occurrence was positively associated with the abundance of *Verrucomicrobiae*, *Verrucomicrobiaceae*, *Verrucomicrobiales*, *Akkermansia*, and *Butyrivibrio* in the gut (122). Another Mendelian randomization study found that PCa development was significantly correlated with gut *Ruminococcus torques* group, *Oscillibacter*, *Barnesiella*, *Butyricicoccus*, and *Ruminococcaceae UCG005* (123). For BC, a Mendelian randomization study identified *Bilophila* as a key gut microbiota species distinguishing BC patients from healthy individuals (124). In contrast, in mouse models, *Faecalibaculum* was the primary gut microbiota species differentiating normal mice from BC mice (125). Additionally, based on TCGA data, researchers observed that aggressive BC was enriched with *Oleomonas*, *Cellulomonas*, *Rhodopirellula*, *Cycloclasticus*, *Candidatus Paracaedibacter*, *Prosthecobacter*, *Aphanizomenon*, and *Thiothrix* in the TME (126). BC urinary microbiota also showed significant enrichment of *Rhodanobacter*, *Cutibacterium*, *Alloscardovia*, *Moryella*, and *Anaeroglobus* compared to healthy controls (127). Differences in study methods, including microbiota sampling and research approaches, contribute to the variability in results. These inconsistent findings within and across locations highlight the need for standardized methodologies in microbiota research. This standardized procedure should include sample collection, DNA extraction, sequencing, and bioinformatics analysis. Additionally, a comprehensive microbiota database needs be developed based on these standards, incorporating data from respiratory, vaginal, oral, skin, urological, and gut microbiota, rather than only focusing on gut microbiota. Furthermore, the project should consider collecting data on other microbial species, such as phages, fungi, and viruses, making it a substantial and resource-intensive endeavor. Notably, a project with these objectives has been initiated at The National Institute for Biological Standards and Control (https://www.pharmabiotic.org/microbiome-standardisation-efforts-progressing-at-the-nibsc-mhra/). Moreover, some public databases, such as the BIC database (http://140.112.52.86:8888/bic/) and TCMbio database (https://microbiomex.sdu.edu.cn/), also provide microbiota information, promoting microbiota exploration. Currently, studies primarily focus on elucidating the correlations between gut microbiota and urological tumors or treatment outcomes. However, this represents just one facet of the intricate relationship between urological tumors and microbiota. The full scope of this relationship encompasses complex interactions among urine microbiota, oral microbiota, gut microbiota, vasculature microbiota, intratumoral microbiota, the TME, and various therapeutic interventions. Numerous unexplored fields within this realm await further investigation.

In a previous review, Dr. Ma *et al*. (128) defined intratumoral microbes and their products as the tumor microbe microenvironment and they proposed some underlying mechanisms though which intra-tumoral microbes and their products mediating the interaction between tumor cells and immune cells. Based on the current evidence, we can conclude that TME consists of tumor cells, immune cells, stroma cells, intracellular microbe and extracellular microbe, and inorganic substances. The interactions between living cells includes direct contacts and bioactive molecules within the inorganic substances and the latter is predominant. In our opinion, we need to understand microbiota from both macroscopic and microscopic perspectives. Overall, we classified the microbiota into four levels: microorganisms outside the biological barrier, microorganisms within vasculature system, microorganisms within tissue, ECM and intracellular microorganisms. We cannot ensure whether these four layered microbes are able to physically transport to each other, but we can speculate that the properties of microorganisms and their derivatives have to undergo assimilation from the outside to the inside due to existence of innate and adaptive immune responses. On the other hands, the existence of microbiota and current evidence are indicative of growing inspirations from the understanding of tumor cells and immune or non-immune cells. Both myeloid and lymphoid haematopoietic cells must extravasate from the bloodstream into the tumor tissue to contain or eradicate malignant solid tumors. They also need to migrate to different specialized niches within the TME to interact functionally with non-haematopoietic stromal cells, with cancer cells, and with each other. Collectively, these interactions control the outcome of naturally occurring or therapeutically generated antitumor immune responses by regulating local immune cell survival, proliferative growth, differentiation, and their execution of pro-tumor or antitumor effector functions (129). These interactions are all coordinated and heavily reliant on the migratory chemical cues that chemokines and their receptors give and physical cues that ECM provides. During the local distribution of microbiota, we

characterized the important role of complement system, ECM, and chemokines, for a large family of chemotactic cytokines, and their receptors. The former is necessary to maintain the microbiota hemostasis and immune activation and the latter two play multifaceted roles in the recruitment and positioning of cellular constituents of the TME functional organization (92,93,129).

Based on the above findings, we proposed a hypothesis of microbiome-mediated secretory phenotype (MMSP) which plays an important role in human diseases, including cancers. MMSP may encompass the range of secretory profiles induced or influenced by microbial presence, activity, or interaction within or around host cells. Therefore, MMSP should be categorized into two subtypes based on their secretory source. The first subtype is the original MMSP, which is produced by microbiota themselves, including enzymes, antibiotics, and metabolic by-products. For example, butyrate, a bacterial metabolite, triggers the differentiation of Treg cells and IL-10-producing T cells, fostering an anti-inflammatory microenvironment through the activation of GPR109A, thereby mitigating colon carcinogenesis (130). The second subtype is secondary MMSP, which is secreted by microbiota-influenced cells such as normal epithelial cells, glandular cells, immune cells, or cancer cells. Secondary MMSP may consist of toxins, chemokines, inflammatory cytokines, proteases, and other factors. Different microbes can secrete distinct types of original MMSP, which can culture either a pro-tumor or anti-tumor TME by influencing immune cells and immune factors. Similarly, various microbes can activate different cells to produce different forms of secondary MMSP, contributing to the modulation of the TME. Furthermore, anti-tumor treatments may affect microbiota to generate various MMSP, which, in turn, may influence the efficiency of these therapies. Microbiota in different location may interact each other by secreting MMSP. Specifically, MMSP is the messenger which promotes the intricate interactions and communications between distinct microbial communities residing in various human body sites. In a similar study involving butyrate, it was observed that patients who responded to oxaliplatin treatment exhibited elevated serum butyrate levels compared to non-responders. This observation highlights the potential role of microbial metabolites as MMSP (131). Recently, Jingushi *et al.* (132) examined and compared bacterial DNA in serum extracellular vesicles from five healthy donors and seven RCC patients using 16S rRNA metagenomic analysis. They found that serum extracellular vesicles from RCC patients contained higher levels of Cutibacterium acnes DNA compared to those from healthy individuals. Cutibacterium acnes DNA was shown to promote RCC proliferation and angiogenesis, contributing to cancer progression. This study strongly supports the hypothesis that MMSP serves as a communication pathway among different locations in the human body. Human microbiota is a complicated microbiota network consisting of oral, gut, urine, vasculature, respiratory, vaginal (female) and intra-tumoral microbiome, where MMSP is expected to play an important role in their interactions. Furthermore, interactions within the internal microbiota or between microbiota and host cells can profoundly impact host health and disease. This hypothesis still needs to be explored and identified in many future studies.

Several of the most common preclinical models used in urological cancer research involve the use of mice – in particular xenografts and patient-derived xenografts (133). However, the microbiota between mice and human are quite different and they also change dynamically with time, disease stage, and environmental stimuli. Microorganisms, cancer, interventions, and hosts comprise an extensive and intricate network. More advanced models might be considered such as preclinical models including organoids and emerging bioengineering like microfluidics, nano-delivery materials, bioprinting, and microbiome editing, and their anti-tumor effects and induced immune response tested in preclinical experiments. More advanced microbiota analysis technologies, such as artificial intelligence, kinds of probe, and single-cell microbiome omics analysis, should be developed to improve the depth, breadth, and accuracy of sequencing identification (134-136). Moreover, it is currently challenging to isolate the intra-tumor microorganisms identified from the microbiota analysis due to various environmental contaminants and limitations of biobanks for microbial sequence alignment. This increases the difficulty of deepening our understanding of TME. Looking forward, despite the existing obstacles, including the need for better animal models and improved microbiota analysis tools, microbiota research holds significant potential for understanding the pathological mechanisms underlying urological malignancies. It also offers the promise of developing more potent therapeutic strategies to improve the quality of life for patients. What's more, we might leverage the key perspectives of integrated tumor biology to identify the optimal therapeutic nodes at systematic level rather than only focusing on the certain

risk factors of microbiota in cancer patients due to the evolving patient conditions and environmental variants.

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Footnote

Conflicts of Interests: The authors have no conflicts of interest to declare.

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