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Review Article

Microbiota and the landscape of the prostate tumor microenvironment

Kasmira R Gupta[1], Natasha Kyprianou[1,2]

[1]*Department of Urology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA;* [2]*Oncological Sciences and Pathology & Cell Based Medicine, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA*

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Abstract: Prostate cancer remains one of the most common causes of cancer-related death in men globally. Progression of prostate cancer to lethal metastatic disease is mediated by multiple contributors. The role of prostate microbiota and their metabolites in metastasis, therapeutic resistance to castration resistant prostate cancer (CRPC), and tumor relapse has yet to be fully investigated. Characterization of microflora can provide new mechanistic insights into the functional significance in the emergence of therapeutic resistance, identification of novel effective targeted therapies, and development of biomarkers during prostate cancer progression. The tumor microenvironment (TME) and its components work concurrently with the prostate microbiota in promoting prostate cancer development and progression to metastasis. In this article, we discuss the growing evidence on the functional contribution of microbiota to the phenotypic landscape of the TME and its effect on prostate cancer therapeutic targeting and recurrent disease.

Keywords: Microbiota, prostate cancer, epigenetic regulation, tumor microenvironment, cell plasticity, mesenchymal phenotype

Introduction

Prostate cancer is the second leading cause of death in men worldwide. While there have been significant advances in detection and treatment, the 5-year survival rate of men diagnosed with metastatic hormone-sensitive prostate cancer is approximately 30% [1]. *Genetic* aberrations work concordantly with the tumor microenvironment (TME), which serves a critical role in cell survival and tumor development. The TME is biologically heterogeneous and is composed of stromal, epithelial, endothelial, and immune cells, such as T-lymphocytes, B-lymphocytes, macrophages, myeloid-derived suppressor cells, neutrophils and cancer-associated fibroblasts (CAF) [2]. Paracrine signaling between the cancer cells and the TME allows for activation of signaling pathways that promote angiogenesis, proliferation, and metastasis to ectopic sites [3]. The cellular communications within the TME can be dictated by the external environment (lifestyle, diet, and microbiota) [2]. Characterization of the cellular populations that inhabit niches of the TME can help clarify mechanisms of immunosuppression and metastasis. Significantly, identification of the microbiota and factors of the TME that contribute to immune resistance can lead to the development of potential therapeutic measures regarding eradication of prostate cancer [2]. This review focuses on the functional contribution of microbiota within the TME on prostate cancer progression to metastasis and its impact on the emergence of therapeutic resistance.

A rapidly growing body of evidence indicates that prostate microbiota within the TME may significantly contribute to the initiation of prostate cancer and progression to metastasis [4, 5]. Chronic inflammation in the prostate is common in adult tissues, and pathogenic microorganisms are being investigated as potential stimulants of prostatitis [5]. In fact, there are numerous infectious bacteria that have been

proven to cause bacterial prostatitis, such as *Streptococcus anginosus* and *Anaerococcus lactolyticus* [5, 6]. Inflammation of the prostate has been implicated as a main cause for the progression of prostate cancer, due to studies demonstrating that patients treated with anti-inflammatory drugs show significant decreases in prostate cancer risk [6]. Moreover, when exposed to bacterial or viral infections, patients show elevated levels of inflammatory factors, such as IL-6, IL-8, TGF-β, and TNF-α [4, 6, 7]. During chronic inflammation, microorganisms can modulate the expression of these inflammatory chemokines and cytokines [4, 6, 7]. Increased release of inflammatory factors support tumorigenesis through evading and dampening the immune response, as well as promoting epithelial-mesenchymal transition (EMT), angiogenesis, and metastasis [4, 6, 7]. Additionally, once secreted into the TME, the cytokines can induce the expression of oncogenes, such as VEGF, which then upregulate the NF-κB, EGFR, and TLR signaling activities, ultimately contributing to tumor cell proliferation and survival [4].

The most common types of bacteria found within the prostate TME are *Escherichia coli* and *Neisseria gonorrhoeae.* Interestingly, both contain the endotoxin lipopolysaccharide (LPS) within their cell walls [4]. Upon bacterial cleavage, the LPS released into the TME stimulates tumor invasiveness and promotes the EMT by upregulating the activities of the IL-6/STAT3, AKT/GSK-3β, and β-catenin pathways [4]. In addition to endotoxins, bacteria also release exotoxins, such as toxic necrosis factor 1 (CNF1), which work to activate the Cdc42-PAK1 signal axis, thus stimulating prostate cancer development [4]. The most common atypical bacteria, mycoplasma, also contributes to tumor progression through its associated proteins. For instance, the mycoplasma chaperone protein, DnaK, binds to and deactivates p53 to inhibit DNA repair while the mycoplasma protein p37 promotes the metastatic potential of tumor cells by inducing the P13K/AKT and MAPK/RAS signaling cascades [4]. Multiple studies have suggested a close relationship between viruses and prostate cancer, specifically human papillomavirus (HPV), adenovirus, BK polyomavirus (BKPyV) and EB viruses [4]. Recent studies revealed that upon HPV infection, expression of tumor suppressor genes p53 and pRb, as well as E-cadherin, were all down-regulated. These findings indicate that HPV infection may play a crucial role in metastasis through controlling anti-tumor mechanisms within cancer cells [4]. Attractive as this concept might be, one also must consider that some bacteria present in the TME induce signaling pathways that exhibit anti-tumor properties. For instance the bacteria *Staphylococcus aureus* expresses an enterotoxin that causes apoptosis of prostate cancer cells through the downregulation of certain lncRNAs [4]. The exotoxin, Botulinum toxin A, is also secreted by bacteria, and can enter tumor cells through the SV2 receptor, therefore inducing phosphorylation of phospholipase A2 (PLA2), which effectively interrupts tumor cell proliferation [4]. While the exact roles of the different types of microbiota in the TME are not fully elucidated, there is promising evidence that the microorganisms in the TME play a vital role in prostate cancer progression, and can be of therapeutic value when developing targeted treatments [4]. Emerging potential treatments involving microbiota include immunotherapy as well as targeted therapy using microorganisms. Therapeutic viral-based vaccines can activate the immune system, causing cytotoxic and humoral immune responses to prevent tumor growth [2]. Furthermore, several studies focus on the specific microorganisms present in the TME that deliver exogenous genes and metabolic products to cancer cells to induce growth and inhibit apoptosis [4, 6, 8].

Hypoxia is strongly associated with progression to metastasis, tumor invasion, and biochemical recurrence [4]. Mechanistic activation of hypoxia-inducible factor-1 (HIF-1) by hypoxia within the TME, facilitates the phenotypic adaptation of cells within the TME to hypoxic conditions [9]. Thus, HIF-1α activation involves induction of genes associated with phenotypic EMT, increased vascularity (VEGF), proliferation, and metastasis, ultimately conferring clinical resistance against standard of care chemotherapeutic drugs [9]. However, one may argue that therapies that employ anaerobic bacteria that can survive in hypoxic regions of the TME may provide a better alternative. For instance, *Salmonella typhimurium*, a facultative anaerobe, triggers apoptosis of PC-3, LNCaP, and DU-145 human prostate cancer cell lines [4]. Another facultative anaerobe, *Serratia marces-*

cens, suppresses the activity of IAP family inhibitors, thus initiating a caspase cascade that leads to apoptosis activation in prostate cancer cells [4]. Moreover, natural and genetically-engineered oncolytic viruses have been proven to specifically dissolve cancer cells while leaving normal cells unharmed [4]. Mammalian orthoreovirus (MRV) can inhibit HIF-1α to induce apoptosis in hypoxic regions, as well as down-regulate the expression of Akt, AR, and PSA in prostate cancer cells [4]. In a study, where microRNAs were inserted at the 3'UTR of the HSV-1 viral gene in MRV, the oncolytic virus was able to selectively target prostate cancer cells without affecting normal cells [4]. Technologies such as ultrasound targeting can facilitate the transport of oncolytic viruses to cancer cells, potentially reducing side effects and enhancing therapeutic efficacy [4].

Interlacing microbiota with the phenotypic landscape of the TME

Cell plasticity

The process of epithelial-mesenchymal transition (EMT) creates an opportunity for epithelial-derived tumors to become invasive and metastasize. Indeed, there is a large body of evidence in diverse solid tumors that identifies the central role EMT plays in metastasis: EMT endows cells with migratory and invasive properties, induces stem cell properties, prevents apoptosis and initiates metastasis [10]. EMT is largely regulated by transcriptional events that cause tumor epithelial cells to undergo long-term phenotypic changes in their cell polarity and adopt the physical characteristics of mesenchymal fibroblast-like cells [11]. It is the signaling activities of mesenchymal cells that facilitate migration and survival in an anchorage-independent, anoikis-defying mode in prostate cancer progression [12]. The other critical steps of the cancer cell metastatic journey involve the degradation of the extracellular matrix (ECM) with subsequent detachment of cancer cells from the ECM and neighboring cells, which is promoted by the transcriptional repression of cell-cell junctions and desmosomes [12]. Transformation into a mesenchymal phenotype facilitates extravasation and invasion into the blood and lymphatic system for migration to distant tissues [11]. However, malignant progression is a fluctuating, reversible process. Therefore, EMT is not solely caused by permanent genetic modifications, but is rather controlled by more dynamic factors, such as the TME [12].

The process of EMT is functionally coordinated by diverse components of the TME [13]. Contributors to the molecular and phenotypic landscape of the TME are CAFs, integrins, and proteases. CAFs typically replace smooth muscle cells in the stromal compartments of impacted prostate glands, and they induce the expression of ECM-remodeling enzymes as well as Vimentin, a structural protein that replaces E-cadherin during EMT interconversion [13]. This is a dynamic phenomenon navigated by the cell plasticity that characterizes tumor cells. Furthermore, the reorganization of the ECM in the context of the TME is vital to the processes of cell invasion and migration out of their original niches that characterize metastatic tumor cells [11]. Integrins, a family of membrane glycoproteins, are also reported to assist in tumor cell proliferation, survival, and invasion through binding to a multitude of ECM elements and facilitating cytoskeletal reorganization for migration [13]. One of the most significant contributors to cell plasticity and the phenotypic landscape of the TME are proteases, whose expression is often upregulated by bacterial microbiota. Proteases are typically secreted from a diverse array of cells in the TME, such as macrophages, fibroblasts, and neutrophils [13]. Proteases such as Matriptase and Hepsin, which are Type II transmembrane serine proteases, specifically help to break down the basement membrane of epithelial cells [13]. The most widely recognized proteases in terms of metastasis and invasion are matrix-metalloproteinases (MMP), which are involved in the degradation of collagen and fibronectin in the ECM [13, 14]. In non-diseased states, MMPs work to remodel the ECM and function in tissue repair; however, dysregulation of MMPs can induce a series of diseases and promote malignancy [13].

Phenotypic EMT may be disrupted by anoikis, a form of apoptosis induced upon cell detachment from the ECM [15]. In this manner, cells undergoing EMT are blocked from migrating and metastasizing to distant sites. Tumor cells can develop anoikis resistance to evade cell death through a myriad of mechanisms, thus

allowing them to travel throughout the lymphatic and circulatory systems to secondary sites [15]. Recent studies have shown that anoikis-resistant cells are dependent on Transforming Growth Factor-Beta (TGF-β), a serine threonine membrane kinase. In the presence of TGF-β, anoikis-resistant cells exhibit upregulated activity of Snail and P13K/Akt pathways [15]. Activation of the Snail pathway leads to increased transcription of EMT genes, facilitating the tumor cell's transition into a mesenchymal phenotype. The P13K/Akt pathway is a highly conserved signal transduction pathway that inhibits caspase-3-mediated apoptosis and anoikis while promoting the transcription of genes involved in angiogenesis and metabolism [15]. As secretors of TGF-β and promoters of androgen production, microbiota may play a crucial role in conferring anoikis-resistance in metastatic castration-resistant prostate cancer (CRPC) cells. With increased TGF-β, the signaling pathways previously mentioned can better facilitate a conversion to a mesenchymal phenotype to allow for metastasis of tumor cells to more distant sites [15]. Studies have discovered a strong link between the androgen receptor (AR) and TGF-β, indicating that they form a positive feedback loop to promote anchorage-independent survival [15]. Microbiota often secrete androgens, which bind to AR to promote the growth and proliferation of prostate cancer cells. Increased activity levels of AR stimulate TGF-β activity, thus facilitating EMT and preventing EMT-MET interconversions to contribute to easier metastasis of tumor cells [13]. The interplay between AR and TGF-β may be a crucial cause of therapeutic resistance against CRPC treatments that work to shift tumor cells towards an epithelial phenotype or make them more anoikis-sensitive [15].

During prostate cancer progression to metastasis, the prostate contains signaling interactions among regulators of cell lineage plasticity that contribute to phenotypic EMT-MET interconversions. Upon tissue damage, cytokines and growth factors are secreted to activate the stromal fibroblasts, endothelial cells, and epithelial cells within the TME [13]. The epithelial cells consequently loosen their attachments to the ECM with help from proteases and integrin signaling and are forced to migrate through the remodeled matrix. Epithelial cells eventually lose their cell-cell adhesions with each other and their apical-basal polarity, indicating the conversion from an epithelial to mesenchymal phenotype [13]. Interestingly enough, there is evidence to suggest the cell can enter a dormant state with low metabolic activity that inhibits its proliferative capacity after undergoing EMT, thus requiring the cell to convert to MET before attaining a proliferative state again [16]. Inhibition of EMT-inducing factors and promotion towards reversal of the epithelial to mesenchymal phenotype (MET to EMT interconversion) has been shown to stimulate cell division and metastatic progression [16]. The enhanced plasticity that characterizes the interconversion between epithelial and mesenchymal states has become associated with poor patient outcomes, which highlights the complexity of EMT-targeting therapies and the need for new phenotypic targeted therapeutics to impair metastatic disease [16].

The process of EMT promotes resistance against taxane chemotherapies such as docetaxel (1st line taxane chemotherapy), as proven by low E-cadherin levels and upregulated mesenchymal markers in drug resistant cells [17]. A major regulator of EMT induction is TGF-β, which activates Smad2/3 proteins to induce expression of EMT transcriptional regulators (Snail, Twist), conferring cells with stem cell-like qualities [17]. Aberrant TGF-β signaling leads to transient EMT-MET interconversions, which confers certain mesenchymal survival capabilities to epithelial cells [18]. Furthermore, there is a wealth of evidence profiling the EMT phenotypic landscape such that personalized signatures for prostate cancer patients with advanced disease can be developed to detect therapeutic resistance and treatment response [17]. In addition, a recent study was conducted in which treatment of therapy resistant prostate cancer with cabazitaxel (2nd line taxane chemotherapy) caused a phenotypic redifferentiation by actively reversing EMT to MET [17]. Thus, the phenotypic EMT-MET interconversion dynamic emerges as a viable target for circumventing therapeutic resistance and increasing tumor vulnerability to androgen-deprivation therapy (ADT).

Chromatin provides the platform for epigenetic regulation

The signaling events that occur throughout the TME often impact the chromatin and pheno-

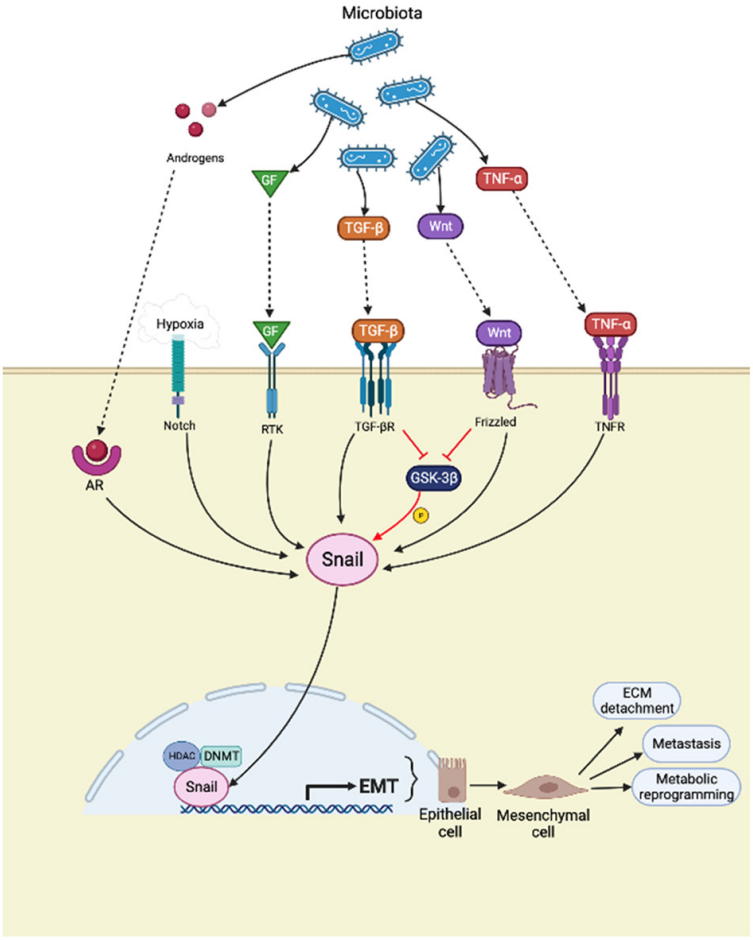

Figure 1. Extracellular signals from inflammatory factors, growth factors, androgens, hypoxia, and Wnt signaling lead to direct activation of Snail as well as inhibition of GSK-3β to prevent phosphorylation of Snail. The Snail transcription factor enters the nucleus and binds to epigenetic modifiers, such as HDACs and DNMTs, to upregulate the expression of EMT genes (Vimentin, N-cadherin, MMPs, fibronectin, β-catenin). Activation of EMT genes facilitates tumor cell ECM detachment, metastasis, and metabolic reprogramming.

typic landscape of prostate tumors [19]. Epigenetic modifications involve alterations of gene transcription through acetylation, methylation, and phosphorylation [2]. DNA methyltransferases (DNMT) often hypermethylate chromatin in prostate cancer to silence tumor suppressor genes, whereas DNA hypomethylation often leads to over-activation of oncogenes that have crucial roles in tumorigenesis and metastasis [19]. Histone modifications, such as acetylation, are typically carried out by histone acetyltransferases (HAT) on lysine residues of histone N-terminal tails to neutralize the electrostatic charge that holds DNA around the nucleosome, thus loosening the coiling of DNA and increasing transcription of target genes. Conversely, histone deacetylases (HDAC) remove acetyl groups to tighten chromatin around histones and silence genes [19].

Many of the signaling effectors secreted by microbiota, including TGF-α, TGF-β, and the Wnt pathway, induce EMT through the activation of EMT-transcription factors, such as *Snail, Twist, Slug,* and *Zeb* [20]. These EMT transcriptional regulators have both a DNA-binding domain as well as a domain that interacts with epigenetic modifying enzymes to carry out chromatin alterations [20]. Thus, TGF-β and Wnt both downregulate glycogen synthase kinase-3 beta (GSK-3β), which phosphorylates and targets degradation of Snail and β-catenin. Snail is an EMT-inducing transcription factor that contains a C-terminal zinc-finger DNA binding motif as well as an N-terminal SNAG domain that binds to a series of epigenetic regulators, including HDACs and DNMTs (**Figure 1**) [20]. ZEB1, another EMT-transcription factor, forms a repressor complex with Sirt1, an HDAC, and binds the E-cadherin gene promoter to block transcription. ZEB1 not only alters expression of EMT genes, but also regulates SETD1B, a histone methyltransferase, in which SETD1B further activates ZEB1 to form a positive feedback loop driving continuous chromatin modification [11]. The activity of the chromatin-modifying enzymes that work in conjunction with EMT-inducing transcription factors add acetyl and methyl groups to chromatin, thus reducing expression of target genes such as E-cadherin, occludin, and claudins while increasing expression of mesenchymal genes such as N-cadherin, fibronectin, and Vimentin [20]. Moreover, DNMTs often hypermethylate promoter or exonic regions to silence genes, resulting in the

inactivation of vital tumor suppressor genes [21]. The Adenomatous Polyposis Coli (APC) protein acts alongside GSK-3β to inhibit Snail and β-catenin in the Wnt pathway in normal cells; however, in prostate cancer, the APC promoter is often hypermethylated to prevent APC expression, leading to Wnt signaling and EMT [19]. The extent of epigenetic reprogramming associated with MET implies that the reversible nature of epigenetic alterations allows for cell plasticity [14].

In addition to the cytokine secretion by inflammatory cells and microbiota, CAFs secrete NRG1, a molecule that binds to ERBB3, an activator of the PI3K-AKT pathway that reduces DNA hypermethylation of cell survival and proliferation genes [22]. CAFs are also involved in secreting WNT16B, which activates the Wnt pathways and stimulates β-catenin entry into the nucleus. Nuclear localization of β-catenin allows for binding to transcriptional activators, TCF/LEF, which induce epigenetic chromatin modifications and increase expression of drivers of cell cycle progression, such as C-myc and Cyclin D1 [22]. While epigenetic modifications greatly impact cell plasticity and prostate cancer progression, further mechanistic exploration of the impact of TME paracrine signaling on the chromatin landscape of tumor cells will provide valuable new insights into the functional contribution of epigenetic modifiers to tumor progression [2].

Contribution of microbiota to therapeutic resistance

Microbiota directly contribute to the therapeutic resistance of prostate cancer cells through the production of androgens, impacting signaling pathways of cell survival, apoptosis, and metabolic reprogramming [8]. Androgens binding to AR drive prostate tumor growth, and their biological activity can be eliminated pharmacologically or surgically via ADT [23, 24]. ADT is the standard of care for advanced prostate cancer; however, patients who are initially responsive to ADT often develop resistance and progress to CRPC [23]. Numerous studies have shown that ADT instigates the activation of tumor microbiota that synthesize androgens from androgen precursors. By providing a supply of androgens, tumor microbiota contribute to the onset of CRPC and curtail the effects of ADT [8]. Studies in mice treated with antibiotics to limit tumor microbiota populations demonstrated a reduction in circulating androgens and AR in tumor cells, thus delaying the emergence of CRPC [8]. For instance, microbial species found in prostate tumors in mice, such as *Akkermansia muciniphila* and *Oscillospiraceae*, utilize a CYP17A1-like bacterial enzyme to synthesize androgens. In response to abiraterone, a CYP17A1 inhibitor, the production of steroid hormones was decreased, inhibiting tumor growth [8]. However, the depletion of androgens by targeting certain species of microbiota could potentially lead to the stimulation of other androgen-producing bacteria as well as antibiotic resistance of the original androgenic microbiota. A recent study showed that antibiotic exposure altered the microbial composition of the TME, leading to gut dysbiosis, and activating the inflammatory signaling pathways [25]. Significantly enough, the amount of *Proteobacteria* and LPS increased upon antibiotic treatment, and the elevated LPS levels assisted in prostate cancer progression by activating the NF-κB-IL6-STAT3 axis [25]. Furthermore, the LPS-activated inflammatory pathways resulted in chemotherapeutic resistance against docetaxel, a standard treatment for CRPC [25].

Microbiota and racial disparities

Understanding the differences in prostate microbiomes between patients of different racial/ethnic origins requires further investigation as more biologically relevant insights are generated towards the impact of microbiota in cancer outcomes. Recent evidence identified a number of specific microbial taxa that correlated with specific ethnicities and are heritable [26]. Thus, there exists a plausible link between genetic patterns of ancestry and the abundance of certain microbiota [26]. Statistically, men from Africa are at greater risk for chronic inflammation and aggressive prostate cancer [27]. In light of the previously discussed link between prostate microbiota and inflammation, the microbial composition of the TME may be a main contributor to the ethnic differences in risk presentation [27]. Recent studies prove that prostate samples from African men show heightened bacterial richness compared to non-African samples, thus indicating that the bacterial populations could be key drivers of aggressive disease [27]. Specifically, *Escheri-*

chia and *Acidovorax* bacterial populations are significantly abundant in African males in comparison to males of European and Australian ethnic backgrounds. Both *Escherichia* and *Acidovorax* are well-known infectious pathogens; however, *Escherichia* is particularly associated with bacterial prostatitis, in which inflammation is triggered largely through the JAK/STAT pathway [27]. Targeting specific microbiota species with anti-inflammatory mediators have proven to reduce inflammation. Significantly, testosterone has suppressive effects on uropathogenic *Escherichia coli* by downregulating JAK/STAT signaling and preventing the release of inflammatory cytokines, such as IL-6 and IL-8 [28]. While prostate microbial composition may begin to explain the racial disparities in clinical outcomes of prostate cancer, the genetic components behind microbial differences are still being investigated. Furthermore, the specific profile of bacterial populations responsible for increased prostate cancer risk and their mechanisms of action have yet to be elucidated, emphasizing the necessity for further research in racial and ethnic disparities [26].

Conclusions and future directions

The human microbiome provides information on the patient's health and disease, including cancer and consequently towards exploitation of the diagnostic value of microorganisms [4]. A recent study found that cyclophosphamide (an anti-cancer drug) is significantly effective in mice because of its ability to lower the population of *Bacteroidetes* and increase *Firmicutes*, which remarkably promoted an anti-tumor response [29]. Therefore, a possible route of future analysis is observing the structural qualities of the microbiota present in prostate tissue samples or prostatic fluid to determine their involvement in the antitumor response and their role as bacterial biomarkers [4]. The major clinical challenge in the treatment of prostate cancer patients is our limited ability to eradicate recurrent tumors following treatment [4]. Microbial targeted immunotherapies are under development, such as anaerobic bacterial therapies and oncolytic virus vaccines [4]. Moreover, clinical trials focused on increasing the efficacy of immunotherapy, such as fecal microbiota transplants, are also underway [30].

The role of smooth muscle cells, endothelial cells, and fibroblasts, and their signaling interactions with the tumor epithelial cells is collectively critical in defining the epigenetic landscape of prostate tumors [22, 31, 32]. The TME's patterns of modulating chromatin structure in prostate cancer through paracrine signaling or metabolic reprogramming towards metastasis is not completely understood [13, 22, 31]. Only a few clinical trials are testing the efficacy of small molecule inhibitors that target bromodomain and extra-terminal proteins (BET), DNMTs, and HDACs to control methylation and acetylation patterns on chromatin [31]. Using epigenetic modulators as actionable targets for drug development may provide new avenues for effective targeted treatments, while minimizing the severity of side effects, compared to standard-of-care drugs [31]. Moving forward, dissection of the dynamic interplay between the TME, microbiota, and tumor cells is critical to maximize therapeutic response to targeted treatment of advanced CRPC [33-35].

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Disclosure of conflict of interest

None.

Abbreviations

ADT, Androgen Deprivation Therapy; APC, Adenomatous Polyposis Coli; AR, Androgen Receptor; BET, Bromodomain and Extra-terminal Proteins; BKPyV, Polyomavirus BK; CAFS, Cancer-Associated Fibroblast; Cdc42, Cell Division Control Protein 42; CNF1, Toxic Necrosis Factor 1; CRPC, Castration-Resistant Prostate Cancer; CYP17A1, Cytochrome P450 17A1; DNMT, DNA Methyltransferase; EB, Epstein-Barr Virus; ECM, Extracellular Matrix; EGFR, Epidermal Growth Factor Receptor; EMT, Epithelial-Mesenchymal Transition; GSK-3β, Glycogen Synthase Kinase-3 Beta; HAT, Histone Acetyltransferase; HDAC, Histone Deacetylase; HIF-1α, Hypoxia Inducing Factor-1alpha; HPV, Human Papillomavirus; HSV-1, Herpes Simplex Virus-1; IL-6, Interleukin-6; IL-8, Interleukin-8; lncRNAs, Long Noncoding RNAs; LPS, Lipopoly-

saccharide; MAPK, Mitogen-Activated Protein Kinase; MET, Mesenchymal Epithelial Transition; MMP, Matrix Metalloproteinase; MRV, Mammalian Orthoreovirus; NF-κB, Nuclear Factor Kappa B; NRG1, Neuregulin 1; PAK1, P21 (RAC1) Activated Kinase 1; PI3K, Phosphatidylinositol 3-Kinase; PLA2, Phospholipase A2; PSA, Prostate-Specific Antigen; RAS, Rat Sarcoma; Rb, Retinoblastoma; Sirt1, NAD-Dependent Deacetylase Sirtuin-1; STAT3, Signal Transducer and Activator of Transcription 3; TCF/LEF, T-Cell Factor/Lymphoid Enhancer Factor; TGF-α, Transforming Growth Factor-Alpha; TGF-β, Transforming Growth Factor-Beta; TLR, Toll-Like Receptor; TME, Tumor Microenvironment; UTR, Untranslated Region; VEGF, Vascular Endothelial Growth Factor; Wnt, Wingless/Integrated; ZEB-1, Zinc Finger E-Box-Binding Homeobox 1.

Address correspondence to: Natasha Kyprianou, Department of Urology, Icahn School of Medicine at Mount Sinai, New York, New York 10029, USA. Tel: 212-241-6696; E-mail: natasha.kyprianou@mountsinai.org

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