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Racial differences in prostate tumor microenvironment: implications for disparate clinical outcomes and potential opportunities

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ABSTRACT

Disparities in cancer incidence and outcome are common among the racial and ethnical minorities in the United States and are of significant social and clinical concern. Prostate cancer is the most commonly diagnosed non-cutaneous malignancy in American men and exhibits substantial racial disparities with African American men bearing the highest burden in terms of incidence and mortality. A multitude of factors, including socioeconomic, behavioral, and access to healthcare, have been implicated as the underlying causes of such disparities. More recent data also suggest that there are inherent molecular and biological differences in prostate tumors of patients having distinct racial backgrounds. Tumor microenvironment has tremendous impact on the course of cancer progression and clinical outcome and may also contribute to the racial disparities observed in prostate cancer. Therefore, a better understanding of critical differences in the tumor microenvironment components may provide newer directions to study the biological causes of prostate cancer health disparities and may identify novel therapeutic targets. This review discusses the findings related to the tumor microenvironment differences between African American and Caucasian American prostate cancer patients and makes suggestion regarding their potential significance in prostate cancer disparities.

KEYWORDS: Prostate cancer, racial disparity, tumor microenvironment

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1.0. Introduction

Prostate cancer (PCa) is the most commonly diagnosed non-cutaneous malignancy and the second leading cause of cancer-related death in American men [1, 2]. Among all the cancers, PCa not only shows extreme variations in its potential to cause morbidity and death in men but also displays great variations in geographic and racial distribution [1, 2, 3, 4]. In the United States, despite significant improvements in cancer diagnosis and treatment strategies, African American (AA) men suffer disproportionately from PCa with over 80% higher incidence rates than men of European American (CA, Caucasian American) origin [5, 6, 7, 8]. AA men are also more likely to be diagnosed at a younger age and present with more advanced and aggressive disease stages [8-12] compared to men with CA ancestry. Accordingly, for AA men, the lifetime risk of developing PCa is 1 in 6, while that for CA men is 1 in 8. AA men are also greater than twice as likely to succumb to the disease compared with CA men as the PCa specific mortality in AA men is 1 in 23 whereas it is 1 in 42 in CA men [1, 2, 7].

In order to overcome the disparity that affects AA population negatively and to develop personalized therapeutic approaches, we need to identify and understand the factors that drive PCa tumor progression and metastasis in AA men. Over the years, a number of such interconnected factors including socioeconomic status, lifestyle and dietary issues, problems with accessing healthcare have been identified as probable causes of this epidemiological disparity in PCa incidence and mortality [1, 2, 8]. Interestingly, several newer lines of evidence have also demonstrated genetic and biological variations among patients of different racial backgrounds. The androgen hormonal axis, the androgen receptor (AR), and its signaling pathway play critical roles in PCa progression [13].Several aspects of the AR pathway have also been implicated in PCa associated racial differences [14-16]. However, in addition to androgens and AR signaling, the crosstalk between epithelial cells and cellular components of the tumor microenvironment (TME), such as mesenchymal stem cells, endothelial cells, fibroblasts/myofibroblasts, and immune cells also plays an integral role in PCa progression and metastasis [2,17]. The immune cells as well as the endothelial cells forming the blood vessels in the PCa TME, secrete growth factors and cytokines to induce PCa cell proliferation and spread [2, 17]. Increasing evidences now indicate that the TME components may also be a significant contributor to the racial disparity observed in PCa incidence, aggressiveness and clinical outcomes between AA and CA populations [2, 18-20]. Therefore, we have reviewed the pertinent data to discuss the potential contribution of the TME to the observed racial disparity associated with PCa (Table 1).

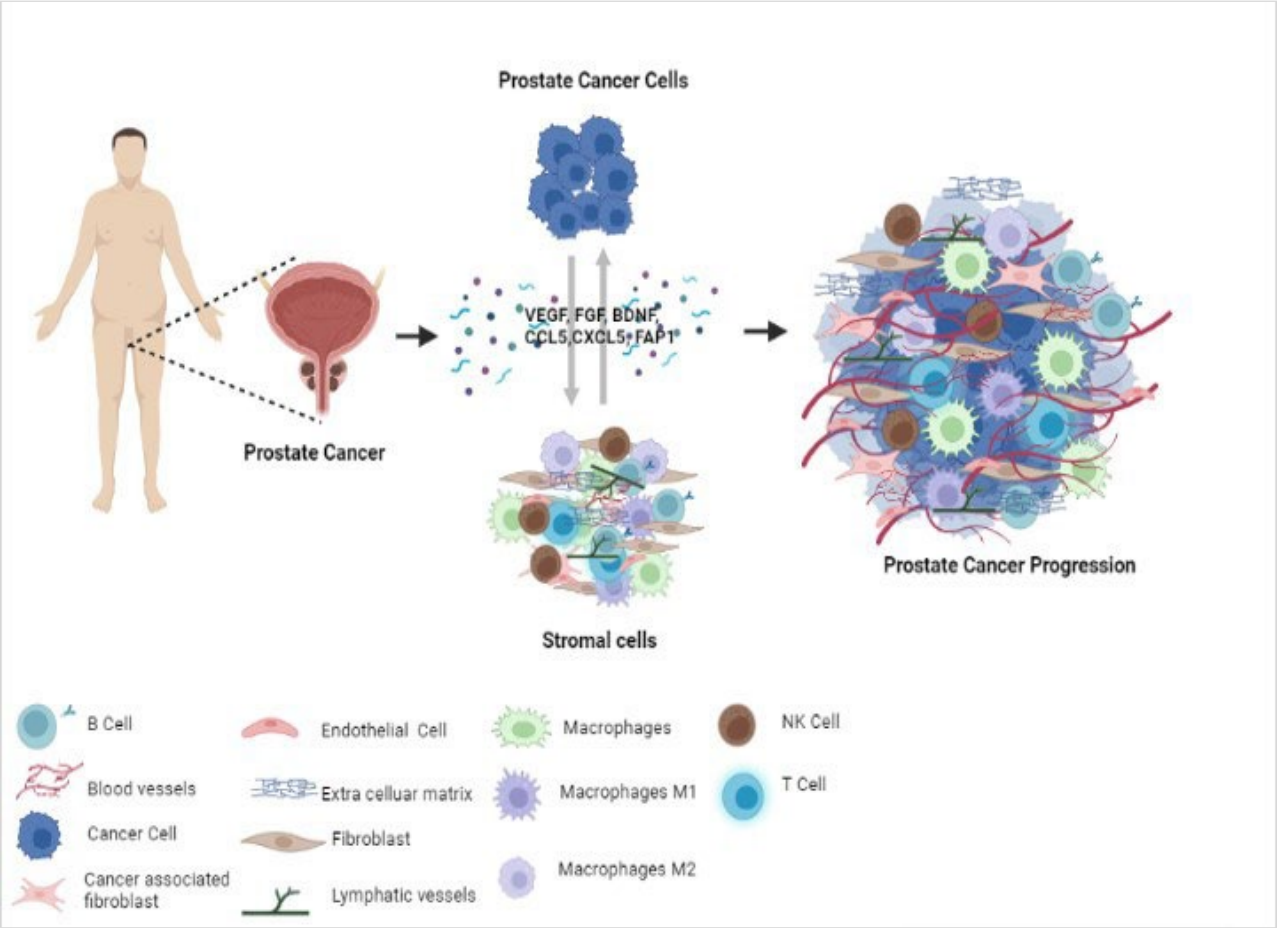
Table 1. Role of stromal cells in AA and CA PCa.			
Cell type	Role in PCa	Differences in AA and CA PCa	References
Fibroblasts	• Secrete chemokines, cytokines, growth factors (brain derived neurotrophic factor and chemokines like CCL5, CXCL5, SDF1-alpha and soluble factors such as VEGF, bFGF, HGF) • Promote tumor growth and metastasis	• Pro-inflammatory cytokines and growth factors [brain-derived neurotrophic factor (BDNF), VEGF, and fibroblast growth factor 7 (FGF7)] are significantly elevated in AA PCa • Higher expressions of myofibroblast activating markers [αSMA, vimentin, and FAP1] and mesenchymal stem cell marker, CD90, in cancer associated fibroblasts (CAFs) of AA PCa	2,19
Immune cells	• Inflammation promotes initiation and progression	• Increased lymphocytic infiltration in AA PCa tissues • Pro-inflammatory cytokines (interferon-alpha (IFNα), IFNγ, tumor necrosis factor-alpha (TNFα), and Interleukin 4 and Interleukin 13) are upregulated in PCa of AA men • Increased NK cell activity in AA PCa	2, 28, 34-36
Endothelial Cells	• Form neovesels to support tumor growth and metastatic progression	• Increased VEGF secretion in AA PCa • Higher MVD in AA PCa tissues	2,19, 44, 50

2.0. Prostate Cancer Microenvironment

Prostate, a tubule-alveolar gland is primarily composed of prostatic epithelial cells surrounded by the stromal components [17, 21]. The gland has three distinct zones; peripheral, central, transition, and a mixed zone called the anterior fibro-muscular zone or stromal zone [17, 21, 22]. It is mainly composed of four major epithelial cell types- basal cells, neuroendocrine cells, epithelial stem/progenitor cells, and secretory luminal cells [17, 22]. The stroma consists primarily of fibroblasts, myofibroblasts, endothelial cells, immune cells, nerve cells and smooth muscle cells [17, 22].

The development and progression of PCa is a complex process and the disease is extremely heterogeneous from molecular, cellular and clinical standpoints [23]. In most cases, PCa originates in prostatic epithelial cells. Therefore, studies on PCa development and progression have mainly focused on these cells [22, 23]. However, epithelial cells are not sole players contributing to PCa tumorigenesis; the stromal cells in the TME also play critical roles in PCa development and progression [2, 17, 24]. The crosstalk between the stroma and the epithelium is a major driver of PCa pathogenesis and disease progression [24, 25]. The interaction between the epithelial or cancer cells and the non-epithelial or stromal cells in PCa is mediated by a variety of paracrine factors secreted both by cancer cells as well as by the stromal cells [2, 25] **(Figure 1).** Several studies have emphasized the contribution of altered/reactive stromal microenvironment characterized by increase in the numbers of myofibroblasts and fibroblasts and significant decrease in the numbers of smooth muscle cells in tumorigenesis and progression of PCa [17, 25].

Figure 1: Interaction between PCa cells and the stroma (Created by BioRender)



Regarding the disproportionate burdens of PCa between AA and CA populations, while most studies have focused on genetic differences within different prostate tumor subtypes, emphasizing mostly on PCa cells, a handful of studies have also indicated how differences in PCa TME can affect tumor progression among men with different racial and ethnic backgrounds [18, 19]. Altered gene expression profiles of fibroblasts, immune cells and angiogenic components was noted between the TME of AA and CA men with PCa [18-20, 26-27]. In a study involving PCa samples from patients of AA and CA backgrounds, a total of 677 genes associated with 103 pathways were identified to be differentially expressed in the PCa TME [20]. Furthermore, pathway analysis and disease association studies have revealed a significant difference in tumor inflammatory response and cytokine secretion between AA and CA patient samples [18, 20, 21, 28, 29].The differences in TME of AA and CA PCa patients may account for the differences observed in tumor growth, progression and therapeutic response. In the following sections, we will therefore discuss the racial differences observed in three important cellular components of the TME in PCa: cancer associated fibroblasts (CAFs), immune cells and endothelial cells.

2.1. Fibroblasts

The stromal fibroblasts play a major role in normal prostate development as well as in PCa progression [2, 17, 25]. Cancer associated fibroblasts (CAFs) form a major component of TME and they actively communicate with PCa cells both via direct contact

and via soluble mediators such as chemokines, cytokines, growth factors secreted by both of the cell types [2, 17, 25, 30, 31]. This bidirectional communication between PCa cells and CAFs is crucial for tumor progression and metastasis. CAFs secrete growth factors like brain derived neurotrophic factor and chemokines like CCL5, CXCL5, SDF1-alpha and soluble factors such as VEGF, bFGF, HGF that promote PCa growth and progression [2, 19]. Studies have shown CAFs can differentially impact PCa progression in AA and CA patients. In a study where prostate fibroblasts from PCa specimens of AA and CA patients with similar clinicopathologic characteristics were isolated, it was noted that pro-inflammatory cytokines and growth factors [brain-derived neurotrophic factor (BDNF), VEGF, and fibroblast growth factor 7 (FGF7)] were significantly elevated in CAF isolated from AA PCa samples compared to CA PCa [19]. In addition, myofibroblast activating markers [αSMA, vimentin, and FAP1] and mesenchymal stem cell marker, CD90, showed significantly higher expressions in AA CAFs compared with CA CAFs [19]. With increased myofibroblastic components and presence of a population of mesenchymal-like cells (CD90+) it was inferred that AA-derived cells would show increased response to growth factors compared with CA-derived cells [19]. On the other hand, the expression of Caveolin1 (CAV1) that is a membrane-associated protein , whose expression in cancer cells increases with progression but loss in PCa stroma correlates with reduced relapse-free survival [19, 32, 33], was found to be lower in AA CAFs compared with CA CAFs. Upon exposure of PCa cells to conditioned media from fibroblasts isolated from AA and CA PCa patients, it was seen that there was increased proliferation and migration *in vitro* when PCa cells were exposed to conditioned media from AA prostate fibroblasts compared to CA prostate fibroblasts [19]. Furthermore, this study demonstrated that regardless of the racial background of PCa cells, growth and/or proliferation of PCa cells was significantly increased when conditioned media from AA patients' fibroblasts was used (19). In addition, the study also reported an increased collagen deposition and myofibroblasts forming the 'reactive stroma' and elevated expression of fibroblast specific marker, tenascin-C, in the extracellular matrix (ECM) of AA PCa patients [19]. High expression of tenascin-C in CAFs is associated with poor prognosis in PCa [34].Taken together; these data suggest that CAFs in AA PCa patients produce significantly higher levels of growth factors that enhance the tumorigenicity of PCa cells compared with CAFs in CA PCa patients.

2.2. Immune Cells

Although PCa is considered as a poorly immunogenic tumor, chronic inflammation has been consistently shown to be associated with the development and progression of the disease [35]. Immune cells form the cellular arm of inflammatory responses and presence of inflammatory cells in PCa TME is well documented.Only a few studies however have explored the immunological differences observed in the TME of AA and CA PCa.[36]. Very recently, it was reported that there is over-representation of immunogenic TME in AA PCa patients, with significantly higher inflammatory cytokines and lymphocytic infiltrates which increases the potential for better response to immunotherapy in these patients [37] . Studies have reported a significant difference in both the numbers and types of inflammatory cells and inflammatory responses between AA and CA PCa populations. Differences were noted between AA and CA PCa patients in expression of chronic inflammatory cytokines, such as interferon-alpha (IFNα), IFNγ, tumor necrosis factor-alpha (TNFα), Interleukin (IL) IL-1β, IL 4, IL 6, IL 8 and IL 13. These pro-inflammatory cytokines show significant

upregulation in PCa of AA men [20, 38]. IL-6 promotes migration of cells and helps to evade apoptosis through STAT and PI3K pathways and is considered immunosuppressive as it helps to recruit myeloid derived suppressor cells (MDSC) to the TME [37, 39]. IL-8 activates neutrophil and plays a role in cell proliferation and invasion. Higher levels of IL-8 expression in PCa was associated with higher tumor grade but this association was comparable in AA and CA PCa [37, 40]. A recent study that was conducted using grade, stage matched AA and CA PCa, has reported an increased lymphocytic infiltration in AA PCa tissues compared to PCa tissues of CA origin [28]. Upon further analysis of the lymphocytic population, the study reported a higher presence of plasma cells in TME of AA PCa that correlated with IFNγ expression and increased inflammation observed in these tissues [28]. High expression of IgG was also noted in these AA PCa samples, which suggested more antibody secretion by these cells [28]. In addition, increased activity of NK cells, which primarily drives antibody dependent cellular toxicity, have been reported in AA PCa tissues compared to tissues from CA patient [28]. A different study also reported that AA PCa had higher expression of CD4+ and CD8+ T-cell markers in TME [38]. In contrast, there is also a report that indicated no difference in T-cell infiltration between AA and CA PCa but increased regulatory T-cells in AA PCa that correlated with disease recurrence [41]. Poor disease prognosis associated with lymphocytic TME infiltrates may be due to their association with more aggressive tumors, or as the infiltrating T-cells were dysfunctional, or as were immunosuppressive regulatory T-cells [37, 42].

Macrophages comprise a major portion of the immune cells in the TME. M1 type or classically activated macrophages which are anti-tumorigenic and M2 type or alternatively activated macrophages which are pro-tumorigenic have been shown to be present in the PCa TME. In the TME, the tumor-associated macrophages (TAMs) are converted from a M1-type to the M2-type phenotype that secrete numerous growth factors, which influence diverse processes during PCa progression.The density and type of TAMs present in PCa thus provide prognostic information [2, 43]. AA PCa patients show increased TAM numbers compared to CA PCa patients as both CD68+ (M1), and CD163+ (M2) cells were significantly higher in AA PCa tissues [2].

A study investigating the role of inflammation and immune genes in AA PCa characterized 124 TME and immune response genes in AA PCa patients [44]. It was reported that 22% of total AAM patients showed adverse pathology features, high genomic risk (53%) and higher expressions of immune-response genes some of which along with their functions have been included in Table 2.

Table 2: Immune response genes elevated in AA PCa patients compared to CA PCa patients.

Gene Name	Expression in AA PCa patients	Role in cancer	References
Cluster of differentiation 2 (CD2)	⬆	Immunomodulatory in the TME; associated with delayed disease progression; enhances tumor immunogenicity and may improve response to immunotherapy.	44, 45

Cluster of differentiation 3 (CD3)	↑	Activates cytotoxic T cells (CD8+ naive T cells) and T helper cells (CD4+ naive T cells).	44, 46
Cluster of differentiation 4 (CD4)	↑	Immunosuppressive; may help in identifying patient subset that would benefit from immunotherapy.	44, 47, 48
Cluster of differentiation 45 (CD45)	↑	Regulates lymphocyte survival, cytokine responses, and TCR signaling; altered CD45 could result in severe combined immunodeficiency.	44, 49
Cluster of differentiation 96 (CD96)	↑	Inhibits function of CD8+ T cells; regulates NK cell effector function and cellular metastasis.	44, 50
C-C Motif Chemokine Ligand 5 (CCL5)	↑	Promotes angiogenesis and metastasis; increases drug resistance; promotes self-renewal of PCa cells.	44, 51
C-X-C Motif Chemokine Ligand 9 (CXCL9)	↑	Inhibits cytokine secretion from T cells; promotes PCa progression.	44, 52
C-X-C Motif Chemokine Ligand 10 (CXCL10)	↑	Increase infiltration of pre-adipocytes and TAMs in PCa TME; promotes migration and invasion of PCa cells.	44, 53
C-X-C Motif Chemokine Ligand 11 (CXCL11)	↑	Promotes PCa cell migration and invasion.	44, 54
Signal transducer and activator of transcription 1 (STAT1)	↑	Tumor suppressor in early PCa stages; promotes drug resistance.	44, 55
Indoleamine 2,3-dioxygenase 1(IDO1)	↑	Mediates immunosuppression; associated with significantly worse clinical outcomes.	44,56
Matrix metallopeptidase 9 (MMP9)	↑	Promotes angiogenesis.	18, 57
Autocrine motility factor receptor (AMFR)	↑	Mediates AMF-mediated cell migration and metastasis.	18, 58

Taken together, the TME in PCa exhibits an immunosuppressive microenvironment and manifests a unique immune repertoire in AA population characterized by increased inflammatory mediators and significant enrichment of proinflammatory immune pathways creating a tumor supportive environment that negatively associates with disease outcomes. However, a study also indicates that there is no significant association between inflammatory infiltrate and inflammation and the difference in PCa incidence and outcomes in different racial groups [59, 60].Therefore, more studies are needed to draw a conclusion regarding

contribution of immune microenvironment to PCa associated racial disparity.

2.3. Endothelial Cells

In addition to the fibroblasts and immune cells, endothelial cells form a major cellular component of the TME. Endothelial cells form new blood vessels from existing vasculature by a process termed angiogenesis to meet the nutrient and oxygen requirements of the rapidly dividing cancer cells. Additionally, these cells by forming neovessels provide routes for dissemination of cancer cells to other parts of the body [61-67]. In order to propagate and form new blood vessels the endothelial cells in TME respond to growth factors secreted by cancer cells and cells in TME including endothelial cells themselves , such as vascular endothelial growth factor (VEGF) and fibroblast growth factor (FGF). PCa, like other solid tumors depends on angiogenesis and overexpression of proangiogenic factors like VEGF and FGF have been shown to be associated with poor PCa prognosis [65, 68-71].

VEGF is the most prominent cytokine regulating the process of angiogenesis [65, 70, 72, 73]. In PCa, the expressions of VEGF and/or its receptor VEGFR-2 are directly correlated to tumor Gleason grade, metastatic potential, and progression-free survival (PFS). In AA PCa TME increased VEGF secretion by fibroblasts may impact tumor angiogenesis [71]. Microvessel density (MVD) a surrogate marker assessing angiogenic response in tissues has been shown be higher in PCa tissues collected from AA patients compared to patients with CA background. [2, 19]. These differences in expression of angiogenic factors and angiogenic response observed between PCa of AA and CA men could differentially influence PCa growth, metastasis and clinical outcomes in these two populations.

3.0. Clinical implications of the racially different tumor microenvironment composition in prostate cancer

TME in PCa patients with different racial backgrounds show prominent genetic variability which influences their ability to synthesize, secrete and, respond to growth factors which results in differential growth, progression and therapeutic responses [2, 17, 19, 20, 24]. With the differences observed in TME, it is more likely that AA PCa patients may respond differently to different therapeutic strategies. Recent evidence indicates that even though immunotherapy has not been very successful in PCa, AA patients might benefit from it due to the differences in the immune landscape. In the PROCEED (NCT01306890) trial for receiving immunotherapy with sipuleucel-T for metastatic castration resistant prostate cancer (mCRPC), AA PCa patients showed a higher survival advantage than CA PCa patients [74]. In the PSA-matched set, median overall survival (OS) for AA patients was 35.3 and that for CA patients was 25.8 months and in the all patient set, OS of AA patients was 35.2 monthsas compared to 29.9 months for CA patients. mCRPC AA patients with lower baseline PSA showed even longer OS of over 4.5 years compared to 2.8 years for CA patients. The better response to immunotherapy shown by AA PCa patients proves the differences in immune response in AA and CA PCa patients [35]. AA PCa patients have been predicted to have higher response score to DNA damage and alkylating agent-based chemotherapy whereas CA PCa has a higher response score to microtubule-based chemotherapy [44]. Other studies have reported that the regular use of aspirin can significantly reduce both the risk of developing metastatic PCa and disease recurrence in AAM [75, 76] by targeting the pro-inflammatory cyclooxygenase/ thromboxane A2 pathway [77]. Evidence also suggests reduced mortality due to PCa in AAM

using aspirin [78].Furthermore, TME facilitates therapeutic resistance by modification of stromal components to promote invasion, angiogenesis, and metastases. Patient response to therapy depends strongly on activation of tumor stroma. The presence of myofibroblasts, that show higher expressions in AA patients than CA patients, predicts biochemical recurrence in PCa patients [79]. CAFs were also shown to induce chemoresistance through induction of EMT [80]. Interaction of TAMs and cancer stem cells (CSCs) can result in resistance to ADT therapy. CSCs help in TAM remodeling and TAMs promote the stem-like properties of CSCs and drug resistance by acting through the IL-6/STAT3 signaling pathway [81].

4.0. Conclusion and future perspective

The TME is a key contributor to PCa progression and determinant of clinical outcomes. The stromal cells and the extracellular milieu of the TME regulate the plasticity of the phenotypic traits of PCa cells. The interaction between PCa cells and surrounding TME components (immune, vascular, and stromal) are therefore being studied extensively to understand its broader role in pathobiology and disease outcomes [2, 17, 19, 20, 24] using traditional *in vitro* and *in vivo* experiments and recently by fluorescence-activated cell sorting or laser microdissection with RNA sequencing and spatial transcriptomics [82, 83, 84]. The recent technique of multiplex immunofluorescence (mIF) with tyramide signal amplification helps to gather maximum information from a single tissue section with accurate classification of the TME cell population [85]. Use of single-cell RNA transcriptome sequencing (scRNA-seq) can indicate the cell heterogeneity and help to analyze cellular interactions [82]. The use of these techniques will further help to identify the role of the modulated genes in individual TME components of AA and CA PCa.

Data related to the role of TME in race-associated cancer health disparity has only recently begun to emerge in prostate and other cancers. Further studies involving larger datasets from diverse patient populations would provide more strengths to TME differences and their association with clinical outcomes and clinicopathologic progression of cancer. Similarly, more efforts should also be made to determine the exact contribution of TME to differential PCa progression using appropriate experimental models and delineate the underlying molecular mechanisms. Unlike the cancer cells, cells of the TME are genetically stable, which make them attractive targets for cancer management (prevention and treatment) and to reduce the risk of acquiring therapy resistance leading to treatment failure and recurrence. A better understanding of the role of the TME will also help in the development of race-specific biomarkers and therapeutic targets leading to personalized approaches for risk prediction, diagnosis, monitoring, and management of PCa.

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Conflicts of interest

The authors declare that they have no conflicts of interest with the contents of this article.

Authors' contributions

Conception and design: DC. Initial manuscript writing: SG, CS, and DC. Review and revision of the manuscript: SG, CS, SS, APS and DC.

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