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Author manuscript

Prostate. Author manuscript; available in PMC 2023 January 25.

Published in final edited form as:

Prostate. 2022 June ; 82(8): 883–893. doi:10.1002/pros.24333.

Immune mechanisms behind prostate cancer in men of African ancestry: A review

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Abstract

Background: Men of African ancestry (AA) with prostate cancer suffer from worse outcomes. However, a recent analysis of patients treated with the dendritic cell vaccine sipuleucel-T for prostate cancer suggested that AA patients could have improved outcomes relative to whites.

Methods: We conducted a focused literature review of Medline-indexed articles and clinical trials listed on clinicaltrials.gov.

Results: We identify several studies pointing to enrichment of inflammatory cellular infiltrates and cytokine signaling among AA patients with prostate cancer. We outline potential genomic and transcriptomic alterations that may contribute to immunogenicity. Last, we investigate differences in host immunity and vaccine responsiveness that may be enhanced in AA patients.

Conclusions: AA patients with prostate cancer may be enriched for an immunogenic phenotype. Dedicated studies are needed to better understand the immune mechanisms that contribute to existing cancer disparities and test immune-based therapies in this population.

Keywords

African ancestry; cancer disparities; cancer vaccines; immunology; prostate cancer

1 | INTRODUCTION

Prostate cancer remains the most incident and prevalent non-cutaneous malignancy in US men, accounting for up to 20% of new cancer diagnoses; it is also the second leading cause

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CONFLICTS OF INTEREST

Daniel Sentana-Lledo: None. Oliver Sartor: Consultant for Advanced Accelerator Applications (AAA), Astellas, AstraZeneca, Bavarian Nordic, Bayer, Blue Earth Diagnostics, Inc., Bristol Myers Squibb, Clarity Pharmaceuticals, Clovis, Constellation, Dendreon, EMD Serono, Fusion, Isotopen Technologien Meunchen, Janssen, Myovant, Myriad, Noria Therapeutics, Inc., Novartis, Noxopharm, Progenics, POINT Biopharma, Pfizer, Sanofi, Tenebio, Telix, and Theragnostics; receives grant or research support from Advanced Accelerator Applications, AstraZeneca, Bayer, Constellation, Dendreon, Endocyte, Invitae, Janssen, Merck, Progenics, Sanofi, and SOTIO. Steven P. Balk: None. David J. Einstein: Funding to institution from Bristol Myers Squibb, Cardiff Oncology, and Puma Biotechnology for clinical trials; discounted research sequencing from Foundation Medicine.

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of cancer death among US men.[1] However, men of African ancestry (AA) with prostate cancer have higher incidence (1.8×) and mortality (2.2×) compared to white patients.[2] Potential contributing factors include tumor-specific biology, medical comorbidities, access to and receipt of care, and other social determinants of health. Several studies have shown that in equal access to care settings (e.g. the VA system), the differences in prostate cancer mortality were comparable across AA and other populations.[3–5] However, there is also growing evidence that AA men may have unique biological phenotypes of prostate cancer.[6–9] In addition to tumor biology, host immunity may also be different in AA men and shape the antitumor immune response.[10,11] Characterizing these unique phenotypes could have significant implications for personalized therapeutic approaches, including immunotherapies. Recently, data has emerged on an observed survival advantage in AA patients with metastatic castration-resistant prostate cancer (mCRPC) who had received sipuleucel-T, a cell-based form of immunotherapy.[12,13] This latest finding, along with others in the literature, raises the question whether prostate cancer patients of AA can particularly benefit from immunotherapy.

At this point, it is crucial to emphasize that race is a social construct that has deep historical and cultural connotations. There is ongoing debate in the medical literature about whether using race as a proxy for biological differences in patient populations further perpetuates health inequities,[14] or rather the resulting “color blindness” exacerbates existing disparities.[15] Importantly, reported race often mixes together multiple populations, limiting the generalizability of findings in studies (e.g., patients with ancestors from sub-Saharan Africa can have different genomics than those with Caribbean predecessors).[16] In addition, the concept of race dichotomizes a range of ancestry. Recently, the concept of “genetic ancestry” has emerged as a more appropriate surrogate to tease apart biological traits within populations.[17,18] Keeping these clarifications in mind, there is a need for dedicated studies in AA patients to better inform treatment decisions and close the gap on existing inequities. This review aims to identify distinct and recurrent phenotypes in immune pathways found in AA prostate cancer, with the hope of promoting studies with AA representation that can help reduce prostate cancer disparities.

2 | METHODS

Peer reviewed articles included in this review were obtained from searches in publicly available journal databases—PubMed, Embase, Cochrane, Web of Science—for the period up to 04/2021, containing combination of the keywords “prostate cancer,” “African ancestry,” “African American,” “Black,” “cancer disparities,” and the specific topic of interest (e.g., “genetics”). Additional targeted searches were carried out for articles on “cancer vaccines” and “immunotherapy” that were not necessarily limited to prostate cancer, as well as other noncancer pertaining topics like “immunology” and “vaccines.”

3 | RESULTS

3.1 | Clinical observation: Increased effectiveness of sipuleucel-T in AA with mCRPC

Sipuleucel-T is a therapeutic immune stimulating cancer vaccine approved for treating mCRPC after the pivotal phase III IMPACT trial showed an overall survival benefit.[19] The

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vaccine contains autologous dendritic cells (DCs) and other antigen presenting cells (APCs) activated ex vivo to a fusion protein of prostatic acid phosphatase (PAP) with granulocyte-macrophage colony-stimulating factor. Building on the findings of prior studies,[20,21] the IMPACT trial showed a prolonged median survival of 4.1 months in mCRPC patients who received sipuleucel-T compared to placebo (25.8 months vs. 21.7).[19] The survival effect observed was as long as 13 months in patients with low baseline PSA in a subgroup exploratory analysis.[22] The effect on OS was not matched by PSA responses or progression-free survival benefits, suggestive of possible delayed immune effects. Indeed, sipuleucel-T was shown to induce a robust, durable humoral and cellular immune response —in particular, the activation of APCs that led to production of antibody titers to the fusion protein was associated with a survival benefit.[23] While sipuleucel-T also induced T-cell proliferation (although particular T-cell subsets were not specified), there was no associated change in survival.[19,23] A deeper analysis on the antibody production after sipuleucel-T administration identified “antigenic spread,” or off-target immune response to tumor-associated antigens (TAAs) such as PSA or LGALS3, which was additionally associated with improved survival.[24] Last, to complete the understanding of immune mechanisms derived from sipuleucel-T, neoadjuvant use of the vaccine in localized prostate cancer found T-cell recruitment and activation, predominantly of CD4 helper T-cells, at the tumor microenvironment (TME).[25] Despite its recommendation as an option in the treatment of mCRPC, uptake of sipuleucel-T has remained relatively low. In a recent large retrospective study, sipuleucel-T was selected as treatment in approximately 10% of mCRPC patients; importantly, administration of sipuleucel-T to AA patients was not significantly different than to other patient populations.[26]

Participants in the IMPACT trial included 6.7% (n = 23/341) AA patients, but no AA-specific data was reported. However, a subsequent subgroup analysis of AA participants in several sipuleucel-T phase III trials identified a signal of a significantly improved OS of 30.7 months in AA patients receiving sipuleucel-T (compared to an overall OS of 3.9 months in all participants), although AA comprised ~6% (n = 43/737) of the sample size.[27] In another study, AA patients appeared to have greater rates of PSA stabilization in response to sipuleucel-T.[28] It is possible that differential tumor PAP expression is partly behind this increased response to sipuleucel-T given its mechanism of action. Indeed, elevated serum levels of PAP had previously been observed in a higher percentage (85% vs. 27%) of AA men with locally advanced prostate cancer, compared to whites; notably “race” was designated by the investigators and not self-reported.[29] Recently, an analysis of the observational multicenter registry PROCEED included roughly twice the proportion of AA patients than in IMPACT (11.6%, n = 221/1902). The observed median survival was 30.7 months (there was no placebo comparison group to determine survival benefit), but importantly, this study identified AA as an independent predictor of prolonged survival. Furthermore, the median survival was 9.5 months longer in AA patients than in whites when controlling for PSA (35.3 vs. 25.8) and 5.3 months longer without PSA matching (35.2 vs. 29.9).[13] After sipuleucel-T, both populations received similar antineoplastic treatment and had similar rates of adverse events. The reasons behind these observed differences in AA patients remain largely unexplored. In a subsequent analysis of biomarkers obtained from PROCEED participants, higher baseline inflammatory cytokines, such as interleukin

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(IL)-4 and IL-10, have been observed in mCRPC AA patients compared to whites, which were significantly more augmented after receiving sipuleucel-T. Interestingly, while the AA cohort had higher OS, there were no race-dependent differences in humoral response or antigenic spread.[30] These findings raise the hypothesis that AA men may have a uniquely immunogenic phenotype of prostate cancer. Below, we highlight the research performed thus far that could explain these differences.

3.2 | Established differences in tumor immune microenvironment

The TME of prostate tumors is composed of immune cells, cancer-associated fibroblasts, blood vessels, and secreted molecules such as cytokines and growth factors.[31] Traditionally, prostate cancer has been viewed as a "cold" and poorly immunogenic tumor.[32] However, there is growing evidence that an immunogenic TME may be over-represented among AA patients, with significantly higher expression of inflammatory cytokines and lymphocytic infiltrates,[33–36] raising the potential for responsiveness to immune therapies.

Examining cytokine profiles, higher levels of IL-6, IL-8, IL-1B, and CXCR4 have been observed in AA tumors compared to whites and were linked with increased tumor grade.[37] Interleukin expression is particularly interesting as a biomarker of inflammatory AA tumors. IL-6 is a proinflammatory cytokine, promoting cell migration and evasion of apoptosis through interactions with STAT and PI3K pathways,[10] however, its overall effects can be considered immunosuppressive as it attracts myeloid derived suppressor cells to the TME.[38] Additionally, IL-6 was one of several inflammatory paracrine mediators enriched in tumor stromal fibroblasts from AA patients relative to white patients.[39] IL-8 acts as a neutrophil activator with a role in cell proliferation and invasion. The evidence behind IL-8 appears mixed, as a study demonstrated a link between higher levels of IL-8 expression from prostate epithelium and higher tumor grade but the effect was comparable across AA and white tumors.[40]

Furthermore, tumor-infiltrating immune cells and expression of programmed death-ligand 1 (PD-L1) in the TME may indicate increased inflammatory signaling. Presence of intratumoral T-cells (particularly CD8+) and PD-L1 expression are associated with higher risk of biochemical recurrence.[41–43] One study of prostatectomy samples demonstrated increased PD-L1 expression in AA vs non-AA tumors; interestingly, these PD-L1 positive tumors were linked with CD8+ infiltration.[44] Moreover, a recent study identified enriched populations of lymphocytes, particularly plasma cells, in the TME of AA patients, independent of age, PSA level, or genomic alterations. Increased B-cell infiltrates in the TME were associated with prolonged disease-free survival in this localized prostate cancer cohort.[36] This was further corroborated in a different study where AA tumors had higher expression of CD4+ and CD8+ T-cell markers at the TME, but there was no difference in PD-1/PD-L1 or CTLA-4 expression.[33] In contrast, another study found no difference in the density of T-cell infiltration in prostate cancers in AA men versus whites, but did find that among AAs, increased regulatory T-cells (but not CD3+ or CD8+ cells overall) correlated with disease recurrence.[45] Additionally, the presence of PTEN loss and ERG fusion (both less common in AA patients, as discussed below) were linked with T-cell infiltration

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regardless of ethnicity. Notably, confidence intervals were wide, requiring validation in other cohorts.

The poor prognosis associated with lymphocytic TME infiltrates may be because they are associated with more aggressive tumors, or that these T-cells are dysfunctional or actively immunesuppressive.[46] Indeed, immunosuppressive regulatory T-lymphocytes are frequently found in the TME of prostate cancer, as noted above.[47–49] In contrast, stem-like progenitor T-cells marked by the transcriptional factor TCF-1 may be responsible for expansion in response to vaccines and checkpoint inhibitors,[50,51] and their presence in antigen-presenting cell niches may correlate with decreased risk of relapse in other tumor types.[52] Further studies are required to better describe the role of T-cell infiltrates in AA prostate cancer, particularly with an eye towards predicting the response to PD-1/PD-L1 inhibitors. Other types of immune cells in the TME, for example macrophages and neutrophils, are generally regarded as inflammatory and protumorigenic, while natural killer cells (NKs) and DCs are responsible for innate antitumor effect and increased antigen presentation, respectively, and are associated with improved outcomes.[48,53,54] However, there have not been dedicated studies evaluating these immune cell populations in AA patients.

Based on the current evidence, there appears to be higher expression of cytokines and the interferon-gamma-triggered PD-L1 in AA men, reflecting more immunogenic tumors. Data on T-cell subsets and other immune cells remains incomplete. A better understanding of the immune cell subpopulations present in the TME will be needed for better patient selection and co-targeting of unique mechanisms of immunotherapy resistance.

3.3 | Potential genomic contributors to tumor immunogenicity

The current understanding of prostate cancer genetics and tumor biology is largely derived from studies performed in homogeneous, largely white, populations, limiting external validity.[55,56] However, over the past two decades, dedicated research on AA patients has shed some light on tumor-specific differences. These findings are highlighted in several review articles.[6,9,31,57,58] Here, we specifically explore the growing literature on genomic ancestral differences seen in AA prostate cancer, and whether these might or might not be related to observed differences in tumor immunogenicity.

While a large body of work has evaluated the role of single nucleotide polymorphisms (SNPs) in increasing the susceptibility of prostate cancer in AA men,[58–62] none found a direct link between polymorphisms and higher risk through immune-mediated mechanisms. In turn, studies evaluating germline alterations have been generally underpowered to identify differences in AA compared to other populations.[58] For instance, a study of early-onset AA prostate cancer identified germline alterations in DNA damage repair (DDR) pathways like BRCA1/2, BRIP1, ATM, and PMS2, although their relatively low frequency (<10%) was insufficient to determine whether these alterations were more or less prevalent than in an unselected population.[63]

As noted below, DDR alterations have been associated with response to immune checkpoint inhibitors as well as potential immune-mediated interactions with PARP inhibitors (PARPi), making this question of particular relevance for immunotherapy in AAs. A recent study

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revealed an increased number of actionable somatic mutations in metastatic AA patients compared with other cohorts, particularly in DDR genes such as BRCA1 or MSH6.[64] Furthermore, another recent study identified a high (>35%) prevalence of driver somatic mutations in AA tumors affecting DDR genes, such as ATM and BRCA2, compared to whites. It also identified a higher prevalence of mutations in ZMYM3, a protein that links BRCA1 with damaged chromatin and thus indirectly affects DDR mechanisms[65] These studies contrast with another study where neither alterations in DDR genes like BRCA2 or ATM, nor proportion of microsatellite instability, appeared to be more frequent in AA cohorts.[66]

Loss of key tumor suppressor genes and activation of oncogenes may impact not only tumorigenesis but also the tumor immune microenvironment. TMPRSS2-ERG fusion and PTEN deletion are prevalent somatic alterations in prostate cancer in predominantly white cohorts.[53,67] Interestingly, AA patients consistently have less frequent ERG fusion[68–71] and higher rates of intact PTEN.[66,69–71] No relationship was found among white patients between tumors featuring ERG fusion and higher expression levels of immune-related genes (such as interleukins and CTLA-4).[72] There is a signal that there may be increased macrophage and T-lymphocyte infiltration in tumors with higher ERG fusion, but further studies, specifically in AA patients, are needed.[73] PTEN activity has been shown to regulate adaptive immunity in in vitro studies, such as participating in T-cell development and proliferation.[74] In breast cancer and melanoma, PTEN loss has been linked with decreased T-cell infiltration and low efficacy of PD-1 inhibitors.[75,76] In prostate cancer, PTEN loss is associated with higher grade tumors and increased metastatic potential.[46,53] This has also been observed in AA patients, where PTEN-deleted tumors were linked with a higher rate of biochemical recurrence in AA patients, irrespective of ERG fusion.[69,77] Since AA prostate cancer appears to have intact PTEN more often, this might correlate with increased T-cell infiltration. Notably, ERG fusion and/or PTEN loss actually correlated with *decreased* T-cell infiltration in one study described above,[45] but it is possible that this T-cell population was primarily immunosuppressive.

3.4 | Potential transcriptomic contributors to tumor immunogenicity

Several pathways involved in immune response appear to have enhanced expression in AA with prostate cancer. A landmark microarray study found enrichment of genesets associated with immune response, antigen presentation, lymphocyte function, and cytokine signaling in AA tumors.[35] Among several upregulated chemokine ligands and receptors, CXCR4, a chemokine receptor, was specifically linked with higher metastatic potential and was specifically upregulated in tumors versus surrounding benign tissue in AAs but not in whites. CXCR4 has been shown in other malignancies to promote tumor metastasis by activating proliferation pathways through the MEK/ERK signaling cascade and activation of nuclear factor kappa B (NF-κB).[78,79]

These findings were corroborated by a more recent study using transcriptomic data from a much larger set of microarray gene probes.[33] Geneset enrichment analysis revealed enrichment of several immune-related pathways, similar to the prior study, including IFN alpha and gamma response and TNF alpha signaling via NF-κB. Expression of IFN alpha

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and gamma, as well as markers of CD4 and CD8 T-cells, were enriched in AAs, with lower level of hallmark genomic DNA repair scores. Six immune-related genes were validated to have differential expression by race in The Cancer Genome Atlas RNA-sequencing data, including interferon-induced transmembrane protein 3 (IFITM3), interferon alpha inducible protein 6 (IFI6), interferon induced protein 44 like (IF44L), and CD38, and also correlated with increased risk of biochemical recurrence in AAs. The interferon-stimulated genes are involved in regulation of viral response and may have immunosuppressive effects; similarly, CD38 is involved in generation of immunosuppressive adenosine and is a potentially actionable target with therapies inhibiting adenosine signaling.

The link between these potentially immunosuppressive immune pathways and aggressive biological behavior suggests that immunogenic tumors may be forced to harness immunosuppressive pathways as a survival mechanism. In that vein, a different study revealed that MICA, an MHC-associated protein, had decreased expression in AA tumor cells, which had a borderline correlation with lower survival.[80] MICA is a stress-induced ligand for the NKG2D receptor on NKs and some T-cells but can be cleaved by tumors, potentially resulting in *decreased* innate immune recognition and activation in AA tumors. Antibodies targeting MICA are currently being developed to decrease its proteolytic shedding and increase NK-cell activation.[81]

Last, a study evaluating chromosomal copy number alterations in AA tumors identified that, compared to whites, there was a higher prevalence of altered chromosomal regions that corresponded to genes involved in immune function, such as T-cell proliferation and activation, which in turn affected gene expression of immunoglobulin-related genes.[82] This mirrors findings of increased immunoglobulin gene expression[35] and increased plasma cells[36] in AA tumors, pointing to adaptive immunity as a potentially upregulated immune response correlated with improved outcomes.

Clearly, there may be multiple pathways up- and downregulated in a complex balance of immune responses, and it is unlikely that one single genomic or transcriptomic difference will fully explain the differential effectiveness of sipuleucel-T in AA patients. However, multiple studies highlight distinct alterations seen in AA tumors that affect immunogenicity, such as a possible increase in DDR deficiency and lower prevalence of PTEN loss, that could have downstream effects in immune mediated pathways. Similarly, upregulation of genes involved in cytokine signaling and lymphocyte activity could reflect existing immune response. Combined, these findings raise the possibility that these tumors could show enhanced immunotherapy responsiveness, but also identify potential key immunosuppressive barriers. Finally, we also need to understand the context in which tumors arise: the host immune response.

3.5 | Potential host immunity differences contributing to enhanced immunotherapy response

Priming the immune system to fight cancer is a focus of active esearch given the success of immunotherapies in treating a variety of tumors. As such, it is critical to detect and understand population-specific differences in host immunity. Variations in immune development in AA patients can be traced to selective genetic drift, generally to infectious

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pathogens (e.g., malaria).[16] Here we list the potential differences in innate and adaptive immunity in AA that could play a role in tumor oncogenesis and response to treatment.

The innate immune system is the rapid, nonspecific arm of immunity. It is most susceptible to inherited genetic variants as it needs to quickly identify and confront pathogens.[83] Together with the adaptive response, innate immune cells can provide immune surveillance against the development of new cancers.[10] While the initial inflammatory environment is beneficial to eliminate tumors, uncontrolled chronic inflammation increases the risk of developing prostate cancer.[11] Toll-like receptors (TLR) are the most characterized of the pattern-recognition mechanisms. TLRs are present in APCs such as DCs and macrophages, but also in tumor cells. Activation of TLRs causes a robust local inflammatory response through release of cytokines and launches adaptive immunity.[84,85] Some African populations developed extensive TLR polymorphisms as means to cope with endemic pathogens,[86] showing the highest haplotype diversity compared to other groups.[87] There is extensive literature on the role of TLRs in prostate cancer, which has previously been reviewed.[85] There is conflicting evidence on whether they combat or contribute to tumor growth, which is not surprising given the disparate roles of TLR signaling pathways in immune function. For instance, TLR-3 is associated with inhibiting tumor growth by inactivating the PI3K/AKT pathway,[88] while TLR-4 promotes tumor development via VEGF and TGF-b.[89] In AA cohorts, there is interest in linking TLR polymorphisms with prostate cancer risk—a good example is that SNPs in TLR-2 and TLR-6 appear to confer higher risk in AA patients compared to whites.[83,84] TLR-2 and TLR-6 work as a heterodimer that recognize mostly bacterial patterns but also viral agonists and lead to the activation of the NK-kB pathway.[85] It is plausible that these TLR polymorphisms produce higher affinity to tumor-associated ligands, or cause increased signaling in downstream pathways that lead to the recruitment of a potent inflammatory response at the TME. Therefore, while there is significant TLR diversity in AA patients, the mechanistic link with prostate cancer development is still unclear. In turn, cytokines are molecules that coordinate the innate and adaptive immune response.[10] Cytokine gene polymorphisms also significantly differ across populations.[90,91] Variations in cytokine production and release have been associated with increased prostate cancer susceptibility.[92] Specifically, a study observed an increased risk of prostate cancer in AA patients who had the combination of SNPs in IL-1 and IL-10 genes; these were not observed in whites.[93] As part of innate immunity, APCs recognize tumor antigens released from killed tumor cells and travel to lymphoid tissue to present these antigens to CD4 T-cells.[94] One study found enhanced costimulatory function in T-lymphocytes after antigen presentation by APCs in healthy AA patients,[95] which offers a potential mechanism behind the enhanced effects of sipuleucel-T in AA prostate cancer.

Adaptive immunity is a highly selective process that plays a critical role in combating cancer. Unfortunately, there is limited research examining differences in adaptive immunity in AA patients. An older study identified a slightly higher proportion of lymphocytes in the leukocyte count of AA men, but no difference in B- or T-cell subpopulations.[96] Additionally, alterations in B-cell receptors and downstream signaling in B-lymphocytes were observed in healthy AA men, although the clinical significance of this finding is unknown.[97] Some studies have pointed to differential antibody responses to TAAs in AA patients with prostate cancer, suggesting distinctive B-cell and CD4-T-cell responses to tumors. Antibodies to

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nucleophosmin 1 have been observed in association with prostate cancer, and relative to non-AAs, titers among AAs were particularly different between those patients with cancer versus benign prostatic hypertrophy.[98] Among AA patients, certain immunoglobulin allele variants may be associated with reduced antibody response to cyclin B1, overexpressed in some prostate cancers; this would be expected to decrease immune surveillance and promote metastasis.[99] Serum from AA patients had generally stronger immunoreactivity to cell-line antigens in another study; differential reactivity was noted between AA and non-AA patients' antitumor-antigen autoantibodies to the same epitope in different contexts, an effect seemingly mediated by differential response to posttranslational modifications of the epitopes.[100] Since autoantibodies may also be observed in healthy individuals, further work will be needed to associate these antitumor-antigen antibodies with different clinical outcomes or response to immunotherapies. It could be particularly interesting to investigate whether any antigen-spreading from sipuleucel-T treatment includes autoantibodies and/or clonally expanded T cells against these targets.[101]

Altogether, there seem to be differences in AA host immunity, with polymorphisms in TLRs emerging as the most consistent differences, but further research is needed to explain its role in prostate cancer.

3.6 | Vaccine immunogenicity in patients of AA

Vaccines may be used prophylactically, to prevent infections, or therapeutically, to enhance antitumor immunity. In patients with active cancer who are receiving treatment, there may be baseline immunodeficiency.[102] Therefore, development of effective cancer vaccines must critically consider the characteristics that affect vaccine immunogenicity, including host factors (such as age and comorbidities), and specifics to vaccine design like antigen selection, timing of administration, and need for boosters.[103] Notably, genetic ancestry has been evaluated as a possible influence to vaccine efficacy.

A number of studies in the infectious disease literature examined the effect of genetic ancestry in children receiving childhood immunizations. The overarching conclusion from this body of work is that, compared to other cohorts, AA children appear to have higher humoral and cellular response to vaccination, whether it is against measles,[104] rubella,[105] or pertussis[106]—a notable exception being smallpox.[107] The source of this augmented vaccine response among AA children seems to stem from genetic differences in both innate and adaptive immunity, such as polymorphisms in cytokines and TLRs, as discussed earlier.[105]

In AA adults, the enhanced immunogenic effect of vaccines is also described, however, this is somewhat dampened by immunosenescence, as both antibody production and cellular response to a vaccine can become quantitative and qualitatively affected by aging.[108] The relationship between genetic ancestry and response to the influenza vaccine has been the most studied. AA adults were able to produce higher antibody titers than whites independently of prior flu vaccination,[109] but there was an age-dependent decrease in cellular response.[110] Moreover, a few studies focused on therapeutic HIV vaccines found mixed results regarding genetic ancestry. For instance, there was no change in immunogenicity in recipients of a DC vaccine,[111] while a post-hoc analysis of several trials on a recombinant vaccine reflected higher titers of HIV-neutralizing antibody in AA

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patients.[112] Still, this effect appeared dependent on vaccine type and clinical implications were unclear. Finally, it is worth highlighting that the ongoing vaccine literature on Covid-19 presents an unprecedented opportunity to explore the immunogenicity generated in AA populations.

In summary, there is some evidence that AA may confer increased immunogenicity to infectious vaccines. Whether this effect has a genetic basis remains to be seen; potential confounders could be prior pathogen exposure or the living environment during upbringing.[97,100] Nevertheless, immunosenescence can present an important obstacle to therapeutic vaccine efficacy in elderly patients regardless of genetic background.

3.7 | Immunotherapy in prostate cancer

Compared to other malignancies, the role of immunotherapy in prostate cancer has thus far been marginal based on lack of efficacy observed in clinical trials. To date, the only Food and Drug Administration-approved immunotherapy for prostate cancer remains the cellular vaccine sipuleucel-T.[113] As we will discuss below, insufficient recruitment and lack of validation in AA cohorts remains a common theme across immunotherapy trials.

Other cancer vaccines have had less success in prostate cancer. PROSTVAC, a poxvirus vector vaccine which targets PSA as its TAA, had promising preliminary data for prolonging OS in mCRPC, however the phase III trial was stopped early for meeting criteria for futility. Of note, the study only included around 5% AA patients.[114] Additional trials of PROSTVAC and other prostate cancer vaccines, like GVAC, have failed to show clinical benefit, although some are still underway.[115,116] Outside of prostate cancer, the only currently approved cancer vaccine is T-VEC for melanoma, not specifically examined in AA cohorts given the rare incidence of melanoma in this population.[117] There are multiple trials underway on cancer vaccines, including several in combination with checkpoint inhibitors.[118–120]

In turn, checkpoint inhibitors are a booming class of cancer immunotherapy that target inhibitors of T-cell regulation, including cytotoxic T-lymphocyte associated protein 4 (CTLA-4) and programmed cell death receptor/ligand 1 (PD-1/PD-L1).[118] In prostate cancer, ipilimumab monotherapy has failed to show a survival benefit in mCRPC patients. The phase III trial included 5% AA patients and suggested a trend towards improved OS in the AA cohort, but the study was underpowered for this subset analysis.[121] Similarly, phase II trials of pembrolizumab in mCRPC demonstrated low response rates.[122,123] Interestingly, a trial testing the addition of avelumab in AA men with mCRPC progressing on androgen signaling inhibitors was stopped early for rapid clinical progression in the initial cohort.[124] This raises the hypothesis that the observed immunogenic phenotype in AA patients might not be associated with response to PD-1 inhibition, but rather might respond to other checkpoint inhibitors or other immunotherapy approaches. Alternatively, the immune microenvironment may be sufficiently tilted towards immunosuppression as a result of prior hormonal therapies to prevent response to PD-1 inhibition,[125] presumably in a race-independent manner, but this approach could be effective in an earlier disease setting and in AA patients.

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DDR deficiency may be associated not only with response to PARPi[26] but also immune checkpoint inhibitors.[127,128] There are conflicting reports as to whether DDR deficiency is more prevalent in in AA patients,[64,66,67,129,130] but if true, then this could have implications for patient selection for checkpoint inhibitors and potentially combinations of checkpoint inhibitors with PARPi. Notably, PARPi may have effects beyond their role in DDR. In DDR-deficient breast cancer models, PARPi treatment activates STING signaling and downstream PD-L1 expression and lymphocyte infiltration.[131] Several trials are underway to investigate PARPi in combination with checkpoint inhibitors in prostate cancer, including in nonselected populations.[132,133] Enrollment of AA patients will be crucial to determine the effectiveness of these strategies in this population.

In sum, the use of immunotherapy in prostate cancer is a rapidly growing field, with multiple strategies being tested in clinical trials. Elucidating the specific immune pathways that become activated with these novel immunotherapies should become a priority to predict whether AA patients could expect greater clinical benefit. Unfortunately, these studies frequently fail to report the ethnicity of their study population, which greatly prevents subgroup analysis of the response of AA patients. This is a broader concern across oncology, where the proportion of AA cancer patients enrolled in immunotherapy trials is not reported. This “color blindness” can also negatively affect tracking of recruitment of minority patients to cancer studies.[134] Attempts to find dedicated research of immunotherapy in AA patients across all cancer types yielded a single retrospective study that suggested improved response to nivolumab in non-small cell lung cancer.[135] At the very least, data on self-reported race or ethnicity should be included to allow for subgroup exploratory analysis. Ultimately, the future goal would be to better stratify study populations based on their genetic ancestry as a much more precise and clinically relevant tool. Based on the evidence of improved survival in AA cohorts who received sipuleucel-T, focused research on immunotherapy in underrepresented populations is crucial and long overdue to reduce cancer disparities.

4 | CONCLUSIONS

Prostate cancer disparities in AA patients are complex and multifactorial (see Figure 1 for a visual summary of the evidence discussed). On an immunological basis, the strongest evidence to date has been at the TME. The findings point towards a uniquely inflammatory phenotype, including higher levels of interleukin expression and tumor infiltrating lymphocytes. Variations in AA tumor genomics and transcriptomics, as well as host immunity, may additionally affect the body’s immune response to prostate cancer. Here, the most promising leads are increased expression of immune-related genes and more frequent host genetic variations that developed as a result of genetic drift. Last, AA may grant enhanced immunogenicity to vaccination, including therapeutic cancer vaccines like sipuleucel-T.

All in all, the evidence (or lack thereof) found in the studies above underscores the urgent need to perform dedicated studies of prostate cancer in patients of AA, particularly on immunotherapy and biomarkers. In this review, we have identified multiple areas of future research to better understand prostate cancer disparities. The hope would be for further validation of PROCEED’s results in other large, AA prominent, cohorts. The highest level

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of evidence would naturally result from prospective studies comparing sipuleucel-T, alone or in combination to novel therapies, to current standard of care treatments in mCRPC. Adequate representation from AA cohorts could be achieved via pre-specified accrual or enrolling clinical sites that serve a racially diverse patient population. Furthermore, an in-depth analysis of TME composition and activity in AA patients, specifically those that received sipuleucel-T, could open a myriad of opportunities for researching the biology behind survival advantage in this population. Recent dedicated studies focused on AA patients, such as a trial evaluating enzalutamide vs bicalutamide use in mCRPC,[136] are a promising start. However, representation of AA patients in prostate cancer and oncology clinical trials remains scarce and not reflective of the general population. Low accrual of AA patients to clinical trials has been linked with socioeconomic and cultural barriers.[137] Overcoming these obstacles is an area of active work, requiring investigator as well as institution-wide initiatives.[138] Still, given the differences in treatment response observed with sipuleucel-T in AA mCRPC patients, there is tremendous reward in elucidating the biology of prostate cancer and immunotherapy in the AA population to eliminate long-standing cancer disparities.

ACKNOWLEDGEMENTS

This work was supported by the Prostate Cancer Foundation Challenge 18CHAL09 (Steven P. Balk, David J. Einstein), P50 CA090381 (Steven P. Balk), Developmental Research Project P20 CA233255 (Steven P. Balk, David J. Einstein), and Department of Defense W81XWH-17-1-0350 (David J. Einstein) and W81XWH-16-1-0431 (Steven P. Balk).

Funding information

U.S. Department of Defense, Grant/Award Numbers: W81XWH-16-1-0431, W81XWH-17-1-0350; Dana-Farber/Harvard Cancer Center, Grant/Award Numbers: P20 CA233255, P50 CA090381; Prostate Cancer Foundation, Grant/Award Number: 18CHAL09

DATA AVAILABILITY STATEMENT

Data sharing is not applicable to this article as no new data were created or analyzed in this study.

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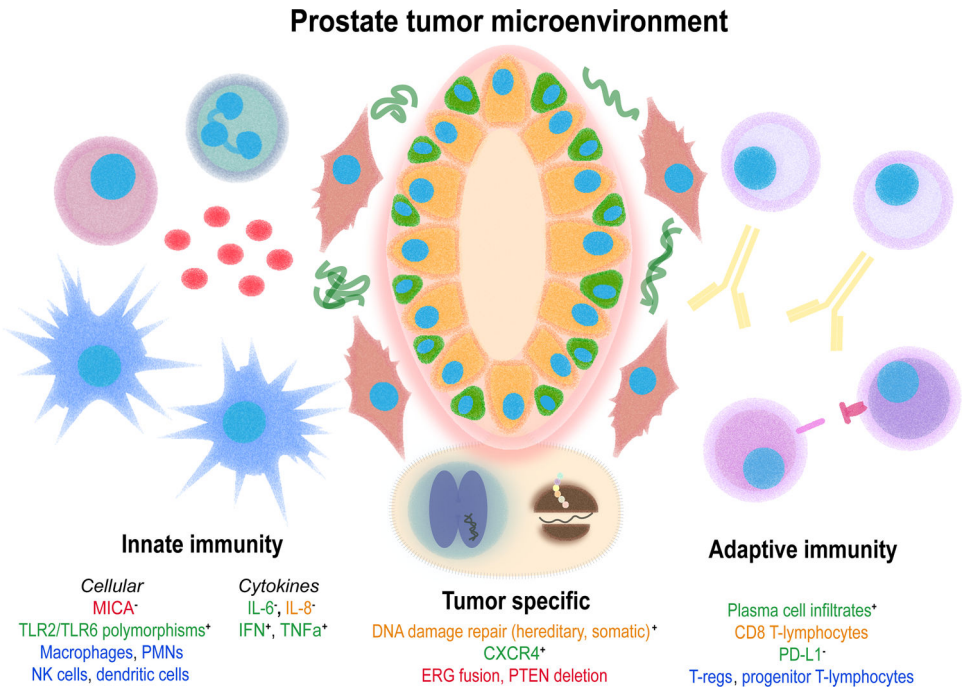

FIGURE 1.

Summary of differences with an immune basis in prostate cancer in men of African origin. Font color reflects whether the relationship is more (green) or less (red) prevalent in AA, or if the data is mixed (orange) or unknown (blue). Where appropriate, + and − reflect pro- or antiinflammatory effects in the tumor microenvironment, respectively