Immune Resistance in Prostate Cancer

Subjects: Allergy

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Utilizing the immune system to treat cancer has been a revolutionary development and has quickly become the standard treatment for many cancer types, superseding other targeted and systemic therapies. By targeting cancer cells and avoiding the toxicities of chemotherapy and radiation, immunotherapy offers a less toxic, yet, in many types of cancers, highly efficacious alternative. With regard to PCa, the interaction between prostatic epithelial cells and the immune and non-immune cells that make up the tumor microenvironment (TME) have been shown to have an important role in the complex changes that occur and ultimately result in disease progression, development of resistant metastases, and the overall resistance to both conventional and experimental therapies.

Keywords: immunotherapy ; metastatic castration resistant prostate cancer ; tumor microenvironment ; immune resistance ; combination therapies ; immune checkpoint inhibitors

1. Introduction

Androgens have a key role in the pathogenesis of prostate cancer (PCa), and treatment modalities altering androgen receptor signaling pathways are the standard of care for advanced and disseminated disease. However, despite the initial effectiveness of androgen deprivation therapy (ADT), resistance to therapy occurs in approximately 30–50% of patients, resulting in castration-resistant prostate cancer (CRPC) for which there are very limited, generally not curative, systemic treatment options [1][2].

Utilizing the immune system to treat cancer has been a revolutionary development and has quickly become the standard treatment for many cancer types, superseding other targeted and systemic therapies [3]. By targeting cancer cells and avoiding the toxicities of chemotherapy and radiation, immunotherapy offers a less toxic, yet, in many types of cancers, highly efficacious alternative [4]. With regard to PCa, the interaction between prostatic epithelial cells and the immune and non-immune cells that make up the tumor microenvironment (TME) have been shown to have an important role in the complex changes that occur and ultimately result in disease progression, development of resistant metastases, and the overall resistance to both conventional and experimental therapies [1][5].

To date, however, patients with advanced PCa have not yet benefited to the same extent as those with more “immunologically hot” or “responsive” tumors such as melanoma, lung cancer, renal cell carcinoma or urothelial carcinoma [3][6][7]. In fact, PCa has been classified as a “cold tumor” with minimal response to immune-related treatment modalities [8][9][10]. Low tumor-associated antigen expression, decreased major histocompatibility complex (MHC) presentation of tumor antigens, tumor suppressor and DNA repair enzyme defects, and poor immune-modulating signaling are some key processes that have a role in this complex tumor environment, altering the overall anti-tumor response [8][11]. Efforts have been made to target these immune evasion mechanisms in CRPC. Currently ongoing preclinical and clinical trials are reporting encouraging results on combination-based therapies. However, other than pembrolizumab, which was approved for advanced solid tumors from the US Food and Drug Administration (FDA) in 2017 for high microsatellite instability (MSI) and in 2020 for high tumor mutational burden (TMB), sipuleucel-T, an immunotherapy based on the infusion of antigen presenting cells (APCs) which has demonstrated improvements in survival without a significant response rate, remains the only FDA-approved immunotherapy for mCRPC [12][13].

A greater understanding of the TME and methods for utilizing the host immune system to halt and eliminate tumor growth is needed to improve therapies. In this review, we set out to identify and explore key immune resistance mechanisms that lead to treatment failure in the immunosuppressive TME of PCa, and focus on therapeutic strategies (**Figure 1**) and approaches that target the immunosuppressive TME and seek to overcome these resistance mechanisms.

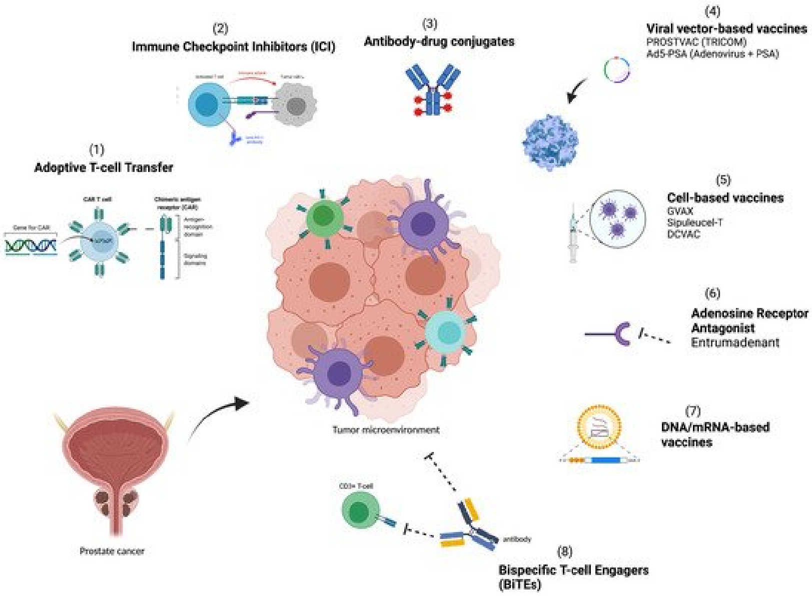

Figure 1. Immunotherapeutic categories designed to overcome immune resistance mechanisms in the tumor microenvironment of prostate cancer: (**1**) adoptive cell transfer, (**2**) Immune checkpoint inhibitors, (**3**) antibody–drug conjugates, (**4**) viral vector-based vaccines, (**5**) cell-based vaccines, (**6**) Adenosine receptor antagonists; (**7**) DNA/mRNA-based vaccines, and (**8**) Bispecific T-cell engagers.

2. Immune Resistance Mechanisms in Prostate Cancer

In most solid tumors, effective immune responses within the TME rely on an increased infiltration and activation of immune cells, increased mutational burden within the cancer cells, expression of these tumor antigens on the cell surface, functional immune signaling pathways, and appropriate tumor suppressor functions [14][15]. Mechanisms that bypass these coordinated cellular functions ultimately result in immune evasion and subsequent malignant disease progression, and are thought to be critical factors in limiting the response to immune therapies [16].

Neoantigen expression on the cell surface of tumor cells via MHC Class-I/Class II molecules and activation of APCs and CTLs is essential in generating an anti-tumor immune response leading to tumor cell apoptosis [17]. TMB is a quantitative measure of the total number of mutations per coding region. Because some cancers result in a higher TMB, there is a subsequent increase in tumor neoantigen expression and thus anti-tumor immune response [17]. PCa, however, has low somatic TMB and thus decreased neoantigen expression compared to other tumor types [8]. In fact, one study found mean somatic mutational rates at a frequency of 0.9 per megabase, approximately 10 times lower than reported for melanoma [18]. This highlights a potential lack of T-cell co-stimulation and activation in the PCa TME, which prohibits the generation of a powerful adaptive immune response following antigen presentation; a key step in immunotherapy effectiveness [8].

Interferons (INF1) are a group of immunostimulatory cytokines released in response to cellular detection of invading pathogens [8]. Activation and expression of INF1 gene has also been shown to be crucial in mounting an efficient anti-tumor immune response through the release of cytokines that ultimately lead to an increase in the expression of immune costimulatory molecules, activation of adaptive immune cells, and an increase in TIL killing [19].

Interferon-gamma, INF-γ, a potent cytokine known to modulate tumor immunity and tumoricidal effects, has been shown to be highly elevated in patients with PCa after radiation [20]. Kundu et al. found that IFNγ can induce epithelial-to-mesenchymal transition in PCa cells leading to the downstream activation and expression of IFN-stimulated genes, PCa cell death and tumor regression [20][21]. Further animal models have also demonstrated that loss of tumor-intrinsic type I IFN can occur in proliferating PCa cells in bone and that the loss suppresses anti-tumor and therapeutic responses, in addition to promoting bone PCa cell activation and cancer progression [22]. These all highlight the importance of INF1 and their role in an anti-tumor immune response.

3. Therapies Targeting Immune Resistance

Preclinical studies have focused on targeting prostate-specific cancer stem cells. Cancer stem cells are a subpopulation of cancer cells with self-renewing capabilities, which are distinguished by the types of proteins expressed on their cell surface. Common cell-surface markers used in the identification of PCa stem cells include CD44, CD133, and epithelial cell adhesion molecule (EpCaM) [23].

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4. Combination Strategies

Due to the complex nature of immunotherapy, multifaceted combination therapies are being investigated. Trials are underway to study various permutations of treatments that include antigen vaccines, DNA vaccines, and checkpoint inhibitors. One study is examining the effect of a neoantigen DNA vaccine combination with PROSTVAC, nivolumab and ipilimumab (NCT03532217). Another trial is evaluating ipilimumab in combination with GVAX [28]. Pembrolizumab combination therapies in mCRPC are being investigated in KEYNOTE-365 (NCT02861573) a phase Ib/II study mentioned in the previous section with four different study medications (pembrolizumab, docetaxel, enzalutamide, Olaparib, abiraterone, and prednisone). Ongoing studies are investigating combination Sipuleucel-T with atezolizumab (NCT03024216), ipilimumab (NCT01804465), radiation (NCT02463799, NCT01818986, NCT01807065), and chemotherapy (NCT01420965). A list of ongoing studies is included in **Table 1** .

Table 1. Current ongoing clinical trials of immunotherapeutics in prostate cancer.

Agent (s)	Mechanism	Clinical Phase	Indication	Clinical Trial ID
DCVAC/PCa/docetaxel/prednisone	Autologous DC vaccine + chemotherapy	III	mCRPC	NCT02111577 (VIABLE)
Ad/PSA	Adenovirus-based vaccine with PSA gene	II	mCRPC	NCT00583024
W_pro1/cemiplimab	mRNA-based vaccine monotherapy complexed with liposomes +/− IC	I/II	mCRPC	NCT04382898 (PRO-MERIT)
CAR T cell-PSCA (BPX-601)	Autologous T cell-based vaccine	I/II	mCRPC	NCT02744287
CAR T cell-PSMA	CAR T cell-based vaccine	I	mCRPC	NCT01140373

Agent (s)	Mechanism	Clinical Phase	Indication	Clinical Trial ID
Entrumadenant/zimberelimab/enzalutamide/docetaxel/AB680	Adenosine receptor antagonist + ICI + CD73 inhibitor + ADT + chemotherapy	I/II	mCRPC	NCT04381832 (ARC-6)
AMG160/pembrolizumab	PSMA-targeting Bispecific T-cell Engager + ICI	I	mCRPC	NCT03792841
HPN424	PSMA-targeting Bispecific T-cell Engager	I/II	mCRPC	NCT03577028
PROSTVAC/Ipilimumab/Nivolumab/Neoantigen DNA vaccine	Viral vector-based vaccine + ICI+ DNA vaccine	I	HSPC	NCT03532217
Pembrolizumab/enzalutamide/docetaxel/olaparib/abiraterone/prednisone	ICI + ADT + PARP inhibitor + chemotherapy	I/II	mCRPC	NCT02861573 (KEYNOTE-365)
Atezolizumab/Sipuleucel-T	ICI + DC Vaccine	Ib	mCRPC	NCT03024216
Ipilimumab/Sipuleucel-T	ICI + DC Vaccine	II	mCRPC	NCT01804465
Sipuleucel-T/CT-011/Cyclophosphamide	DC Vaccine + ICI + chemotherapy	I	mCRPC	NCT01420965
Nivolumab/Ipilimumab/Cabazitaxel/Prednisone	ICI + chemotherapy	II	mCRPC	NCT02985957 (CheckMate 650)

mCRPC metastatic castration-resistant prostate cancer; ICI immune checkpoint inhibitor; HSPC hormone-sensitive prostate cancer; PSA prostate-specific antigen; PSMA prostate-specific membrane antigen; DC dendritic cell; ADT androgen deprivation therapy; CAR T chimeric antigen receptor T cells; PARP poly ADP ribose polymerase.