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REVIEW ARTICLE

Role of Immune Components and Immunotherapy in Prostate Cancer Treatment

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Abstract

Prostate cancer (PCa) is a prevalent malignancy among men, with advanced stages often presenting significant treatment challenges despite traditional therapies such as surgery, radiation, and hormone therapy. Recent advancements in immunotherapy have introduced new strategies to harness the immune system's potential in combating this disease. This review explores the roles of various immune components in PCa and evaluates the impact of emerging immunotherapeutic approaches. Immune components, including tumor-infiltrating lymphocytes (TILs), dendritic cells (DCs), and cytokines, play crucial roles in the tumor interaction with the immune system. TILs, particularly CD8+ T cells, can influence prognosis, while DCs are pivotal in antigen presentation and T cell activation. However, these components often face functional suppression within the immunosuppressive tumor microenvironment of prostate cancer, which includes regulatory T cells and myeloid-derived suppressor cells (MDSCs). Immunotherapy strategies have progressed, with notable approaches including checkpoint inhibitors, cancer vaccines, adoptive cell therapy, monoclonal antibodies, and oncolytic virus therapy. Checkpoint inhibitors, such as PD-1/PD-L1 and CTLA-4 inhibitors, aim to restore T cell activity against cancer cells but have shown variable efficacy in PCa. Sipuleucel-T, a cancer vaccine, has demonstrated survival benefits in metastatic castrate-resistant prostate cancer (mCRPC). Adoptive cell therapies, including CAR T-cell and TIL therapies, are being investigated for their potential to target prostate-specific antigens (PSA). Monoclonal antibodies and oncolytic viruses offer additional mechanisms to target cancer cells directly and stimulate immune responses. This review highlights the promise and ongoing progression of immunotherapy in addressing the complexities of PCa treatment.

Keywords

Prostate Cancer, Immune components, Immunotherapy, Tumor-infiltrating lymphocytes, Dendritic Cells (DCs), Sipuleucel-T

Introduction

Prostate cancer (PCa) remains one of the most common cancers affecting men worldwide [1]. Current diagnostic approaches cannot predict PCa at a treatable stage of the tumor. Despite advancements in diagnosis and treatment, the prognosis for advanced PCa often remains poor [1,2]. Traditional treatments, including surgery, radiation, and hormone therapy, have shown varying degrees of success. The innate immune system is essential for the early response to PCa given that it affects the growth and spread of the tumor. Key innate immune components within the prostate cancer microenvironment include macrophages, dendritic cells, neutrophils, and natural killer (NK) cells. These components interact with cancer cells and other elements of the tumor microenvironment to modulate immune responses [3].

The introduction of immunotherapy has provided new avenues for treatment, leveraging the body's immune system to combat PCa. Understanding the role of immune components in prostate cancer and how immunotherapy can be effectively utilized is critical for advancing treatment strategies and improving patient outcomes [4]. The immune system plays a complex and multifaceted role in PCa. Helper T cells and cytotoxic T lymphocytes (CTLs) are a few of the several T cell subtypes that make up the important component known as tumor-infiltrating lymphocytes (TILs). CTLs, particularly CD8+ T cells, are crucial for recognizing and killing cancer cells [5,6]. Their existence within malignancies is frequently associated with a better prognosis, indicating that they may be involved in regulating the growth of tumors. However, their functionality can be impeded

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by the immunosuppressive tumor microenvironment (TME) typical of PCa [5,6].

Immunotherapy represents a promising frontier in PCa treatment, offering several innovative approaches to enhance the immune system's ability to target and eradicate cancer cells. One of the most studied classes of immunotherapy agents, checkpoint inhibitors, target immune checkpoints that normally inhibit T cell activity [7,8]. PD-1/PD-L1 inhibitors, such as pembrolizumab and nivolumab, work by blocking the interaction between PD-1 on T cells and PD-L1 on tumor cells, thereby enhancing T cell-mediated anti-tumor responses. Although these inhibitors have shown impressive results in other cancers, their efficacy in PCa has been mixed, prompting ongoing research to identify biomarkers that predict response and optimize treatment regimens [7,8]. Cancer vaccines are designed to stimulate the immune system against cancer-specific antigens. Sipuleucel-T (Provenge) is the most established PCa vaccine, involving the infusion of a patient's dendritic cells, which are exposed to prostatic acid phosphatase (PAP) antigen [9,10]. This approach has been shown to extend survival in patients with metastatic castrate-resistant prostate cancer (mCRPC), though its impact on progression-free survival is limited. The integration of immunotherapy into PCa treatment represents a significant advancement, offering hope for improved outcomes in advanced disease stages. However, challenges remain, including overcoming the immunosuppressive tumor microenvironment, identifying predictive biomarkers, and optimizing combination therapies. Continued research is essential to refine these approaches and realize the full potential of immunotherapy in PCa management.

PCa vaccines represent an evolving area of cancer immunotherapy. While Sipuleucel-T remains a standard treatment for advanced PCa, other vaccines like Prostvac-VF, PSA-TRICOM, and GVAX are under active investigation to enhance efficacy and overcome resistance mechanisms [9-18]. Combining these vaccines with immune checkpoint inhibitors like ipilimumab shows promise for improving patient outcomes. Ongoing clinical trials and research are crucial for advancing these therapies and optimizing their use in PCa treatment.

Recently, the exploration of immunotherapy has emerged as a promising area in the fight against PCa. This review article aims to explore the role of immune components in PCa and explore how immunotherapy is a response and treatment strategy.

Role of Immune Components in Prostate Cancer

One of the most prevalent cancers in males PCa, presents numerous barriers to efficient treatment, especially when the disease is advanced. The interaction between PCa and the immune system is complex, involving various immune components that can influence PCa progression and response to therapy. Understanding these interactions is crucial for developing effective immunotherapeutic strategies.

Tumor-Infiltrating Lymphocytes (TILs)

Tumor-infiltrating lymphocytes (TILs) are a key component of the immune response within the tumor microenvironment (TME) [5,6]. These comprise a range of T cell subtypes, including helper and cytotoxic T lymphocytes (CTLs). CTLs, particularly CD8+ T cells, play a vital role in recognizing and killing cancer cells. In prostate cancer, the density and functionality of TILs can significantly impact PCa prognosis. High levels of CD8+ T cells within prostate tumors have been associated with better clinical outcomes [5,6]. These cells can directly kill cancer cells by recognizing and binding to tumor-specific antigens presented on major histocompatibility complex (MHC) class I molecules. However, in prostate cancer, CD8+ T cells often face challenges due to the immunosuppressive TME, which can inhibit their activity. These cells help orchestrate the immune response by providing help to other immune cells, including CTLs and B cells. They can be subdivided into different subsets, such as Th1, Th2, and regulatory T cells (Tregs) [5,6]. Th1 cells are generally associated with anti-tumor responses, while Th2 cells and Tregs can promote PCa progression and immune tolerance [5,6].

Regulatory T Cells (Tregs)

Tregs are essential for preserving immunological homeostasis and averting autoimmune reactions. In the context of PCa, Tregs often accumulate in the TME and suppress anti-tumor immune responses [19,20]. They achieve this through the production of immunosuppressive cytokines, such as IL-10 and TGF-β, and by directly inhibiting the function of other immune cells, including CTLs [19,20].

Dendritic Cells (DCs)

Dendritic cells are professional antigen-presenting cells (APCs) that play a central role in initiating and regulating immune responses. They capture process, and present antigens to T cells, thereby linking innate and adaptive immunity [21,22]. In PCa, the function of DCs can be compromised, impacting the overall immune response. DCs are crucial for presenting tumor antigens to T cells. However, PCa can alter DC function through various mechanisms, such as the secretion of immunosuppressive cytokines like TGF-β and IL-10 [21,22]. This can lead to impaired DC maturation and antigen presentation, thereby reducing the effectiveness of T-cell activation. Furthermore, different subtypes of DCs, such as plasmacytoid DCs and myeloid DCs, have distinct roles in immune regulation. Plasmacytoid DCs are known for producing type I interferons and can have

both anti-tumor and pro-tumor effects depending on their activation state. Myeloid DCs are more involved in antigen presentation and can be significantly affected by the TME [21,22].

Macrophages

Macrophages are versatile immune cells that can adopt different functional states depending on the signals they receive [23,24]. In the TME, macrophages often exhibit an M2-like phenotype, which is associated with tumor promotion. M1 macrophages are typically involved in pro-inflammatory responses and can kill tumor cells. In contrast, M2 macrophages are generally associated with anti-inflammatory responses, tissue repair, and tumor progression. By producing cytokines and growth factors that encourage angiogenesis and inhibit potent immune responses, M2 macrophages in PCa might accelerate tumor development [23,24].

Tumor-associated macrophages (TAMs)

TAMs are a significant component of the TME and can influence tumor progression through various mechanisms [25,26]. They can suppress anti-tumor immunity while stimulating angiogenesis, metastasis, and tumor cell growth. Targeting TAMs or modulating their phenotype represents a potential therapeutic strategy [25,26].

Cytokines and chemokines

Cytokines and chemokines are critical for regulating immune responses and can significantly impact tumor behavior. In PCa, the balance between different cytokines and chemokines can influence disease progression and treatment outcomes. Cytokines such as tumor necrosis factor-alpha (TNF-α) and interferon-gamma (IFN-γ) play roles in initiating anti-tumor immune responses [27]. However, their effects can be modulated by other components of the TME. For example, TNF-α can have both pro-tumor and anti-tumor effects depending on the context. Cytokines like interleukin-10 (IL-10) and transforming growth factor-beta (TGF-β) are often elevated in PCa and contribute to immune suppression [27,28]. IL-10 can inhibit the activation of T cells and DCs, while TGF-β can suppress the function of various immune cells, including CTLs and DCs. Another, these small signalling molecules attract immune cells to the site of inflammation or tumor. In PCa, the expression of certain chemokines can influence the recruitment of immune cells such as Tregs and TAMs, thereby affecting tumor progression and response to therapy [27,28].

In PCa, the immunological components of the TME are crucial in determining how the disease progresses and if a patient responds to therapy. Tumor-infiltrating lymphocytes, dendritic cells, macrophages, and various cytokines and chemokines all contribute to the complex interactions between the immune system and the tumor. Understanding these components and their interactions is essential for developing effective immunotherapies and improving treatment outcomes for PCa patients. Ongoing research into the mechanisms of immune evasion and the development of targeted therapies continues to provide new insights and potential strategies for harnessing the immune system in the fight against PCa. Summarizes the key immune components present in the PCa microenvironment, and their roles in tumor progression as shown in Table 1. The simple presentation of immunological components linked to tumor-infiltrating lymphocytes (TILs), dendritic cells, macrophages, cytokines, and chemokines in PCa-associated responses and treatment strategies are shown in Figure 1.

Role of Immunotherapy in Prostate Cancer Treatment

Immunotherapy represents a transformative approach to cancer treatment, harnessing the body's immune system to target and eradicate cancer cells. In PCa, immunotherapy has evolved significantly, with several strategies demonstrating promise in clinical trials and practice. Immunotherapy represents a promising frontier in the treatment of PCa, with several approaches showing potential to improve patient outcomes. Cancer vaccines, immune checkpoint inhibitors, and adoptive cell therapies each offer unique mechanisms for enhancing the immune response against PCa. While significant progress has been made, ongoing research is crucial to address the challenges and limitations associated with these therapies. By combining immunotherapies, identifying predictive biomarkers, exploring novel targets, and personalizing treatment approaches, the field of PCa immunotherapy holds great promise for advancing patient care and improving long-term outcomes. The overview, mechanism of action and clinical status of immunotherapy strategies in PCa are given in Table 2. A basic summary of immunotherapy for PCa treatment includes immune modulators, adoptive cell therapy, monoclonal antibodies, cancer vaccines, checkpoint inhibitors, and oncolytic virus therapy, depending on the patient's condition and response are shown in Figure 2.

Checkpoint inhibitors

A group of immunotherapy medications known as checkpoint inhibitors have the purpose of inhibiting proteins that suppress immune responses. The PD-1/PD-L1 and CTLA-4 pathways are two major targets for checkpoint inhibitors [7,8]. PD-1/PD-L1 inhibitors associated drugs such as pembrolizumab and nivolumab target the PD-1 receptor on T cells or its ligand PD-L1 on tumor cells. While these therapies have shown remarkable efficacy in several cancers, their effectiveness in PCa has been limited [7,8]. Research is ongoing to identify biomarkers that could predict which patients might benefit from PD-1/PD-L1 inhibitors. Furthermore, Ipilimumab is a CTLA-4 inhibitor

Table 1: List of immune components within the prostate cancer microenvironment and their roles in influencing tumor progression and treatment response.

Immune Component	Description	Role in Prostate Cancer	References
Tumor-Infiltrating Lymphocytes (TILs)	T cells that infiltrate the tumor microenvironment, including CD8+ cytotoxic T cells and CD4+ helper T cells.	CD8+ T cells recognize and kill cancer cells, associated with a better prognosis. CD4+ T cells can promote or suppress anti-tumor responses depending on their subset (e.g., Th1, Th2).	[5,6]
Regulatory T Cells (Tregs)	A subset of CD4+ T cells that suppress immune responses and maintain tolerance.	Tregs often accumulate in the TME and inhibit anti-tumor immunity through cytokine secretion (e.g., IL-10, TGF-β) and direct suppression of CTLs.	[19,20]
Dendritic Cells (DCs)	Professional antigen-presenting cells that process and present antigens to T cells.	DCs are crucial for initiating T-cell responses. In prostate cancer, their function can be impaired by the TME, reducing effective T cell activation.	[21,22]
Macrophages	Versatile immune cells can adopt different functional states, including M1 (pro-inflammatory) and M2 (anti-inflammatory).	M2 macrophages in prostate cancer support tumor progression by secreting cytokines and growth factors that enhance angiogenesis and tissue repair while suppressing anti-tumor immunity.	[23,24]
Tumor-Associated Macrophages (TAMs)	Macrophages found within the tumor microenvironment, often exhibit an M2-like phenotype.	TAMs promote tumor growth, metastasis, and angiogenesis while inhibiting anti-tumor immunity. Targeting TAMs is a potential therapeutic approach.	[25,26]
Cytokines and Chemokines	Signaling molecules that regulate immune responses and influence tumor behavior.	Pro-inflammatory cytokines (e.g., TNF-α, IFN-γ) can initiate anti-tumor responses, whereas anti-inflammatory cytokines (e.g., IL-10, TGF-β) contribute to immune suppression. Chemokines attract immune cells, influencing their recruitment to the tumor site.	[27,28]

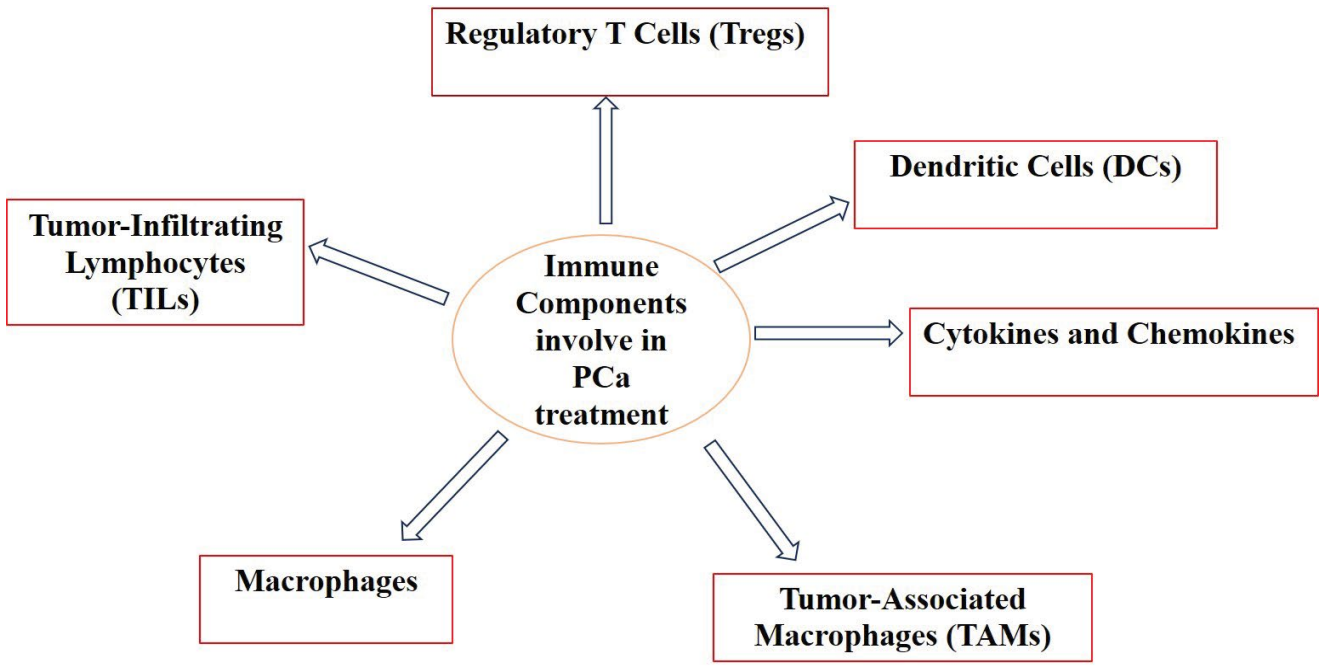

Figure 1: Simple presentation of immune components in prostate cancer associated with tumor-infiltrating lymphocytes (TILs), dendritic cells, macrophages cytokines, and chemokines.

that enhances T-cell activation and proliferation. Although primarily used in melanoma, it has shown some promise in PCa, especially in combination with other therapies [7,8].

Adoptive cell therapy

Adoptive cell therapy involves modifying a patient's immune cells to better target cancer. This includes strategies like Chimeric Antigen Receptor (CAR) T-cell therapy and tumor-infiltrating lymphocyte (TIL) therapy [29]. Thus, CAR T-cell therapy involves engineering T cells to express receptors that target specific cancer antigens. For PCa, researchers are exploring CAR T-cells

Table 2: Immunotherapy strategies, description, mechanism of action, and clinical status in prostate cancer.

Immunotherapy	Description	Mechanism of action and clinical status	References
Checkpoint Inhibitors	Drugs that block proteins used by tumors to evade immune detection, such as PD-1/PD-L1 inhibitors.	Restore T cell function and enhance the immune response against tumor cells. Nivolumab (PD-1) and atezolizumab (PD-L1) have shown promise in trials.	[7,8]
Prostate Cancer Vaccines	Vaccines are designed to elicit an immune response specifically against prostate cancer cells.	Stimulate the immune system to recognize and attack prostate cancer cells. Sipuleucel-T is FDA-approved for advanced prostate cancer.	[9,10]
CAR-T Cell Therapy	T cells are genetically modified to express chimeric antigen receptors (CARs) targeting prostate cancer antigens.	Enhance T cell recognition and killing of prostate cancer cells. Under investigation, with early trials showing promise.	[29]
Oncolytic Virus Therapy	Use of genetically modified viruses to selectively infect and kill tumor cells.	Directly lyse tumor cells and stimulate an anti-tumor immune response. Early phase trials are ongoing, showing potential.	[30,31]
Immune Modulators	Agents that modulate the immune response to enhance anti-tumor activity.	Enhance the overall immune response against prostate cancer. Agents like Interleukin-2 and various experimental drugs.	[32]

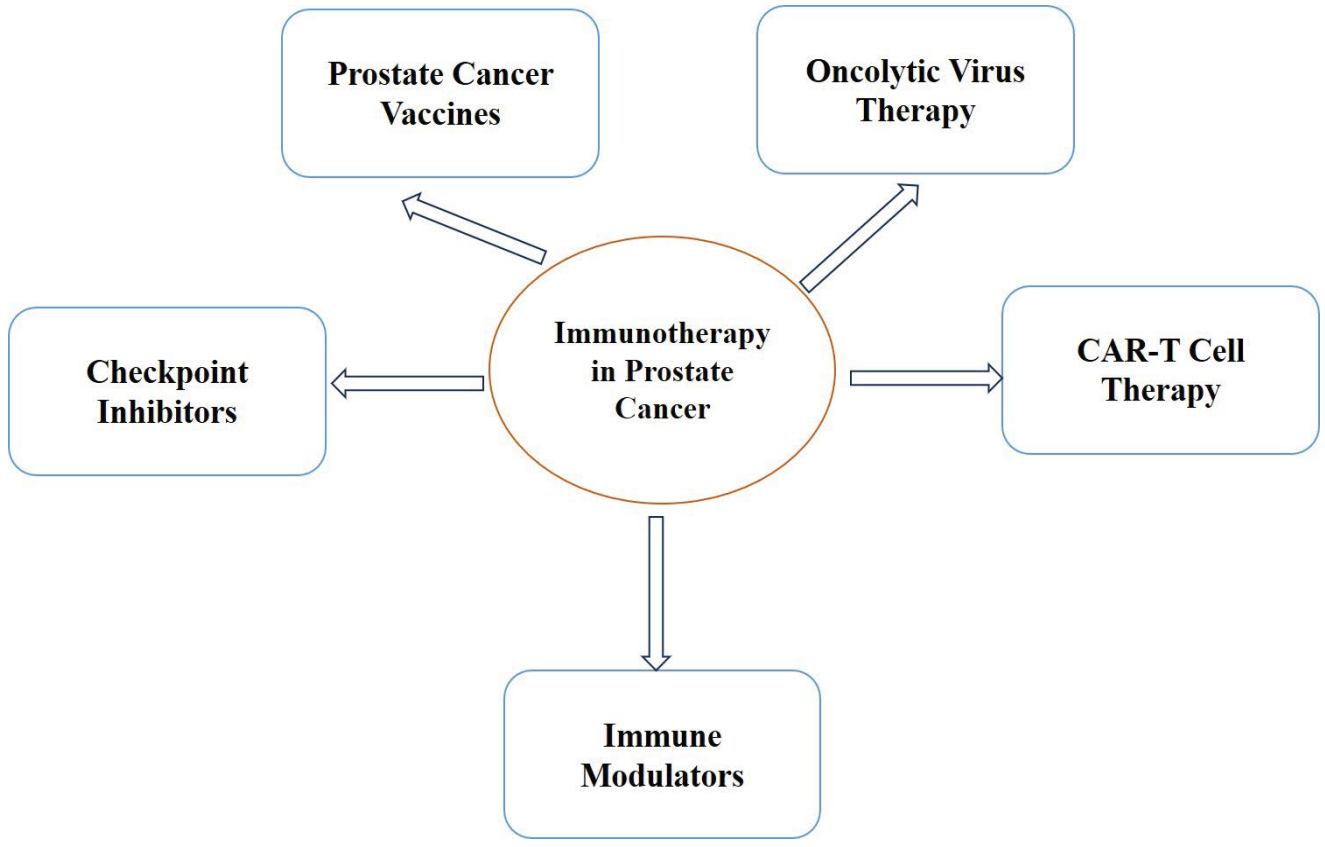

Figure 2: Simple overview of immunotherapy in prostate cancer treatment like checkpoint inhibitors, cancer vaccines, adoptive cell therapy, monoclonal antibodies, oncolytic virus therapy, and immune modulators depending upon the response of the patient condition.

targeting prostate-specific membrane antigen (PSMA) and other antigens. Although CAR T-cell therapy has shown substantial success in hematological cancers, its application in solid tumors like PCa faces challenges, including the identification of suitable targets and overcoming the tumor microenvironment [29]. This approach involves isolating TILs from a patient's tumor, expanding them in the lab, and reinfusing them into the

patient. While TIL therapy has been successful in other cancers, its application in PCa is still under investigation [29].

Monoclonal antibodies

Monoclonal antibodies are designed to specifically bind to cancer cells or associated molecules, marking them for destruction by the immune system. Agents like enzalutamide and abiraterone, although primarily androgen receptor inhibitors, can also have immune-modulatory effects. Other monoclonal antibodies being investigated include those targeting PSMA or other prostate cancer-specific antigens [33].

Oncolytic virus therapy

Oncolytic virus therapy utilizes genetically modified viruses that selectively infect and kill cancer cells while stimulating an immune response against the tumor [30,31]. Adenoviral and vesicular stomatitis virus (VSV)-based therapies are being explored for PCa. These viruses can be engineered to produce tumor antigens or other immunostimulatory factors to enhance their therapeutic effect [30,31].

Immune modulators

Immune modulators are drugs that can alter immune system function to enhance anti-tumor responses agents like lenalidomide and thalidomide, known for their effects on multiple myeloma, are being investigated for their potential to modulate immune responses in PCa [32].

Role of Vaccines in Prostate Cancer Immunotherapy

Cancer vaccines stimulate the body's immune system to target and destroy cancer cells. The goal of PCa vaccinations is to prime the immune system to identify and eliminate PCa cells. These vaccines generally focus on enhancing the immune response against prostate-specific antigens or other tumor-associated targets.

Sipuleucel-T (Provenge)

An autologous dendritic cell-based vaccine that targets PAP and PSA. Approved for metastatic castration-resistant prostate cancer (mCRPC), it improves overall survival but not progression-free survival [9]. Sipuleucel-T remains a standard treatment for mCRPC, with ongoing research exploring combination therapies and its use in earlier stages of the disease [10].

Prostvac-VF

A viral vector-based vaccine using modified vaccinia Ankara (MVA) and fowl pox vectors to express PSA and costimulatory molecules. It aims to enhance T cell-mediated immune responses [11]. Clinical trials have shown it can extend overall survival. Research continues to optimize its efficacy and investigate combination approaches with other therapies [12,13].

GVAX

A vaccine using genetically modified PCa cells to secrete GM-CSF, enhancing immune response against PCa [15,16]. Clinical studies are being performed to evaluate its efficacy and safety. Earlier studies showed promise in inducing immune responses against PCa [15,16].

PSA-TRICOM

Combines PSA with costimulatory molecules (TRICOM) to enhance T-cell activation [14]. Clinical

Table 3: Current status of vaccine treatment prostate cancer-associated immunotherapy.

Vaccine	Description	Current Status	References
Sipuleucel-T (Provenge)	An autologous dendritic cell-based vaccine that targets prostate-specific antigen (PSA) and prostatic acid phosphatise (PAP).	Approved by FDA for metastatic castration-resistant prostate cancer (mCRPC). Shown to improve overall survival. Ongoing studies explore combination therapies.	[9,10]
Prostvac-VF	A viral vector-based vaccine using modified vaccinia Ankara (MVA) and fowlpox vectors expressing PSA and costimulatory molecules.	In clinical trials, it has shown promise in extending overall survival. Investigated for use in combination with other therapies.	[11-13]
PSA-TRICOM	A vaccine that combines PSA with a triad of costimulatory molecules (TRICOM) to enhance T-cell activation.	Clinical trials have shown mixed results, with some evidence of prolonged survival. Research continues optimizing efficacy.	[14]
GVAX	A vaccine that uses genetically modified prostate cancer cells to secrete GM-CSF, a cytokine that stimulates immune responses.	Ongoing clinical trials to assess its efficacy and safety. Shown to induce immune responses against prostate cancer in earlier studies.	[15,16]
PSA-TRICOM + Ipilimumab	Combines PSA-TRICOM with ipilimumab, a CTLA-4 inhibitor, to enhance immune response through checkpoint blockade.	Trials are investigating the combined approach for improved efficacy in advanced prostate cancer. Initial results are promising.	[17,18]

trials have demonstrated mixed results, with ongoing research to improve its effectiveness and identify optimal PCa patient populations [17,18].

The summary of the current status of notable PCa vaccines, including recent updates is given in shown in Table 3.

PCa immunotherapy involves a multifaceted approach, including understanding the roles of various immune components, harnessing innate immune mechanisms, and developing effective vaccines. The interaction between these elements shapes the efficacy of current treatments and informs ongoing research. Vaccines combined with other therapy modalities, such as checkpoint inhibitors, may improve patient outcomes for those with PCa. Continued research is essential to enhance the efficacy of these strategies and tailor treatments to individual patient needs.

Conclusion

There are several difficulties since PCa tumor microenvironments are immunosuppressive. Factors such as the presence of regulatory T cells, MDSCs, and an abundance of immunosuppressive cytokines can inhibit effective immune responses. Strategies to overcome these barriers include combining immunotherapy with other treatments like chemotherapy or targeted therapy. Identifying biomarkers that predict response to immunotherapy is crucial. Current research focuses on genomic, transcriptomic, and proteomic biomarkers that could help stratify patients and personalize treatment approaches. Combining immunotherapy with other treatment modalities, such as hormone therapy, radiation, or targeted therapy, is an active research area. These combinations aim to enhance the effectiveness of immunotherapy by overcoming resistance mechanisms and improving overall treatment outcomes. Advances in personalized medicine offer the potential to tailor immunotherapy to individual patients based on their unique tumor and immune profiles. This approach requires ongoing research to understand the complex interactions between cancer and the immune system. Immunotherapy has emerged as a promising approach in the treatment of PCa, offering new hope for patients with advanced disease. The complex and numerous interactions between immune components and the tumor microenvironment impact the efficacy of different immunotherapeutic approaches. While significant progress has been made, ongoing research is essential to overcome current limitations and optimize immunotherapy for PCa. Future studies will likely continue to explore combination therapies, novel immunotherapeutic agents, and personalized approaches to improve patient outcomes.

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