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Review

Immune phenotypes of prostate cancer cells: Evidence of Epithelial immune cell-like transition?

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Abstract Prostate cancers (PCa) have been reported to actively suppress antitumor immune responses by creating an immune-suppressive microenvironment. There is mounting evidence that PCas may undergo an ''Epithelial Immune Cell-like Transition'' (EIT) by expressing molecules conventionally associated with immune cells (e.g., a variety of cytokines/receptors, immune transcription factors, Ig motifs, and immune checkpoint molecules), which subsequently results in the suppression of anti-cancer immune activity within the tumor microenvironment. Recent progress within the field of immune therapy has underscored the importance of immune checkpoint molecules in cancer development, thus leading to the development of novel immunotherapeutic approaches. Here, we review the expression of select immune checkpoint molecules in PCa epithelial and associated immune cells, with particular emphasis on clinical data supporting the concept of an EIT-mediated phenotype in PCa. Furthermore, we summarize current advances in anti-immune checkpoint therapies, and provide perspectives on their potential applicability.

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1. Introduction

Prostate cancer (PCa) is the most commonly-diagnosed non-cutaneous cancer and the second leading cause of cancer-related death in North American males. Although PCas typically present as androgen-dependent cancers, and initial androgen ablation can lead to substantial remissions, they frequently return in an androgen-independent, castration-resistant form. Within the last few years, a number of new agents have been developed and approved for treatment of metastatic castration-resistant prostate cancer (mCRPC). These include second generation anti-androgen agents (abiraterone acetate and enzalutamide), cytotoxic drugs (cabazitaxel), and radiopharmaceuticals (radium-223 dichloride) [1—4]. However, while these advancements have significantly improved patient survival and quality of life, and slowed disease progression, relapse invariably occurs. Therefore, there still remains an urgent need for novel therapeutic targets and agents for mCRPC.

During the past decade, immune therapy has become one of the most active and prolific areas of cancer research. Sipuleucel-T, an autologous cellular immune therapy, is the first therapeutic cancer vaccine and currently the only FDA-approved immune therapy for PCa. Recent advances have also underscored the crucial role of immune checkpoint molecules in facilitating cancer development, thus leading to numerous novel immunotherapeutic approaches. In particular, studies have demonstrated that PCa cells employ various mechanisms, including the aberrant expression of immune checkpoint molecules, in order to elude the immune system. Therefore, these insights have served to provide corroborating evidence for the "Epithelial Immune Cell-like Transition" (EIT) hypothesis [5]. In this review, we will revisit the EIT concept with regards to the expression of immune checkpoint molecules on PCa cells, with an emphasis on clinical data. Additionally, we will summarize current advances in immune checkpoint-based therapies and provide perspectives on their potential applicability.

2. EIT and PCa

Although the immune system plays an invaluable role in the elimination of cancer cells, there is mounting evidence that epithelial cancers avoid immune destruction by expressing certain immune genes and products (e.g., cytokines and immune-inhibitory molecules) not physiologically-expressed by the originating normal tissues. On the basis of these observations, we propose that the immune-suppressive activity of epithelial cancers may arise from acquired immune-suppressive characteristics via a trans-differentiation process we term EIT. These properties could enable cross-talk between cancer and immune cells, thereby facilitating evasion of immune surveillance and co-optation of immune mechanisms to promote tumor growth.

Recent reports have confirmed that PCa cells are able to use various mechanisms in order to evade the immune system (Fig. 1). Unsurprisingly, the presence of multiple immunosuppressive cell types within the PCa microenvironment has been found to be associated with a poor prognosis. In particular, an increased number of regulatory T cells (the archetypal immunosuppressive cell type), have been found within the peripheral blood of PCa patients [6—8]. Furthermore, M2 macrophages and myeloid-derived suppressor cells (MDSCs) also appear to be significant contributors in maintaining the immunosuppressive microenvironment, with multiple reports associating increased numbers with poor prognosis in PCa patients [9—12]. Conversely, the abundance of cytotoxic natural killer (NK) cells within the PCa tumor could potentially confer a protective effect [13].

Mechanistically, several well-known immunosuppressive molecules have been implicated in the inhibition of cytotoxic cell functions within the PCa microenvironment. For example, the cytokine milieu of the prostate tumor was found to contain high levels of TGF-β, and in conjunction with decreased expression of activating receptors (NKp46 and NKG2D) and increased expression of the inhibitory receptor ILT2 on NK cell surfaces, suppress the cytotoxic immune response against PCa cells [14]. Furthermore, high levels of the NKG2D ligand have been found on the surfaces of PCa-derived exosomes, resulting in the downregulation of NKG2D on NK and $CD8^+$ T cells, thus inhibiting their activation [15]. Additionally, the upregulation of CSF1 and IL1β in *Pten*-null prostatic epithelium have been shown to facilitate the immunosuppressive effects of MDSCs, inhibiting T cell proliferation via high levels of arginase-1 and iNOS expression [16].

Standard therapies used for the treatment of PCa have also been found to induce immune suppression. In particular, upregulation of CSF1 following radiotherapy results in an increased MDSC population in PCa patients. When a selective inhibitor of CSF1R was administered in conjunction with radiation, the treatment suppresses tumor growth more effectively than with irradiation alone. This indicates that an alleviation of the immunosuppressive tumor microenvironment can enhance anticancer therapeutic effects [17]. Additionally, androgen deprivation therapy, the current first-line treatment for metastatic PCa, has been shown to mediate immune suppression via impairment of initial T cell activation priming and IFN-γ production [18]. Furthermore, although there have been reports suggesting that concurrent immune therapy and castration could initially enhance the number and function of cytotoxic $CD8^+$ T cells, the synergy is short lived and ultimately offset by a parallel expansion of regulatory T cells [19].

Finally, the increased expression of immune checkpoint molecules has also been observed in PCa, thus indicating an important immune-suppressive mechanism underlying PCa development. Below, we will focus on the details of expression, function, and clinical applications of these immune checkpoint molecules in PCa.

3. Immune checkpoint molecules and PCa — expression and function

3.1. PD-1/PD-L1

First described by Ishida et al. in 1992 [20], programmed death 1 (PD-1) is a transmembrane glycoprotein and T cell co-inhibitory receptor expressed on T cells, B cells, NK cells, dendritic cells (DCs), and activated monocytes [21].

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