Engineering 12 (2022) 12–15

Contents lists available at ScienceDirect

Engineering

journal homepage: www.elsevier.com/locate/eng

Views & Comments

DNA Damage Response Inhibitor and Anti-PD-L1 Therapy for Prostate Cancer: Development of Predictive Biomarkers

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1. Introduction

Although androgen receptor biosynthesis and signaling inhibitors have significantly improved outcomes in patients with castration-resistant prostate cancer (CRPC), there is still a dearth of effective treatment options for men with advanced prostate cancer. Recent studies have shown that DNA damage and altered DNA damage response (DDR) pathways may contribute to the progression of prostate cancer to CRPC. More than 25% of men with metastatic CRPC (mCRPC) are enriched for germline or somatic alterations in DDR genes [1,2]. Based on previous work, which established one of the first clinically implemented examples of a synthetically lethal approach for cancer therapy, initial clinical trials demonstrated significant responses to poly(adenosine diphosphate-ribose) polymerase (PARP) inhibition in CRPC patients with deleterious defects in DDR signaling and DNA repair genes that are prevalent in mCRPC (mainly breast cancer susceptibility gene 2 (*BRCA2*) variants) [3,4]. This work led to intensive focus on PARP inhibitors (PARPis) as the first targeted therapy for CRPC and resulted in breakthrough therapy designations from the US Food and Drug Administration (FDA) for three PARPis, olaparib, rucaparib, and niraparib, for the treatment of CRPC patients with specific *BRCA2*-mutant mCRPC [5–8]. DDR inhibitors (DDRis) have rapidly expanded to include inhibitors of other pathways, including ataxia telangiectasia and Rad3-related (ATR) kinase, which, together with ataxia-telangiectasia mutated (ATM), serves as a key regulator of replication stress response (RSR) signaling [9–11].

2. DDR-targeted therapies induce intrinsic immune signaling in prostate cancer cells

Recent preclinical studies of PARPis in combination with immune checkpoint therapy (ICT) have shown the potential for additive benefits in *BRCA*-mutant and *BRCA1/2* wild-type cancer cells. These studies showed that PARPis can induce immune activation through a variety of mechanisms, including the activation of the tumor cell innate immune pathway cyclic guanosine monophosphate–adenosine monophosphate synthase (cGAS)–stimulator of interferon genes (STING) signaling and expression of immune checkpoint protein programmed cell death ligand 1 (PD-L1) through induction of type I interferon (IFN) expression and IFN regulatory factor 3 activity [12–17], and through inactivation of glycogen synthase kinase 3β to stabilize the PD-L1 protein [18]. A recent study has shown activation of the cGAS–STING signaling pathway by ATR inhibitors (ATRis) in CRPC preclinical models and demonstrated synergistic suppression of prostate cancer growth by combining ATRi treatment with anti-PD-L1 antibody ICT *in vivo* [19]. While parallels between the known mechanism (s) of immune activation can be drawn between PARPis and ATRis, analysis of specific mechanisms of action between these agents revealed potentially pivotal roles for tumor cell-expressed immune checkpoint proteins, such as PD-L1 in the regulation of type I IFN, tumor cell-intrinsic, and autocrine signaling pathways in response to DDRis as important modulators of therapy outcome [19]. For example, in contrast to PARP inhibition, ATRis induced PD-L1 protein downregulation through the activation of checkpoint kinase 1—cell division cycle 25C–cyclin-dependent kinase 1—speckle-type pox virus and zinc finger protein E3 ligase complex signaling axis, which resulted in an autocrine, IFN-β–IFN-α receptor 1-mediated apoptotic response in CRPC models [19]. The results of this and other studies raise the question of whether, in addition to PD-L1, the expression of other immune checkpoint protein B7 family members, which are functionally regulated by IFNs and interferon regulatory factors (IRFs), play an important role in DDRi and ICT combination therapy responses in prostate cancer and other malignancies.

3. Expression of B7 immune checkpoint protein family members in cancer

As summarized in Table 1, the B7 immune checkpoint protein family contains at least ten transmembrane or glycosylphosphatidylinositol (GPI)-linked to cell membrane (B7-H4) protein members. All B7 protein family members are structurally related and feature extracellular immunoglobulin V (IgV)–IgC domains that bind to their respective receptors on lymphocytes, which regulate T cell immune responses through signaling activities. Although early studies characterized the expression of B7 protein family members in immune cells, recent investigations have expanded the expression pattern of B7 protein family members

https://doi.org/10.1016/j.eng.2022.01.002
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Table 1
B7 immune checkpoint protein family.

B7 checkpoint protein family ligand	Ligand alias	Extracelluar domian structure	Expression in immune cells	Tumor expression	Receptors	Regulating response of T-cell
B7-H1	CD274, PD-L1	IgV–IgC	T cells, B cells, DCs, monocytes	+	PD-1	Inhibition
B7-H2	ICOS-L, GL-50, B7h, B7RP-1	IgV–IgC	T cells, B cells, DCs, macrophages	+	ICOS	Inhibition
B7-H3	CD276	IgV–IgC–IgV–IgC (human) IgV–IgC (mouse)	T cells, B cells, DCs, monocytes	+	TREML2? TLT-2?	Activation/ inhibition
B7-H4	B7S1, B7x, Vtcn1	IgV–IgC	T cells, B cells, NK cells, DCs, monocytes	+	Unknown	Inhibition
B7-H5	VISTA, platelet receptor GI24, Dies1, PD-1H	IgV–IgC	T cells, DCs, macrophage, neutrophils	–	CD28H	Inhibition
B7-H6	NCR3LG1	IgV–IgC	Unknown	+	NKp30	Activation
B7-H7	HHLA2	IgV–IgC–IgV	T cells, B cells, DCs, monocytes	+	CD28H	Activation/ inhibition
B7-1	CD80	IgV–IgC	T cells, B cells, DCs, monocytes	+	CD28, CTLA-4	Inhibition
B7-2	CD86	IgV–IgC	T cells, B cells, DCs, monocytes	+	CD28, CTLA-4	Inhibition
B7-DC	CD273, PD-L2	IgV–IgC	DCs, monocytes	+	PD-1	Inhibition

CD: cluster of differentiation; ICOS-L, B7h: inducible costimulatory ligand; B7RP-1: B7-related protein 1; B7S1: B7 superfamily member 1; B7x: B7 homolog x; Vtcn1: V-set domain containing T cell activation inhibitor 1; VISTA: V-domain immunoglobulin-containing suppressor of T cell activation; Dies1: differentiation of embryonic stem cells 1; PD-1H: PD-1 homolog; NCR3LG1: natural killer cell cytotoxicity receptor 3 ligand 1; HHLA2: human endogenous retrovirus subfamily H long terminal repeat associating protein 2; CTLA-4: cytotoxic T lymphocyte-associated antigen 4; TREML2, TLT-2: triggering receptor expressed on myeloid cells like transcript 2; CD28H: CD28 homolog; NKp30: natural killer-activating receptor; DCs: dendritic cells.

to a wide variety of cell types in various tissues, especially in malignant tumors [20–34]. Importantly, B7 immune checkpoint proteins are extensively modified posttranslationally, and like many other membrane and secreted proteins, are glycosylated at their extracellular IgV–IgC domains, which are required for their functional activities. Interestingly, while glycosylation and glycan structure alteration of cell surface proteins are universal features of many cancer cells, altered glycosylation in cancer cell-expressed B7 protein family members reportedly block their interactive immune cell recognition functions, which can be restored by de-glycosylation [35–39]. Recent studies have revealed that, to metastasize, tumor cells utilize mechanistically diverse pathways involving inhibitory immune checkpoints to escape immune responses. Targeting the function of these immune checkpoint proteins has emerged as a new treatment that may effectively prevent cancer progression [40]. Among the pathways of inhibitory immune checkpoints, the PD-L1/programmed cell death 1 (PD-1) immune checkpoint pathway has emerged as a key regulator of adaptive immune response and has been shown to promote evasion of the immune system during metastatic progression of many cancers [41–43]. For this purpose, inhibitors that block the interaction of PD-L1/PD-1 have been developed as therapeutic anticancer drugs and are combined with other drugs to maximize the efficacy of cancer treatment [44].

4. Tumor cell-expressed PD-L1 as a therapeutic target and predictive biomarker for ICT

PD-L1 (B7-H1, CD274) belongs to the B7 immune checkpoint protein family. PD-L1 is expressed on the cell membrane surface of many types of cells, including T cells, B cells, dendritic cells, macrophages, and non-lymphoid cells, such as mesenchymal stem cells, epithelial cells, endothelial cells, and brown adipocytes. PD-L1 was also reported to be expressed in tumor cells of various origins. PD-L1 is the ligand for its receptor PD-1, an immune cell inhibitory receptor expressed on the surface of activated T and B cells [41,45]. PD-1 is activated through PD-L1 binding and suppresses effector T cell activity within tissues and tumors, which promotes the survival and metastasis of PD-L1-expressing tumor cells. Interestingly, in addition to the cell membrane presentation of PD-L1 protein (membrane PD-L1, mPD-L1), it has been reported that PD-L1 can be secreted into the extracellular space or serum and that the secreted form of PD-L1 (sPD-L1) contains a C-terminal, which is distinct from mPD-L1. sPD-L1 is generated from alternatively spliced PD-L1 mRNA or as an extracellular peptide fragment domain from the membrane-bound PD-L1, which is shed through the activities of matrix metalloproteinases (MMPs) or a disintegrin and metalloproteinases (ADAMs) [46–49]. More recently, studies have revealed that PD-L1 can be present in the cytoplasm (cytoplasmic PD-L1, cPD-L1) and, by acetylation at K263, can be translocated into the nucleus (nuclear PD-L1, nPD-L1) and recruited to chromatin to functionally regulate mRNA transcription of a range of genes including oncogenic/stemness genes. In particular, PD-L1 can regulate the message RNA (mRNA) transcription of a network of genes critically involved in regulating immune responses, such as other checkpoint protein members of the B7 family and cytotoxic T lymphocyte-associated antigen 4 (CTLA-4) [50,51]. As summarized in Table 2 [46–53], like "classic" mPD-L1, these non-membrane bound PD-L1s were detected using immunoblotting (IB), immunohistochemistry (IHC), and enzyme-linked immunosorbent assay (ELISA) in immune and cancer/tumor cells

Table 2
Compartment localization of PD-L1 protein.

Cellular compartment	Source	Detection	References
Membrane and extracelluar vescle	PD-L1 mRNA translated full length protein	IB, IHC	[52,53]
Cytoplasma and nucleus	PD-L1 mRNA translated full length protein	IB, IHC	[50,51]
Extracellular space and serum	Alternative spliced PD-L1 mRNA translated full length protein; extracellar domain (peptides fragment) of mPD-L1 shed by MMP13, ADAM10, or ADAM17	ELISA	[46–49]

with specific anti-PD-L1 antibodies. Importantly, detection of PD-L1 through these methods can substantially affect therapy decisions with regard to the selective clinical use of anti-PD-L1/anti-PD-1 and the interpretation of the results of PD-L1 detection post-therapy. Taken together, the results of these studies suggest a crucial role for tumor cell- and immune cell-expressed PD-L1 in tumor immune evasion and tumorigenesis and potentially as an early predictive biomarker of response to ICT.

Numerous FDA-approved clinical trials have tested immunohistochemically detected tumor cell- and tumor microenvironment (TME) cell-expressed PD-L1 as a predictive marker for ICT response in patients with certain cancers, including melanoma, triple-negative breast cancer, and non-small cell lung cancer [54–58]. These studies showed the value of anti-PD-L1 immunostaining as a predictive biomarker for response to immunotherapy agents. However, as an increasing number of preclinical and clinical studies have tested PD-L1 expression as a predictive biomarker, important questions have arisen regarding the biological and clinical significance and utility of this marker. Questions regarding the overall efficacy and use of anti-PD-L1 ICT in prostate cancer and the relatively low level of detection of PD-L1 in prostate cancer tissues present a challenging scenario. However, efforts to understand and use anti-PD-L1 ICT for the treatment of CRPC, as well as recent preclinical studies and clinical trials that have tested anti-PD-L1 as a single agent and in novel combinations, have yielded increasingly promising results [19,59,60]. Overall, substantial challenges remain for the development of PD-L1 as a predictive biomarker for anti-PD-L1-based ICT in many cancers. Much work needs to be done to overcome these barriers, especially for CRPC.

5. Development of tumor cell-expressed PD-L1 as a therapeutic target and predictive biomarker for ICT in prostate cancer—The challenges

First, due to the extreme heterogeneity of prostate cancer, sampling bias can be one of the greatest obstacles to the accurate assessment of PD-L1 expression in prostate cancer biopsies. As tumor biopsies often contain a limited number of evaluable tumor cells and sample handling is variable, immunostaining analysis can be suboptimal and not representative of prostate cancer lesions. Thus, in addition to immunohistochemical detection, other detection protocols and methods, such as reverse transcription quantitative real-time DNA polymerase chain reaction, IB, or ELISA, should be evaluated and considered for PD-L1 analysis. Second, as we discussed earlier, tumor-expressed PD-L1 can be located in the serum, extracellular matrix, cell membrane surface, cytoplasm, or nucleus. Importantly, different posttranslational modifications of PD-L1 have been identified in association with these different compartments. While glycosylation of PD-L1 is required for membrane and extracellular matrix localization, secretion, and ligand functionalities, these modifications may block or reduce the exposure of PD-L1 peptide antigens recognized by PD-L1 antibodies. Additionally, PD-L1 glycosylation can potentially be altered in cancer cells, which may further compromise the detection of cancer cell-expressed PD-L1 via specific PD-L1 antibodies. A recent report has shown that *in vitro* enzymatic removal of N-linked glycosylation significantly enhances PD-L1 detection by a several methods, including IB, immunofluorescence, ELISA, and IHC [61]. However, as alterations in glycosylation of proteins are a universal observation in cancer cells, the applicability and utility of this approach require intensive validation in clinical samples, especially in extremely heterogeneous tumors, such as prostate cancer. The development of antibodies that recognize different posttranslationally modified forms of PD-L1 and their extensive characterization (including cellular distribution) are needed. Third, cell-type-specific functional analysis of various forms of PD-L1 should be prioritized for future translational research. Although tumor and immune cells (including macrophages and lymphocytes) are often scored independently for PD-L1 expression using IHC, there is only minimal information regarding the functional significance of PD-L1 in these discrete cell types in cancer, including tumor response to anti-PD-L1 therapy. In addition, the development and application of better quantitative analysis and computational biology approaches would likely improve the utility of these clinical biomarker studies in the short term.

In summary, the expression patterns of tumor cell- and immune cell-expressed PD-L1 in multiple cancers, including prostate cancer, are complex. In addition, various PD-L1 posttranslational modifications in tumors are difficult to detect via immunohistochemical methods and may confound the interpretation of PD-L1 protein expression in highly heterogeneous prostate cancer tumor samples. Thus, the development of PD-L1 antibodies that recognize different post-translationally modified PD-L1 molecules and their extensive characterization (including cellular distribution) are needed. Furthermore, basic and translational research into the potentially different, compartmentalized functions of PD-L1 in prostate cancer cells and tumor-associated macrophages and lymphocytes must be prioritized to address the knowledge gaps that exist regarding the clinical significance of PD-L1 IHC. These research efforts will likely require the development of more quantitative analytical approaches using computational biology, as well as specific biochemical and protein engineering methods. Overall, increased research in these areas could lead to more accurate identification and management of prostate cancer patients who could benefit from anti-PD-L1 ICT.

Acknowledgments

We acknowledge the editorial assistance of Sarah E. Townsend. We also acknowledge the support from MD Anderson National Cancer Institute (NCI) Prostate Cancer SPORE (P50 CA140388) and the NCI Cancer Center Support (P30 CA16672).

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