

Comparison of PD-L1 and B7-H3 in Cancer Immunotherapy

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Abstract

PD-L1 and PD-1 inhibitors have achieved great success in the treatment of patients of a wide spectrum of cancers. However, only a fraction of cancer patients benefits from this therapy. Therefore, it is quite urgent to find another target for immunotherapy. Recently we published one article (Young-hee Lee et al., Cell Research, 2017, 27: 1034-104), which showed that B7-H3 knockout mice and the mice treated with anti-B7-H3 neutralizing antibody displayed slower tumor growth in several tumor types. More interestingly, combining blockade of B7-H3 and PD-1 resulted in synergistic effect on inhibition of tumor growth. So in this paper, we compare PD-L1 and B7-H3 in the terms of expression pattern, mechanism of action, the sites of action in tumor evasion and clinical inhibitors. These suggest that B7-H3 is a promising target for cancer immunotherapy.

Keywords: PD-L1; B7-H3; Cancer immunotherapy

Introduction

Recently we published one paper entitled 'inhibitor of the B7-H3 immune checkpoint limits tumor growth by enhancing cytotoxic lymphocyte function' in cell research (Young-hee Lee et al., Cell Research, 2017, 27(8): 1034-1045). In this study, we found that B7-H3 knockout mice and the mice treated with anti-B7-H3 neutralizing antibody displayed slower tumor growth in several tumor types, which is dependent on NK and CD8⁺ T cells. More interestingly, combining blockade of B7-H3 and PD-1 resulted in synergistic effect on inhibition of tumor growth. Based on this study and others studies, B7-H3 are a promising target for immunotherapy against cancer. Thus, we compare B7-H3 with PD-L1 in the context of cancer immunotherapy.

Expression of PD-L1 and B7-H3

PD-L1 is a type I trans-membrane protein consisting of one IgV and one IgC domains [1]. The expression of mRNA encoding PD-L1 has been found in all normal tissues in humans and mice. However, constitutive expression and location of PD-L1 protein on cell surface are rare and have been found in only a fraction of

tissue macrophages-like cells in the liver, lung or tonsil [2]. PD-L1 is expressed on dendritic cells (DCs), macrophages, B cells and T cells. For non-hematopoietic cells, vascular endothelium epithelia, liver pancreatic islets, placenta and eye express surface PD-L1. Aberrant PD-L1 is expressed on a broad spectrum of cancers. Interferons (α , β and γ) are the potent inducers for PD-L1 expression.

B7-H3 is a type I trans-membrane protein with its sequence similarity to the extracellular domain of other B7 family members. Murine B7-H3 contains one IgV and one IgC domains [3,4]. In humans, but not mice, B7-H3 has an alternate isoform containing a tandem repeat of IgV and IgC domains (VCVC) and this isoform is the more common form expressed [4]. B7-H3 is widely expressed in both lymphoid and nonlymphoid organs at RNA level, but the expression of B7-H3 protein is more restricted to cell types such as activated DCs, monocytes, T cells, B cells, and NK cells. IL-10 regulates B7-H3 expression in cancerous cells. Tumor-Associated Macrophage (TAM)-derived IL-10 was shown to upregulate B7-H3 expression on murine lung cancerous cells. In particular, coculture with regulatory T cells, IFN γ , LPS, or anti-CD40 in vitro stimulation all induces the expression of B7-H3 on DCs. Recent studies found that aberrant B7-H3 was expressed on a wide variety of cancers.

The Receptors for B7-H3 and PD-L1

The receptors for PD-L1 have been found to be PD-1 and CD80. PD-1 belongs to CD28 family and it has a cytoplasmic Immunoreceptor Tyrosine-Based Inhibitory Motif (ITIM), as well as an immunoreceptor tyrosine-based switch motif (ITSM) that has been found to be capable of recruiting the phosphatases SHP-1 and SHP-2 [5]. PD-1 is inducibly expressed on CD4⁺ and CD8⁺ T cells, NKT cells, B cells and monocytes upon activation [6].

Hashiguchi et al. found that murine and human B7-H3 can specifically bind to Triggering Receptor Expressed on Myeloid cells (TREM)-like Transcript 2 (TLT-2) and this interaction enhances T cell responses. However, these findings cannot be repeated by several other labs. Thus, the receptor(s) for B7-H3 has not been conclusively identified until now. B7-H3-Ig protein binds a counter-receptor on activated T cells [3,4], indicating that its putative receptor is expressed on activated T cells. Moreover, Zhang and colleagues [7] found that a putative

receptor for B7-H3 was detected on monocytes and peritoneal macrophages from septic patients but not on monocytes from healthy donors, suggesting that its receptor on monocytes and macrophages is induced by disease environment.

The Roles of PD-L1 and B7-H3 in T Cell Responses

The interaction between PD-L1 and PD-1 upon TCR activation leads to phosphorylation of PD-1, which recruits the phosphatase SHP-2 to shut down the TCR-mediated activation of PI3K-Akt and Ras-MEK-ERK pathways and TCR-mediated activation of T-bet/STAT1 by dephosphorylation, thus resulting in arrest of cell cycle progression and inhibition of effector function of T cells [8-10]. It is beyond question that PD-L1 signaling strongly inhibits T cell responses. The interaction of PD-L1 and PD-1 not only dampens T cell immunity, but also correlates with carcinogenesis and cancer progression. Current data indicate that this pathway mediates inhibitory signals in T cells and anti-apoptotic signals in the tumor cells in tumor site with minimal expression in other organs, which has been proposed as one of the major mechanisms of tumor immune escape [11].

The ligation of B7-H3 with its unidentified receptor(s) induces T cell activation as well as T cell inhibition in human and mouse system. This could be explained by that B7-H3 has more than one putative receptor, one for T cell activation and the other for T cell inhibition. Thus, it is quite urgent to be determined whether this hypothesis is true and identify B7-H3 signaling pathways.

The Sites of PD-L1 and B7-H3 in Tumor Evasion

Both B7-H3 and PD-L1 are expressed on myeloid cells as well as tumor cells. However, the inhibitory signaling to T cells to promote tumor evasion comes mainly from PD-L1 on tumor cells, not from host immune cells. Recent finding from Arlene sharpe group [13] strongly suggests that PD-L1 on tumor cells is sufficient for immune evasion in immunogenic tumors and inhibits CD8⁺ T cell cytotoxicity. In our recently published paper, B7-H3-deficient mice showed reduced growth of multiple tumors and anti-B7-H3-treated KO mice had similar tumor growth as the B7-H3 KO mice, suggesting that it is B7-H3 expressed on host immune cells that exerts its pro-tumor capacity. All suggest that B7-H3 might control neo-antigen-specific T cell activation during cognate interactions between antigen-presenting cells (APCs) and T cells in secondary lymphoid organs, while PD-L1 suppress effector T cell responses in Tumor Microenvironments (TMEs). The immunological roles of PD-L1 and B7-H3 are non-redundant in anti-tumor immunity.

PD-L1/PD-1 Inhibitors and B7-H3 Inhibitors

PD-L1 inhibitors and PD-1 inhibitors have been generated to block PD-L1/PD-1 signaling pathway, leading to normalized effector functions. Both inhibitors have shown great clinical

success in patients with a variety of cancers. So far there is no clinically significant difference observed between PD-1 antibodies and PD-L1 antibodies approved by FDA in terms of adverse event profiles. Slightly higher rates of infusion reactions were detected with PD-L1 antibody (BMS-936559) than PD-1 antibody (BMS-96558) [12]. In terms of antitumor activity, both anti-PD-1 and anti-PD-L1 antibodies have shown responses in overlapping multiple tumor types.

Several anti-B7-H3 antibodies have been used in clinical trials, although B7-H3 binding partner(s) remains unknown. One of those antibodies, MGA271, mediates potent antibody-dependent cellular cytotoxicity against a broad range of tumor cell types, which is being tested in several phase I/II clinical trials. The safety of MGA271 in combination with pembrolizumab (anti-PD-1 antibody) is in a clinical trial (NCT02475213), which is given to patients with B7-H3-expressing melanoma, SCCN, NSCLC, and other B7-H3 expressing cancers. We are looking forward to the result and hope they will produce synergistic anti-tumor effect.

Conclusion

Recently PD-1/PD-L1 inhibitor therapy in cancer patients results in VISTA upregulation [14], another immune checkpoint, which might be one of the adaptive resistances for PD-L1/PD-1 inhibitors. It is yet to be determined that PD-L1/PD-1 inhibitor therapy can upregulate B7-H3 expression. Although PD-L1 and B7-H3 have similar expression patterns, they function in different sites to promote cancer progression (Table 1), suggesting they are non-redundant in tumor evasion. Thus, combination of PD-L1/PD-1 inhibitors and B7-H3 inhibitors can result in synergistic anti-tumor effect theoretically. In addition, our data strongly suggests that blocking PD-L1/PD-1 signaling pathways and B7-H3 signaling pathways achieve synergistic benefits in murine cancer models. Before this finding is translated to the treatment of human cancer, it is pretty crucial to find B7-H3 receptor(s) in order to better explain the involvement of its pathway in immune responses and cancer development.

Table 1: Comparison of PD-L1 and B7-H3.

Immune Checkpoints	Structure	Expression		Sites of action
		Ligand	Receptor	
PD-L1	IgV-IgC	APCs, tumor cells	PD-1, CD80	Tumor
B7-H3	IgV-IgC-IgV-IgC or IgV-IgC	APCs, tumor cells	Unknown	Lymphoid organ

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Disclosure of Potential Conflicts of Interest

The authors declare that there are no conflicts of interest to disclose.

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