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Non-Redundant Roles of New Immune Checkpoints in Cancer Evasion

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Commentary

Although FDA-approved inhibitors of immune checkpoints have made great success in the treatment of advanced cancer patients, the patient response rates are still low in most cases. It is quite urgent to explore the role of new checkpoint pathways in cancer immunity. Recently we reviewed three new inhibitory B7 family checkpoint molecules, B7-H3, B7S1 and VISTA. In this article, we compare their expression patterns and the sites of action. More importantly, non-redundant roles of new immune checkpoints in cancer evasion are also discussed (Table 1).

T cell activation is fine-tuned by co-stimulatory or co-inhibitory receptors to amplify or dampen TCR signal, respectively. Tumor cells have exploited this to escape immune attack via overexpressing surface ligands of those co-inhibitory receptors (also known as immune checkpoints). The Immune checkpoint blockade has already become one of cancer therapies, which represent a new, efficient alternative to the standard management for multiple cancer types. Ipilimumab is a human monoclonal antibody against CTLA-4 and FDA approved it for the treatment of metastatic melanoma in 2011 on the basis of survival benefit [1]. Nivolumab, pembrolizumab and atezolizumab, which inhibit PD-1/PD-L1 signaling pathway, have also been approved by FDA to treat advanced patients with certain cancer types [2-4]. However, the patient response rates are low in most cases. Moreover, combinational blockade of CTLA-4 and PD-1 gives rise to better efficacy than single inhibitor in melanoma [5] and lung cancer [6], implying that blocking single immune checkpoint is not sufficiently effective and combinatorial targeting of immune checkpoints is highly required. Thus, it is quite necessary to explore the role of new immune checkpoint pathways in cancer immunity.

Recently we reviewed three new inhibitory B7 family checkpoint molecules, B7-H3, B7S1 and VISTA [7]. Both B7-H3 and B7S1 are expressed on myeloid cells as well as tumor cells, while VISTA is predominantly expressed within myeloid compartment, not by tumor cells. The difference in expression patterns suggests that VISTA might control neo-antigen-specific T cell activation during cognate interactions between antigen-presenting cells (APCs) and T cells in secondary lymphoid organs. B7-H3 and B7S1, in addition to providing inhibitory signals to T cells in the lymph nodes, which is similar to VISTA, they also suppress effector T cell responses in tumor microenvironments (TMEs). Therefore, B7-H3 inhibitors as well as B7S1 inhibitors enable effector T cells to directly recognize and kill tumor cells, but not VISTA inhibitors. The immunological roles of VISTA and B7-H3 or B7S1 are non-redundant in anti-tumor immunity.

Besides membrane isoforms, B7-H3 and B7S1 also exist in soluble forms, which are generated by proteases. The levels of serum B7-H3 and B7S1 are pretty high in patients with some types of cancers, indicating that they might be a valuable blood marker for predicting the progression and prognosis of those cancer patients. Interestingly, soluble B7S1 is a decoy molecule to block the inhibitory functions of membrane B7S1 [8], implying the potential of soluble B7S1 in the treatment of cancer patients. Whether soluble B7-H3 is a decoy molecule is needed addressing. So far, serum VISTA has not been reported.

Immune Checkpoints	Expression		Expression	
	Ligand	Receptor	Isoform	Sites of action
B7-H3	APCs, tumor cells	Activated T cells, Mo and MØ	Membrane;	Lymphoid organ,
			Soluble	Tumor
B7S1	APCs, tumor cells	Activated T cells, MDSCs	Membrane;	Lymphoid organ,
			Soluble	Tumor
VISTA	APCs, T cells	Activated T cells	Membrane	Lymphoid organ,

Table 1: Comparison of new immune checkpoints

In addition to APCs, tumor cells express B7-H3 and B7S1. The mechanisms that regulate the expressions of B7-H3 and B7S1 in tumor cells are poorly understood. B7-H3 in kidney cancers can directly regulated by miRNA-187, while B7-H3 in osteosarcoma and colorectal cancers is a direct target of miRNA-124 and miRNA-143, respectively. B7-H3 in prostate cancer is directly regulated by androgen receptor. Therefore, it is highly warranted to validate which factors are involved in regulating B7-H3 expression in other cancer types. Functionally, B7-H3 in/on tumor cells promotes tumor progression. Lung cancer-expressing B7-H3 modulates abnormal lipid metabolism via FASN [9], and B7-H3 in breast cancer and melanoma promotes aerobic glycolysis [10]. Furthermore, colorectal cancer-expressing B7-H3 promotes EMT by activating the PI3K-Akt pathway and upregulating Smad1 expression [11]. B7S1 expressed in/on tumor cells has been proposed to promote epithelial cell transformation in ovarian, breast, lung and esophageal carcinoma. In cervical cancer, B7S1 promotes oxygen consumption rate, ATP production, and mitochondrial membrane potential and mass, which suggest that B7S1 expressed in cervical cancer has a role in the regulation of mitochondrial function. Taken together, B7-H3 and B7S1 not only play immunologic roles in suppressing T cell activation, but also non-immunological roles in promoting tumor growth. However, the non-immunological roles of B7-H3 and B7S1 in tumor progression are quite different based on the

above evidences, indicating that they function non-redundantly in tumor evasion.

The binding partners of those three immune checkpoints have not been identified yet. All these three can bind its corresponding counter-receptor on activated T cells to suppress T cell activation. It is beyond question that both B7S1 and VISTA provide inhibitory signals to T cells. However, the effect of B7-H3 on T cells is controversial. It was reported that B7-H3 has a co-stimulatory effect and a co-inhibitory effect on T cell activation, which may be explained by more than one receptor on T cells for B7-H3. In addition to activated T cells, B7-H3 can also bind to monocytes and peritoneal macrophages from septic patients [12] while B7S1 is able to bind to MDSCs. These indicate that B7-H3 signaling can regulate the function of monocyte and macrophage while B7S1 signaling has an effect on MDSCs. It is of note that VISTA also functions as co-inhibitory receptor expressed on T cells, indicating it can directly transduce inhibitory signals to T cells [13]. Nonetheless, their binding counter-partners are seriously needed to be identified before we understand the actions of these pathways in T cells and other immune cells.

B7-H3, although, has a coinhibitory function and a costimulating function on T cells, antibodies targeting B7-H3 are being tested in a phase I/II clinical trials. B7S1, no targeting antibodies have been investigated in any disease indication clinically, but it remains a high priority candidate in cancer immunotherapy. In the CT26 colon cancer model, targeting VISTA and PD-L1 simultaneously achieve optimal tumor-clearing therapeutic efficacy, whereas targeting each molecule alone was less effective [14]. Right now we are looking forward to the result from the clinical trial about CA-170 (NCT02812875), which can target the PD-L1/PD-L2 as well as VISTA checkpoints. Hopefully CA-170 treatment results in optimal efficacy.

Conclusion

Those three B7 immune checkpoints act non-redundantly to help cancer cells escape from immune surveillances. They show different expression patterns and different sites of actions. B7-H3 and B7S1 are expressed on APCs and tumor cells, while VISTA is expressed on APCs and T cells. Therefore, VISTA mainly suppresses T cell activation in secondary lymphoid organs, resulting in suppression of T cells. In contrast, B7-H3 and B7S1 can disable effector cells to recognize and kill tumors in the TMEs, leading to cancer evasion. Furthermore, tumor-expressing B7-H3 and B7S1 have different non-immunological roles in tumor progression. PD therapy (PD-1 inhibitors and PD-L1 inhibitors) has made big success in treatment of wide spectra of cancers, but there are still 60-80% of patients who don't respond to it. Whether combinatorial targeting of other immune checkpoint can help those non-responding patients needs to be further investigated. This series of study will ultimately unleash the power of the immune system and improve clinical responses in cancer patients.

Conflicts of Interest

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

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