



B7 Gene Family: Promising Immunotherapeutic Checkpoint in Cancers

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Abstract

The B7 gene family plays critical roles in regulating adaptive cellular immunity by either co-stimulating or co-inhibiting T cell functions. And the oncogenic roles of B7 family have already been identified in various cancers, with the immune checkpoint inhibitors of PD-L1/PD-1 and CTLA-4/B7 being successfully applied in cancer treatment.

Introduction

The B7 gene family was reported to play critical roles in regulating adaptive cellular immunity by either co-stimulating T cells after selectively binding to T cell ligands of CD28 and CD28H or co-inhibiting T cells after binding to cytotoxic T lymphocyte-associated protein 4 (CTLA-4) and programmed cell death-1 (PD-1). Of all its ten members in B7 family, B7-H2, B7-H6 and B7-H7 were described to stimulate activation of naive T cells and B7-DC, B7-H4 and B7-H5 were found to inhibit T cell response, whereas B7-1 and B7-2 were demonstrated to provide both stimulatory and inhibitory signals [1]. Due to their contributive roles in adaptive cellular immunity, B7 members have gained more and more attention in triggering cancerous development especially at the aspects of immune evasion, as cancer development was to some extent thought to be attributed to disturbance of immune surveillance [2]. Wu S et al. [3] reported that overexpression of B7-H3 correlates with aggressive clinicopathological characteristics in non-small cell lung cancer and Wu L et al. [4] showed that B7-H4 was extremely overexpressed in oral squamous cell carcinoma (OSCC) and also indicated a poor prognosis of low overall survival rates, which firmly identified the role of B7 family in the pathogenesis of tumor formation. Besides the role of promoting cancer development, B7 family members were also reported to induce drug resistance, for example B7-H1 (PD-L1)/PD-1 interaction induced chemotherapeutic resistance in myeloma probably through the PI3K/AKT signaling pathways [5].

Our previous studies used existing and publically available data from cBioPortal to investigate various aspects of B7 family members and their corresponding receptors in various cancers, and finally depicted the vigorously oncogenic roles of B7 family in breast cancer as it demonstrated the highest amplification. We found out that all the 10 members in B7 family were over-expressed in breast cancer [1] at varying frequencies, which were consistent with existing reports in other cancers. Amplification of B7 members in breast cancer was actually related to gene amplification and/or DNA methylation as described in our studies. Yet other mechanisms mediating upregulation of B7 members in breast cancer should also be carefully clarified, for example the proto-oncogene Myc was reported to bind to the promoter of B7-H6 to amplify its expression [6]. Importantly, among all the B7 family members, only B7-H6 gene amplification was significantly associated with worse overall survival in breast cancer patients [1], perhaps by binding to its corresponding receptor NKp30 on NK cells and impairing NK cell-dependent interferon-gamma (IFN γ) production and cytolytic function [7]. However, this needs further experimental identification.

As for their proto-oncogenic roles in various carcinogenesis process especially to induce immune evasion by suppressing T-cell function, immune checkpoints of B7 family got considerable attention in the context of anticancer immunotherapy. Immunotherapy with antibodies against B7-CD28 family members, including PD-L1/PD-1 and CTLA-4/B7 (B7-1, B7-2), were already introduced into cancer treatment and reported to shift treatment paradigm with improved clinical outcome in various solid cancers such as NSCLC [8]. Nicolazzo C et al. [9] intriguingly found out that Non-Small-Cell Lung Carcinoma (NSCLC) patients with PD-L1-negative Circulating Tumor Cells (CTCs) all obtained a clinical benefit after treatment, while patients with PD-L1 positive CTCs

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all suffered progressive disease, which indicated a therapeutic escape in PD-L1 positive NSCLC cells. Another study, however, indicated that activation of PD-L1-specific T cells may directly modulate immunogenicity of dendritic cell (DC)-based cancer vaccine. In that case PD-L1 epitopes could be co-applied to augment the effectiveness of cancer vaccines and other immunotherapeutic agents [10]. Thus, it's too complicated to simply describe the role of PD-L1/PD-1 axis in cancerous immunotherapy, and many studies should be conducted to take into consideration of cancerous backgrounds.

Several antibodies against PD-L1/PD-1 axis and CTLA-4/B7 axis have already been put into clinical trials, and some reported results really excited physicians and patients. Anti-PD-L1 antibodies (BMS-936559 and avelumab) and anti-PD-1 antibodies (nivolumab and pembrolizumab) were all reported to be applied to ovarian cancer patients at different trial stages, and varying benefits including Complete Response (CR) and Partial Response (PR) were observed in patients [11]. Ipilimumab and tremelimumab were two kinds of anti-CTLA4 antibodies. In a pivotal, randomized, double-blind phase III study conducted in 2010, ipilimumab, regardless of the presence or absence of the gp100 peptide vaccine, improved overall survival in patients with unresectable stage III or IV melanoma, with a 1-year survival rate of 46% for ipilimumab alone versus 25% for gp100 alone. On the other hand, remelimumab failed to confer a statistically significant survival advantage over standard-of-care chemotherapy in a phase III trial in patients with advanced melanoma [11]. Besides their anti-cancerous benefit in treatment, studies also emphasized their adverse immunological effects. Thus patients accepting B7-CD28 immune checkpoint inhibitors treatment should be carefully evaluated in order to achieve a maximum anti-tumor effect with a minimum treatment period to lower adverse effects.

Conclusion

B7 family members played irreplaceable roles in cancerous development, especially at the aspect of immune evasion, and the immune checkpoint inhibitors of B7-CD28 pathways provided new visions of anti-cancer strategies.

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