B7-H4 is a positive regulator of antitumor immunity

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Members of the B7 family of molecules provide positive or negative signals that modulate T cell function. Notably, the co-inhibitory molecules CTLA-4 and PD-1 that bind to B7-1 (CD80) and B7-2 (CD86) or PD-L1 (B7-H1/CD274) and PD-L2 (B7-DC/CD273), have proven to be important targets for cancer immune therapy. Melanoma and non-small cell lung cancer patients treated with antibodies specific for either CTLA-4 or PD-1 show encouraging responses that approximately range between 20–35%. Therefore, it is critical to evaluate the role of other B7 family members as candidates for new therapeutic targets.

B7-H4 is a member of the B7 superfamily that negatively regulates T cell responses. In addition, B7-H4 expression is increased on tumors and has been shown to be a negative prognostic marker for many cancers. Unexpectedly our recent study demonstrated that B7-H4 inhibited tumor growth and was required to promote effective antitumor responses.

We also generated WAP-gp/MMTV-PyMT and RIP-gp/Tag2 mouse models, which expressed the lymphocytic choriomeningitis virus (LCMV) glycoprotein (gp) as a defined endogenous antigen. This provided a target molecule and the opportunity to use LCMV as a live viral vaccine for the induction of an antitumor response. We confirmed that B7-H4 had a negative regulatory role on T cells during LCMV infection but unexpectedly showed that B7-H4 was a positive mediator of vaccine induced antitumor immunity.

To determine if B7-H4 expression was critical on hematopoietic or non-hematopoietic cells, bone marrow chimeric mice were generated. Our results demonstrated that B7-H4 expression by the non-hematopoietic compartment was critical for an efficient antitumor immune response. This suggests a new role for B7-H4 expression on the tumor tissue for promoting antitumor immunity.

We observed a correlation between B7-H4 and the expression of major histocompatibility complex I (MHC I) in both mouse mammary tumors and primary human breast cancer samples. In mice, the absence of B7-H4 coincided with reduced MHC I expression. Notably, there was a decrease in Granzyme B expression in CD8+ T cells infiltrating tumors lacking B7-H4. Furthermore, experiments suggested that the expression of MHC I and B7-H4 were linked, as siRNA knockdown of B7-H4 in tumor cell lines resulted in downregulation of MHC I. Our work also demonstrated that IFNγ can induce the upregulation of B7-H4 in vitro, and...
that this was dependent upon T or NKT cells \textit{in vivo}.

Previous studies also suggested a role for other cytokines including IL-6 and IL-10 in inducing B7-H4 expression in immune cells.\textsuperscript{7} Recent findings demonstrate that hypoxia induces B7-H4 expression in cancer cell lines in an hypoxia-inducible factors (HIF)-1\textalpha-dependent manner. Notably, analysis of publicly available gene expression datasets of 414 patients with multiple myeloma showed that B7-H4 expression was positively correlated with the expression CA-9, an endogenous hypoxia marker.\textsuperscript{8} Although the mechanism of B7-H4 upregulation in cancer cells is not fully understood, these data suggest a role for stress signals in the tumor microenvironment in regulating B7-H4 expression. B7-H1 (PD-L1) was also shown to be induced by IFN\textgamma\textsuperscript{9} as well as under hypoxic condition through HIF-1\textalpha\textsuperscript{10} in cancer cells. These results support the concept that stress signals could be important inducers of members of the B7 family in different tumor settings.

Our data demonstrated that B7-H4 expression by non-hematopoietic cells in the tumor microenvironment is essential for optimal antitumor immune responses. This is in contrast with the negative regulatory role in T cell responses that has been defined for B7-H4. It is possible that B7-H4 may have at least two independent receptors that signal different outcomes and are differentially expressed under certain conditions. Further studies are required to understand the molecular mechanisms that define how the B7 family of molecules regulate immunity.

\textbf{Disclosure of Potential Conflicts of Interest}

No potential conflicts of interest were disclosed.

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