IDENTIFYING THE ROLE OF B7-H4 AS A SUPPRESSOR OF TUMOR INFILTRATING LYMPHOCYTES AND A TARGET FOR IMMUNOTHERAPY IN BREAST CANCER

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Background Immune checkpoint inhibitors (ICI) have improved patient survival in some cancer types but yielded limited success in breast cancer. Combinations of ICI (α PD-L1/PD-1) and chemotherapy have been FDA-approved for metastatic TNBC patients, and potentially in the early breast cancer setting, but many patients remain non-responsive to ICI. B7-H4 is a B7 family ligand with proposed immunosuppressive functions being explored as a cancer immunotherapy target and may be associated with resistance to α PD-L1. We confirmed an inverse expression pattern between B7-H4 and PD-L1 in breast tumor cells, which has previously been noted by others. B7-H4 was expressed in immune-excluded tumors, while PD-L1 was expressed in immune-infiltrated tumors. Based on these findings, we hypothesized ectopic B7-H4 expression would induce α PD-L1 resistance through immune cell suppression in vivo.

Methods Using an immunocompetent and α PD-L1-sensitive EMT6 orthotopic mammary cancer model, we induced ectopic expression of B7-H4 and performed animal survival studies to assess therapy response, and RNA analysis to assess changes to cell signaling among tumor infiltrating immune cells. Finally, we performed transcriptomic correlation analyses from the cancer cell line encyclopedia dataset to identify potential regulators of B7-H4 in breast cancer.

Results In the α PD-L1-sensitive EMT6 mammary cancer model, tumors with cell-surface B7-H4 expression were more resistant to immunotherapy. Additionally, tumor infiltrating immune cells had reduced immune activation signaling based on transcriptomic analysis. We also observed strong correlation with B7-H4 mRNA and epithelial cell markers, in contrast to gene expression markers of mesenchymal cells.

Conclusions Our data support the hypothesis that B7-H4 induces tumor resistance to α PD-L1 ICI through an immunosuppressive function. Additionally, the strong correlation of B7-H4 to epithelial cell markers suggests a potential regulatory mechanism of B7-H4 expression independent of PD-L1 regulation.

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