Evaluating the role of B7-H4 as a suppressor of tumor infiltrating lymphocytes and a target for immunotherapy in breast cancer

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Abstract

- Immunotherapy has seen broad success across cancer types and has become a key aspect of TNBC treatment, but some patients fail to respond.
- B7-H4 (VTCN1) is an alternative immune checkpoint ligand in the CD28/B7 family of molecules, like PD-L1.
- We observed both high and low B7-H4 expression on several mammary cancer cell lines.
- B7-H4 is exclusively expressed on cells bearing epithelial markers.
- mRNA expression data from a variety of human breast cancer cell lines corroborate this strong positive correlation of B7-H4 expression on epithelial cells.
- B7-H4 may act as an alternative mechanism of immunologic escape in breast cancer.

Background

(A) We quantified CD8 T cell infiltration as described by Guresco et al. J Clin Invest. 2019. (B) We found both low and high B7-H4 expression in TNBC tumors. (C) B7-H4 expression was more often on the MR and ID tumors. (D) Tumors with high B7-H4 expression had worse overall survival. (E) We performed digital spatial profiling to identify protein expression in different regions of interest (ROI) and found PD-L1 and STING expression on tumor cells in a subset of SR tumors. We also found EpCAM expression on MR tumors, and CD44 expression on SR tumors. Data generated by Paula Gonzalez-Ericcson, M.D.

B7-H4 is expressed on EpCAM+ murine mammary cancer cells

(A) We screened a panel of murine mammary cancer cell lines and found both high and low expression of B7-H4. (B) Those cells that were B7-H4+ were also EpCAM+ in multiple cell lines.

B7-H4 expression is not regulated by interferon

(A) We investigated models of enforcing cell transition into EMT and measured expression of B7-H4. (B) When these cell populations were separated by differential trypsinization, we found only the epithelial cells expressed B7-H4. (C) These data were further confirmed by quantitative PCR of the heterogenous, epithelial, and mesenchymal cells, compared to an EMT6 negative control.

Conclusions & Future Directions

- Immunotherapy has seen broad success in a variety of tumor types, including breast cancer.

- B7-H4 is expressed in breast cancers and correlates with epithelial markers.

- B7-H4 expression is not regulated by interferon stimulation, unlike PD-L1, but may be regulated by mesenchymal to epithelial transition in tumors.

- I will investigate models of enforcing cell transition into EMT and measure changes in B7-H4 expression.

To determine whether B7-H4 is an alternative mechanism of immunologic escape in breast cancer, I will test whether enforced expression of B7-H4 causes EMT6 tumors to be resistant to anti-PD-L1 immunotherapy in vivo.