Blockade of TIGIT-PVR Axis can Treat Breast Cancer

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This review covers the identification and application of anti-TIGIT antibodies as checkpoint inhibitors for the treatment of triple-negative breast cancers. The original article, *Targeting the TIGIT-PVR Immune Checkpoint Axis as Novel Therapeutic Option in Breast Cancer*, was published by Stamm et al. in Oncoimmunology in October of 2019.[1]

Checkpoint blockade with antibodies targeting cytotoxic T-lymphocyte-associated protein 4 (CTLA4) and programmed cell death protein -1 (PD-1) has recently been approved by the FDA as a treatment for a variety of malignancies.[2,3] These studies have inspired several groups to evaluate additional checkpoint inhibitors to identify additional therapeutic options for cancer treatment.[4] T cell Immunoreceptor with Ig and ITIM domain (TIGIT) are one such new target for cancer immunotherapy. TIGIT is expressed on activated T cells, natural killers, and regulatory T cells. TIGIT binds to poliovirus receptor (PVR) ligands that are expressed on tumor cells and Antigen Presenting Cells (APCs) in the tumor microenvironment.[5] PVR initially binds to DNAX Accessory Molecule-1 (DNAM-1), a co-stimulatory receptor, that activates immune responses. However, TIGIT's high binding affinity to PVR outcompetes its binding to DNAM-1 thereby interrupting the co-stimulatory response and subverting both adaptive and innate immune responses.[6,7]

Specifically, this study examines how PVR expression correlates with the prognosis of triple-negative breast cancer and patient survival. Stamm et al., evaluated 197 tumor samples of breast cancer patients using microarray analysis tools. Each probe set analyzed was divided into cohorts representing Low, Moderate-Low, Moderate-High, and High levels of PVR levels. Correlation analysis demonstrated the association of high PVR protein expression with higher tumor grading, estrogen receptor (ER)- and progesterone receptor (PR)- negativity, and nodal involvement. Additional analysis showed that PVR mRNA levels were also significantly higher in ER- and PR-negative breast cancers and as well as in human epidermal growth factor receptor (HER2)-positive and triple-negative tumors in comparison with luminal subtypes. Further, the analysis revealed that high PVR mRNA levels were associated with shorter patient survival and shorter recurrence-free intervals. These results were verified by using two publicly available breast cancer patient cohorts where high PVR expression levels were associated with a poorer overall survival as well as a recurrence-free interval in both datasets.

The authors tested if PVR mRNA levels correlated with protein levels in breast cancer samples by analyzing protein expression in subgroups of breast cancer with a western blot analysis and used acute myeloid leukemia (AML) cell line MV4-11 as a reference. Stamm et al. found a positive correlation between PVR mRNA levels and protein. The results from this experiment were similar to the data obtained from the microarray data. The authors observed high levels of PVR in samples with high grading, ER- and PR- negativity, and in HER2 and triple-negative breast cancer (TNBC) subtypes of breast cancer. Eight different cancer cell lines were observed to have high expression of surface-expressed PVR by flow cytometry. In addition, PVR expression is high in HER2 positive, triple negative basal B, and triple-negative basal A subtypes of breast cancer. Stamm et al., evaluated the impact that an antibody blockade has on PVR expressed on breast cancer cells as well as the impact that an antibody blockade has on the receptor TIGIT on allogeneic immune cells from healthy donor peripheral blood mononuclear cells (HD-PBMCs) in *in vitro* cytotoxic assays. These tests revealed that the addition of blocking anti-PVR or anti-TIGIT antibodies enhanced the cytotoxic effect of immune cells on HER2 positive SKBR3 cell lines and the triple negative cell line MDA-MB-231.

This study shows that high expression of the PVR ligand is strongly associated with poor patient survival and recurrence-free survival in 197 cancer patients as well as a strong association with more aggressive breast cancer subtypes. The finding suggests that the checkpoint molecule PVR is a novel prognostic marker in breast cancer and the blockade of the PVR-TIGIT axis might become a possible novel therapeutic option for the treatment of breast cancer. Future work to explore this potential should focus on analyzing whether blockade of TIGIT in an autologous setting with corresponding tumor-infiltrating lymphocytes in primary breast cancer cells shows the predicted efficacy.

As noted by the authors, preclinical data are always subject to the limitations of their model systems, but the efficacy of other checkpoint inhibitors does raise hopes that these results may point to the introduction of new meaningful players in cancer immunotherapy.

References

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