TIGIT-PVR IS A KEY IMMUNE CHECKPOINT AND THERAPEUTIC TARGET IN HPV-POSITIVE HEAD AND NECK SQUAMOUS CELL CARCINOMAS

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Background Human papillomavirus (HPV)-positive head and neck squamous cell carcinoma (HPV+ HNSCC) is a disease that has moderate response to anti-PD-1/L1 immune checkpoint blockade, with the response rates less than 20% and median progression-free survival less than 3 months. A greater understanding of tumor intrinsic and extrinsic factors that restrict anti-tumor immunity in the tumor immune microenvironment (TIME) is needed to identify other immune checkpoints to enhance therapeutic efficacy.

Methods Two cohorts (TCGA n=72 and a separate cohort n=84) of surgically resected, treatment-naïve HPV+ HNSCC with RNA-seq were analyzed to understand the immune features. In addition, single-cell RNA-seq and TCR-seq were performed on 18 cases to further delineate the immune molecules' interactions. An immune-competent murine HPV+ HNSCC model was used to preliminarily evaluate the therapeutic efficacy.

Results In two bulk-sequenced HPV+ HNSCC cohorts, TIGIT ligands PVR and NECTIN2 were found to associate with an epithelial-to-mesenchymal gene expression signature, suppression of IFN α and IFN γ signaling, a stromal-enriched or immune-excluded TIME, and poor survival. Single-cell RNA-seq of over 72,000 cells of HPV+ HNSCC revealed that the PVR/NECTIN ligand TIGIT was highly prevalent in T-cells (34%), significantly higher than PD1- (20%, $p<0.01$). There is an enrichment of cell-cell interactions mediated by TIGIT-PVR/NECTIN2 in the TIME of HPV+HNSCC versus normal tonsil. TIGIT was the most differentially upregulated immune checkpoint on clonally expanded CD8+T-cells and was abundant on antigen-experienced, tissue-resident memory CD8+T-cell and T-regulatory subsets. TIGIT ligands PVR, NECTIN1, and NECTIN2 were abundant on mature regulatory dendritic cells (DCs), immunosuppressive plasmacytoid (p)DCs, and macrophages, respectively. TIGIT and PD-1 co-blockade in the mEER syngeneic murine model significantly reduced tumor growth, improved survival, restored effector function of HPV16E7-specific CD8+T cells, natural killer cells, and DCs, and conferred tumor re-challenge protection.

Conclusions TIGIT-PVR/NECTIN receptors/ligands are more abundant than PD-1/L1 in the TIME of HPV+ HNSCC. Co-blockade of TIGIT and PD-1 immune checkpoints enhanced anti-tumor efficacy in a CD8+ T-cell-dependent manner and conferred long-term immune protection in a murine model. Our study nominates TIGIT as a therapeutic target for HPV+ HNSCC.

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