PVRIG Is Uniquely Expressed in Tumor Dendritic Cell-rich Niches on Stem-like Memory T Cells and Its Blockade May Induce Immune Infiltration and Activation in Non-inflamed Tumors

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Poorly immune infiltrated cancers pose a significant challenge, with current immunotherapies yielding limited clinical success. Stem-like memory T-cells (T_{SCM}) have been identified as a T-cell subgroup which possesses enhanced proliferative capacity that could expand and differentiate upon priming by dendritic cells (DCs). In this study we investigated the expression of the recently discovered inhibitory receptor PVRIG and its ligand, PVRL2, in the tumor microenvironment (TME).

Leveraging single cell RNA sequencing (scRNAseq) data from diverse cancer indications, we found that in CD8+ T-cells, PVRIG clusters with early differentiation/T_{SCM} genes, unlike other immune checkpoints that cluster with genes related to T-cell exhaustion. In agreement with the scRNAseq data, PVRIG protein expression was increased on CD28+CD8+ early-memory T-cells across cancer indications. Next, we demonstrated that PVRL2, beyond its acknowledged expression on tumor, endothelial, and myeloid cells, exhibits significant expression on intratumoral DC subsets at both scRNA and protein levels. This underscores a novel facet of its expression, potentially impeding the priming of PVRIG+ T-cells.

The observation that PVRIG is uniquely expressed by T_{SCM} cells, and PVRL2 by DCs, led us to evaluate whether these cell populations physically co-localize in the TME, thus potentially allowing PVRIG/PVRL2 interaction. Employing spatial transcriptomic analysis in surgically resected CRC lesions we showed that while CTLA4, PD1, and TIM3 were mainly expressed by tumor infiltrating T-cells, PVRIG and other genes of the DNAM-1 axis were intensely expressed by T_{SCM} in specialized immune aggregates, as well as by T-cells in tumor bed. High resolution spatial mapping of interacting immune and adjacent cells revealed pairs of activated LAMP3+PVRL2+ DCs interacting with CD28+PVRIG+CD8+ T-cells in the intratumoral immune aggregates. Thus, PVRIG/PVRL2 interaction may limit T_{SCM} priming by DCs and blocking this interaction may unleash potent T_{SCM} proliferation, differentiation, and infiltration into tumor regions.
Next, to gain a more comprehensive understanding on the effects induced by PVRIG blockade, we evaluated the immune response in the TME of patients with platinum resistant ovarian cancer and MSS-CRC, treated with the anti-PVRIG antibody, COM701. These two indications are considered less infiltrated, and typically patients with PROC or MSS-CRC display poor response rates to immune checkpoint inhibitors. Treatment with COM701 as monotherapy or in combination with nivolumab resulted in an elevated expression of IFNγ signature genes and of PD-L1 in the TME, and increased tumor CD8+ T-cell infiltration which was accompanied by TCR clonality expansion. Moreover, this immune modulation was associated with clinical benefit. In summary, our study identifies PVRIG as uniquely expressed on T_{SCM} in the TME, with its ligand PVRL2 expressed on activated DCs. Blockade of PVRIG/PVRL2 interaction by COM701 antibody emerges as a promising strategy to induce potent T-cell responses, providing a novel approach overcoming resistance to immunotherapy in immune excluded tumors.