PVRIG is uniquely expressed in tumor dendritic cells-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 possess enhanced proliferative capacity that could expand and differentiate upon dendritic cells (DCs) priming. 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 cells exhaustion. In agreement with the scRNAseq data, PVRIG protein expression was markedly increased on $CD28^+CD8^+$ early-memory T cells across cancer indications. PVRL2, was dominantly expressed on intratumoral DC subsets on both scRNA and protein levels.

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 the tumor regions.

To gain a more comprehensive understanding on the intratumor effects induced by PVRIG blockade, we evaluated the immune response in the TME of patients with poorly immune infiltrated tumors, platinum resistant ovarian cancer and MSS-CRC, indications typically less responsive to immune checkpoint inhibitors. Treatment with COM701, anti-PVRIG antibody, as monotherapy or in combination with nivolumab resulted in an increased tumor T cell infiltration, accompanied by TCR clonality expansion, which were 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.