PVRIG, a novel T cell checkpoint, is preferentially expressed in TLS on stem-like memory T cells, potentially inhibiting their expansion

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Background

Tertiary lymphoid structures (TLS) recently emerged as an intra-tumoral niches of immune-cell aggregates with a predictive value for cancer immunotherapy responses [1]. LAMP3$^+$DCs in the TLS were shown to interact and support the differentiation of stem-like CD8 T-cells into effector-like cells, that then expand in the tumor micro-environment (TME) and may exert anti-tumor responses [2]. We investigated the expression of DNAM-1 axis genes: PVRIG, TIGIT, DNAM-1 and their ligands PVRL2 and PVR in the TME [3].

Methods

MERFISH technology was employed to detect the expression of 350 distinct mRNA transcripts at sub-cellular resolution in CRC sections. Publicly available TME scRNA-seq datasets were analyzed for expression of PVRIG and PVRL2 across immune populations and validated by flow-cytometry. An extensive omics profiling was performed for patients with pre- and on-treatment biopsies from COM701 (anti-PVRIG antibody) and COM701+nivolumab Phase-1 study (NCT03667716).

Results

Spatial distribution of gene transcripts allowed identifying localization of stem-like T-cells in TLS regions of two CRC patients (Figure 1, $p<0.001$). While, CTLA-4, PD-1, and TIM3 were mainly expressed by tumor infiltrating T cells, PVRIG and other genes of DNAM-1 axis were also largely expressed in tumor bed, and even more intensely in TLS ($p<0.05$, Figure 2). Furthermore, high resolution unsupervised scRNA gene co-expression analysis in the TME further validated that while PD-1 is strongly correlated with TIM3, CTLA-4, and other markers of exhausted T-cells, PVRIG uniquely clusters with markers of stem-like T-cells. The PVRIG protein expression was increased on CD28$^+$ stem-like T-cells across indications (Figure 3). RNA and protein expression data identified PVRL2, PVRIG ligand, preferentially expressed across DC-subtypes compared to PD-L1 and PVR (Figure 4). PVRIG blockade could therefore enhance memory T-cell activation by DCs, resulting in their increased expansion and differentiation. Accordingly, COM701 monotherapy induced CD8$^+$ T-cell numbers and immune activation in the TME of ovarian cancer patient (Figure 5). Moreover, MSS-CRC patient with partial response to COM701+nivolumab, demonstrated an

increase in TCR numbers, clonality, T-cell infiltration and activation in the TME (Figure 6). Finally, preliminary analysis of serum from two patients clinically responding to COM701+nivolumab (RECIST criteria), revealed induction of activated-DC markers, compared to non-responders (Figure 7).

Conclusions

By leveraging spatial and scRNA transcriptomics, we identified PVRIG^{+}CD8^{+}T-cells predominantly localized within TLS, interacting with PVRL2^{+}LAMP3^{+}DCs. PVRIG blockade could therefore enhance the differentiation and expansion of stem-like CD8^{+} T-cells into effector-like cells (Figure 8). Accordingly, early clinical data shows increased T-cells infiltration and immune activation in patients treated with COM701 or COM701+nivolumab.

References:

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