IL7R TME EXPRESSION CORRELATES WITH IMMUNOTHERAPY RESPONSE AND IS ASSOCIATED WITH T-CELL STEMNESS WITH DECREASED APOPTOSIS

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Background Anti-PD(L)1 therapy can reinvigorate exhausted Tcells by inducing a proliferative burst of PD1+TCF7+ stem-like Tcells but, Tcells rapidly undergo exhaustion and death, limiting efficacy of therapy. IL7 induces survival and homeostatic proliferation of Tcells. IL7R is associated with memory-stem-like Tcells subset but, the effect of IL7 on cancer-specific TILs remains unknown. We studied gene expression of the IL7/IL7R pathway on single cell transcriptomic analysis in multiple datasets of anti-PD1/PDL1 responder’s and non-responders’ patients.

Methods RNAseq of bulk tumor and scRNAseq of TILs and tumor-specific clonotypes datasets were analyzed prior checkpoint inhibitors treatment from different clinical studies representing a total of 1036 patients for RNAseq analysis and 39 patients for scRNAseq analysis: Melanoma (aPD1+/−aCTLA4), TNBC (Chemotherapy+PDL1), NSCLC (aPD1) and Ovary (Ex vivo aPD-1 response).

Results IL7R and IL7R pathways gene expression on tumor bulk is significantly correlated with better OS or PFS across multiple cancers, as analyzed by PanCancer TCGA and iATLAS datasets (p<0.02; p<0.0001). In Melanoma, NSCLC, Ovarian, TNBC, HNSCC and/or Kidney cancers, we demonstrated a significant higher expression of IL7R and/or IL7R pathway signatures of future ICI responders versus non-responders and confirmed this data by scRNAseq analysis specifically on TILs and tumor-specific Tcell clonotypes. IL7RHigh TILs over-expressing IL7R show upregulation of genes related to stemness and downregulation of genes related to exhaustion. In addition, IL7RHigh TILs are less apoptotic and express significant higher level of BCL2 anti-apoptotic molecule. As TCF7 gene is described as key marker for stemness and anti-PD(L)1 response, we also analysed impact of IL7R+/−TCF7 expression. TCF7 or IL7R expression only are not sufficient to predict ICI response, while the coexpression is predictive to ICI response in Melanoma. scRNAseq and FACs analyses of chronically stimulated human Tcells in vitro show that IL7 significantly promotes long-term survival (up to 5 weeks) and proliferation of stem-like Tcells (TCF7+Tcells), whereas IL2 or IL15 promotes proliferation of Tcells with exhausted phenotype dying after >10 days of culture.

Ex vivo, IL7 fused to an anti-PD1 mAb reinvigorates TILs (IFNg secretion) in human 3D-tumoroids from both anti-PD1 sensitive or not patients.

Conclusions Altogether, our data show that IL7R pathway expression in TILs and tumor-specific Tcell clonotypes are predictive of long-term ICI clinical response. Redirecting IL7 on PD1+Tcells provides stemness, proliferative and survival signals to tumor-specific Tcells capable to induce durable response.

REFERENCES