IDENTIFYING PATIENT SUBSETS FOR CTLA4 AND GITR DEPLETION STRATEGIES IN POORLY T CELL INFILTRATED TUMORS

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Background Many combination immunotherapies have been investigated however identifying subsets of patients who will benefit from each combination has been challenging. While immunotherapy combinations have to date centered on therapeutic targets on immune cells, the expression of immunoncology (IO) targets on cancer cells has not been well studied. We investigated the gene expression landscape across human solid tumors for seven existing IO targets (CTLA4, GITR, CSF1R, IDO1, LAG3, TIM3, and FOXP3) in conjunction with PDL1 to evaluate tumor-intrinsic patterns and potential for IO combinations in specific patient populations.

Methods We used a hierarchical approach on samples from the Cancer Genome Atlas (TCGA). Normalized RNAseq data was converted to quartile rank to define patient populations of PDL1 high/low in combination with high/low from one of the IO targets. Genes differentially expressed between groups were identified by limma voom (fold change >1.5, FDR 0.05). Upstream regulators were predicted by causal networks from Ingenuity Pathway Analysis (z-score >1.95).

Results Patients with PDL1 high expression showed high expression in all seven genes, and those of PDL1 low showed low expression in all genes, consistent with the literature. We identified a unique subset of patients in the PDL1 low setting, however, that demonstrated high CTLA4 or GITR expression, composing 14% and 21% of all tumor samples, respectively. Subsequent analysis of the CTLA4-high/PDL1-low subset indicated that high CTLA4 expression in PDL1 low tumors may represent an intermediate-T cell-inflamed tumor microenvironment (TME) with activated upstream regulators of Type-I IFNγ pathways (IFNG, AHR, TNF, STAT1, NFKB1, IFNA1), which comprised 12% of cervical squamous cell carcinoma, 15% of head and neck squamous cell carcinoma, and 17% of liver hepatocellular carcinoma. Analysis surrounding GITR suggested that high GITR expression in PDL1 low tumors may also represent an intermediate-T cell-inflamed TME. 14% of skin cutaneous metastatic melanoma, 20% of liver hepatocellular carcinoma, 20% of sarcoma, and 11% of testicular germ cell tumor samples fell in GITR-high/PDL1-low group and demonstrated intermediate activation of IFNG, TNF, CD28, AHR, NFKB1, and MYD88. These analyses were not impacted when adjusted by tumor mutational burden across cancer types.

Conclusions High CTLA4 or GITR in the context of low PDL1 may represent an intermediate-T cell-inflamed TME and/or tumor cell-intrinsic expression. Stratification of tumors by T cell-inflamed gene signature, or PDL1 status, as well as expression of a specific therapeutic target may identify patient populations who could benefit from CTLA4 or GITR depletion strategies in IO combination therapies.