1039 A MINIMAL GENE SET TO OVERCOME PHENOTYPIC HETEROGENEITY IN CHARACTERIZATION OF NEOANTIGEN-SPECIFIC TIL IN LUNG CANCER

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Background PD-1/PD-L1 pathway blockade unleashes tumor specific T cells.[1] Neoantigens are the most well-studied tumor antigens, however T cells targeting neoantigens are difficult to detect. Our recent integrated scTCRseq/RNAseq studies on neoantigen-specific TILs in lung cancer illustrated a nearly uniform transcriptional program characterized by high expression of CXCL13 and ENTPD1 (CD39), and low expression of IL7R.[2] We therefore hypothesized that a comprehensive transcriptional profile of neoantigen-specific TIL could be defined that would bypass the need for cumbersome and expensive functional T cell assays, and that these models would be heavily dependent on individual patients and therapeutic response.

Methods Neoantigen- and CEF-specific TILs that were published previously were used to train a gene score with weighting for ENTPD1, CXCL13, and IL7R on TIL from 3 melanoma patients[3] and 2 lung cancer patients.[2] SAVER was used to recover missing data, and the resulting score was termed 'MANAscore'. Both imputed and normalized non-imputation data were studied. Single patient models were constructed first with linear regression and random forest algorithm on imputed and non-imputed data, respectively. Then combining voting models were built using those single models showing high correlation among each other when using them to predict unseen data in lung cancers. ROC curves were used to evaluate the models.

Results A total of 253,161 high quality CD8+ TILs were included, of which 222,987 were from the lung cancer cohort and 30,174 were from the melanoma cohort. As expected, the majority of neoantigen-specific TILs resided in tissue resident memory clusters in both cancers, which demonstrated the similar expression program of neoantigen-specific TIL across cancer types. By using patient-specific models to address issues of patient and therapeutic response heterogeneity, the AUCs for the 3 gene combined voting models are relatively high when testing on lung cancer/melanoma (0.902/0.832 for imputed/non-imputed model) and in an independent head neck dataset (0.8616/0.8625 for imputed/non-imputed model). The proportion of MANA-score^{hi} T cells in patient tumor was correlated with favorable response to ICB and associated with pathological tumor regression after ICB in lung cancer as well, possible reflecting the impact of tumor regression on the expression of a tumor-reactive T cell signature by TIL.

Conclusions Here we show that tumor-reactive TIL gene signatures may need to be optimized on a per-patient level to account for patient and therapeutic response heterogeneity, and that these signatures may be useful pan-cancer biomarkers for ICB response.

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