73 CHARACTERIZATION OF TUMOR-INFILTRATING T-CELL REPERTOIRE IN HUMAN CANCERS

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Background TCR and BCR repertoire profiling is a promising technique that can provide a clinically useful window into the complex interactions between tumor cells and infiltrating lymphocytes. Despite recent advances in repertoire sequencing methods, the characterization of tumor-infiltrating T-cell repertoires has been limited to small sample sizes due to technical and material constraints. In this study, we constructed a large multidimensional database of repertoire data covering a diverse landscape of HLA genotypes and tumor neoantigens from routine clinical sequencing. We present a descriptive summary of repertoire profiles derived from tens of thousands of tumor samples from over fifty different cancer cohorts and characterize the associations between T-cell repertoires and various clinical and molecular features.

Methods To enrich immune receptor transcripts detected by the Tempus RNA-sequencing workflow, hybrid capture probes tiling TCR and BCR genes were used. Repertoire profiling reads were aligned, assembled, and annotated against IMGT reference sequences. Repertoires are profiled as a component of Tempus|xT RNA sequencing and are summarized here for >25 thousand tumor samples from over 50 different cancer cohorts.

Results We demonstrate that the use of TCR/BCR hybrid capture probes is an effective method for enriching immune receptor transcripts in RNA-sequencing data without interfering with downstream transcriptomic analysis. These repertoires were profiled as part of a larger, multimodal DNA/RNA-sequencing pipeline that quantifies a variety of tumor clinical and molecular features. We explored the correlation between high-level repertoire metrics like richness (the number of unique receptor clonotypes in a given repertoire) and clonality/evenness (Shannon entropy) against both gene expression-based metrics (i.e. immune cell infiltration estimates, etc.) and mutational patterns (mutational burden and neoantigen load). Finally, we observed that the repertoire clonality of B-cell and T-cell driven cancers frequently exhibits clear monoclonal dominance for the tumor cells' lymphoid receptors.

Conclusions TCR/BCR repertoire profiling can be incorporated into high-volume clinical RNA sequencing to generate a diverse multimodal dataset for studying the tumor-immune microenvironment. By creating a large-scale database of TCR/BCR repertoire profiles from a variety of tissue, HLA genotypes, and mutational contexts, we can better resolve the molecular and clinical correlates of cancer with host adaptive immunity.

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