Scalable and comprehensive characterization of antigen-specific CD8 T cells using multi-omics single cell analysis

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Understanding the antigen binding specificities of lymphocytes is key to the development of effective therapeutics for cancers and infectious diseases. Recent technological advancements have enabled the integration of simultaneous cell-surface protein, transcriptome, immune repertoire and antigen specificity measurements at single cell resolution, providing comprehensive, scalable, high-throughput characterization of immune cells.

Using the 10x Genomics Single Cell Immune Profiling Solution with Feature Barcoding technology with 14 oligo-conjugated antibodies and 50 Immudex peptide-MHC I Dextramer reagents (pMHC) panels spanning different CMV, EBV, Influenza, HIV and Cancer antigens, we performed multi-omic characterization of ~200,000 CD8+ T cells from four MHC-matched donors. The multi-omic combination of gene expression, paired alpha/beta T cell receptor (TCR) repertoire, cell surface proteins and pMHC binding specificity allowed the identification of CD8+ T cell subpopulations with specificity for pMHCs within our panel. We observed multiple TCRs that bound the same pMHC and identified enriched amino acid motifs within TCR sequences that shared specificities. We compared the CDR3 amino acid sequences of the pMHC-specific TCR clonotypes with previously reported sequences with the same binding specificities to show that we could identify new and known CDR3 sequences. This analytical framework provides a systematic and scalable method for deciphering TCR–pMHC specificity combined with cellular phenotype identity which is critical for developing a better understanding of the adaptive immune response to cancer and infectious diseases and will be key in the development of successful immunotherapies.