THE EFFECT OF HIV ADAPTATION ON HUMAN T CELL FUNCTION AND RECEPTOR DIVERSITY

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The prototypic anti-viral immune response requires the actions of naïve T cells, which differentiate into a specific population of clonotypes with an optimal T cell receptor (TCR) repertoire for viral clearance and anti-viral memory. In HIV, this process is subverted by viral escape (adaptation) from T cells. However, viral mutations that disrupt the HLA-peptide-TCR complex leading to loss of antigen recognition represent only one strategy of adaptation. In many instances adapted viral strains can still be recognised by the host's T cells. We developed a single-cell TCR analysis pipeline to delineate whether responses to the adapted form of the T cell epitope are mediated by the recruitment of new clonotypes or by selection of particular clonotypes with more cross-reactive TCRs. Furthermore, we assessed the effect of these different TCR-Ag-HLA complexes at the scRNA transcriptome level. To isolate single antigen-specific T cells to a select set of HIV CD8+ T cell epitopes, we utilised HLA class I tetramers (for the adapted and non-adapted form) and activation markers (CD69 and CD137) following peptide stimulation in acutely and chronically infected individuals. TCR and RNAseq analysis was performed using the Illumina platform. The affinity of specific TCR combinations with adapted and non-adapted forms of the epitopes was assessed using a Jurkat transfectoma cell line with luciferase activity as the measurable output. We found evidence of cross-reactive T cells to the adapted and non-adapted form of epitopes. A single amino acid change in an epitope corresponded to differences in the scRNA transcriptome signature of HIV-specific T cells with the same TCR combination. The differentially expressed genes between the adapted and non-adapted form of the epitope was dependent on the autologous virus of the subject and likely reflects differences in the responding T cell. Understanding how the TCR diversity of an immune response can be altered or exploited by a pathogen is a fundamental question for HIV vaccine design and for many other pathogens for which natural, vaccine or cell therapy-based immunity is not currently effective or available.

Key words: TCR, adaptation