

COMMITMENT TO CD8+ T CELL EXHAUSTION AND LOSS OF MEMORY T CELL POTENTIAL DEVELOPS DURING PRIMARY CHRONIC HCV INFECTION

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Virus-specific CD8+ T cells (Ag-T) play a pivotal role in the outcome of HCV infection. During HCV infection, both immune escape and CD8+ T cell exhaustion contribute to establishment of chronic infection. To date the characteristics and kinetics of T cell responses and their TCR architecture in early primary HCV infection at single cell level remains unknown. We hypothesized that the onset of both immune escape and exhaustion occur in early phase (<180 days post-infection (DPI)) and that these dynamics contribute to the ultimate immune failure.

HCV infected subjects with longitudinal samples within the first 6 months of primary infection were selected from HITS-p cohort. Autologous MHC-I restricted HCV epitopes were identified, and utilized in IFN- γ ELISpot assay. Dextramers were utilized to detect Ag-T cells in a multi-color flow-cytometry panel for the analysis of activation (CD38), inhibition (PD-1, Tim-3, KLRG-1, 2B4, CTLA-4 and CD160), and differentiation (CD127, CCR7, CD45RO, T-bet and Eomes). Native TCR $\alpha\beta$ repertoire of single Ag-T cells was analysed using established protocol.

CD8+ T cells expressing IFN- γ were detected as early as 45 DPI, however this response rapidly declines in subjects who progress to chronic infection. We also observed a long lasting population of effector memory cells (CCR7^{low} CD45RO^{high}, as well as KLRG1^{high}CD127^{low}) during the first 6 months of infection, and a lack of onset of central memory repertoire. Notably, we also observed early and elevated expression of multiple co-inhibitory markers (PD-1, KLRG1 and 2B4) targeting both conserved as well as escape HCV variants. Longitudinal analysis of Ag-T cells TCR repertoire at the single cell level showed heterogeneous evolution of the repertoire diversity, with partial convergence in response to occurrence of immune escape. This analysis shows that regardless of immune escape primary HCV infection is characterized by early onset of exhaustion and prolonged phase of effector memory cells.