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Contribution ID: **350** Type: **Oral Presentation**

A systems immunology approach to study immune responses against viral infection

Monday, 9 July 2018 15:30 (30 minutes)

CD8+ T (CTL) cells play a pivotal role in protection from viral infection. Better understanding of the heterogeneous phenotypes of T cell subsets evolving during an immune response is timely needed for development of T cell based vaccines that can provide long-term immune protection. Viruses causing chronic infections such as HIV and HCV, trigger a T cell response characterised by functional exhaustion, and accumulation of immune escape variants. We have developed a single cell approach to identify and link functional phenotype, gene expression profile, TCR diversity and T cell avidity with the onset of exhaustion and its relationship with immune escape.

We analysed a cohort of prospectively followed subjects from acute primary HCV infections to disease outcome (clearance and chronicity). Antigen specific (Ag-) CTL were identified via epitope discovery and functional validation via IFNγ-ELISPOT. Index sorting was utilised to link surface phenotyping with gene expression profile. Full length TCRαβ repertoire was identified from scRNAseq data using novel tools. Exhaustion was detected early on in the acute phase of infection and in CTL targeting conserved but also immune escape epitopes. Single cell RNAseq showed a distinct gene expression profile of exhausted T cells compared to the less differentiated subsets. In contrast, Ag-CTL in subjects that cleared HCV, polyfunctional (IFNγ, granzyme, and perforin) responses were found, with a highly diverse TCR repertoire. We discovered a novel T cell clone, characterised by high avidity for viral epitope, elevated IFNγ productions and polyfunctional phenotype.

This systems immunology approach provides new routes to investigate complex T cell dynamics and to identify new mechanisms to exploit in vaccine and immunotherapy.

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Session Classification: Mathematical and experimental approaches to understand immune response to infection

Track Classification: Minisymposium: Mathematical and experimental approaches to understand immune response to infection