AN INVESTIGATION OF CD4+ TCR RECOGNITION OF AN IMMUNODOMINANT HIV EPITOPE IN CONTROLLER INDIVIDUALS

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Background: The role of CD4 T cells in HIV has been overlooked for a long time, due to the elimination of those cells upon infection. However, in elite controller individuals the count of CD4 stays high, as they can control the viral load. We identify a CD4 T cell population specific from controller exhibiting a highly-skewed T cell receptor (TCR) repertoire displaying high affinity and polyfunctionality towards an amazing range of different HLA-DR molecules.

Methods: We undertook structural and functional approaches to gain access for the first time to how CD4 TCR engages with an immunodominant HIV epitope presented by different HLA-DR molecules. We used imaging flow cytometry to observe the formation of immunological synapse between CD4+ T cells and their antigenic target. We assessed the CD4+ T cells cytotoxicity capacity against HIV-infected monocyte-derived dendritic cells. To understand the molecular recognition underpinning high affinity CD4+ TCRs we used X-ray crystallography, and mutagenesis/surface plasmon resonance (SPR) analysis to characterised the key residues driving the interaction.

Results: Our result show that the high affinity CD4+ clones can form mature immunological synapse, giving them the capacity to eliminate HIV-infected cells. We showed that the cytotoxic capability of the CD4+ T cells could be transfer to CD8+ T cells. We solved the structures of a high affinity CD4 TCR in complex with three different HLA-DR molecules presenting the HIV epitope providing the molecular basis of HIV recognition as well as the mechanism underpinning CD4 T cells cross reactivity towards multiple HLA molecules.

Conclusion: Altogether we show that our high affinity HIV-specific CD4+ T cells, form controller individuals, exhibit high functionality, high affinity, cytotoxic capability that can be transfer to CD8+ T cells as well. Our structural analysis, with associated mutagenesis, showed how a single TCR can engage with multiple HLA molecules, providing some exiting possibility to use this information in the design of new therapeutics.