Poster Presentations

[MS5-P36] The Human Immune System vs HIV: A Cat and Mouse Game. Anna Fuller, David K Cole, Pierre J Rizkallah, Andrew K Sewell.

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Cytotoxic T-lymphoctyes (CTLs) can directly kill cells infected with pathogens including viruses, and thus form our main defence against HIV infection. CTLs recognise small peptide fragments derived from protein products digested in the proteasome. These peptides are presented by major histocompatibility complex class I molecules (pMHCI) and are transported to the cell surface where CTLs scan for foreign epitopes through an interaction mediated by the T-cell receptor (TCR).

A number of CTL specific HIV epitopes have been identified and targeted for immune based therapies. However, HIV has the capacity to rapidly mutate its genome during replication and thus evade recognition by CTLs. The p17 Gag-derived (amino acids 77–85) antigen SLYNTVATL (SL9) has been identified as a promising target for HIV based therapies. Firstly, mutation within this epitope is constrained because only conservative mutations result in viable viral particles. Secondly, this epitope is presented by HLA-A*02, which is the most common MHCI allele in Western populations.

We have solved the structure of unbound 868, an HIV specific TCR; in complex with the SL9 index peptide, and with some common SL9 escape mutants. Solving these structures has shown that:

- The peptide changes conformation only very slightly when bound to the TCR.
- There are small differences between the presentation of the escape mutant peptides and the index peptide.
- The 868 TCR binds to the SL9 escape mutants in a very similar way to the SL9 index peptide.
- Upon binding there are small changes in conformation of the peptides.
- The TCR binds to the peptides predominantly through its CDR3 loops, with an induced fit mechanism.
- The CDR3 loops move out of the way to allow the peptide to bind, the largest shift in CDR loops observed.
- There are a high number of contacts between the TCR and pMHC in each complex, which accounts for the high affinity of the interaction between the 868 TCR and these three pMHCs.
- There is a loss of 2 hydrogen bonds at the interface between 868 and A2-SL9 3F6I8V compared with 868 A2-SL9.

In addition to the structural analysis we did a thermodynamic experiment to study the interaction between the 868 TCR and the pMHCs. This showed that the interaction between 868 and A2-SL9 3F6I8V has a different thermodynamic profile compared with the thermodynamic profiles of A2-SL9 and A2-SL9 6I. It also showed that the off rate of the 868 TCR is much faster from A2-SL9 3F6I8V than the other two pMHCs. Our results show how small conformational changes in peptide presentation can affect the binding strategy of the TCR and, in turn, its ability to kill the infected cell. By furthering the understanding of the molecular rules that govern HIV immune evasion, we hope to develop a T-cell based treatment for HIV, including vaccination and adoptive T-cell therapy.

Keywords: Major Histocompatibility complex, T-Cell Receptor, Human Immunodeficiency Virus