

MS036.P04

Unconventional peptide presentation by major histocompatibility class I allele HLA-A*02:01

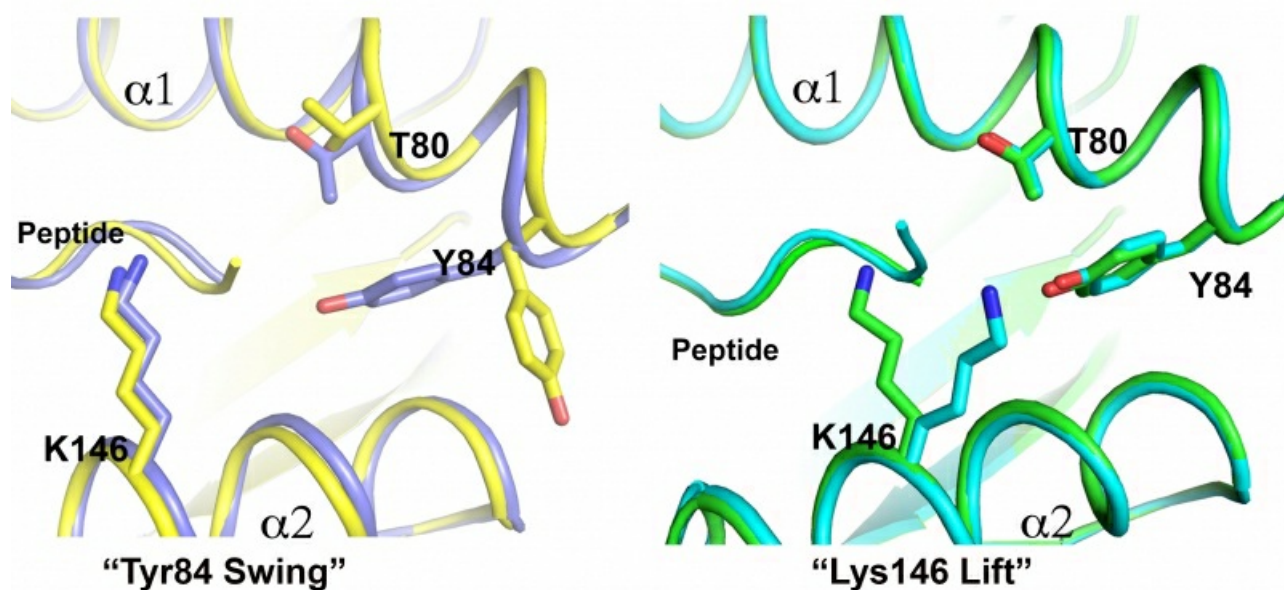
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Peptide antigen-presentation by Major Histocompatibility Class (MHC) I proteins initiates CD8+ T cell mediated immunity against pathogens and cancers. MHC I molecules typically bind peptides nine amino acids in length with both ends tucked inside the major A and F binding pocket. It has been known for a while that longer peptides can also bind by either bulging out of the groove in the middle of the peptide or by binding in a zig-zag fashion inside the groove. In a recent study, we identified an alternative binding conformation of naturally occurring peptides from *Toxoplasma gondii* bound by HLA-A*02:01. These peptides were extended at the C-terminus (PΩ) and contained charged amino acids not more than 3 residues after the anchor amino acid at PΩ, which enabled them to open the F pocket and expose their C terminal extension into the solvent. Here, we show that the mechanism of F pocket opening is dictated by the charge of the first charged amino acid found within the extension. While positively charged amino acid result in the Tyr84 swing, amino acids that are negatively charged induce a not previously described Lys146 lift. Further, we demonstrate that the peptides with alternative binding modes have properties that fit very poorly to the conventional MHC class I pathway, and suggest they are presented via alternative means, potentially including cross presentation via the MHC class II pathway.

(1) Remesh, S.G. et al. (2017) J. Biol. Chem. pii: jbc.M117.776542. doi: 10.1074/jbc.M117.776542

(2) McMurtrey, C. et al (2016) eLife. 5, e12556



Keywords: [MHC I proteins](#), [C-terminal extended peptides](#), [Toxoplasma gondii](#)