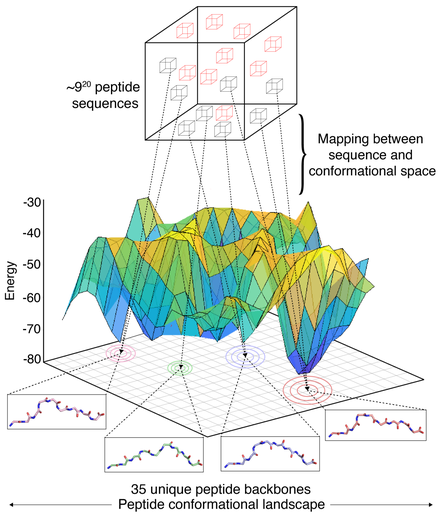
Structural classification of peptide/HLA complexes

Sagar Gupta[1], Santrupti Nerli[3], and Nikolaos G. Sgourakis[2]
[1]School of Arts and Sciences (2024), University of Pennsylvania, Philadelphia, PA
[2]Department of Biochemistry and Biophysics, Perelman School of Medicine, Philadelphia, PA
[3]Department of Biomolecular Engineering, University of California, Santa Cruz, Santa Cruz, CA

sagarg@upenn.edu

Graphical Abstract



Introduction

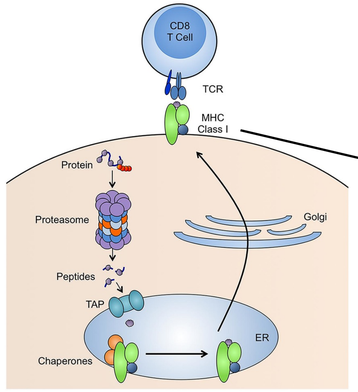


Figure 1
The MHC class I antigen processing and presentation pathway (1). The peptide/MHC-I complex is transported to the cell surface for presentation to CD8⁺ cytotoxic T cells. HLA-I is the human version of MHC-I.

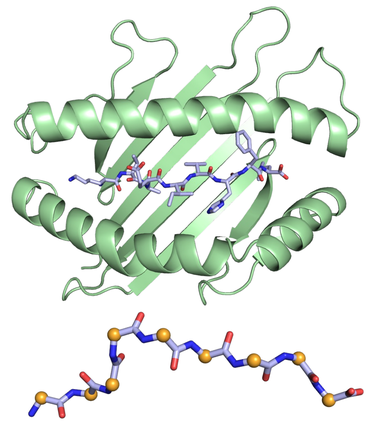


Figure 2
HLA-A*02:01 (green) bound to KVAEIVHFL (blue). The peptide backbone is shown below the pHLA complex with Cα atoms (orange)

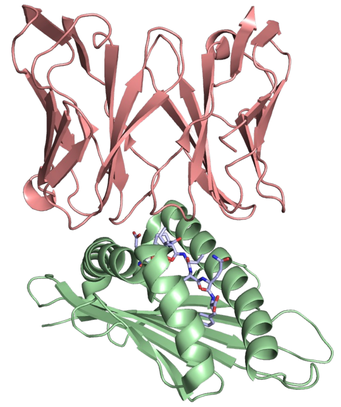
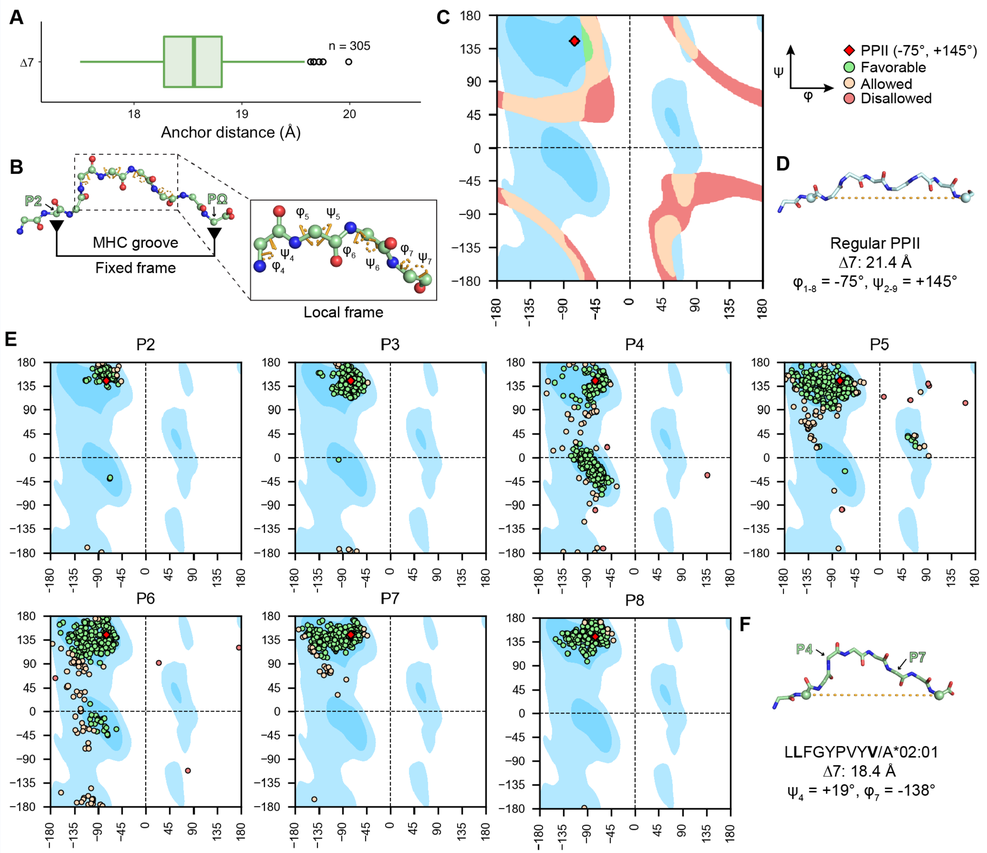


Figure 3
HLA-A*01:01 (green) bound to a cross-reactive peptide (blue) in complex with a T-cell receptor (TCR, red).

Discussion

- Given a conserved anchor distance distribution, a fixed-local frame hypothesis can explain peptide backbone conformational diversity
- Ramachandran plots of dihedral angles (φ and ψ) show that positions 4 to 7 have significant deviation from an ideal backbone conformation
- A greedy algorithm iteratively identifies the most common peptide backbones and ultimately reveals a set of minimal set of 35 unique backbones that can describe the entire conformational space
- A 2D PCA plot reveals that the representative peptide backbones capture “rare” conformations that are poorly represented in existing pHLA structural data
- An exemplar peptide backbone exhibits that peptide backbone identity occurs irrespective of HLA sequence deviations

Results



Conclusions

- Structural diversity of pHLA structures at the peptide backbone level is driven by local structural adaptations at positions 4 to 7 on a fixed overall pHLA binding frame
- The entire set of 295 pHLA structures can be represented by 35 unique backbones, an eight-fold compression
- The complex interplay of divergent peptide and HLA residues can converge to similar peptide backbones
- In the future, representative structures can be used in homology modeling to predict novel pHLA structures

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References

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