HLA3DB: an annotated database of high-resolution pHLA structures

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

Introduction

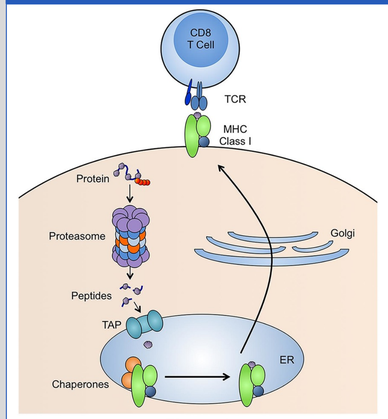


Figure 1
The MHC class I antigen processing and presentation pathway (1). The peptide-MHC class I complex is transported to the cell surface for presentation to CD8 T cells.

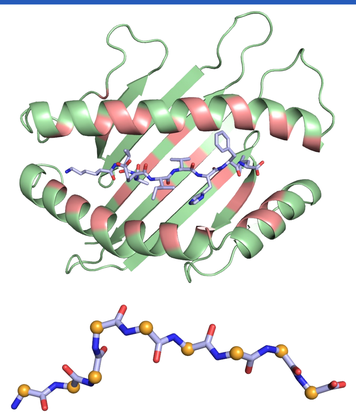


Figure 2
A*02:01 (green/red) bound to KVAEIVHFL (blue). Groove residues (within 3.5 Å peptide) are colored in red. The peptide is shown below the pHLA complex with Cα atoms (orange)

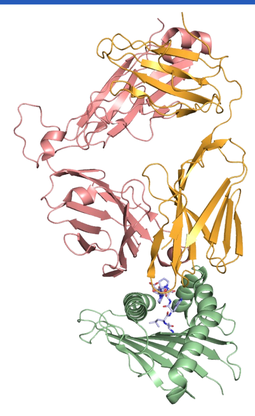
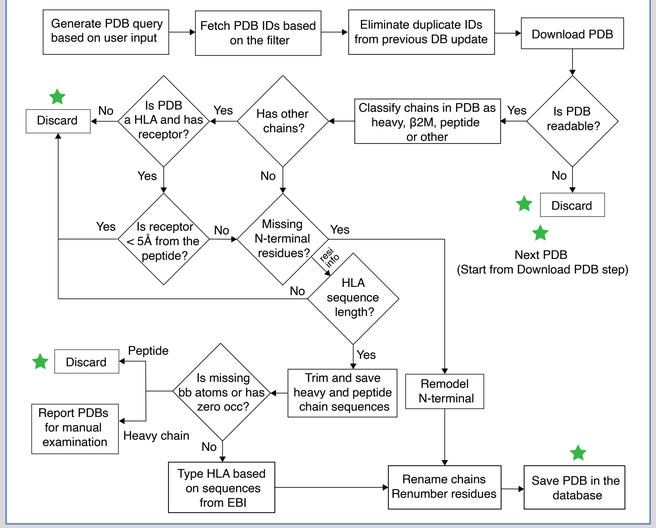


Figure 3
Peptide/HLA (pHLA, blue and green) in complex with T-cell receptor (TCR, red and orange)

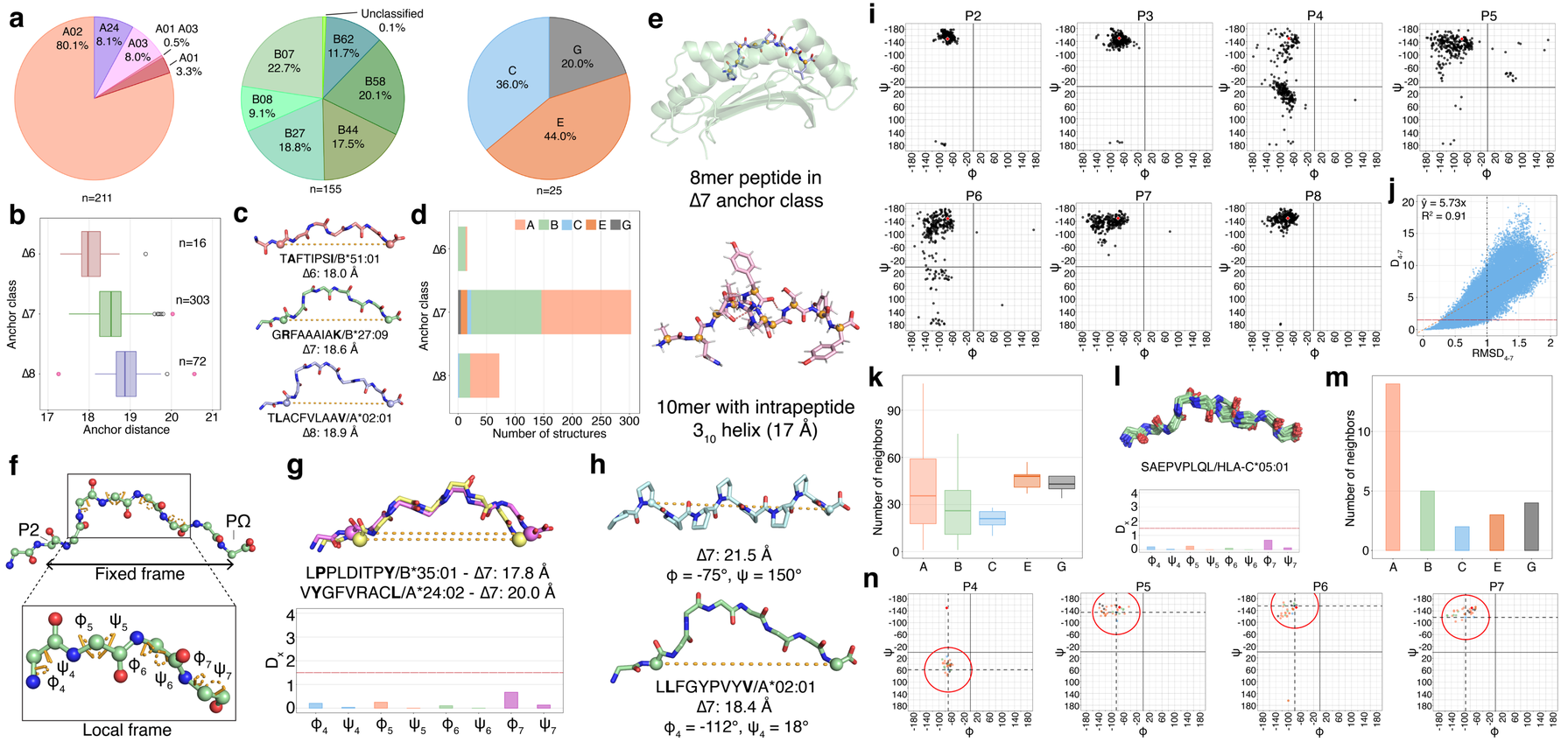
Method



Discussion

- HLA3DB contains 16 8mers, 296 9mers, and 79 10mers for a total of 391 pHLA structures
- There is good coverage of the main HLA-A and HLA-B supertypes
- Increasing sequence separation between anchor residues shows a greater bulge in the middle of the peptide, the region implicated in the specificity of an immune response
- Anchor distances of the peptide is confined by the geometry of the HLA groove
- Conformational diversity can be captured by the dihedral angles (φ and ψ) of P4 – P7
- Distance score is more accurate than RMSD and allows for dimension reduction, reducing noise
- Each structure in HLA3DB has at least one “neighbor,” or structurally similar backbone

Results



Conclusions

- HLA3DB provides a natural sampling of peptide backbone conformations and is dominated by HLA-A*02:01 structures
- Peptides adopt a diverse set of conformations via changes in P4 - P7 of the backbone, rather than drastic overall changes between the anchor residues
- An interplay between P4 - P7 of the peptide and HLA groove can result in similar peptide backbones
- In the future, homology modeling can be used to predict novel pHLA structures

Acknowledgements

Sgourakis Lab:
Nikolaos Sgourakis, Santrupti Nerli, Andrew McShan, Viviane Silva de Paula, Tyler Florio, Georgia Papadaki, Yi Sun, Claire Woodward, Sam Garfinkle, Julia Danon, Michael Young, Omar Ani
Funding:
NIAID (5R01AI143997), NIGMS (5R35GM125034).

References

(1) McCarthy MK, Weinberg JB. The immunoproteasome and viral infection: a complex regulator of inflammation. *Front Microbiol.* 2015 Jan 29;6:21. doi: 10.3389/fmicb.2015.00021.
(2) North B, Lehmann A, Dunbrack RL. A new clustering of antibody CDR loop conformations. *J Mol Biol*. 2011 Feb 18; 406:2. doi: 10.1016/j.jmb.2010.10.030.
(3) Sidney J, Peters B, Frahm N, Brander C, Sette A. HLA class I supertypes: a revised and updated classification. *BMC Immunol*. 2008 Jan 22; 9:1. doi: 10.1186/1471-2172-9-1.