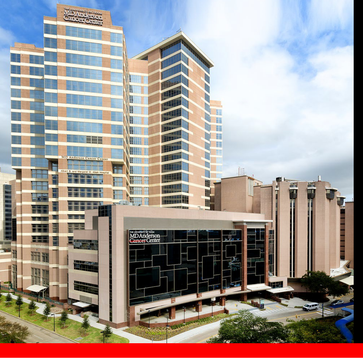

Evaluation of Structural Flexibility and Cross-Reactivity of the T-Cell Receptor

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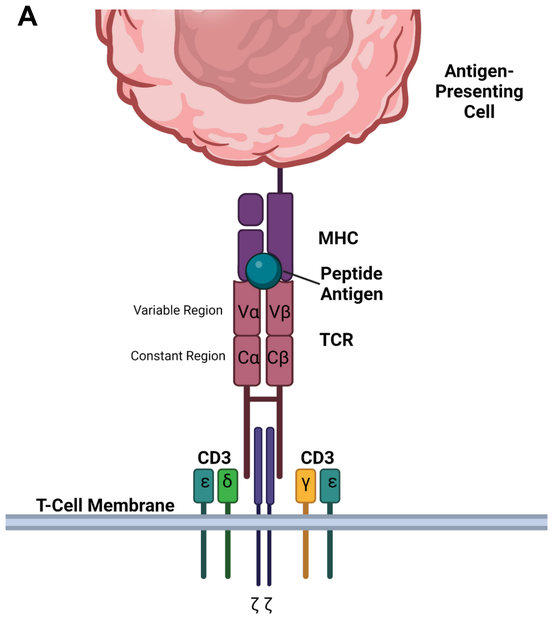
Background

- T-cells have become of interest for cancer therapies due to their ability to recognize and engage with tumor antigens.[1] T-cells receptors (TCR) interact with peptide-major histocompatibility complexes (pMHC) to trigger a response.[2]
- During an immune response, T-cells proliferate until the pathogen is cleared, and a portion of them will develop an antigen-specific memory, allowing a stronger and faster immune response in an event of reactivation.[3]
- There are two parts to each TCR chain (α and β): the variable and the constant region. Within each variable region, there are three complementarity-determining regions (CDR1, CDR2, and CDR3).[2]
- While CDR1 and CDR2 more often interact with MHC helices, CDR3, the most structurally diverse of all loops, engages with peptides to a great extent.[2] To advance therapeutic interventions, a greater understanding needs to be reached through the evaluation of structural flexibility and cross-reactivity of TCR.



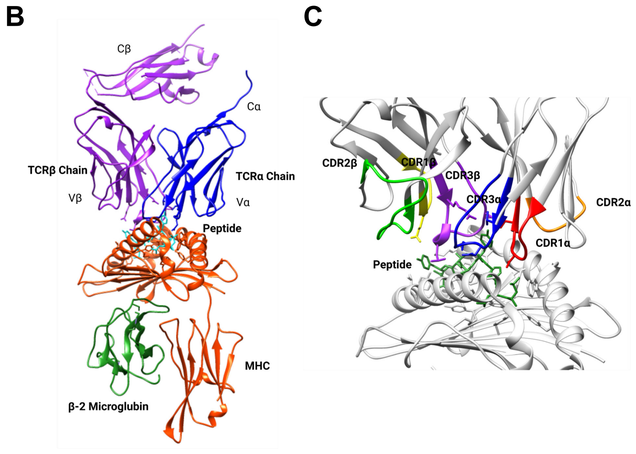


Figure 1: Structures of the TCR-pMHC complex.
(A) TCR chains engage with peptide presented by MHC.
(B) Structures as modeled by bound A6 TCR 1AO7.
(C) CDR loops of bound A6 TCR 1AO7.

Objective

- Explore TCR structural flexibility upon binding to peptide presented by MHC.
- Evaluate role of TCR structural flexibility in cross-reactivity.

Methods

Aim 1: Structural Flexibility

Download bound/unbound TCR complexes from RCSB PDB (38 pairs)[1] → Truncate TCR chains of all PDBs to only include CDR loop regions → Perform RMSD[4], TM-score[4], and IDDT[5] tests between respective loops of bound and unbound TCR

Aim 2: Cross-Reactivity

Download cross-reactive/non-cross-reactive bound/unbound TCR complexes (31 cross-reactive pairs and 8 non-cross-reactive pairs)[1,6] → Aim 1 steps 2-3 → Compare scores between cross-reactive and non-cross-reactive TCR

Results

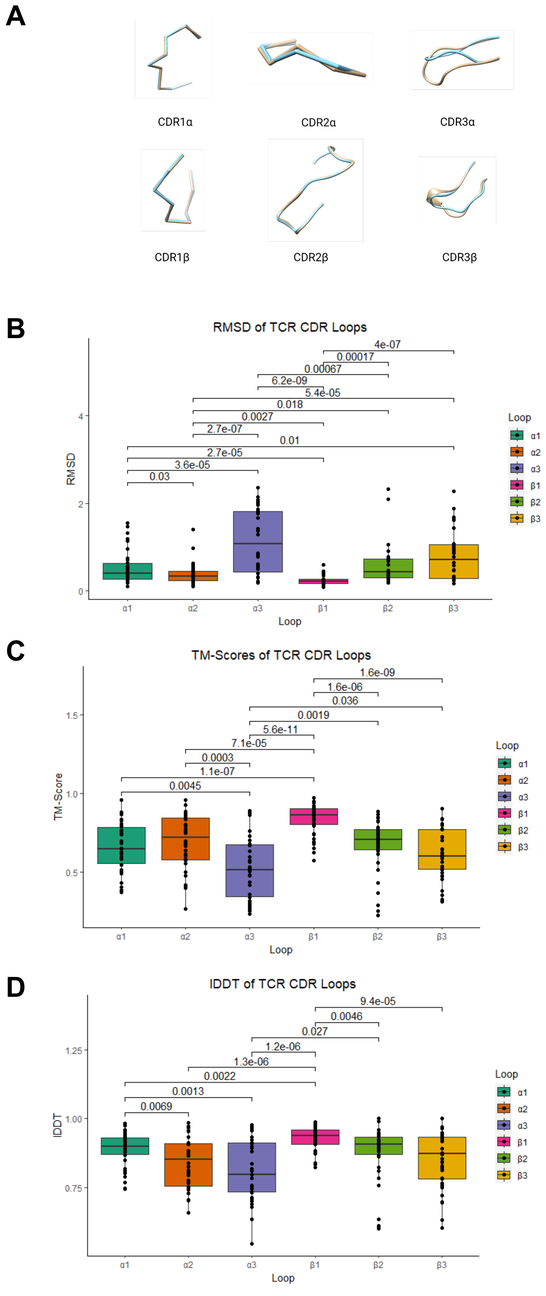


Figure 2: Results for Aim 1: Structural Flexibility.
(A) The backbone of CDR loops adopts different conformations between bound and unbound states (gold: 1AO7 for A6 TCR bound to pMHC; blue: 3QH3 for unbound A6 TCR).
(B) Greatest RMSD range (Å) in CDR3α/β loops.
(C) Lowest TM-score range in CDR3α/β loops.
(D) Lowest IDDT range in CDR3α/β loops.

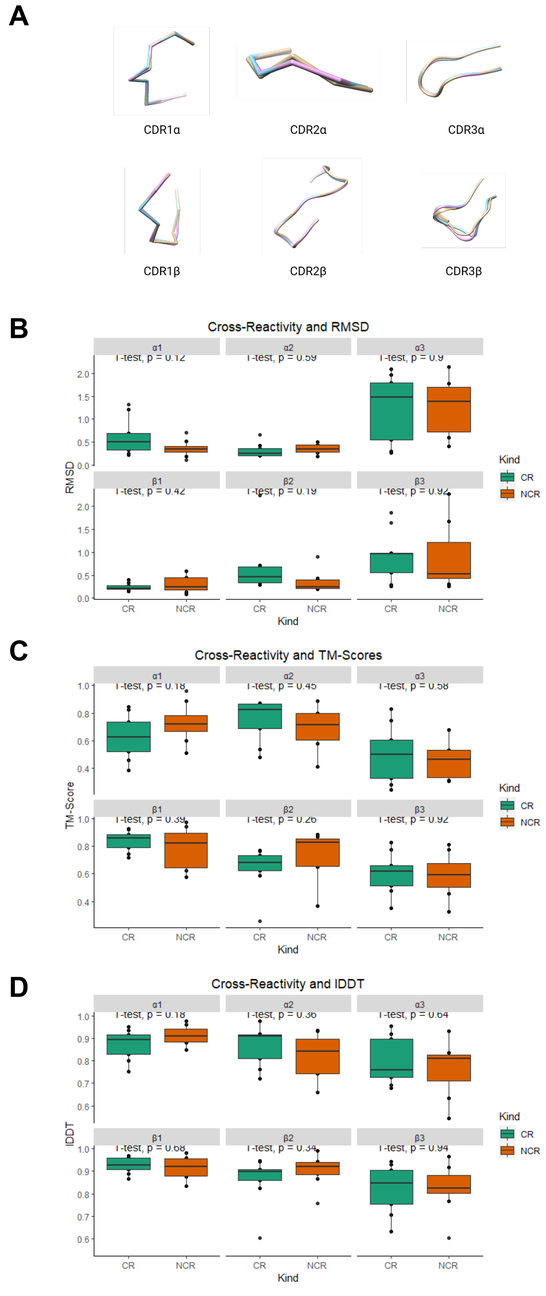


Figure 3: Results for Aim 2: Cross-Reactivity.
(A) The backbone of CDR loops adopts different conformations among three A6 TCR bound to different peptides (gold: 1AO7 bound to LLFGYPVYV; blue: 3H9S bound to MLWGYLQYV; pink: 3PWP bound to LGYGFVNYI).
(B) Greatest RMSD range (Å) in cross-reactive CDR3α/β loops.
(C) Lowest TM-score range in cross-reactive CDR3α/β loops.
(D) Lowest IDDT range in cross-reactive CDR3α/β loops.

Definitions

LYRA 1.0[7]- used to determine CDR regions through input of TCR chain sequences

UCSF Chimera[8]- used to visualize structural differences through alignment function

RMSD- root-mean-square deviation, measures the average distance between corresponding atoms
Higher value indicates greater structural difference

TM-score- template modeling score, measures the alignment and structural similarity between two protein structures
Lower value indicates greater structural difference

IDDT- Local Distance Difference Test, measures the distance differences between atom pairs in model and reference structures
Lower value indicates greater structural difference

Conclusions

- Aim 1: CDR3α/β loops display a greater degree of structural flexibility than other CDR loops.
- Aim 2: CDR3α/β loop-mediated structural flexibility is found in cross-reactivity.

Future Directions

- Increase the number of TCR complexes studied for more definitive conclusions.
- Implement more structural difference methods.[9]
- Evaluate the role of MHC flexibility in cross-reactivity.

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Acknowledgments

Special thanks to the King Foundation and UTMDACC SHP for their support. Diagrams created with Biorender.com. Molecular graphics generated with UCSF Chimera.