**Abstract**

The ability of immune cells to recognize intracellular proteins is vital for adaptive immunity. The specialized and systemic immune cells monitor their microenvironment, discriminate foreign peptides from self-peptides, and defense against microbes and cancers. These processes are mediated by T-cell receptors (TCRs) expressed on T cells. TCR participates in the activation of T-cells in response to peptide fragments bound to major histocompatibility complex (MHC) molecules on antigen-presenting cells (APCs). Immune cells detect a wide range of intracellular proteins via TCR-peptide/MHC interactions. Therefore, the TCR-pMHC interaction leading to T-cell activation is the underlying principle to understand antigen discrimination. To identify the structural conformations of TCRs leading to discrimination in peptide binding, we performed …, applied…,

**Keywords**: TCR, MHC, TCR-pMHC, RosettaDock, protein docking, protein-protein interaction, antigen discrimination

**Introduction**

T cells are an integral component of the adaptive immune responses by detecting a broad range of targets, such as self-antigens, viral oncoproteins, and cancer neoantigens. T-cell receptors (TCR) mediates this process by sensing specific peptides loaded on major histocompatibility complex (pMHC). The TCR does not recognize and bind antigen directly unlike the B-cell receptors. Instead, it senses short peptide fragments presented on MHC molecules. Cytotoxic T cells interact with the MHC class I molecules and kill infected cells or tumors, whereas, helper T cells interact with the MHC class II molecules and activate other immune cells. It has been known that around 4 x unique T cells circulate in the adult human body and each one has multiple TCRs on its surface. This entails a structurally various set of TCRs that can bind and induce immune responses to antigens.

Human T cells express a TCR made up of two polypeptide chains. The most common type of the TCR adopts alpha(α)-beta(β) (95%) chains, and the remaining smaller subset of cells has a TCR with gamma (γ) and delta (δ) chains (5%). Each chain contains two folded domains, membrane-proximal constant (C) and antigen-binding variable (V) domains, and these two chains are maintained by a disulfide bond. The variable regions of a heterodimeric molecule form an antigen-binding site. Each TCR V domain contains six hypervariable loops, known as complementarity-determining regions (CDR). There are CDRα1- CDRα3 in the TCRα chain and CDRβ1- CDRβ3 in the TCRβ chain. CDRs are key structural features for antigen recognition. The CDR1 and CDR2 interact with the MHC’s α-helices for MHC recognition, while the CDR3 contacts the peptide antigen which are the main determinants of target specificity. Like immunoglobulin genes, TCR genes have manifold V, D, and J gene segments in beta chains while V and J gene segments in alpha chains. V(D)J recombination events occur during the development of the thymocyte. The rearrangement of the beta chain takes place first and they will put together after the rearrangement of the alpha chain. This assembly provides a T cell with a unique antigen receptor.

The structures of many bindings of αβTCR with peptide-MHC complexes have now been determined, allowing some of the general insights into antigen recognition. The overall binding modes of crystallized 34complex structures of αβTCR with the MHC-bound peptide in humans have shown that the TCR docks on pMHC in a central diagonal orientation. Typically, the variable α domain (CDR1α, CDR2α, CDR3α) and β domain (CDR1β, CDR2β, and CDR3β) are positioned over the N and C terminus of the peptide, respectively, though the considerable variation in the binding angles. The TCR α chain is oriented over the α2 or β1 helix whereas the TCR β chain is oriented over the α1 helix of the MHC molecules (Castro et al., 2015). It has been known that the structural features of pMHC decide the TCR repertoire~~.~~

Much of what we know about TCR-pMHC assemblies is derived from data on the three-dimensional crystallographic structures found in the Protein Data Bank (PDB ). TCR3d is a curated database and comprehensive TCR structural data resources identified from the Protein Data Bank (PDB) (Gowthaman & Pierce, 2019). The database includes all known TCR structures, TCR-pMHC complex structures with unbound TCR and pMHC, and provides information on loop sequences, peptide binding mode, and interface features. TCR-pMHC complex structures and TCR structures can be further examined based on MHC class and chain information, respectively.

Molecular docking simulation is a powerful method for drug screening, the behavior of nanomaterials, and protein-protein interactions. Protein-protein docking is a computational technology to predict the three-dimensional protein complex structure, given the individual structure of the interacting proteins. Docking approaches suggest the fundamental studies of protein binding modes of complex structures and offer general insights into protein interactions. Several studies have utilized docking to investigate the interaction between the TCR and the pMHC. The most representative study using docking is TCRFlexDock (Pierce & Weng, 2013). TCRFlexDock is a specialized flexible backbone docking method designed to predict the appropriate orientation between the TCR and the pMHC by utilizing twenty crystalized TCR-pMHC structures and each unbound structure of the TCR and the pMHC. It generates 1,000 TCR-pMHC models and scores them using ZRANK to choose the best TCR-pMHC complexes. Also, many databases collect various information of TCR (Zvyagin et al., 2020).

Characterizing these interactions and understanding the fundamentals is therefore an important issue.

Castro, C. D., Luoma, A. M., & Adams, E. J. (2015). Coevolution of T‐cell receptors with MHC and non‐MHC ligands. *Immunological Reviews*, *267*(1), 30–55.

Gowthaman, R., & Pierce, B. G. (2019). TCR3d: The T cell receptor structural repertoire database. *Bioinformatics*, *35*(24), 5323–5325.

Lyskov, S., & Gray, J. J. (2008). The RosettaDock server for local protein–protein docking. *Nucleic Acids Research*, *36*(suppl\_2), W233–W238.

Pierce, B. G., & Weng, Z. (2013). A flexible docking approach for prediction of T cell receptor-peptide-MHC complexes. *Protein Science*, *22*(1), 35–46. https://doi.org/10.1002/pro.2181

Zvyagin, I. V, Tsvetkov, V. O., Chudakov, D. M., & Shugay, M. (2020). An overview of immunoinformatics approaches and databases linking T cell receptor repertoires to their antigen specificity. *Immunogenetics*, *72*(1), 77–84.