A Structural Switch that Couples TCR Ligand Binding to Signaling

The immune system is formed by a complex network of cells that have the ability to kill pathogens (such as viruses and bacteria) while at the same time do not cause autoimmunity or allergy, which could harm the host. One of the main orchestrators of the immune response is the T cell. Each T cell expresses a unique T cell receptor (TCR) which discriminates between infected and healthy cells with remarkable efficiency[1]. T cells are activated by the TCR binding to a molecule expressed on the surface of the target cell, called Major histocompatibility complex (MHC), displaying a short linear antigenic peptide (8-15 amino acids). While T cell activation is correlated with how well a TCR binds to an antigen, exceptions exist in which high potency interactions bind weakly to their target and *vice versa*[2,3]. However, the key parameters behind this discrepancy remained unclear.

A collaborative team of researchers led by Prof. Christopher Garcia (Stanford), and including Profs. Ron Vale (UCSF), Brian Evavold (University of Utah), Mark Davis (Stanford), Jay Groves (UC Berkeley) and Jim Heath and Bill Goddard (Caltech), sought to identify key determinants of T cell activation by studying human T cells that had impaired signaling despite robust binding to antigens. Large libraries of antigen molecules displayed on the surface of yeast were used to identify potent agonists for the previously non-responsive TCR. Interestingly, subtle changes in the peptide antigen elicited major differences in T cell activation. Crystal structures of the TCR bound to agonist and non-agonist ligands were essentially identical (Figure 1; left panel).

When structural and biophysical measurements could not account for these differences, the authors used single-molecule force probes to investigate the nature of these interactions under force. These measurements revealed the emergence of catch bonds at the binding interface of agonist interactions but not non-agonists (Figure 1; middle panel). Catch bonds are intermolecular interactions which initially strengthen the interaction when force is applied to the system before eventual dissociation[4]. To visualize the process of catch bond formation, the authors developed a dynamic molecular model using steered

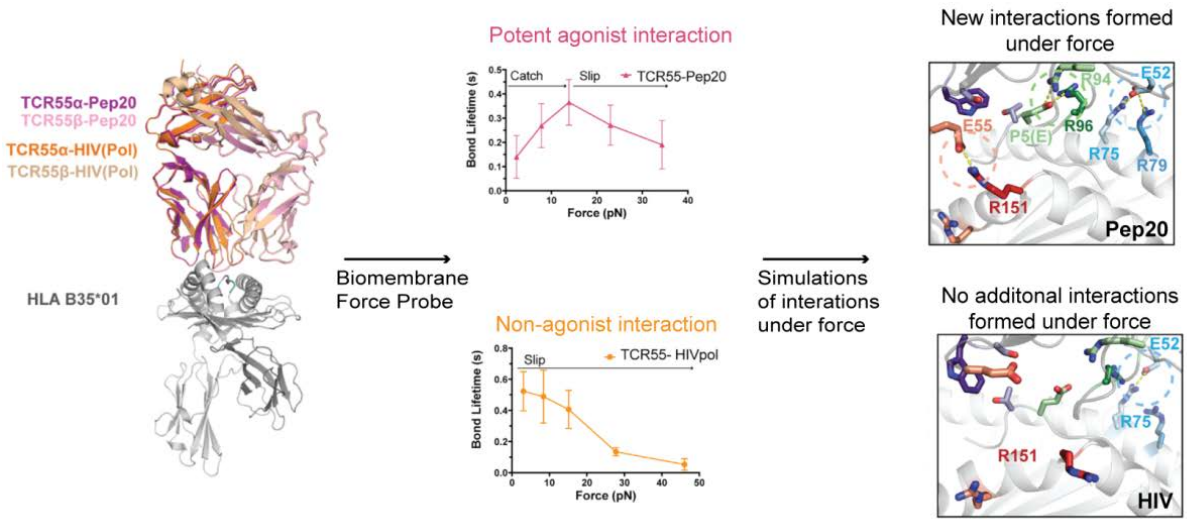

Figure 1. Overlay of TCR55 bound to agonist (HLA B35-Pep20) and non-agonist (HLA B35-HIVpol) peptide-MHC complexes (left panel); Bond life time versus force curves for TCR55 binding to HLA B35-Pep20 (top, pink) and HLA B35-HIVpol (bottom, orange) (middle panel); Snapshots of TCR55 disassociating from Pep20 and forming new bonds (top), compared to TCR55 disassociating from HIVpol where no additional molecular interactions are formed (bottom) (right panel).

molecular dynamics simulations to mimic the effect of mechanical forces experienced at the interface of the T cell and target cell. When force is applied to the activating TCR-antigen interactions, new hydrogen bonds at the TCR-antigen interface emerge, while in the non-agonist interaction no new bonds are formed (Figure 1; right panel).

The visualization of this process would not have been possible without the structural information derived from data collected at SSRL using Beam Line 12-2. Catch bonds represent an additional level of dynamic diversity built in as a proof-reading mechanism to link TCR recognition and subsequent activation. This work revealed a triggering mechanism by which TCR ligation and activation can be decoupled to regulate TCR ligand discrimination. The identification of this dynamic mechanism may provide new avenues for TCR engineering for immunotherapy by enhancing the potency of TCR to tumor antigens through engineering catch bonds.

References

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