Adequate and Simultaneous Accumulation of TCR-pMHC Catch Bonds for early T cell Activation

Yinnian Feng[a], Dibyendu kumar Das[a], Robert J. Mallis[b], Ellis L. Reinherz[c,d] and Matthew J. Lang[a,e]

[a] *Department of Chemical and Biomolecular Engineering, Vanderbilt University, Nashville, TN, USA*
[b] *Department of Biological Chemistry and Molecular Pharmacology, Harvard Medical School, Boston, Massachusetts*
[c] *Laboratory of Immunobiology and Department of Medical Oncology, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA, USA*
[d] *Department of Medicine, Harvard Medical School, Boston, MA, USA*
[e] *Department of Molecular Physiology and Biophysics, Vanderbilt University Medical School, Nashville, TN, USA*

Ligation of the T cell receptor (TCR) by antigen peptides displayed through the major histocompatibility complex (MHC) molecule activates a specific T cell response to foreign invaders. Although the role of mechanical forces in TCR signaling has been previously reported, the mechanism of such force-induced triggering is still unclear. Herein, we studied the role of mechanical force in T cell activation at the single cell level. Bond lifetimes of TCR- agonist peptide MHC (pMHC) at specific rupture forces were measured. We elucidated that the in wild type (wt) T cells, the wt TCR- agonist pMHC interaction is akin to a catch bond whereas in mutant T-cells with a critical structure deletion in the T-cell receptor (dTCR), dTCR- agonist pMHC exhibits bond lifetime deficiencies. The differences seen in bond lifetimes between these two types of cells also affect the T cell triggering process. We find that at robust triggering conditions for wt- T cells where an intracellular calcium flux is observed, d-T cells showed triggering impairment. Meanwhile, a rapid pMHC coated bead displacement, which is regarded as the simultaneous multiple catch bonds accumulation, was observed during the wt- T cell triggering process. Therefore, a T cell triggering model combined both molecular and cellular levels was proposed. At the molecular level, the TCR-pMHC interaction shows a force-induced catch bond and a specific region of the TCR stabilizes such force transduction to extend bond lifetimes. At the cellular level, occurrence of early T cell triggering events requires sufficient pMHC density, adequate force and simultaneous accumulation of catch bonds.