



Molecular Movements Within T-cells that Activate the Immune Responses that Attack Infected or Diseased Cells



K.N. Brazin¹, R.J. Mallis¹, A. Boeszoermyeni¹, Y. Feng², A. Yoshizawa¹, P.A. Rech³, P. Kaur⁴, K. Bi¹, R.E. Hussey¹, J.S. Duke-Cohan¹, L. Song⁴, G. Wagner¹, H. Arthanari¹, M.J. Lang², E.L. Reinherz¹

1. Harvard Medical School; 2. Vanderbilt University; 3. Univ. Complutense de Madrid, Spain; 4. NHMFL

Funding: G.S. Boebinger (NSF DMR-1157490); E.L. Reinherz (NIH AI138489); G. Wagner (NIH GM047467, NIH AI037581); M.J. Lang (NIH AI100643)

T-cells and their surface proteins, T-cell antigen receptors (TCRs), perform immune surveillance to prevent or combat infections, cancers, and other diseases. Here, researchers determined the molecular details of the structure of the TCR α subunit and its dynamic movements during T cell activation.

Experiments at the MagLab involved Electron Paramagnetic Resonance (EPR) and spin labeling techniques. Researchers measured the relative distances between different segments within TCR α and how deep these segments are immersed in lipids mimicking cell membranes. These measurements identified a flexible L-shaped formation of the transmembrane domain of TCR α in the membrane, which undergoes stepwise movements during T-cell triggering as demonstrated by functional and mutational studies. These findings contribute to the conclusion that T-cell activation is initiated via a dissociative mechanism, shifting disposition of individual segments to rearrange TCR membrane topology and weaken its association with another T cell surface protein - CD3.

This study defined the structural movements within the TCR α transmembrane domain linked to fundamental TCR complex mechanobiology and cell activation. The findings provide insight into developing new drugs to fine tune T-cells that combat cancers or other non-malignant diseases.

Facilities and instrumentation used:

EMR Facility (Bruker E680 EPR spectrometer)

Citation: K.N. Brazin, R.J. Mallis, A. Boeszoermyeni, Y. Feng, A. Yoshizawa, P.A. Rech, P. Kaur, K. Bi, R.E. Hussey, J.S. Duke-Cohan, L. Song, G. Wagner, H. Arthanari, M.J. Lang and E.L. Reinherz. *The T-cell Antigen Receptor α Transmembrane Domain Coordinates Triggering through Regulation of Bilayer Immersion and CD3 Subunit Associations.* **Immunity** 49, 1 (2018)

