Mechanosensing by the αβ T Cell Receptor

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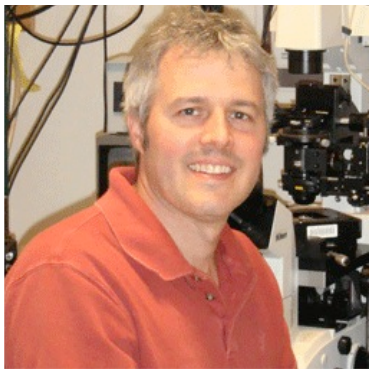

Date and Time: 12—1pm, 29 Jul 2016, Friday

Venue: Perseverance Room, Enterprise Level 5

Abstract

Adaptive immunity begins with ligation between the αβ T cell receptor (TCR) and antigen peptides displayed through the major histocompatibility complex (MHC) molecule. Despite low apparent affinities, T cells achieve exquisite sensitivity where a handful of antigenic pMHC molecules can be detected among a sea (100,000 or more) of irrelevant peptides. In collaboration with the Reinherz lab, we reconciled this paradox by proposing that the αβTCR acts as a mechanosensor. Detection leverages an anisotropic mechanosensing mechanism driven by shear force generated through cell movement to enhance bond lifetime and initiate critical signaling events. We investigate the role of force in T cell receptor triggering using optical tweezers and a series of single molecule assays including a DNA tether spacer technology that permits piconewton force application and nanometer scale displacement monitoring on single cells. Measurements reveal that the FG loop in the β-subunit constant domain (Cβ) allosterically controls both the variable domain module's catch bond lifetime and peptide discrimination via a force-driven conformational transition. Analysis of TCR αβ and preTCR transitions reveal they can be reversible and bond strengthening is associated with the extended state. Broad promiscuous binding is seen in the preTCR, which only contains TCRβ. Mechanosensing capable of triggering cells is achieved with few molecules properly loaded along the shear direction recapitulating the native signaling environment.

Biography

Matthew Lang grew up in Pittsburgh PA. As an undergraduate he studied Chemistry at the University of Rochester earning a BS. He received his PhD in Physical Chemistry from the University of Chicago under the guidance of Graham Fleming where he studied ultrafast solvation dynamics and primary energy transfer steps in photosynthesis. Lang went on to study Biophysics with Steve Block at Princeton and followed the lab to Stanford University where he was a Jane Coffin Childs postdoc. In 2002 Lang moved to Boston Massachusetts and launched his independent academic career at MIT in the department of Mechanical Engineering and the Division of Biological Engineering. He moved to Nashville, Tennessee in 2010 where he joined the faculty of the Department of Chemical and Biomolecular engineering at Vanderbilt University. He is also affiliated with the Department of Molecular Physiology and Biophysics at Vanderbilt University Medical School. The Lang Lab focus surrounds the study of molecular and cellular machinery in particular ClpXP, kinesins, cellulose based motors, T-cell receptors and the mechanics of amyloid fibers. The lab is equipped with single molecule biophysics tools including optical tweezers and single molecule fluorescence and has advanced a number of technical methods in these areas.