LS13-030 - Mechanical Forces in T-Cell Antigen Recognition

Abstract

T-cells readily detect the presence of even a single antigenic peptide/MHC complex (pMHC) among thousands of endogenous pMHCs via clonotypic T-cell receptors (TCRs) on the surface of antigen presenting cells (APCs). The mechanisms underlying this phenomenal sensitivity have remained elusive, but more recent studies suggest mechanical forces to be instrumental. To address their role most directly we will introduce calibrated force sensors into the immunological synapse to allow for quantitative visualization of forces acting between TCR and pMHC on opposing cell surfaces. Sensors will link the pMHC directly to the APC surface and function as a short spring, with fluorescent dyes site-specifically coupled to both ends: the spring collapses in case of zero force, giving rise to high Förster resonance energy transfer (FRET) between donor and acceptor dyes; FRET decreases when the spring is stretched.
Forces exerted on the TCR will be measured in synapses of T-cells contacting functionalized planar lipid bilayers and also physiological synapses between T-cells and APCs. To evaluate their function in ligand discrimination and T-cell triggering, forces will be correlated to the stimulatory potency of chosen pMHCs, TCR-pMHC bond rupture or TCR-proximal signaling, to be monitored simultaneously. We expect to reveal new principles underlying T-cell sensitivity, a true hallmark of adaptive immunity, and to break new ground in studying cell-cell contacts.

Scientific disciplines:
Immunology (50%) | Biophysics (50%)

Keywords:
T-Cell Antigen Recognition, primary TCR-transgenic T-cells,T-Cell Receptor,Immunological Synapse, Mechanobiology, Protein-Protein Interactions, SingleMolecule Microscopy, Force Microscopy, Superresolution Microscopy, FRET

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Further links to the persons involved and to the project can be found under
https://www.wwtf.at/funding/programmes/ls/LS13-030/