

LS24-011 - Designing synthetic antigen-presenting cells to determine the 3D nanoenvironment of T-cell antigen recognition

Abstract

T-cells initiate an immune response by detecting and reacting to rare foreign antigens on the surface of antigen-presenting cells (APCs). The remarkable sensitivity and specificity of this recognition process has puzzled researchers for decades, yet a comprehensive mechanistic understanding is still lacking. This is mainly due to the complexity and dynamics of the cellular interaction, where various accessory proteins create an intricate environment around the antigen:T-cell receptor (TCR) pair, and biochemical stimuli are tightly intertwined with membrane topography and mechanical forces.

We here propose to design a new generation of APC mimics for elucidating the biophysical and biochemical parameters underlying sensitized antigen detection by T-cells. For this, we will recreate the specific 3D nanoenvironment of T-cell antigen recognition by interfacing T-cells with synthetic APCs (sAPCs) that allow for reconstituting, manipulating, and quantifying key parameters. Our approach rests on three pillars: i) a DNA origami-based biointerface for the delivery of biochemical and physical cues with nanometer precision; ii) an sAPC core composed of polymer microparticles with cell-like mechanical properties, and iii) state-of-the-art fluorescence microscopy techniques to directly correlate input with output signals within live T-cell/sAPC interfaces down to the single molecule level. By integrating these sophisticated experimental approaches, we aim to dissect the biochemical and physical parameters contributing to sensitized T-cell antigen recognition and obtain a quantitative description of the underlying molecular mechanisms.

Scientific disciplines:

Biophysics (60%) | Immunology (20%) | Polymer chemistry (20%)

Keywords:

Immunobiophysics Membrane biophysics DNA origami Nanobiotechnology T-cell antigen recognition Single molecule fluorescence microscopy

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Further links to the persons involved and to the project can be found under
<https://www.gmbh.wwtf.at/funding/programmes/ls/LS24-011/>