T cell early mechanosensitivity : a key step in a precise and rapide answer to dangerous situations

Lead supervisor: PH Puech, Laboratoire Adhésion et Inflammation [HDR]
Co-supervisor: Y Hamon, CIML

Abstract

Following infection, an adaptive immunity may develop in the lymph nodes when naïve T lymphocytes encounter Antigen Presenting Cells (APCs) harboring fragments of the pathogens. How those T cells translate rare, diverse, medium affine antigenic signals into a strong, specific and nearly instantaneous response is still widely debated. The T Cell Receptor and the Major histocompatibility complex as its ligand (TCR/MHCp) share unparalleled biomechanical properties, the TCR acting as a mechanosensor molecule, making T cells sensitive to the magnitude as well as the kinetics of force application, and to more global scales of substrate mechanics. We propose to investigate in depth the mechanotransduction properties of the TCR upon APC/T cells contacts, starting from on our recent observation of mechanical changes occurring prior to intracellular signaling (Zak et al. 2019).

Keywords

T cells, forces, cell biomechanics, actin meshwork, plasma membrane, physical models of signaling

Reference

Zak, Alexandra, Sara Violeta Merino Cortés, Anaïs Sadoun, Avin Babataheri, Stéphanie Dogniaux, Sophie Dupré-Crochet, Elodie Hudik, et al. 2019. 'Single-Cell Immuno-Mechanics: Rapid Viscoelastic Changes Are a Hall-Mark of Early Leukocyte Activation'. *BioRxiv*, November, 851634. https://doi.org/10.1101/851634.

Objectives

We defined 3 main questions for this project :
Q1 : How are modulated the mechanical properties of T cells during T/APC contact under forces?
Q2 : What parameters impact on T cell responsiveness (cytoskeleton, membrane nano-organization)?
Q3 : What are the consequences of these inter-cellular forces in term of chronology and magnitude of signalling events ?

Proposed approach (experimental / theoretical / computational)

These objectives will be tackled experimentally, by combining quantitative measurements of forces and mechanics using atomic force microscopy (AFM) indentation or single cell force spectroscopy modes (SCFS) or optical tweezers (OT), already available in Lab. Adhesion & Inflammation. We will develop an innovative force sensing technique as the « lateral AFM » (LatAFM), based on SCFS, coupled to fluorescence microscopy and additionally allowing to control of one of the partner rigidity and shape by aspirating in a pipette. This will be further supported by advanced biophotonic tools based on spot variation fluorescence correlation spectroscopy (svFCS) based on fluorescent molecule diffusion at the plasma membrane, available in CIML. This method enables to document membrane lateral nano-organization on living cells. We will take benefit of the versatile biological system of Cos-7 cells arranged experimentally as APC, which can be further complexified by expressing selective surface molecules recognized by transgenic mice T cells.

Interdisciplinarity

Changes in cell biomechanics converted into biological signals because of cell to cell contacts is of general importance in immunity, both in health and disease. Although lymphocytes are circulating cells, there task is to probe their antigenic environment through constant palpations of neighbouring cell in lymphoid organs, that may dysfunction in autoimmunity or cancer. By nature, this thematic at the border between biology and biophysics is multi- and inter-disciplinary thereby fitting exquisitely in the present call. We will highly benefit of the interaction with Centuri engineering teams for data processing in order to extract quantitative data from the rich experiments we propose, coupling scalar measurement, resolved in time and space, with imaging techniques, to put in tight correlations and if possible, define clear causality links. We will also benefit from them in regard to our development of innovative instrumentation strategies (LatAFM)….

Expected profile

This topic provides a unique approach at the interface of physics and biology for a biologist or an experimental physicist in a young, highly cohesive and multidisciplinary environment (physicists, biologists and physicians) around a theme with strong applications in human health. The candidate should have bases in microscopy and computer programing since the richness of the data may imply to develop data analysis codes, or at least be willing to invest in learning it.