

Crosstalk between cadherins and integrins : a micromechanical approach

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Subjects / Tools-Methodologies

- 1 : Cell mechanics/Optical tweezers
- 2 : Cell-cell and cell matrix adhesion/Micropatterning, videofluorescence
- 3 : Crosstalk/Molecular biology tools - expression of mutants

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Summary of lab's interests

Cell mechanics Cytoskeleton organization and remodelling Dynamics of molecular motors Cell adhesion and migration - structure and growth of adhesive contacts. Mechanotransduction : sensitivity of the cell to its mechanical environment.

Summary of project

In normal or pathologic tissues, variations of the coupling between cell-cell and cell-matrix adhesion systems may deeply affect the stability of the adhesive status of cells, and their mechanical properties. The goal of this thesis will be to understand how the strength and growth dynamics of intercellular adhesions, supported by cadherins, are modulated by the shape and extension of cell-matrix adhesion, supported by integrins. This will be achieved by following the structural changes and the mechanical rigidity of an intercellular contact during its formation, as a function of the conditions of cell adhesion to the extracellular matrix (ECM). The reciprocal crosstalk (perturbation of cell-matrix contacts due to intercellular adhesion) will also be investigated.

Complementary micromechanical and visualization techniques, coupled to molecular biology tools, will be used to probe the stiffness of an intercellular contact, and to observe the remodelling of its structure under an externally applied mechanical stress, in different cell-ECM adhesive conditions. Conditions of spreading on the ECM will be modulated by plating cells on patterns of different sizes micro-printed with fibronectin. The formation of a cell-cell contact will be simulated by bringing a bead coated with cadherin fragments in contact with the cell membrane. After a given incubation period, the bead-cell contact rigidity will be probed by pulling on the bead with an optical trap. The viscoelastic response of the contact will be measured as a function of the incubation time and of the cell-ECM patterned contact area. In the same time the structure and development of the contact will be visualized by fluorescence microscopy.

S180 cells will be used as a biological model, since they can be transfected to express the different adhesive receptors (cadherins, integrins) in a controlled way. It will be possible to compare the properties of intercellular contacts mediated either by type-I cadherins (E- or N-cadherin) or type-II (cadherin-7 or -11), at different expression levels. Also, molecular

biology tools will be used to express cadherins mutants, contact proteins tagged for visualization (beta-catenin, vinculin), or active/inactive forms of effectors acting on the dynamics of the cytoskeleton and of the contacts (Rho, Rac, cdc42, ARP2/3, formin, cortactin&).

The focus will be put on the expected crosstalk effects between cell-cell contacts and cell-ECM contacts. For this scope, the comparative evolution of the structure and of the mechanical properties of intercellular contacts will be followed, in different conditions of cell-ECM adhesion, playing with cell-matrix contact area, spatial repartition and ligand density. The issue is to define the mechanical / chemical / biological conditions under which the integrin-cadherin crosstalk favours the intercellular adhesion or, on the contrary, tends to inhibit it.

This project is partly supported by a grant from ANR "Physique et Chimie du Vivant", and will be held in collaboration with biologists from Sylvie Dufour's group, at Institut Curie (UMR 144-Compartmentation et Dynamique Cellulaires). Candidates are expected to have a background either in physics or in biophysics, and to be motivated for a collaborative experimental work at the interface between physics and biology.