

Investigation of reciprocal crosstalk between cadherins and integrins: a micromechanical study

CrossInteCad - ANR PCV 2007



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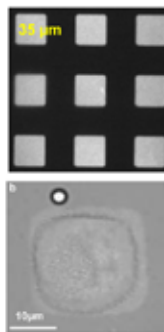
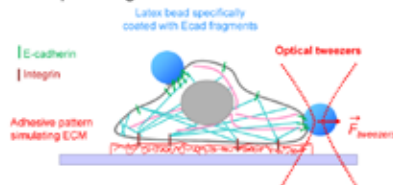
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The goal of the project is to investigate the mechanisms responsible for the growth or the disruption of intercellular contacts mediated by cadherins. We have particularly focused on the structural changes and rigidity variations of these intercellular contacts, induced by the existence (or the absence) of adhesive cell-matrix contacts, and by their spatial distribution. The reciprocal crosstalk (perturbation of cell-matrix contact due to intercellular adhesion) has been also investigated using microforce sensor technique.

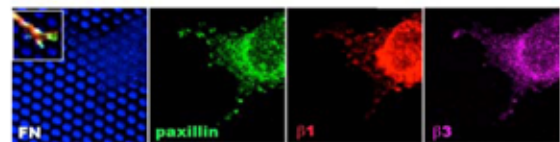
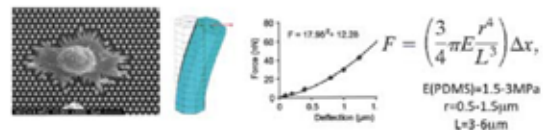
The cellular model is the sarcoma S180 cell line that do not produce any type of cadherins at detectable levels. We have used stably transfected clones producing cadherins; Ecad, Ncad and Cad7 clones express E-cadherin, N-cadherin and type II cadherin-7, respectively.

Cell spreading on fibronectin slows down the formation of cell-cell contacts

Ecad cells are grown on fibronectin (FN) patterns of different sizes. A cell-cell contact is simulated by a micrometric bead coated with Ecad fragments, and incubated during time τ at the cell membrane by means of an optical tweezer. The rigidity and the contact formation velocity are measured as a function of the spreading area A of the cell on FN.

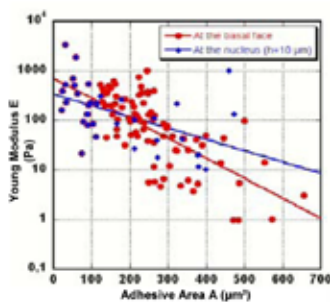


Intercellular contacts stimulate cell pulling force on FN in a Src and PI3K dependent manner



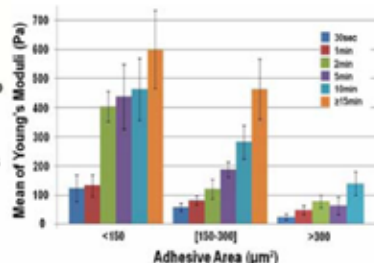
Cells are deposited for several hours on the top of a dense array of micro-pillars and deflect them during the adhesion and migration process. Each pillar acts as sensor of the locally exerted forces that can be simply calculated from the deflection measurements using the equation (du Roure et al., 2005, PNAS 102 (7) 2390-2395), and paxillin, used as a maker of focal adhesions.

Cell-FN spreading area controls the bead-cell contact rigidity



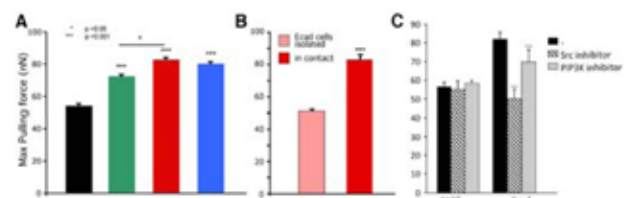
Young's modulus of the bead-cell contact decreases by 3 orders of magnitude when the spreading area varies from 100 μm^2 (spherical cells) to 600 μm^2 (widely spread cells).

Influence of incubation time τ



Contact formation time depends on the cell-FN area:

- 0 < A < 150 μm^2 ~ 2 min
- 150 < A < 300 μm^2 ~ 10 min
- A > 300 μm^2 > 10 min



Isolated Ecad cells exhibit similar pulling force than parental S180 cells. In contrast, in Ecad, cad7 and Ncad cell pairs the intercellular contact mediated by cadherins increases the cell pulling force on FN-coated pillars (A, B). Drug perturbation experiments revealed that Src and PI3K signaling pathways are involved in this process (C). Our results evidence a cadherin-integrin crosstalk that regulates positively the cell-FN adhesion strength.

By different biophysical approaches used to probe cellular micro-rheology and adhesion forces we give new insight on the complex relationship between integrins and cadherin to regulate cell adhesion strength and the mechanical rigidity of the cortex at the contact site.

Publications:

- Negative feedback from integrins to cadherins: a micromechanical study. Alia Al Kilani, Olivier de Freitas, Sylvie Dufour & François Gallet. In revision at Biophysical Journal.
- Src and PI3K signaling pathways are involved in the Cadherin-dependent modulation of integrin-based adhesion strength. Audrius Jaisatis, Benoit Ladoux & Sylvie Dufour. Manuscript to be submitted.

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