

## SINGLE MOLECULE STUDIES TO DECIPHER CADHERIN-MEDIATED CELL ADHESION

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Cell-cell junctions provide tissue integrity and promote cell polarity. Classical cadherins are adhesive receptors involved in controlling the specificity, organization and dynamics of Ca<sup>2+</sup>-dependent cell-cell adhesion, which is crucial for the development and maintenance of tissue architecture and function. Alteration in the expression and functions of cadherins often correlate with the progression to tumor malignancy. Cadherins on neighbouring cells interact through their extracellular subdomain repeats (EC1 to EC5). Their adhesive engagement initiates intracellular signals ranging from cytoskeletal organization to cell polarity, proliferation, or apoptosis that are communicated through their conserved cadherin tail domain. The role of adhesion forces in the signaling process is yet to be understood due to the difficulty in the interpretation of biological responses involving multimolecular organizations.

Our aim is to better understand how cadherins regulate cell contacts stability, and how dynamics and mechanical stress regulate intracellular signaling pathways. Since the EC domain is crucial for their adhesive function, we recombinantly expressed EC domains of different type I and type II classical cadherins. Aggregation assays indicate that these fragments retain biological activity when chemically immobilized on glass beads (Perret et al., 2002). Individual cadherin trans interaction was then analyzed using biophysical approaches such as Laminar Flow Chamber (Perret et al. 2002), Biomembrane Force Probe (Perret et al. 2004) and AFM (du Roure et al., 2006). These studies revealed multiple dissociation events, which could provide distinct properties needed for transient-specific recognition as well as stable tissue formation. Comparison, at the single molecule level, of the kinetics parameters between different cadherins homophilic interactions should help understanding differences in their biological roles. In order to understand how a cell deciphers the information given by adhesive contacts, cadherin-decorated petri dishes are also used. These molecular studies provide a better understanding of the molecular processes used by cadherins for maintenance of cohesion and plasticity of cell-cell adhesion.

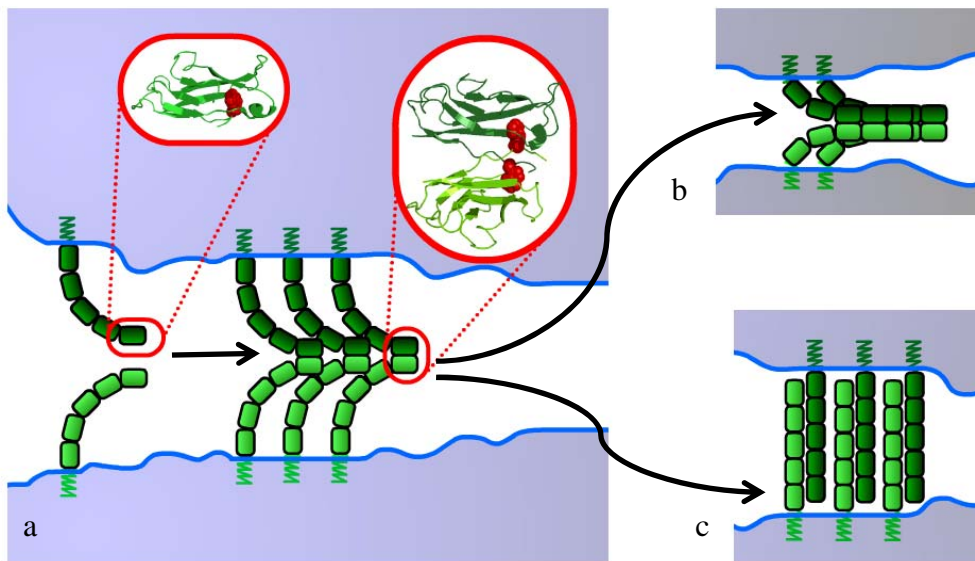
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(a) Schematic drawing of different adhesive surfaces between cadherin molecules leading to adhesive contacts (insert: Trp2 intramolecularly docked, to beta-strand exchange as observed in C/EC15 crystals. (b-c) Deeper interactions have been characterized by BFP between E/EC15 Perret et al., 2004) and C/EC15 by SFA, but never directly visualized.