DO ALL CADHERINS BIND THROUGH THE SAME ADHESIVE INTERFACE?

Chevalier Sébastien,Courjean Olivier, Feracci Hélène[¥]
Centre de Recherche Paul Pascal (CNRS, UPR 8641), Université Bordeaux 1, Avenue du Dr A. Schweitzer, 33600 PESSAC, France
[¥]*feracci@crpp-bordeaux.cnrs.fr*

Classical cadherins are cell surface transmembrane glycoproteins involved in cell to cell adhesion. They play important roles in tissue morphogenesis and in the maintenance of tissue architecture in adults. In addition to their structural function, cadherins contacts are actively remodeled and impact cell movement and migration. Moreover, changes in cell-cell adhesion accompany the transition from benign tumor to invasive malignant cancer, and the subsequent metastatic dissemination of tumor cells.

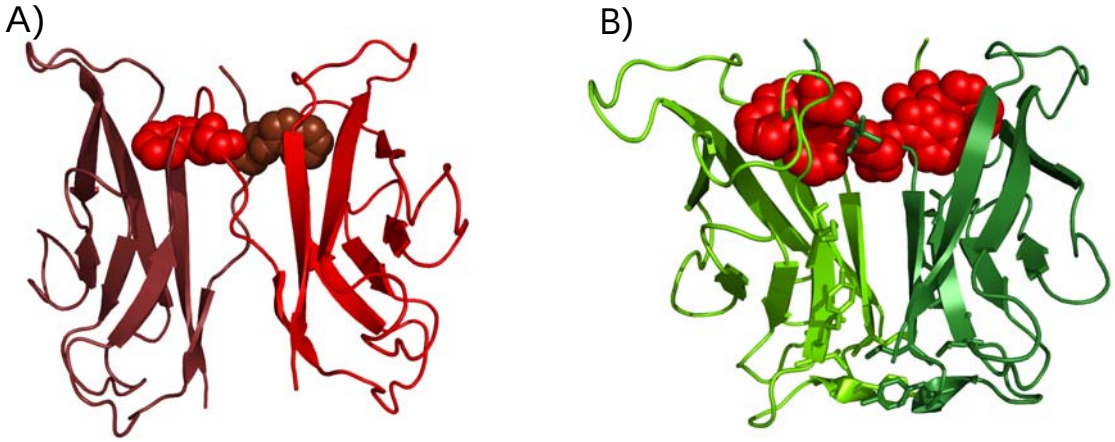
Our aim is to better understand how cadherins regulate cell contacts stability, as well as numerous intracellular signaling pathways. We choose to focus on two cadherins, E(epithelial)-cadherin that is a tumor suppressor, and cadherin-11, as prototypes of type I and type II classical cadherins respectively. Switching between E- and -11 cadherin is often observed in many epithelial cancers. Since the extracellular domain (EC) is crucial for regulating specific Ca^{2+}-dependent homotypic interactions [1], we recombinantly expressed EC domains of E-cadherin and cadherin-11. The E-cadherin [2] and cadherin-11 (unpublished data) fragments retain biological activity when chemically immobilized on glass beads. Individual E-cadherin trans interaction was then analyzed using biophysical approaches such as Laminar Flow Chamber [3]. Our recent studies revealed the importance of the N-terminal beta strand exchange in type I cadherins trans interaction, and the major role played by a key amino acid: the Tryptophan 2 (Trp2). Cristallographic studies revealed that, except for 2 Tryptophan residues in position 2 and 4 instead of one, the homophilic adhesive interface of type I and type II cadherins is very similar suggesting a similar interaction model [4]. Interestingly, our recent dynamic studies combined with molecular biology techniques strongly suggest that despite these similarities, E-cadherin and cadherin-11 interact with completely different adhesive mechanisms. Comparison of the kinetics parameters between E- and -11 cadherins at the single molecule level reveals that type I and type II cadherins have different interaction properties which should help understanding differences in their biological roles (in preparation).

This work was supported by grants from the Association pour la Recherche sur le Cancer, Fondation pour la Recherche Médicale, Ligue Contre le Cancer Dordogne , and the Région Aquitaine.

References:

[1] Perret E, Leung A, Feracci H, Evans E, *PNAS*, **Vol 101** (2004) 16472-16477.
[1] Perret E, Leung A, Morel A, Feracci H, Nassoy P, *Langmuir*, **Vol 18** (2002) 846-854.
[2] Perret E, Benoliel A-M, Nassoy P, Pierres A, Delmas V, Thiery J-P, Bongrand P, Feracci H, *EMBO Journal*, **Vol 21** (2002) 2537-2546.
[4] Patel S, Ciatto C, Chen C-P, Bahna F, Rajebhosale M, Arkus N, Schieren I, Jessel T, Honig B, Price S, Shapiro L, *Cell*, **Vol 124** (2006) 1255-1268.

Figure:



Structural images of A) Type I (Boggon & al., Science, 2002) and B) Type II (Patel & al., [4]) classical cadherins adhesive interfaces. Residues highlighted are Trp2 for type I and Trp2 and 4 for type II cadherins docked in their hydrophobic pocket