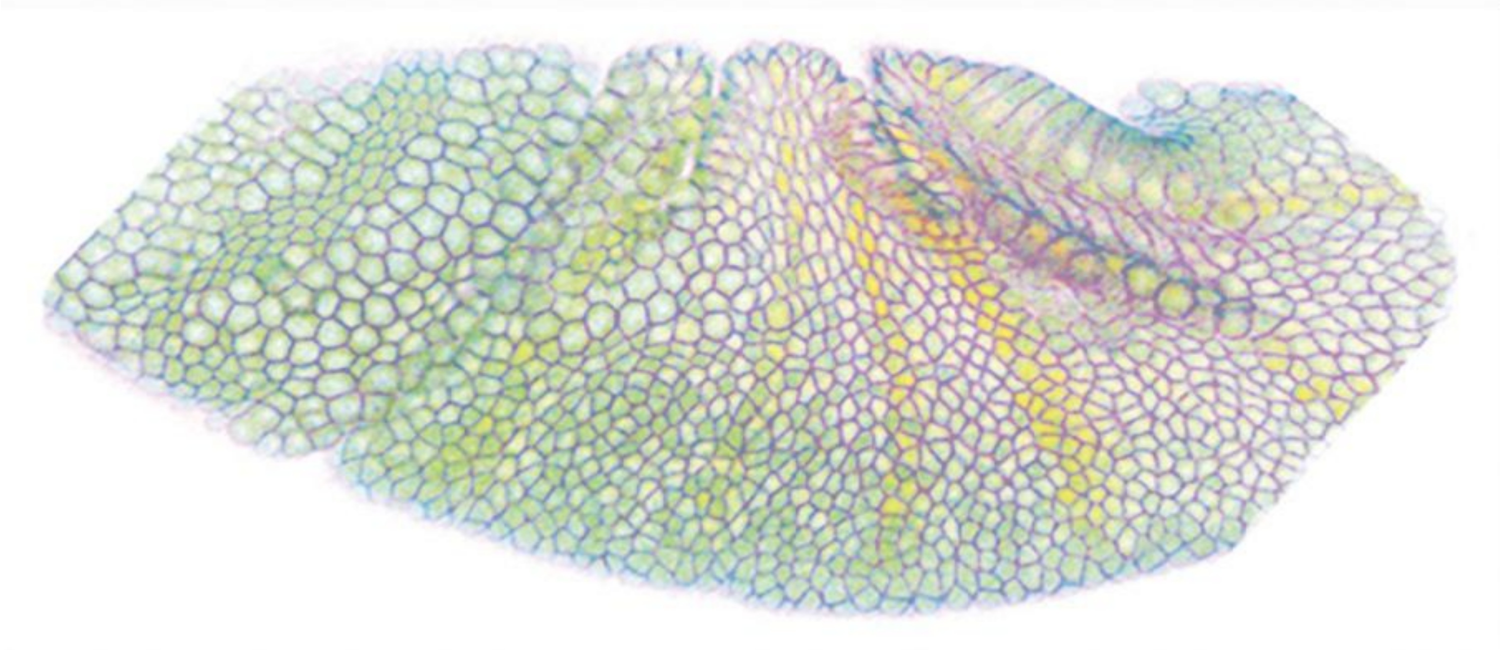
Mechanics of Morphogenesis



Lecture 3: Adhesion: inter- and intra- molecular couplings

Thomas Lecuit
chaire: Dynamiques du vivant

COLLÈGE DE FRANCE
1530

Summary - 31 October

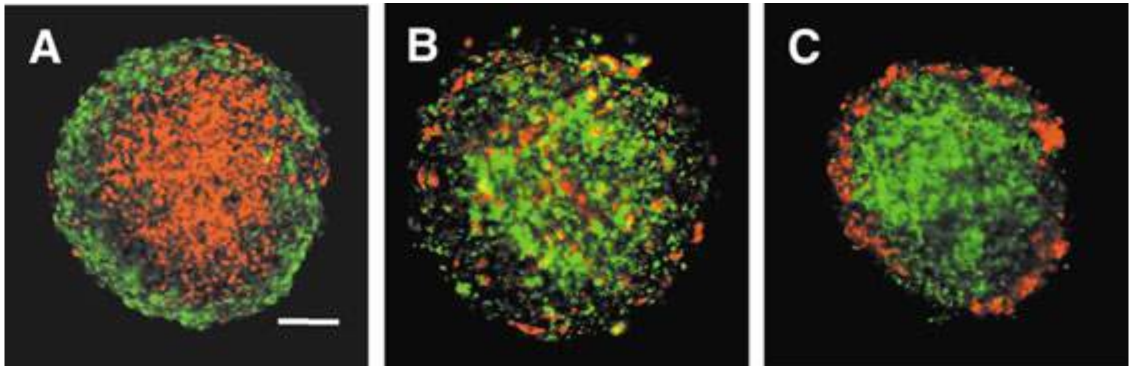
- Adhesion captures the notion of selective/specific aggregation
- Cell sorting phenomena and tissue envelopment behaviours initially interpreted from the standpoint of selective migration (Holtfreter)
- The « differential adhesion hypothesis » (DAH) proposes a purely quantitative description and prediction of cell/tissue behaviours based on surface tension of tissues modelled as fluids approaching thermodynamic equilibrium.
- The discovery of cell adhesion molecules offers an apparent validation of the DAH.
- Discussion of DAH by A. Harris: link between cell surface property dependent on CAMs and reversible work of adhesion?

Quantitative and *Qualitative* determinants of cell sorting

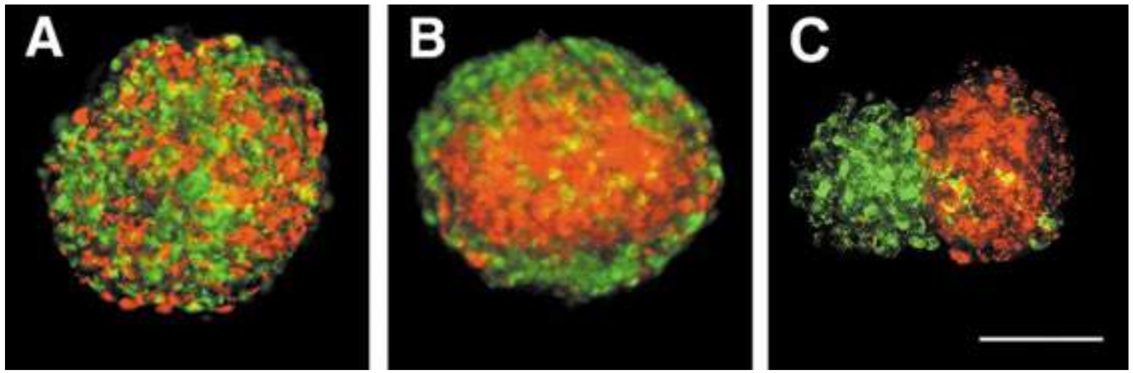
1. Little selective adhesion
2. Quantitative differences seem sufficient for sorting

3. BUT:
No direct measurement of bond strength and adhesion strength

Assumes that [CAM] correlates with adhesion strength



[E-cad] < [P-cad] 2.37 3.55 — [E-cad] = [P-cad] 3.55 3.55 — [E-cad] > [P-cad] 15.8 3.55 10^4 /cell



[N-cad] = [N-cad] — [N-cad] < [N-cad] — [B-cad] = [R-cad]

Duke Duguay,[a] Ramsey A. Foty,[a,b] and Malcolm S. Steinberg[a,*]
Developmental Biology 253 (2003) 309–323

Is cell sorting caused by differences in the work of adhesion?

- Differences between cell aggregates and liquids:

1. Cells are « active particles ». Aggregates are thermodynamically open systems, The final configuration need not reflect minimisation of adhesive free energy.

2. Adhesion is much more than « close range attraction ». The forces that attract cells are not necessarily the same as those that hold cells together.

   Adhesion does not simply arise from H-bonds, van der Waals forces, electrostatic interactions etc.

3. The work of adhesion need not be the same as the work of de-adhesion.

   If there is a *maturation* of adhesion *after* cells are brought into contact (*i.e.* due to cells being active systems) the breakage of adhesive bonds is not the simple reverse of their formation.
   (see Townes and Holtfreter 1955)

4. Adhesion molecules are not distributed uniformly and are mobile units.

   Surface and adhesion are not linearly scaling with one another.

A.K. Harris, *J. Theor. Biol.* (1976) 61:267

Adhesion in multicellular organisms

1. Affinity and Adhesion: a specificity problem

2. Adhesion: a thermodynamic model

3. The molecular framework of adhesion (continued)

4. Evolutionary origin of adhesion mechanisms

5. Adhesion as an active mechanism
    4.1. Clustering
    4.2. Mechanosensation - Mechano-transduction

6. Adhesion and *dissipation*

What are the determinants of adhesion strength?

The molecular nature and strength of chemical bonds

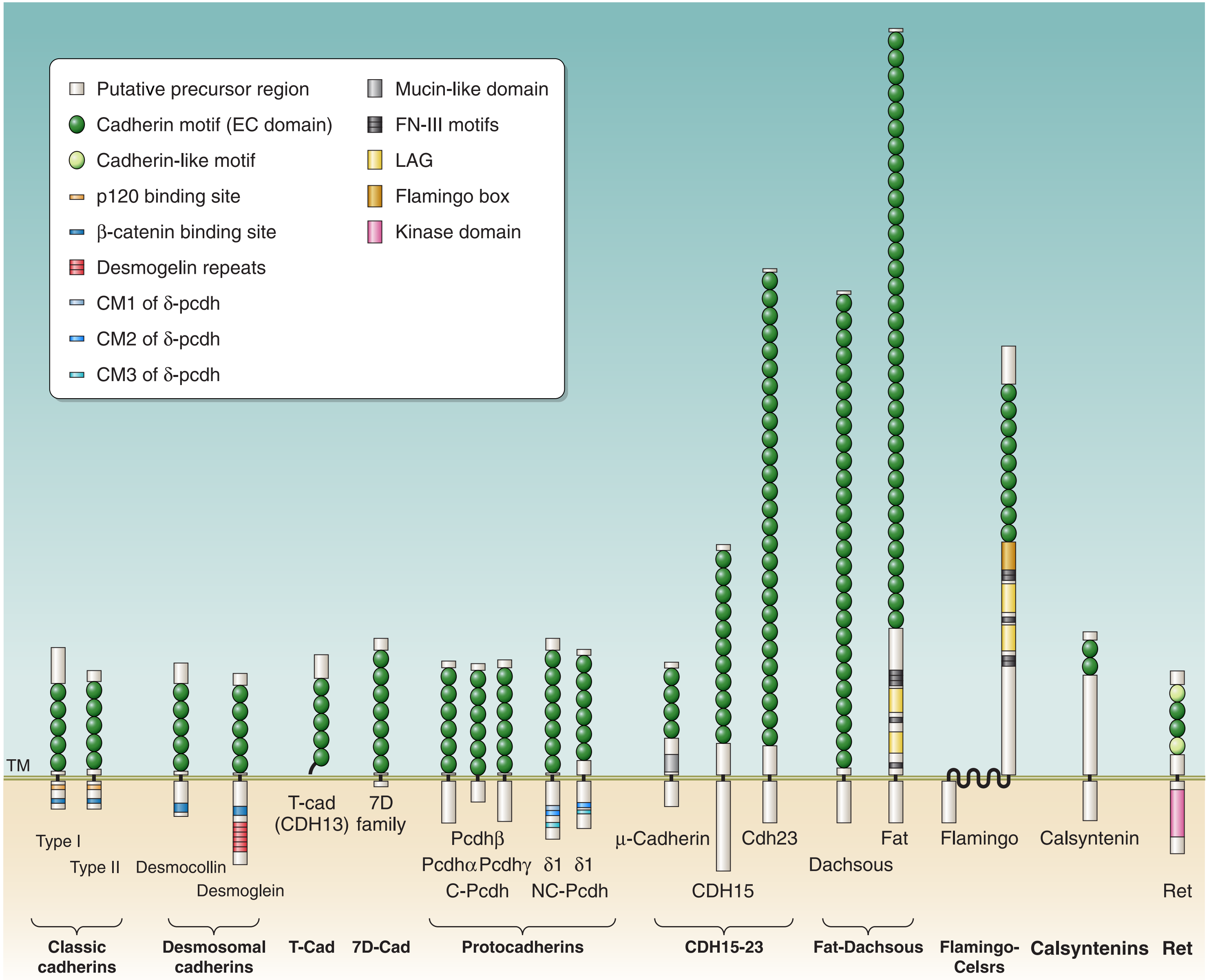
1. The outside view: ectodomain ligation

2. The inside view: coupling to actin

The large family of Cadherins

Physiol Rev 92: 597–634, 2012

Hirano & Takeichi

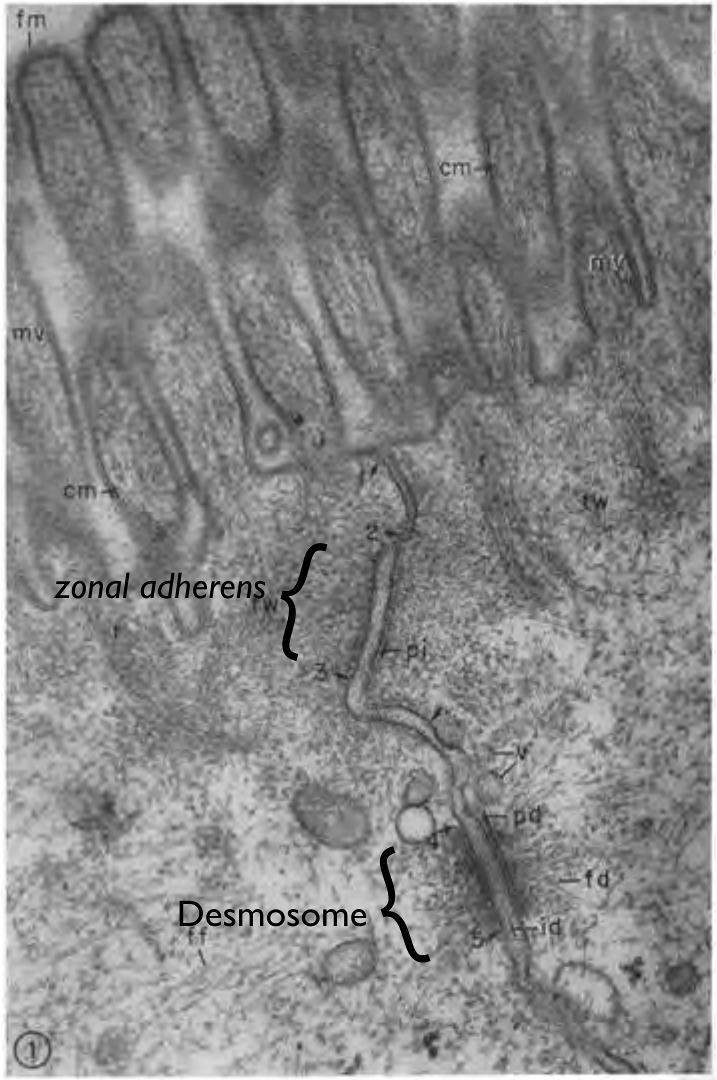


127 Cadherins in the mouse

Molecular Model of Cadherin-based Adhesion

1. Extracellular homophobic ligation

Physiol Rev 92: 597–634, 2012
Hirano & Takeichi



Farquhar M & Palade G. *J. Cell Biol* (1963) 17:375

Molecular Model of Cadherin-based Adhesion

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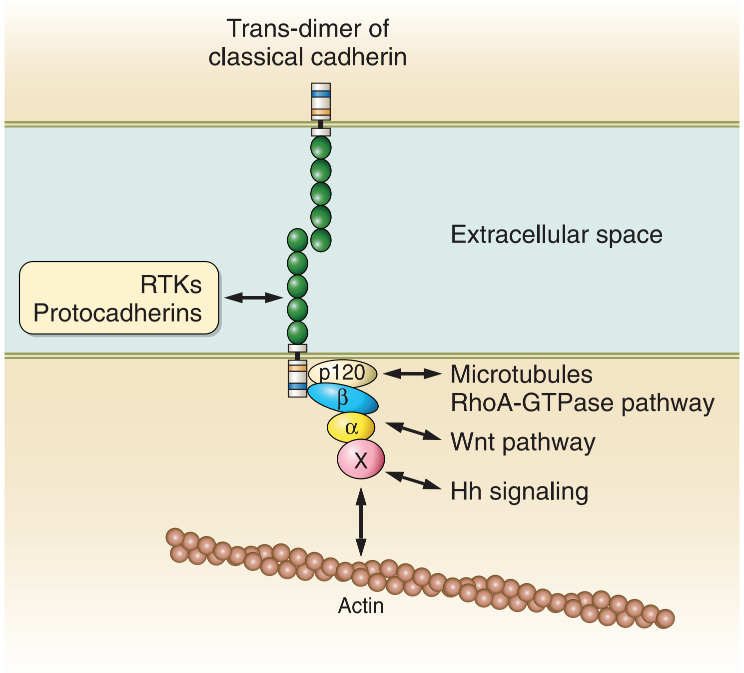
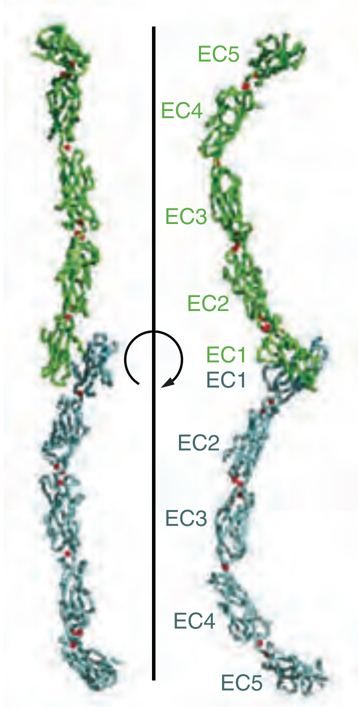
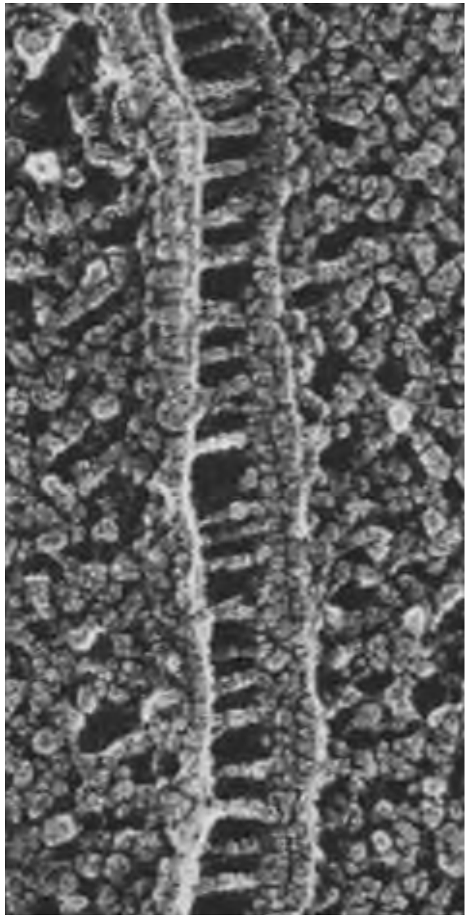
Physiol Rev 92: 597–634, 2012
Hirano & Takeichi



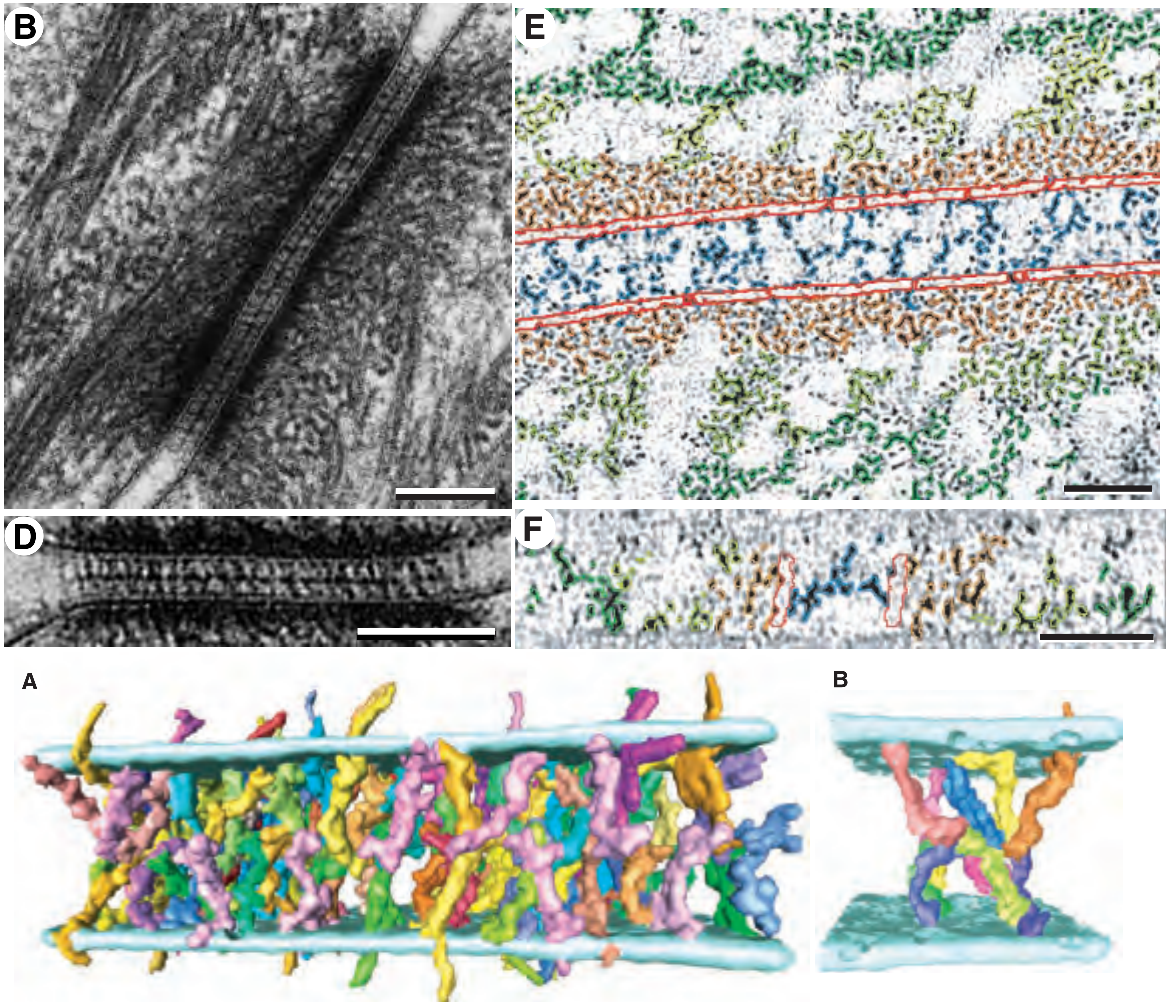




Hirokawa N. and Heuser J.E. *J. Cell Biol* (1981) 91:399

Molecular Model of Cadherin-based Adhesion

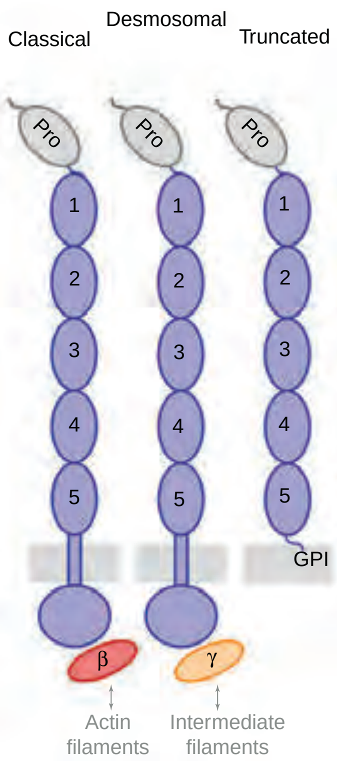
1. Extracellular homophobic ligation

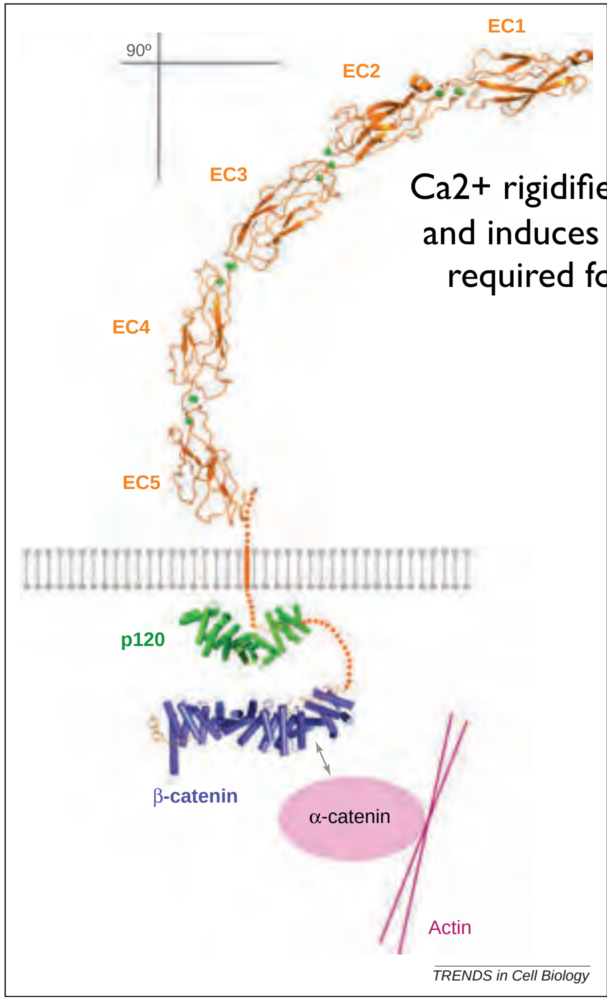


He W., Cowin P. and Stokes DL. *Science*, 302:109 (2003)
see also, Al Amoudi A. et al. *Nature*, 450:832 (2007)

Molecular Model of Cadherin-based Adhesion

1. Extracellular homophobic ligation





Ca2+ rigidifies the ectodomain and induces a crescent shape required for trans-binding

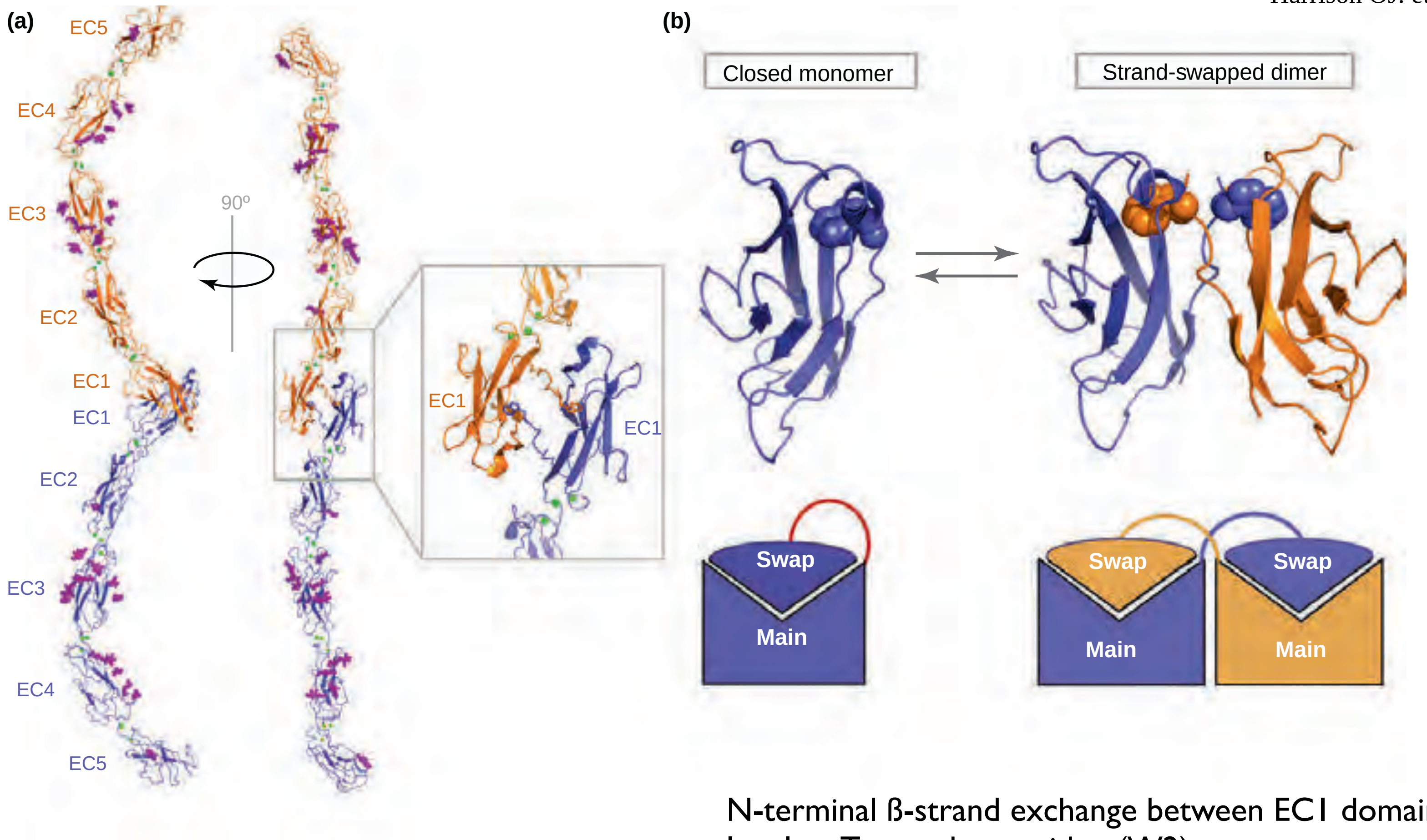
Brash et al *Trends in Cell Biology*, 22: 299 (2012)

B. Honig and L. Shapiro, Columbia Univ.

Molecular Model of Cadherin-based Adhesion

1. Extracellular homophobic ligation

VOLUME 17 NUMBER 3 MARCH 2010 NATURE STRUCTURAL & MOLECULAR BIOLOGY
Harrison OJ. et al

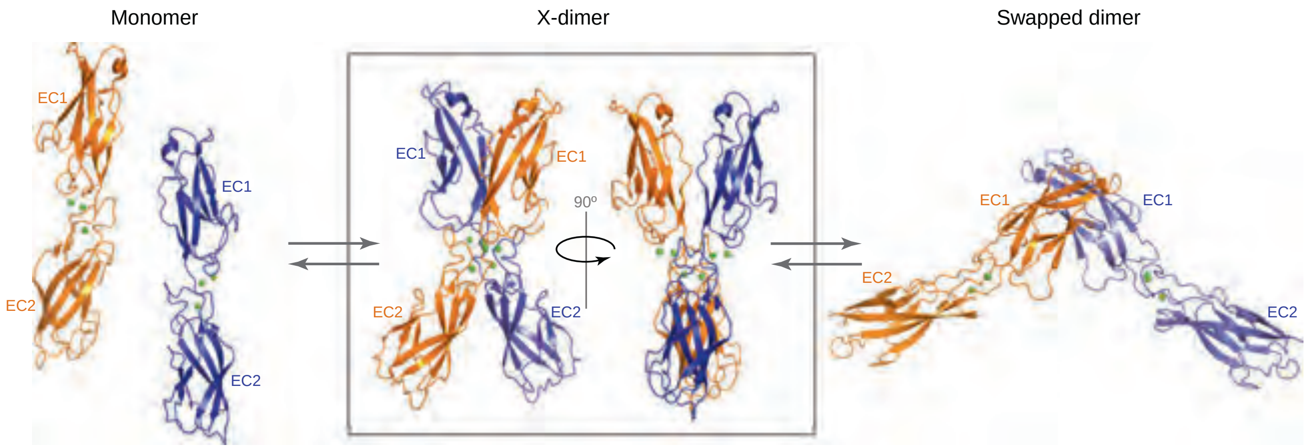


N-terminal ß-strand exchange between EC1 domains
Involves Tryptophan residue (W2)

Molecular Model of Cadherin-based Adhesion

I. Extracellular homophobic ligation

VOLUME 17 NUMBER 3 MARCH 2010 NATURE STRUCTURAL & MOLECULAR BIOLOGY
Harrison OJ. et al



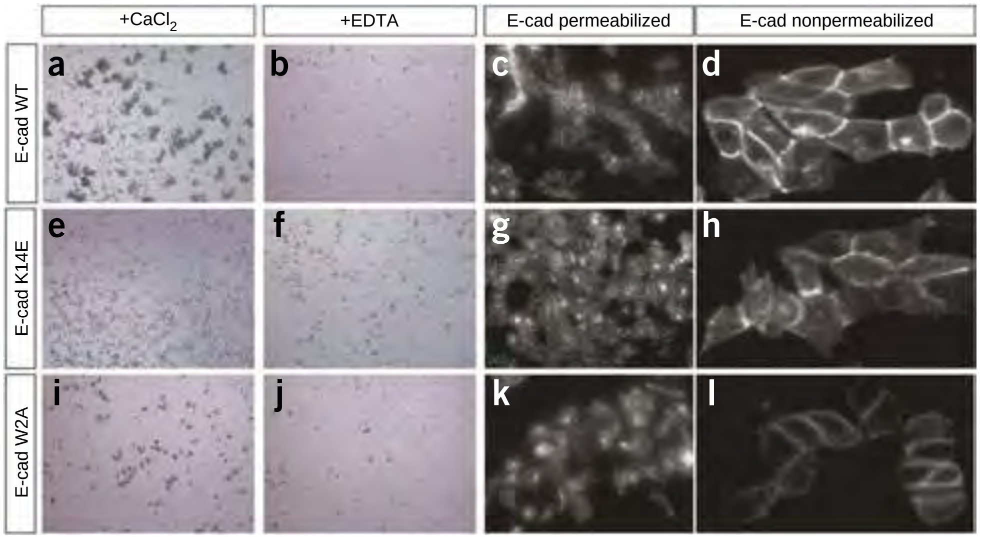
TRENDS in Cell Biology

An « encounter complex » (X-dimer) lowers the activation energy required for domain swapping
X-dimer renders domains swapping kinetically favorable.

X-dimer required for rapid binding
and long-term cell aggregation

X-dimer mutant

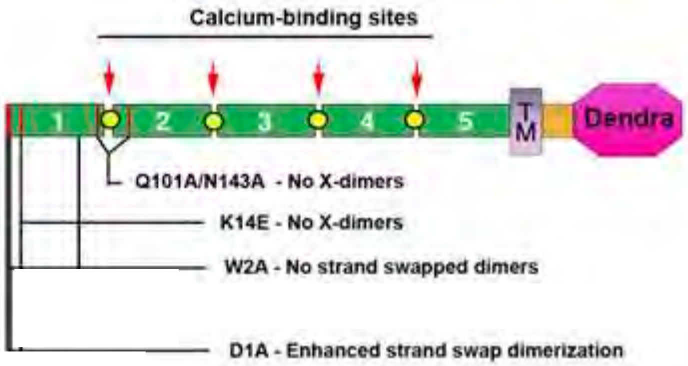
Strand-swap mutant

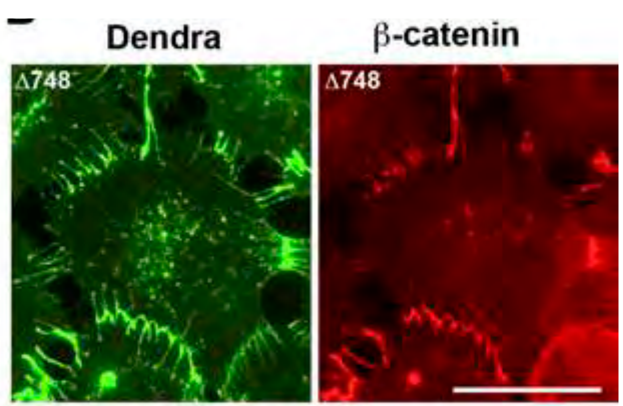


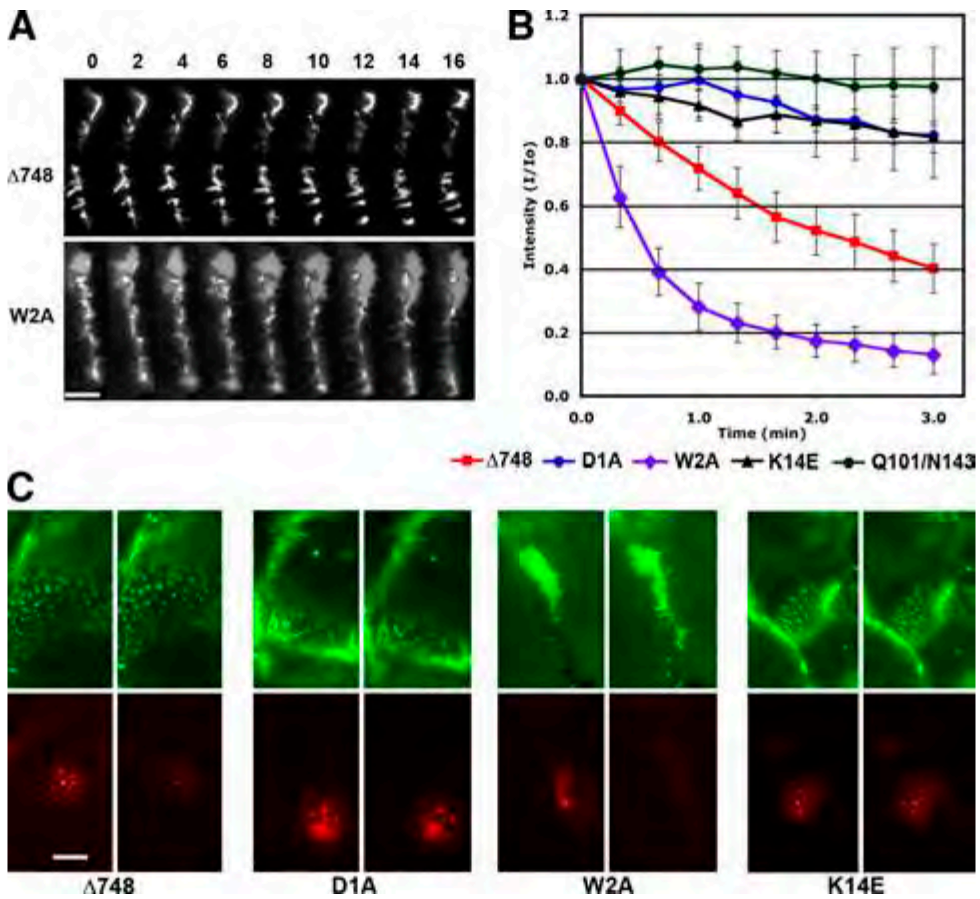
Molecular Model of Cadherin-based Adhesion

1. Extracellular homophobic ligation

X-dimer is required for turnover (K14E mutant more stable)
Strand-swap is required for stable bonds (W2A mutant less stable, D1A more stable)







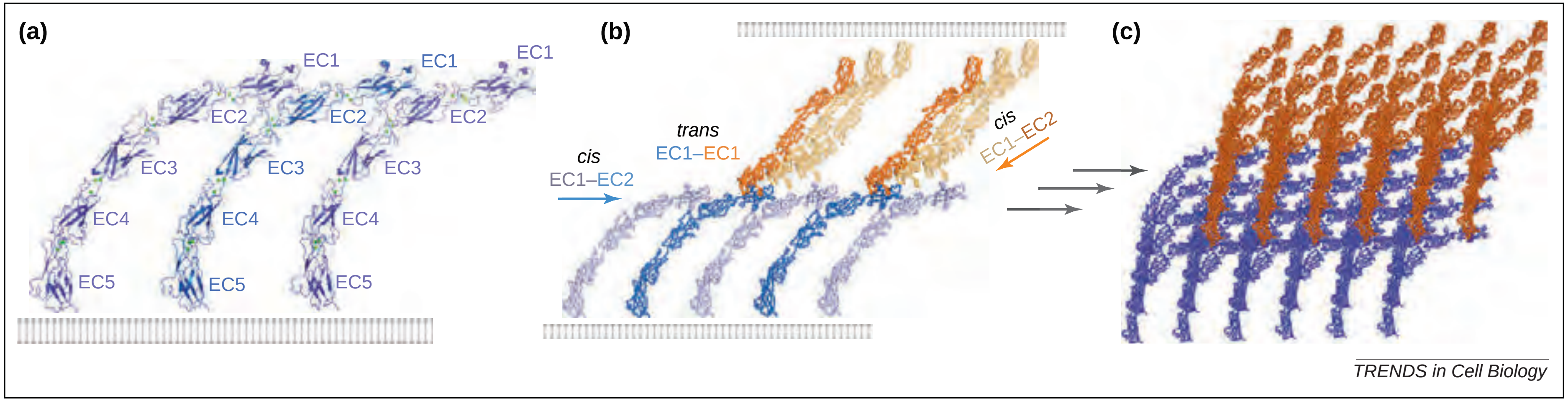
Hong S, Troyanovsky R. and Troyanovsky S. *J. Cell Biology*, 192: 1073 (2011)

Molecular Model of Cadherin-based Adhesion

1. Extracellular homophobic ligation

A model for Cadherin supramolecular assembly based on on the structure of Cis and Trans Cadherin ectodomain interaction

Trans binding via EC1-EC1. Cis binding via EC1-EC2



Structure *19*, 244–256, February 9, 2011
Harrison OJ. et al

Kd E-cad/E-cad: 60-160 μM
Kd N-cad/N-cad: 20-30μM
(bulk: analytical ultra centrifugation)

Katsamba P et al, Ben-Shaul, Shapiro, Honig. *PNAS*. 106-11594. 2009

Molecular Model of Cadherin-based Adhesion

1. Extracellular homo- vs heterophilic ligation

Cadherin-mediated cell sorting not determined by binding or adhesion specificity

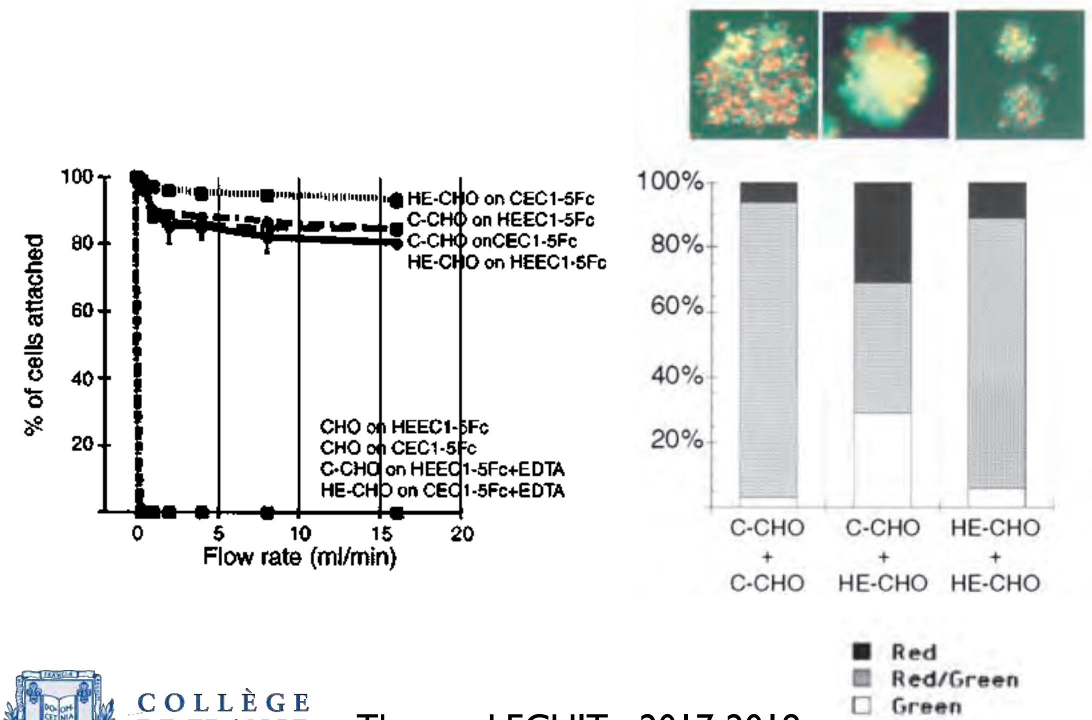
Carien M. Niessen and Barry M. Gumbiner

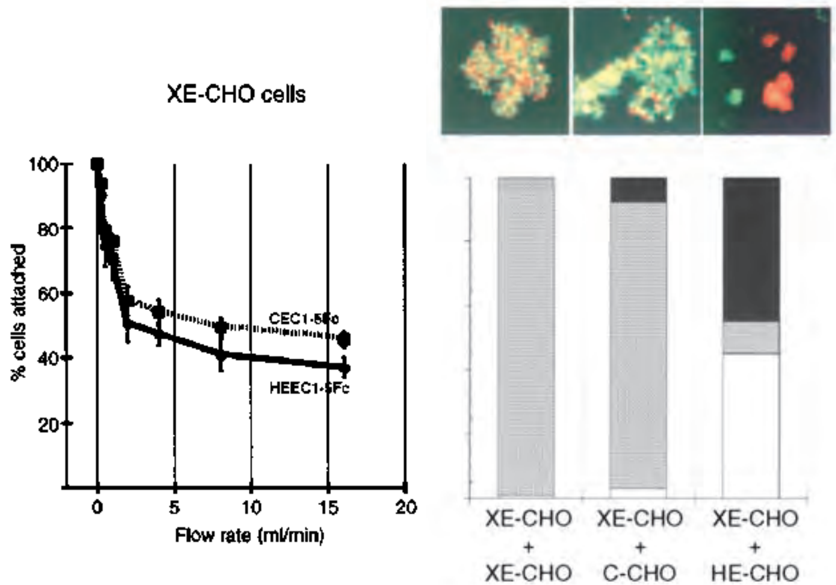
Cellular Biochemistry and Biophysics Program, Memorial Sloan-Kettering Cancer Center, New York, NY, 10021

The Journal of Cell Biology | Volume 156, Number 2, 2002

Cadherins are promiscuous in their binding capacity
Binding capacity is not predictive of cell-sorting behaviour

HE- Human E-cad
XE- *Xenopus* E-cad
C - *Xenopus* C-cad





Molecular Model of Cadherin-based Adhesion

1. Extracellular homo- vs heterophilic ligation

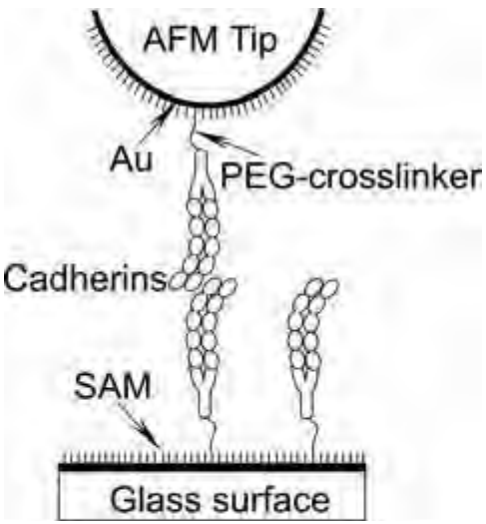
Biophysical Properties of Cadherin Bonds Do Not Predict Cell Sorting*

Received for publication, April 2, 2008, and in revised form, May 21, 2008 Published, JBC Papers in Press, June 15, 2008, DOI 10.1074/jbc.M802563200

Quanming Shi[‡], Yuan-Hung Chien[§], and Deborah Leckband[‡§¶1]

THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 283, NO. 42, pp. 28454–28463, October 17, 2008

Measurement of bond dissociation rates $P(t) = A \times \exp(-k^f_{off} \times t)$



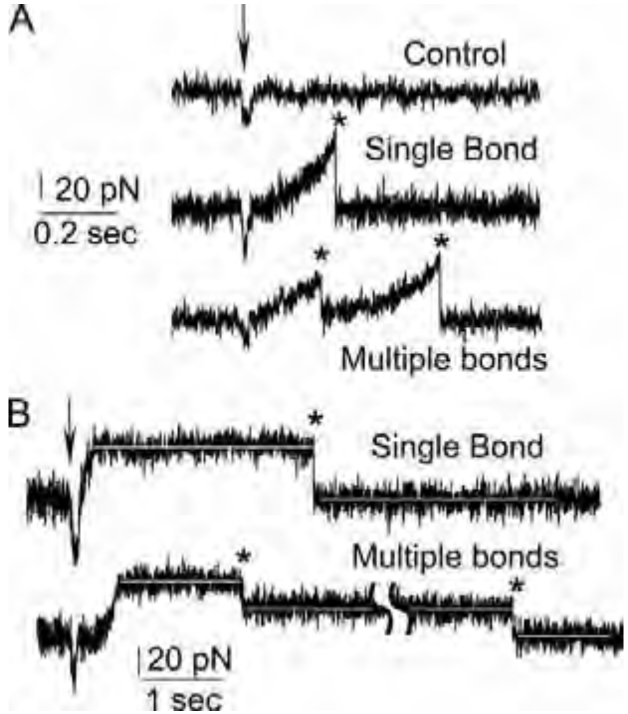


FIGURE 2. **Force time traces of AFM profiles obtained with the steady ramp mode (*A*) and the constant force mode (*B*).**

Ramp

Constant load

Molecular Model of Cadherin-based Adhesion

1. Extracellular homo- vs heterophilic ligation

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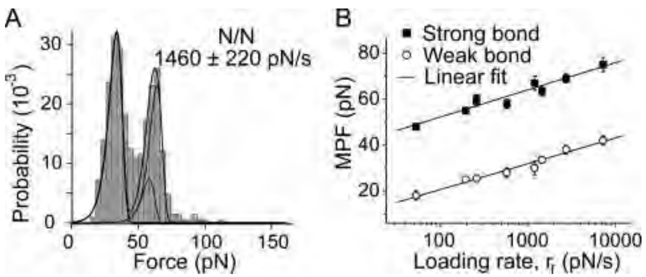
THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 283, NO. 42, pp. 28454–28463, October 17, 2008

Measurement of bond rupture forces: strong and weak forces
All 3 homophilic bonds have the same tensile strength and force spectra



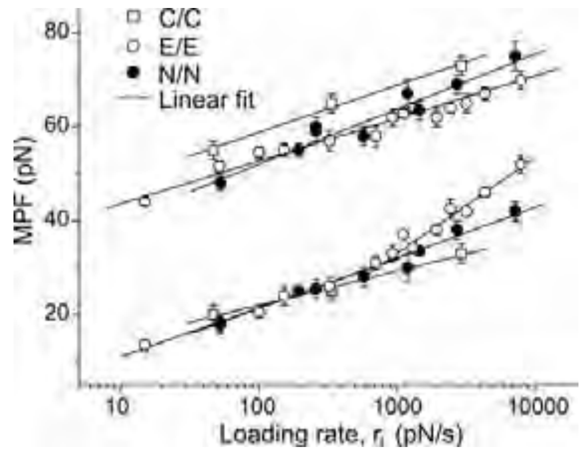


FIGURE 6. **Summary of force spectra for the homophilic cadherin interactions and linear fits to the data.** All three homophilic interactions exhibited two principal peaks over the loading rates examined. The best fit parameters (f_β and k_{off}) for each of the cadherin bonds are summarized in Table 1.

MPF: maximum probability force (from force distribution)

$$MPF_{mp} = f_\beta \times \ln(r_f) - f_\beta \times \ln(k_{off} \times f_\beta)$$

$$k_{off}^f = k_{off} \times e^{-f/f_\beta}$$ (Bell's law)

$$f_\beta = kT/X_\beta$$ thermal force

Molecular Model of Cadherin-based Adhesion

1. Extracellular homo- vs heterophilic ligation

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THE JOURNAL OF BIOLOGICAL CHEMISTRY VOL. 283, NO. 42, pp. 28454–28463, October 17, 2008

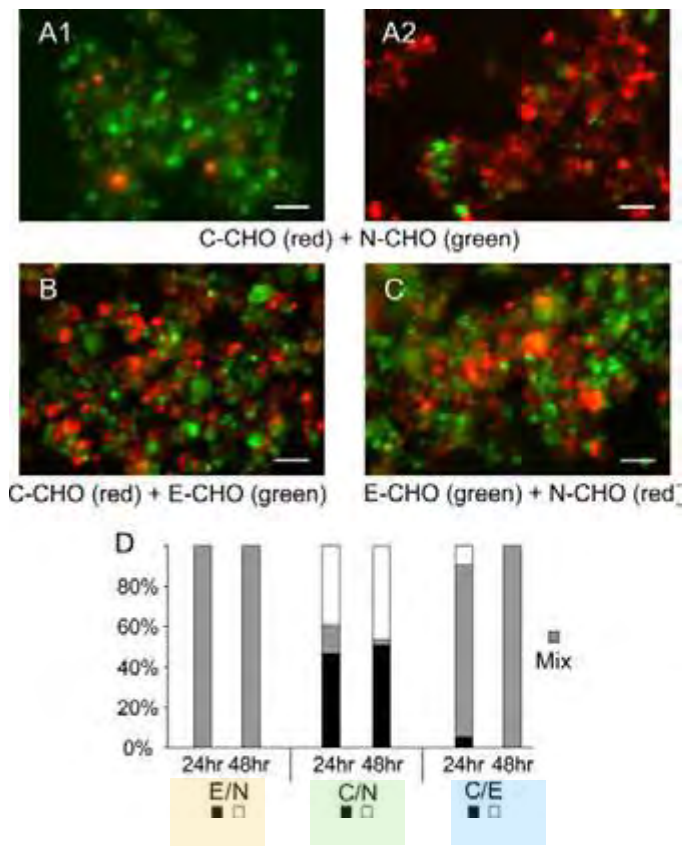
Dissociation rates do not strictly correlate with sorting behaviour

TABLE 1
Dissociation rates and thermal forces of the cadherin bonds determined from linear fits to the force spectra

	Strong bond		Weak bond	
	k_{off}	f_β	k_{off}	f_β
	s^{-1}	pN	s^{-1}	pN
C-CAD/C-CAD	$3 \pm 2 \times 10^{-5}$	4.3 ± 0.4	0.03 ± 0.02	3 ± 0.3
E-CAD/E-CAD	$4 \pm 1 \times 10^{-5}$	4.0 ± 0.2	0.2 ± 0.1	4.5 ± 0.4
N-CAD/N-CAD	$5 \pm 3 \times 10^{-4}$	5.2 ± 0.5	0.2 ± 0.1	4.8 ± 0.3
C-CAD/E-CAD	$9 \pm 6 \times 10^{-5}$	4.3 ± 0.5	0.01 ± 0.005	3 ± 0.4
E-CAD/N-CAD	$4 \pm 1 \times 10^{-4}$	4.6 ± 0.2	2.5 ± 0.9	8 ± 0.4
C-CAD/N-CAD	$9 \pm 8 \times 10^{-3}$	6.3 ± 0.7	0.09 ± 0.06	4.3 ± 0.4

correlation

no correlation



Molecular Model of Cadherin-based Adhesion

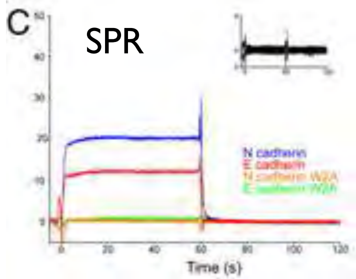
1. Extracellular homo- vs heterophilic ligation

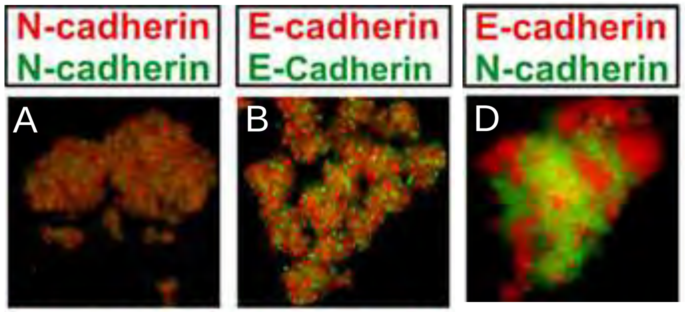
Measurement of Dissociation constants
(bulk analytic ultracentrifugation (AUG)
and surface plasmon resonance (SPR) experiments)

	K_d 25 °C, μM	
Species	N-cadherin	E-cadherin
Mouse	25.8 ± 1.5	96.5 ± 10.6
Human	24.6 ± 5.0	156.0 ± 10.0
Chicken	19.7 ± 2.0	62.0 ± 9.5

AUG

Binding affinities:
NN > NE > EE





Number of transdimers *i*, *j*

$$W(I,J) = -N_{\text{dimer}}(I,J)\Delta g(i,j)$$

Work of adhesion between cells I and J

Trans-dimerisation Free Energy

$$W(I,J) = RTC_iC_jvL\ \ln[K_D(i,j)]/K_D(i,j).$$

L: Avogadro number; v= volume accessible to EC domain

Katsamba P et al, Ben-Shaul, Shapiro, Honig. *PNAS.* 106-11594. 2009

Molecular Model of Cadherin-based Adhesion

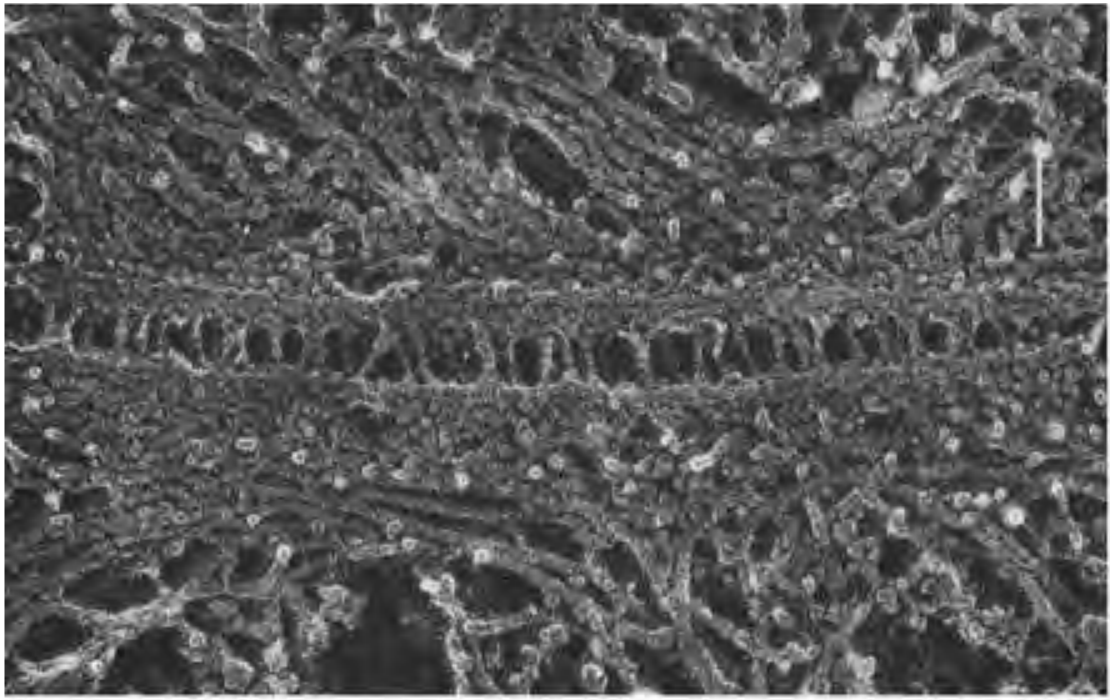
1. Extracellular homo- vs heterophilic ligation does not predict sorting behaviour

- Other features than extracellular Cadherin/Cadherin interaction kinetics and binding energy are required to account for cell sorting behaviour

- Adhesion energy cannot be straightforwardly extrapolated from single molecule Cadherin interaction energy.

Molecular Model of Cadherin-based Adhesion

2. Intracellular F-actin cross linking



Hirokawa N. and Heuser J.E. *J. Cell Biol (*1981) 91:399

Molecular Model of Cadherin-based Adhesion

2. Intracellular F-actin cross linking

The EMBO Journal vol.8 no.6 pp.1711 – 1717, 1989

The cytoplasmic domain of the cell adhesion molecule uvomorulin associates with three independent proteins structurally related in different species

Masayuki Ozawa, Hélène Baribault and Rolf Kemler

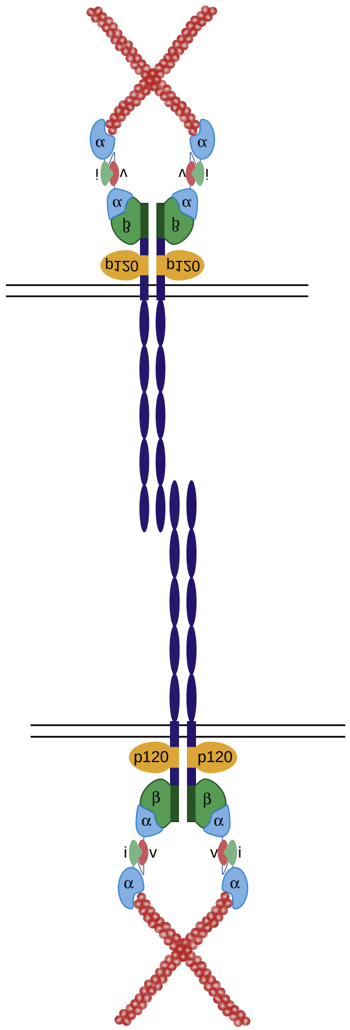
Immunoprecipitation of 3 proteins with Uvomorulin/E-cadherin

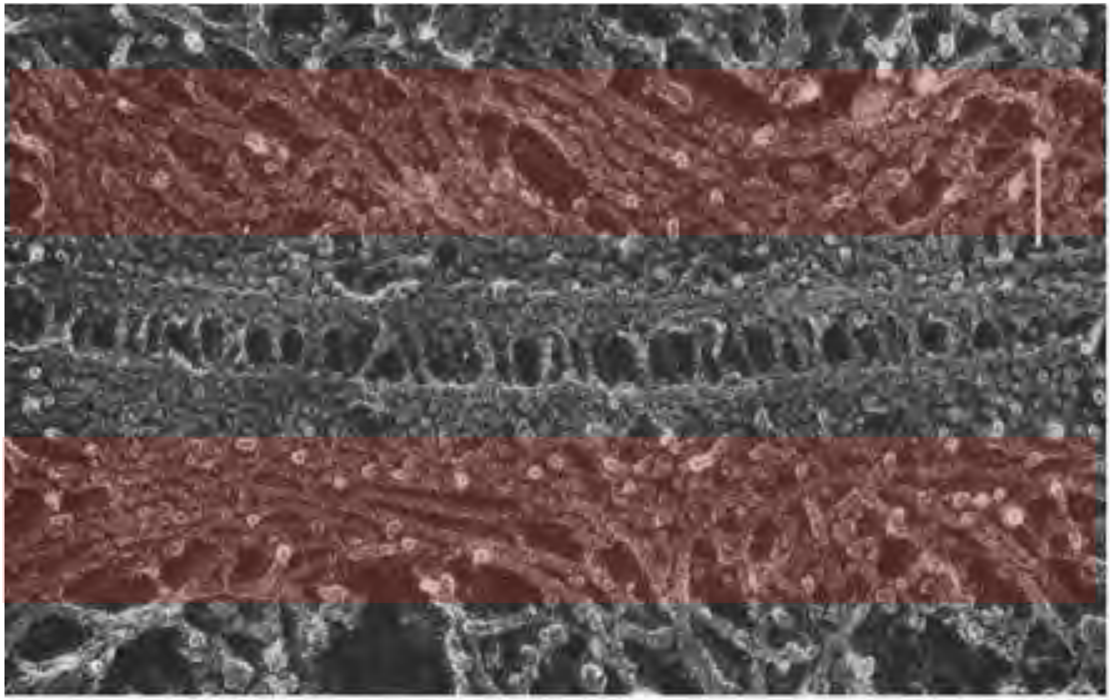
catenins: *link* between E-cadherin and the actin cytoskeleton

This suggests that the 102, 88 and 80 kd proteins constitute a new group of proteins for which we propose the nomenclature of catenin α, β and γ respectively. The characterization of these proteins provides a first molecular basis for a possible cytoplasmic anchorage of uvomorulin to the cytoskeleton.

Molecular Model of Cadherin-based Adhesion

2. Intracellular F-actin cross linking



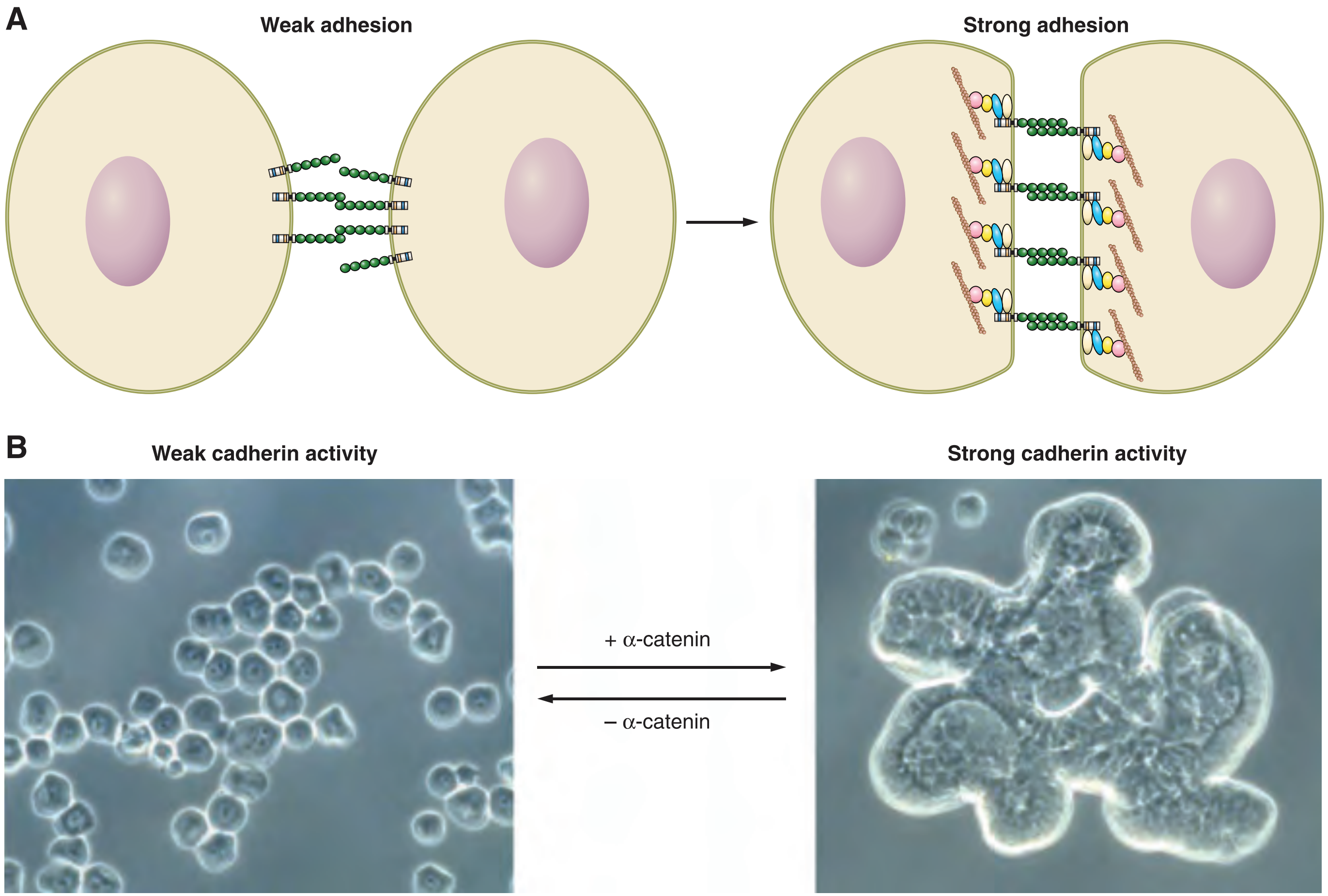


Hirokawa N. and Heuser J.E. *J. Cell Biol* (1981) 91:399

Molecular Model of Cadherin-based Adhesion

2. Intracellular F-actin cross linking

Physiol Rev 92: 597–634, 2012
Hirano & Takeichi

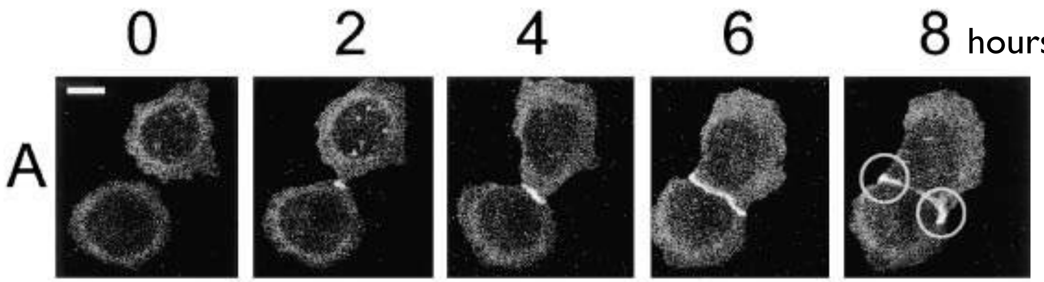


lung carcinoma PC9 cells with or without α-catenin.

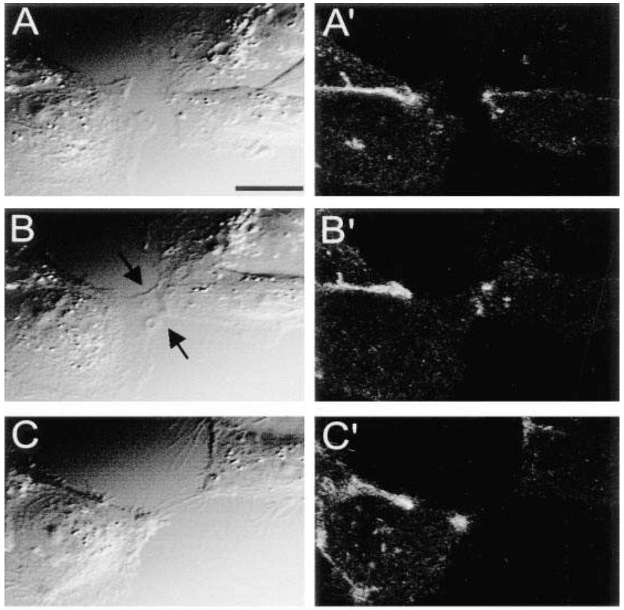
Molecular Model of Cadherin-based Adhesion

2. Intracellular F-actin cross linking

Adams C. … WJ. Nelson, *J. Cell. Biol.* 1998, 142: 1105



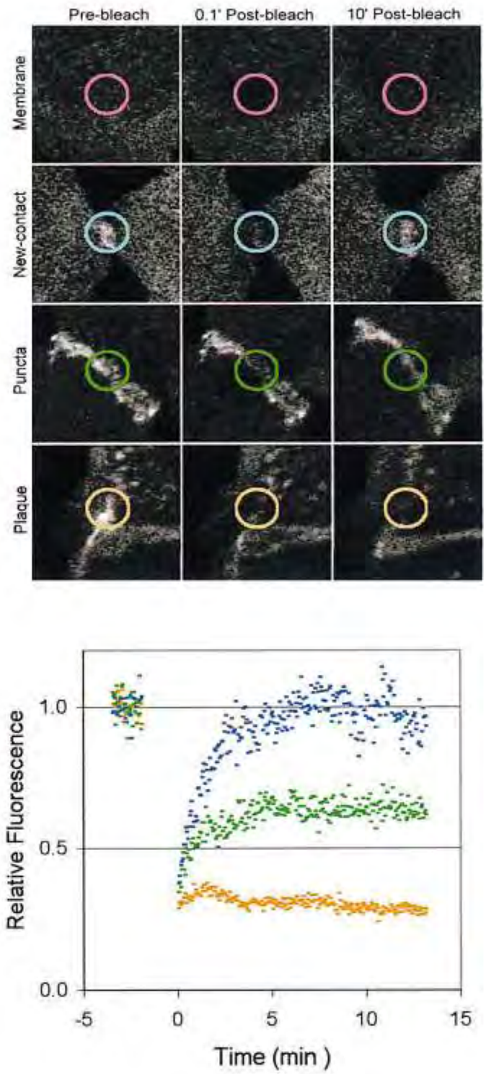
Maturation of adhesion over time
Formation of E-cadherin::GFP aggregates at cell contacts and edges



1 min before CytoD

30 min after CytoD

Contact maturation requires F-actin



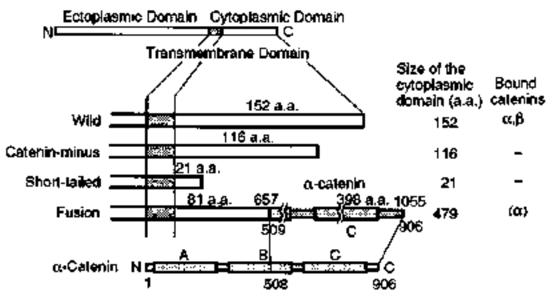
Gradual stabilisation of E-cadherin

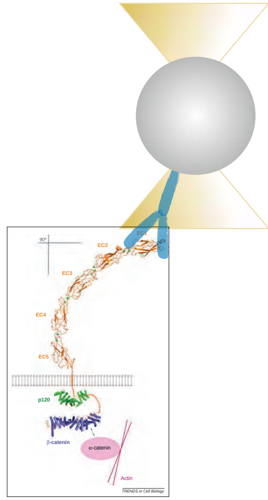
Molecular Model of Cadherin-based Adhesion

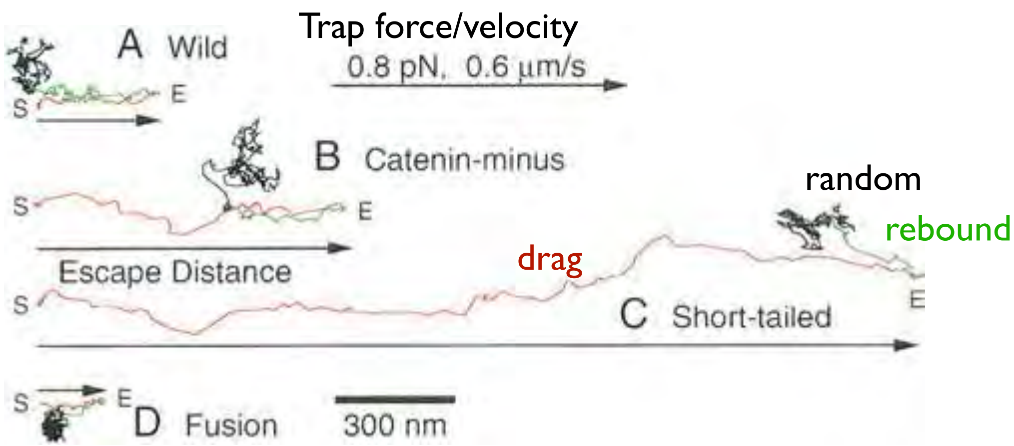
2. Coupling to F-actin: single molecule analysis

Cytoplasmic Regulation of the Movement of E-Cadherin on the Free Cell Surface as Studied by Optical Tweezers and Single Particle Tracking: Corralling and Tethering by the Membrane Skeleton

Sako … Kusumi, *J. Cell. Biol.* 1998

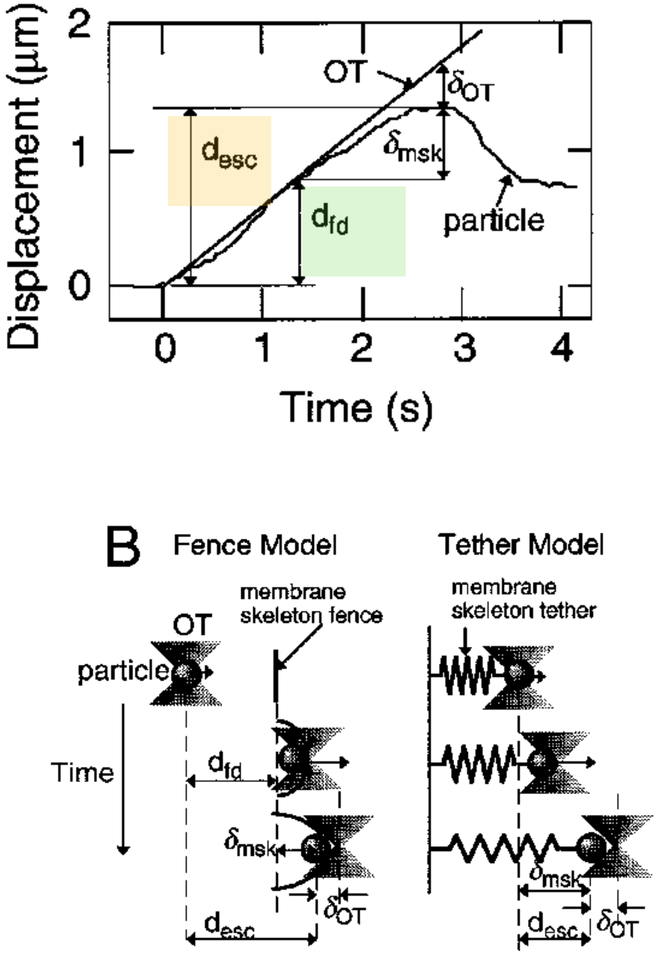


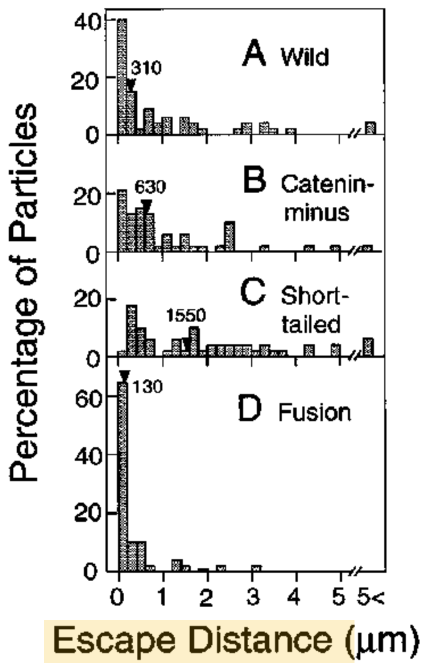


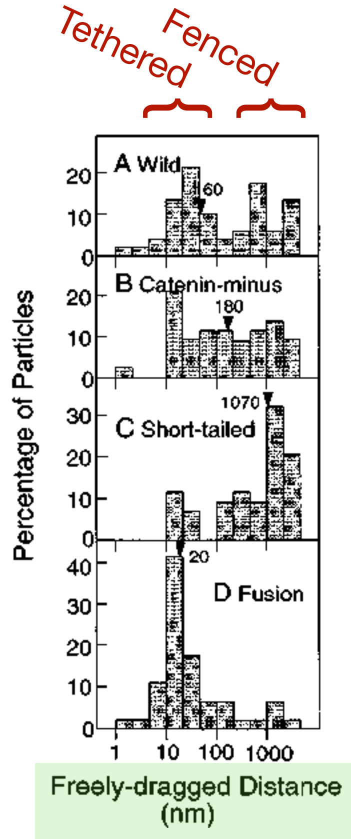


Molecular Model of Cadherin-based Adhesion

2. Coupling to F-actin: tether and fence





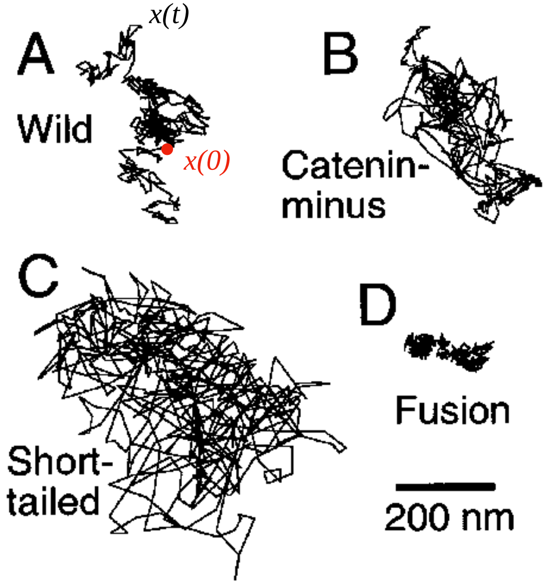


Sako … Kusumi, *J. Cell. Biol.* 1998

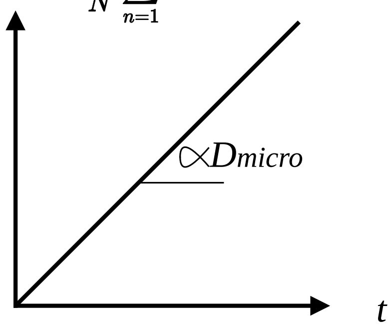
Molecular Model of Cadherin-based Adhesion

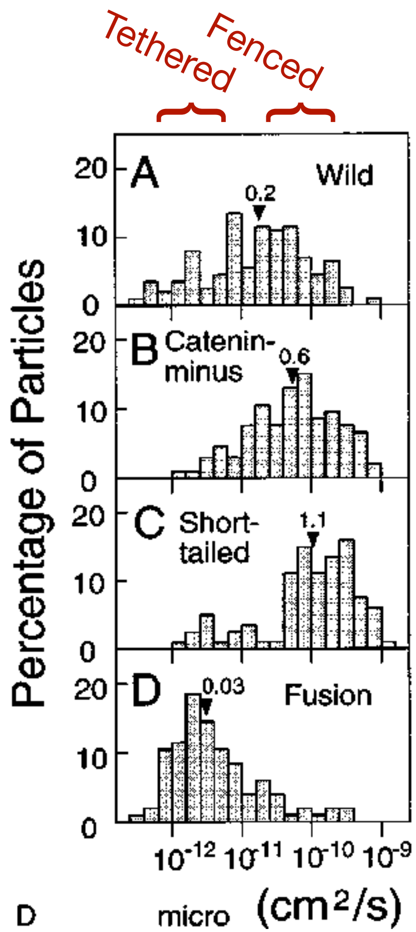
2. Coupling to F-actin: tether and fence

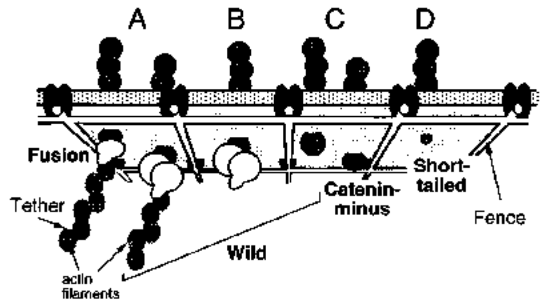
Spingle Particle Tracking



$$\text{MSD} = \frac{1}{N}\sum_{n=1}^{N}(x_n(t) - x_n(0))^2$$







Sako Y. et al Kusumi, A. *J. Cell. Biol.* 140:1227 1998
See also Lambert M. … RM Mège, *J. Cell. Biol* 2002 with N-cadherin

Molecular Model of Cadherin-based Adhesion

2. Coupling to F-actin: tether and fence

- Regulated interaction with F-actin of E-cadherin (and N-cadherin)
- Corraling and Tethering of Cadherins to F-actin: compartmentalised diffusion.

What is the impact:
-on organisation at the plasma membrane, e.g. clustering?
-on dynamic of adhesion? Regulated immobilisation?

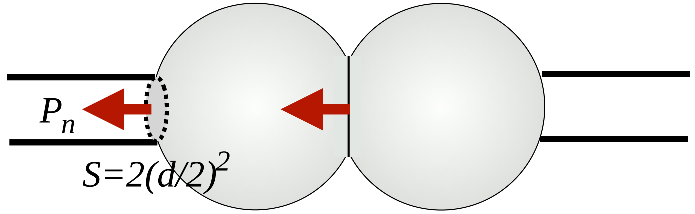
What is the effect of trans-cis homodimerisation on dynamics?

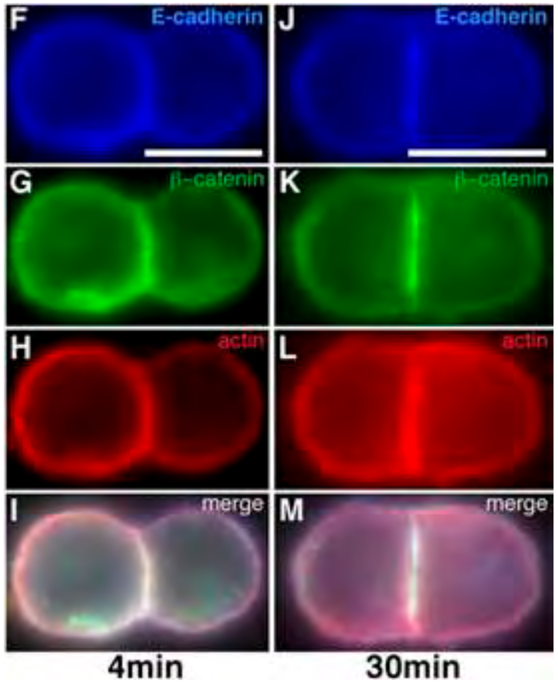
Sako Y. et al Kusumi, A. *J. Cell. Biol.* 140:1227 1998
See also Lambert M. … RM Mège, *J. Cell. Biol* 2002 with N-cadherin

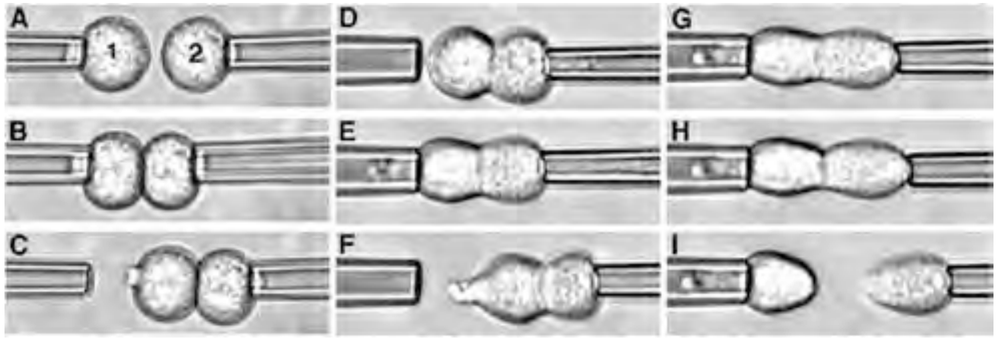
Molecular Model of Cadherin-based Adhesion

2. Coupling to F-actin: contribution to force separation

Y-S. Chu et al, J-P. Thierry and S. Dufour. *J. Cell. Biol.* 167:1183. (2004)







short contact
rapid adhesion

adhesion maturation
stronger contacts

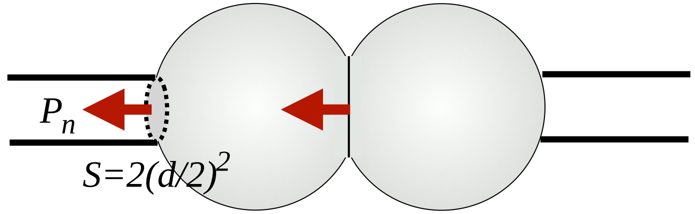
aspiration increased step by step

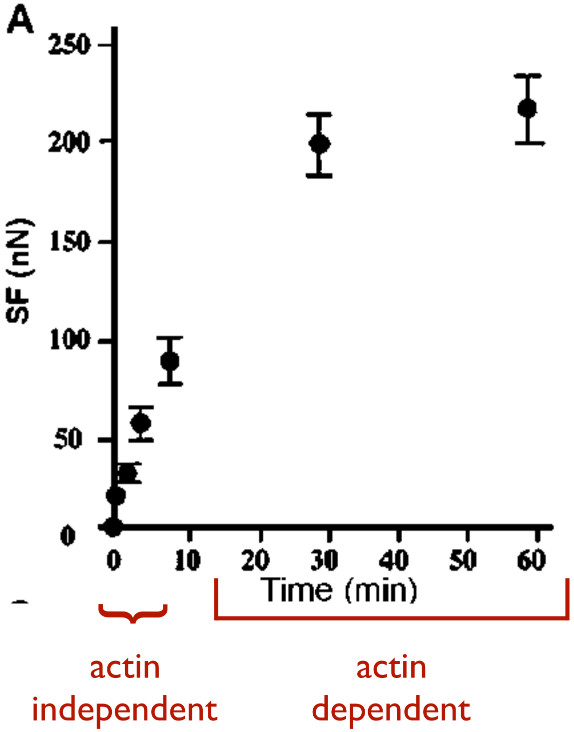
Measurement of: Separation Force (*SF*) = Surface (*S*) x Pressure (*P*)

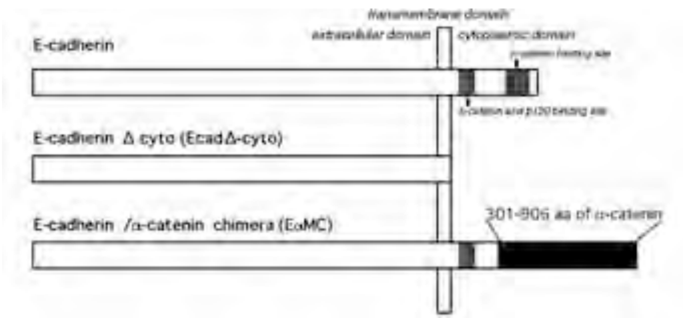
Molecular Model of Cadherin-based Adhesion

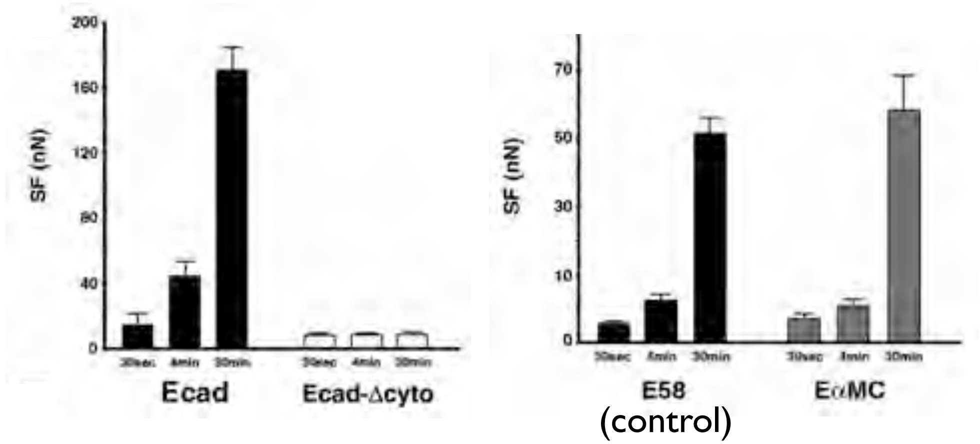
2. Coupling to F-actin: contribution to force separation

Y-S. Chu et al, J-P. Thierry and S. Dufour. *J. Cell. Biol.* 167:1183. (2004)



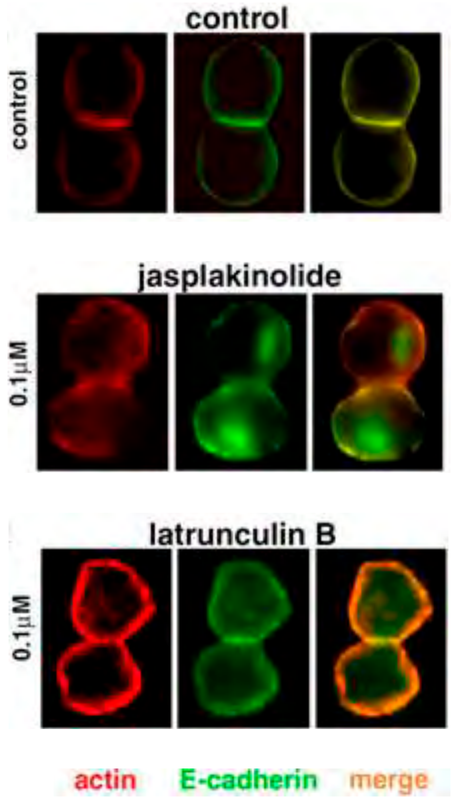


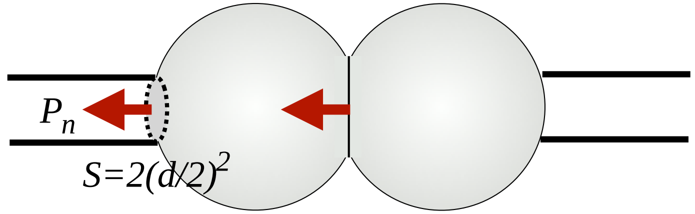


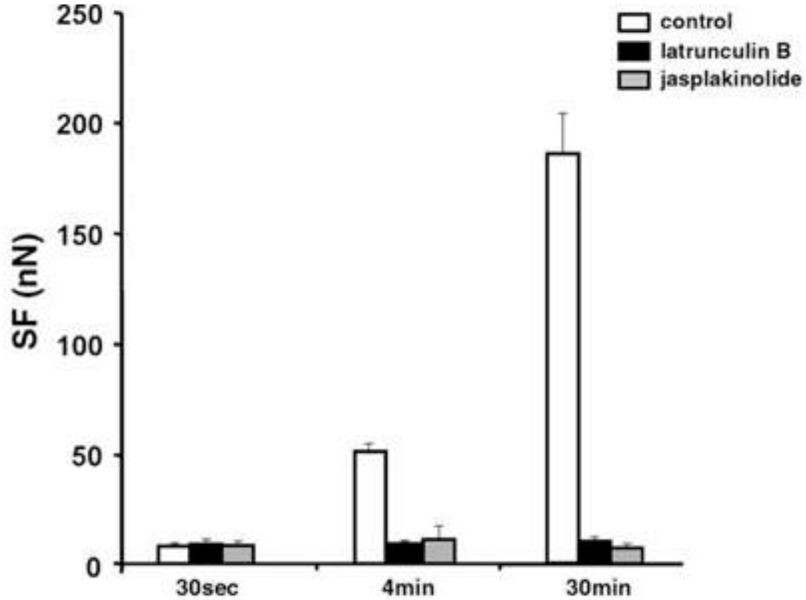


Molecular Model of Cadherin-based Adhesion

2. Coupling to F-actin: contribution to force separation





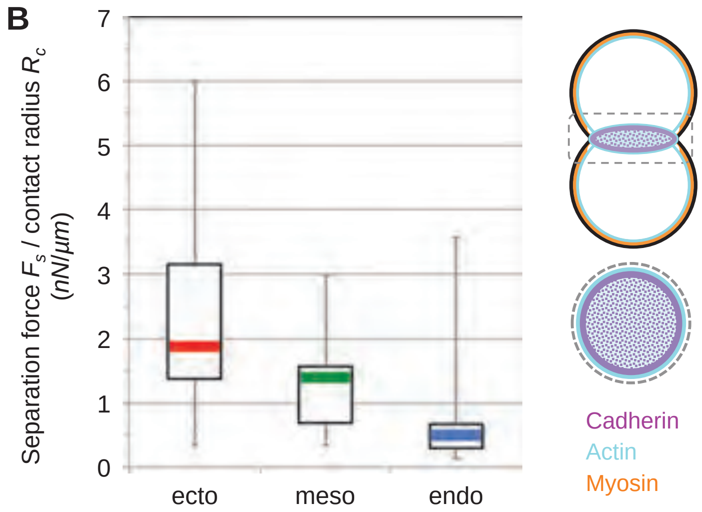


Y-S. Chu et al, J-P. Thierry and S. Dufour. *J. Cell. Biol.* 167:1183. (2004)

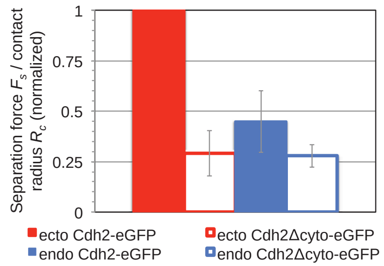
Molecular Model of Cadherin-based Adhesion

2. Coupling to F-actin: contribution to force separation

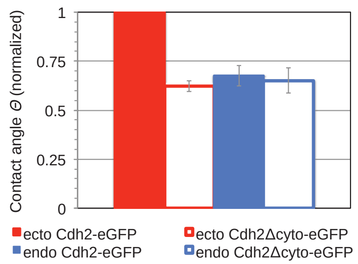
Separation force (normalised to surface)



- The force of adhesion depends on F-actin coupling



Reduction of force separation with reduced coupling to F-actin



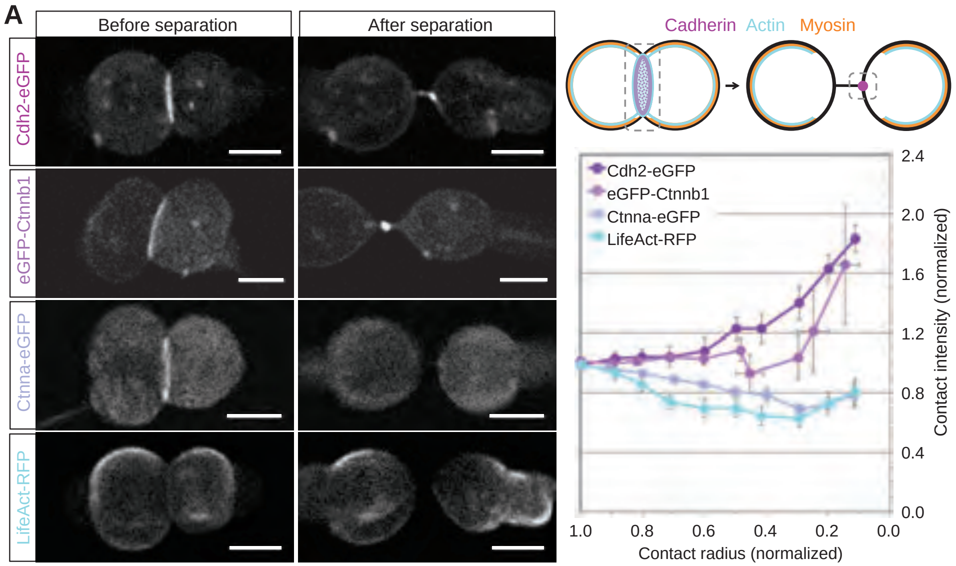
Smaller cell contact with reduced coupling to F-actin

J-L. Maître et al, CP Heisenberg

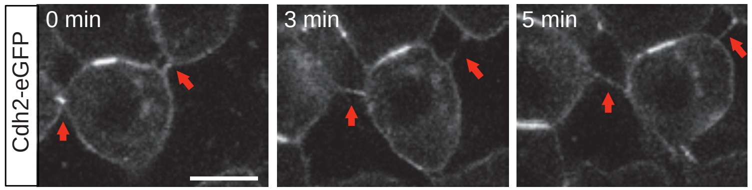
SCIENCE VOL 338 12 OCTOBER 2012

Molecular Model of Cadherin-based Adhesion

2. Coupling to F-actin: contribution to cell-cell contacts



in vitro



in vivo

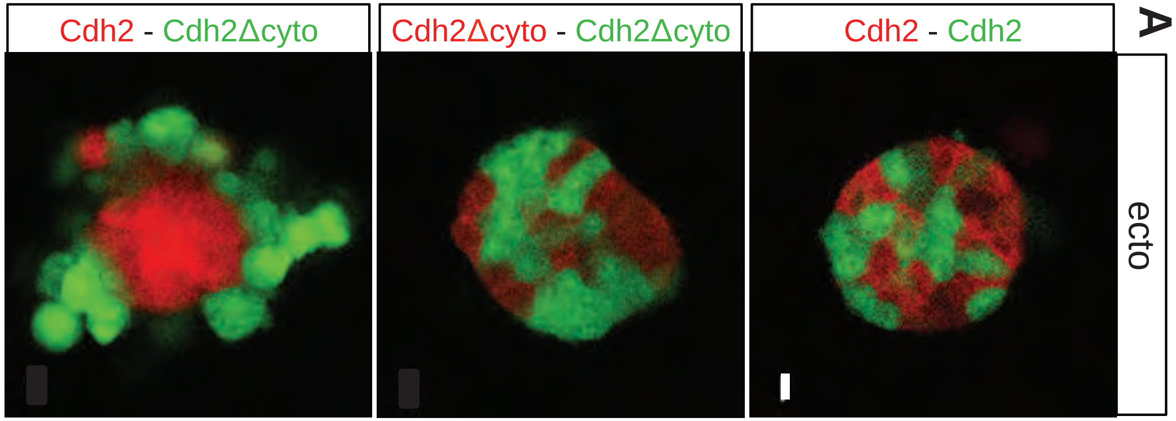
J-L. Maître et al, CP Heisenberg

SCIENCE VOL 338 12 OCTOBER 2012

Molecular Model of Cadherin-based Adhesion

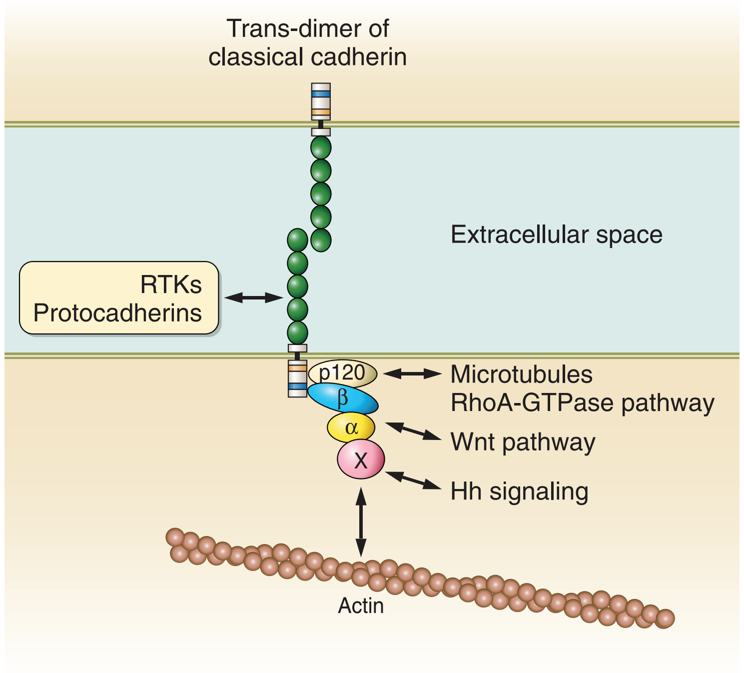
2. Coupling to F-actin: contribution to cell sorting

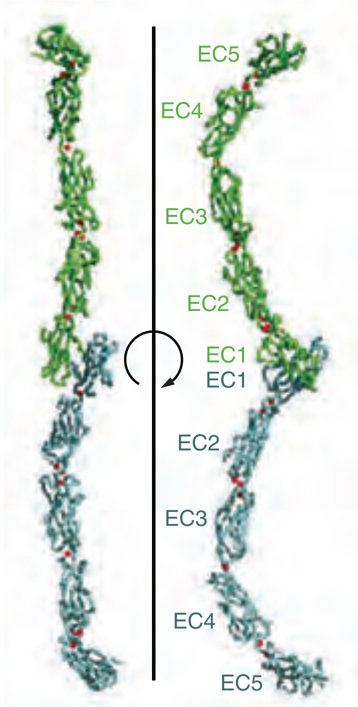
- Cell sorting depends on Cadherin coupling to the actin cytoskeleton



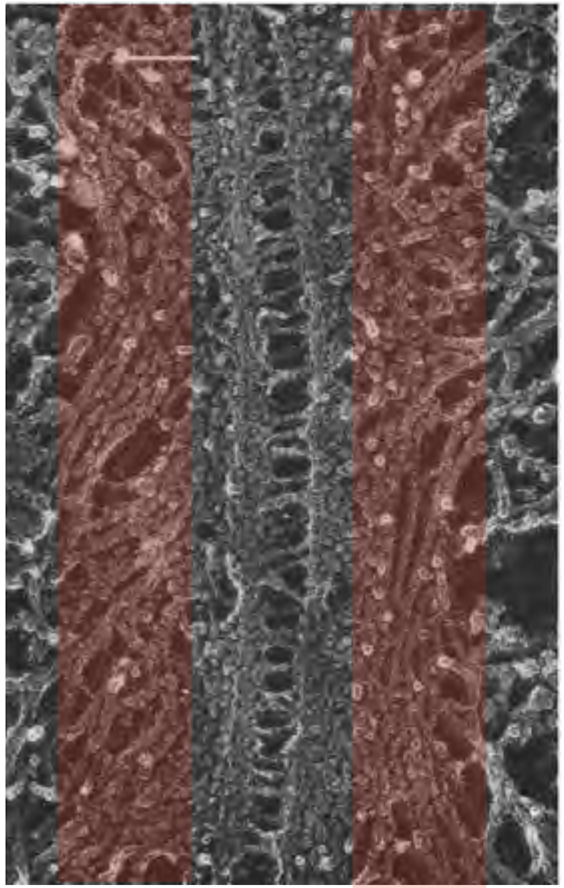
J-L. Maître et al, CP Heisenberg
SCIENCE VOL 338 12 OCTOBER 2012

Molecular Model of Cadherin-based Adhesion





Physiol Rev 92: 597–634, 2012
Hirano & Takeichi



Hirokawa N. and Heuser J.E. *J. Cell Biol* (1981) 91:399

Molecular Model of Cadherin-based Adhesion

Conclusions

- Cell-cell adhesion energy cannot be straightforwardly extrapolated from single molecule Cadherin interaction energy.
- Other features than extracellular Cadherin/Cadherin interaction kinetics and binding energy are required to account for cell sorting behaviour
- Low affinity of single molecule Cadherin homodimerisation: role of molecule organisation in clusters?
- Interaction with F-actin affects diffusivity of Cadherins: impact on clustering?
- Interaction with F-actin accounts for cell-cell force separation and cell sorting: integration of intra-/extra-cellular coupling.

Adhesion in multicellular organisms

1. Affinity and Adhesion: a specificity problem

2. Adhesion: a thermodynamic model

3. The molecular framework of adhesion

4. Evolutionary origin of adhesion mechanisms

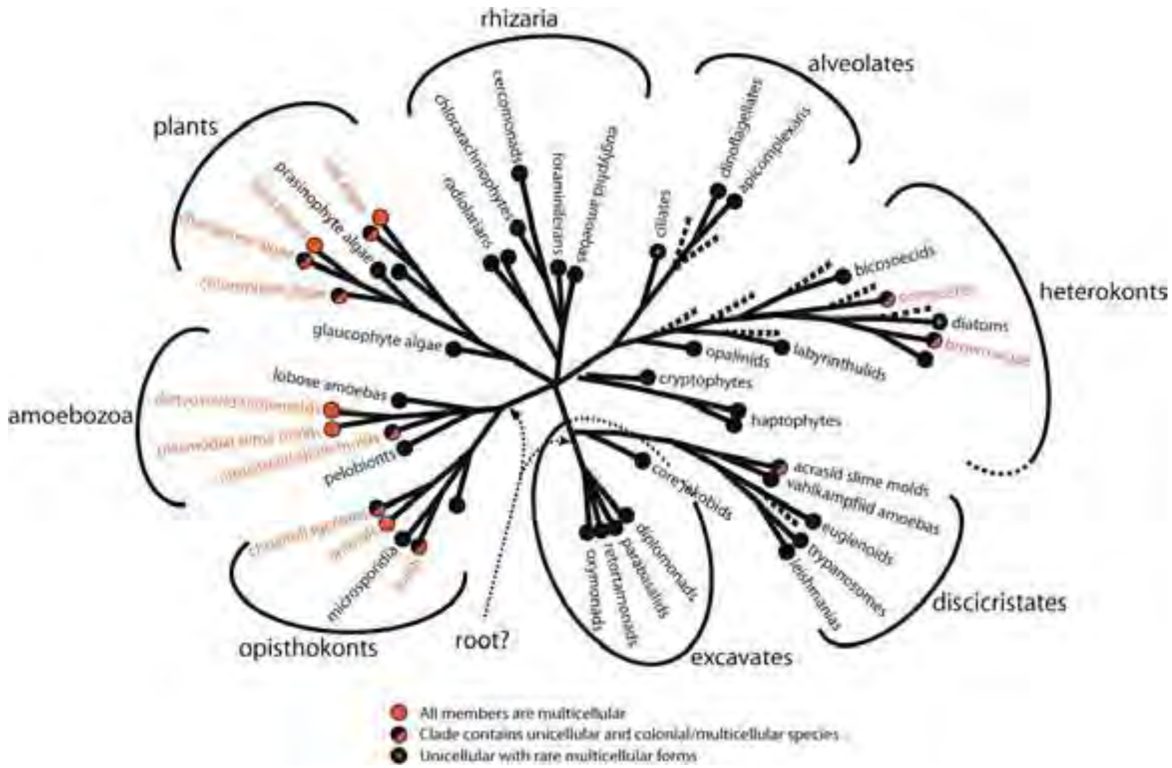
5. Adhesion as an active mechanism

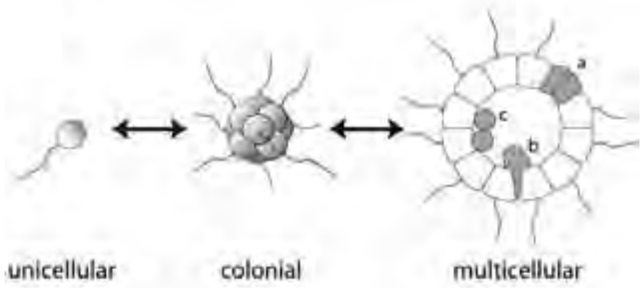
4.1. Clustering

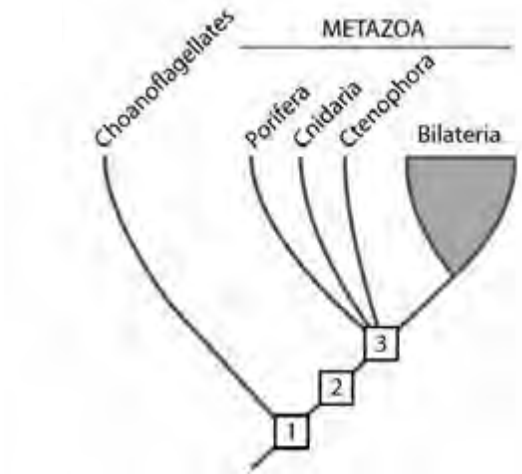
4.2. Mechanosensation - Mechano-transduction

6. Adhesion and *dissipation*

Emergence of multicellularity





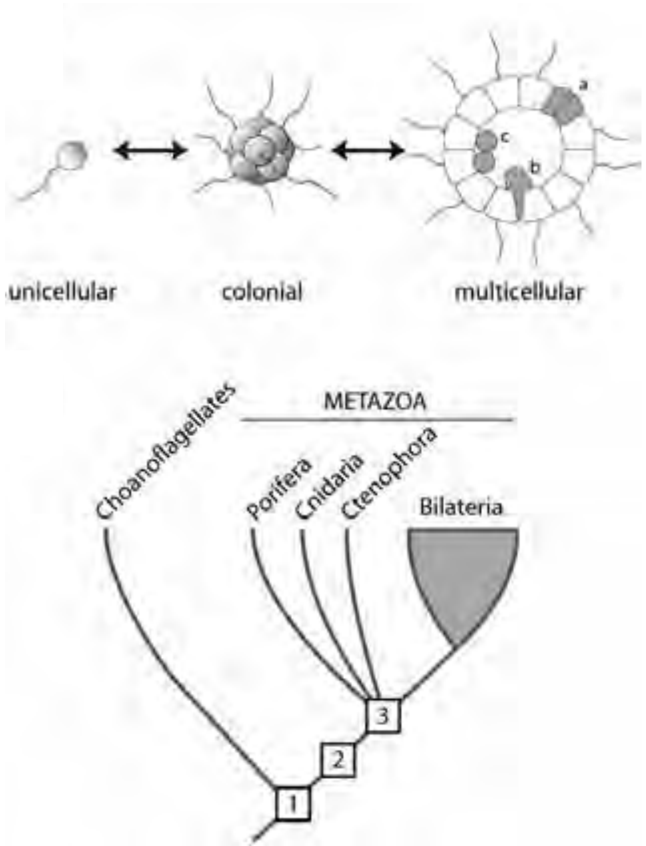


- Multicellularity occurs in at least 16 independent eukaryotic lineages
- Multicellularity: 1) escape from predation; 2) solve motility/division antagonism
- Molecular data support monophyletic origin of all Metazoa, including Porifera (sponges)

King N. *Developmental Cell* 2004

Emergence of multicellularity

- Similarities between choanoflagelates, choanocytes from Porifera, collar cells from Cnidaria and echinoderms suggested that Metazoa originate from choanoflagelate-like ancestors



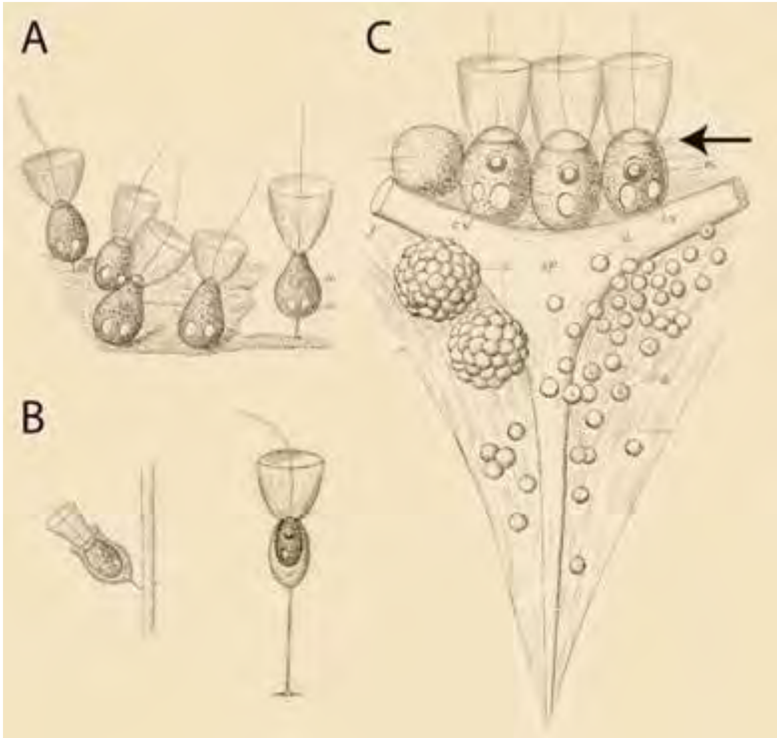
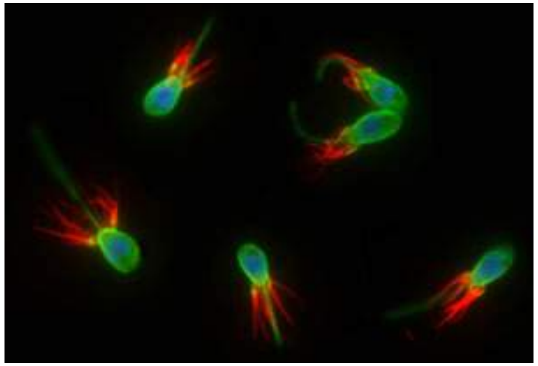


Figure 3. Resemblance between Choanoflagellates and Poriferan Choanocytes

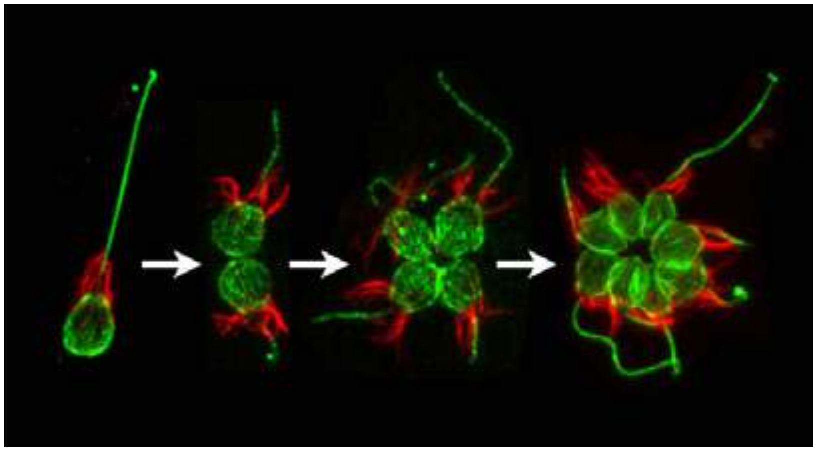
In historical sketches by William Saville-Kent (*A Manual of the Infusoria* [London: David Brogue], 1880–1882), choanoflagellates (A and B) and choanocytes (C) are shown to display similar cellular architectures: a spherical or ovoid cell body and an apical flagellum subtended by a collar of tentacles. Both choanoflagellates and choanocytes use the flagellum to create water currents that propel bacterial food onto the collar for capture. (A) *Monosiga consociata* (as modified from plate IV-19; Saville-Kent); (B) (left) *Salpingoeca convallaria* (as modified from plate IV-13; Saville-Kent), (right) *Salpingoeca infusionum* (as modified from plate VI-8; Saville-Kent); (C) *Leucosolenia coriacea*. Triradiate spicule (sp) and three associated choanocytes (arrow) (as modified from plate X-2; Saville-Kent).

King N. *Developmental Cell* 2004

Choanoflagelates: unicellular or colonial



Monosiga brevicollis

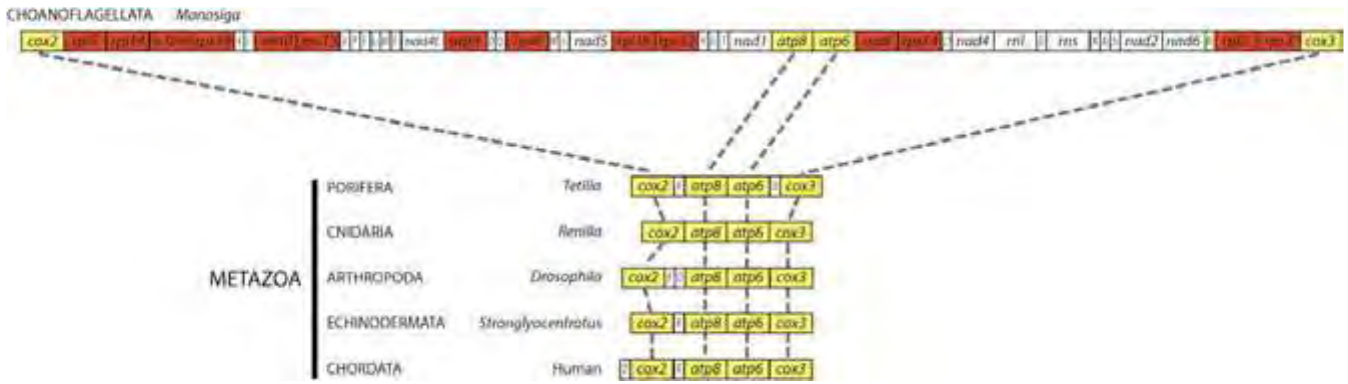


S. rosetta Nicole King. Univ. Berkeley

Kent W Saville *A manual of Infusoria*, 1882

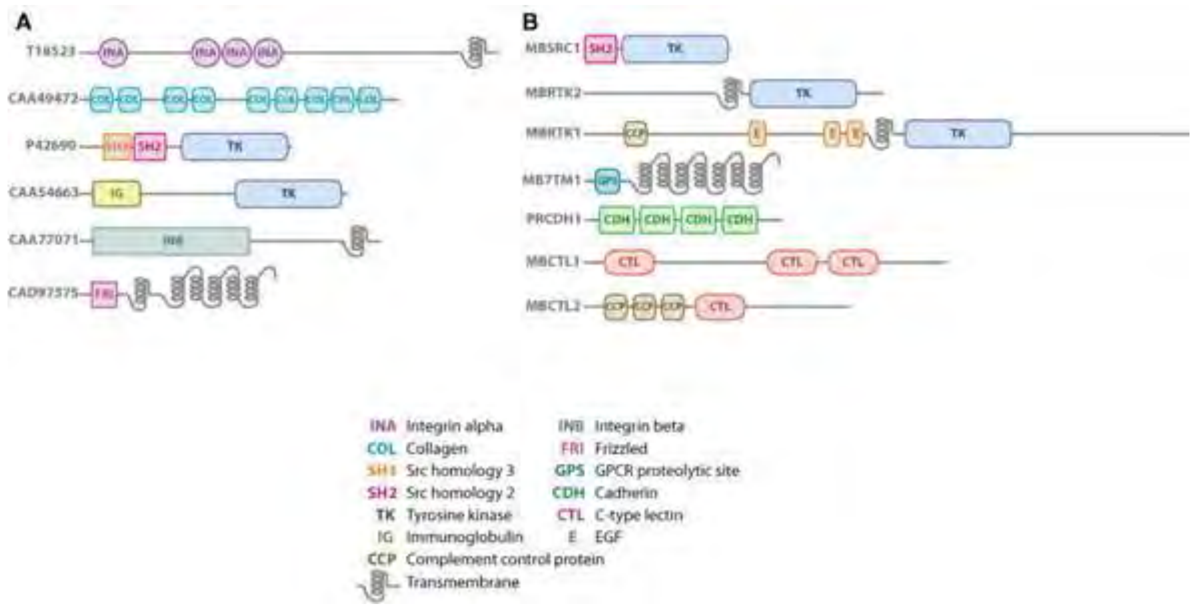
Choanoflagelates: an outgroup of Metazoa

- mtDNA from choanoflagelates is less compact than in Metazoa



- Multiple genes initially thought to be « animal genes » present in choanoflagelates.

Porifera | Choanoflagelates

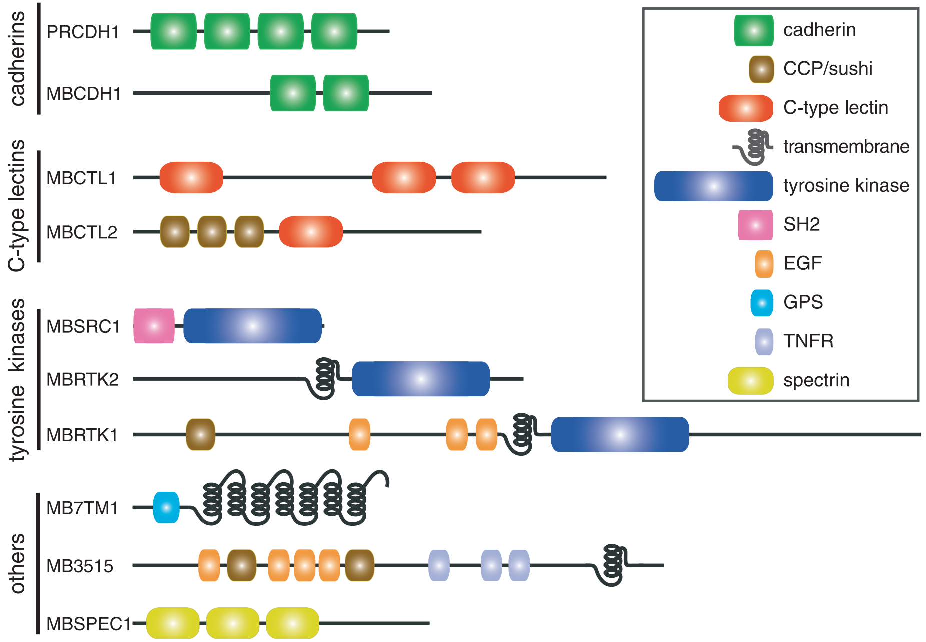


King N. *Developmental Cell* 2004

Evolution of adhesion proteins predates animal origins

- C-type lectins involved in Calcium-dependent sugar recognition.
- Cadherins: Calcium-dependent cell adhesion molecule.

- Function is unknown: binding to bacteria, prey recognition and capture?

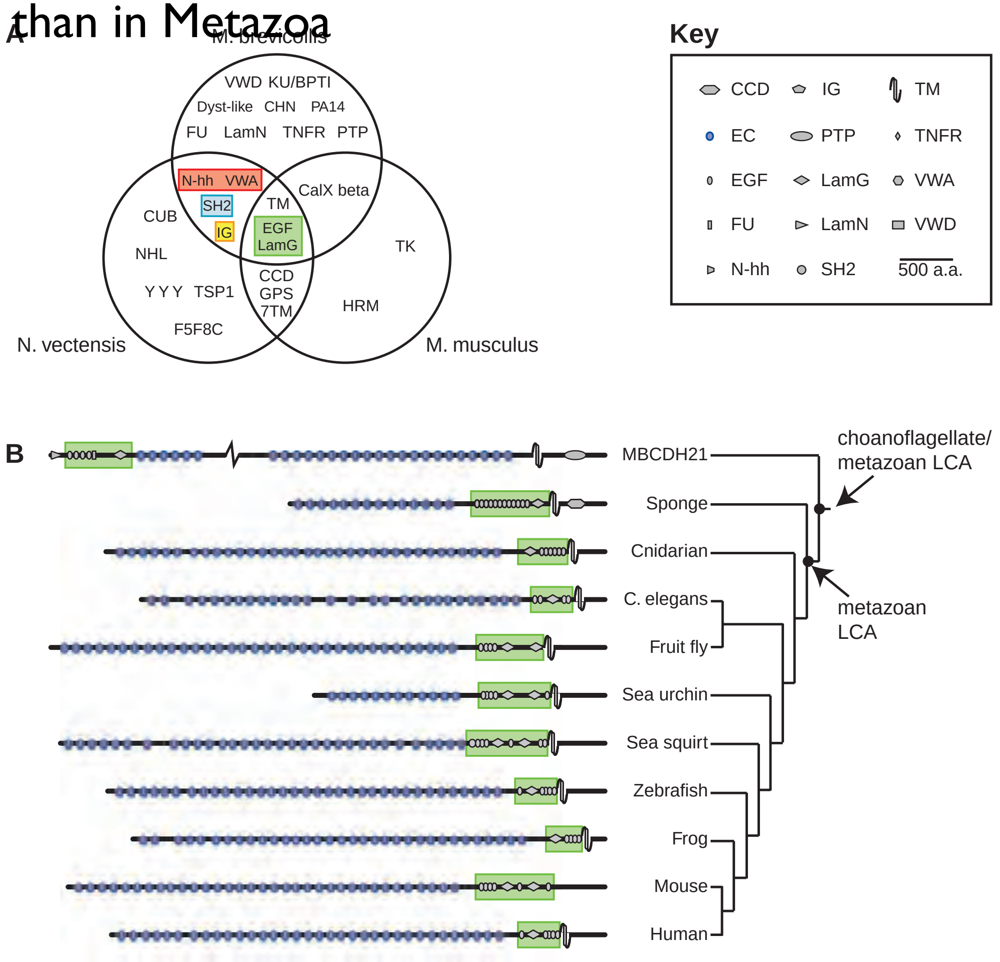


King N, Hittinger C. and Carroll S. *Science*. 301:361-363. 2003

Premetazoan ancestry of Cadherins

- Cadherins: multiple EC domain containing transmembrane proteins together with EGF and LamG domains.
- Equally abundant in choanoflagelates *M. brevicolis* than in Metazoa

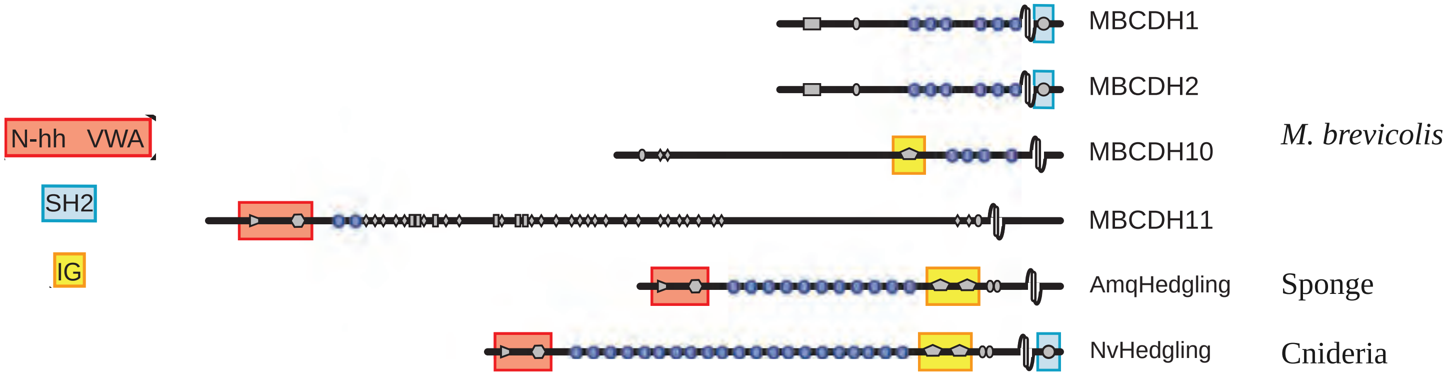
					Metazoa			
						Bilateria		
	Plant	Slime mold	Fungus	Choano-flagellate	Cnidarian	Arthropod	Ascidian	Vertebrate
Genomic content	*Atha*	*Ddis*	*Scer*	*Mbre*	*Nvec*	*Dmel*	*Cint*	*Mmus*
Genes/genome	27,273	13,607	6,609	9,196	18,000	13,601	14,182	32,661
Cadherins/genome	0	0	0	23	46	17	32	127
Normalized cadherin abundance	0	0	0	0.26%	0.12%	0.13%	0.23%	0.39%
EC repeats/cadherin (average)	N/A	N/A	N/A	14.7	11	12.2	6.2	5.2



Abedin M. and King N. *Science*. 319:946. 2008

Premetazoan ancestry of Cadherins

- Cadherins contain signalling domains:
  - SH2: interacts with targets of Tyrosine Kinases
  - N-hh: hedgehog amino-terminal peptide
  - no link to Wnt signaling (ß-catenin)



- Cadherins localise to feeding collar together with F-actin
- But: no ß-catenin identified in choanoflagelates.
- Suggests a signalling function: e.g. recognition of preys, bacteria etc.

MBCDH1/2 F-actin

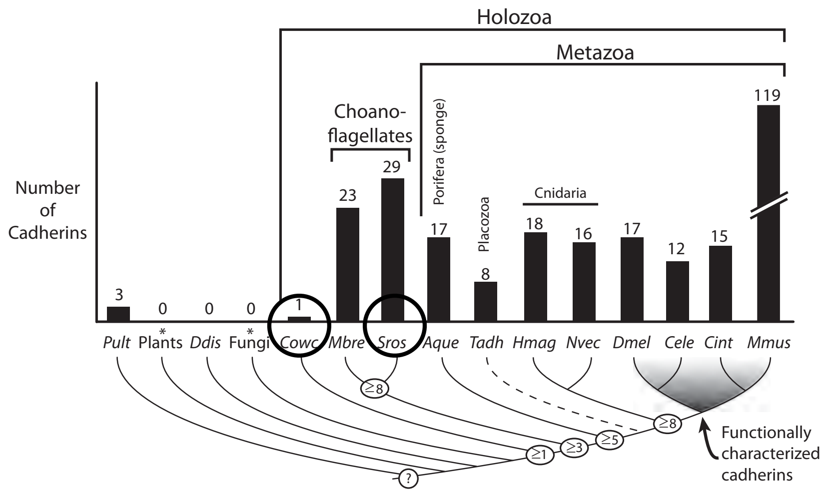
Abedin M. and King N. *Science*. 319:946. 2008

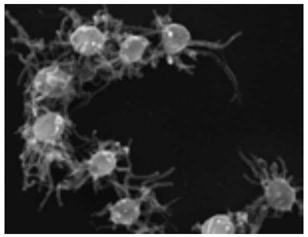
Premetazoan ancestry of Cadherins

Origin of metazoan cadherin diversity and the antiquity of the classical cadherin/β-catenin complex

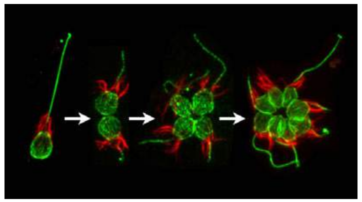
Scott Anthony Nichols[a], Brock William Roberts[b], Daniel Joseph Richter[b], Stephen Robert Fairclough[b], and Nicole King[b,1]

13046–13051 | PNAS | **August 7, 2012** | vol. 109 | no. 32





Capsaspora owczarzaki
Unicellular outgroup
of choanos and metazoans



Salpingoeca rosetta

Choanoflagelate

Oscarella Carmela
Sponge

Nichols SA. et al, and King N. *PNAS*. 109:13046. 2012

Premetazoan ancestry of Cadherins

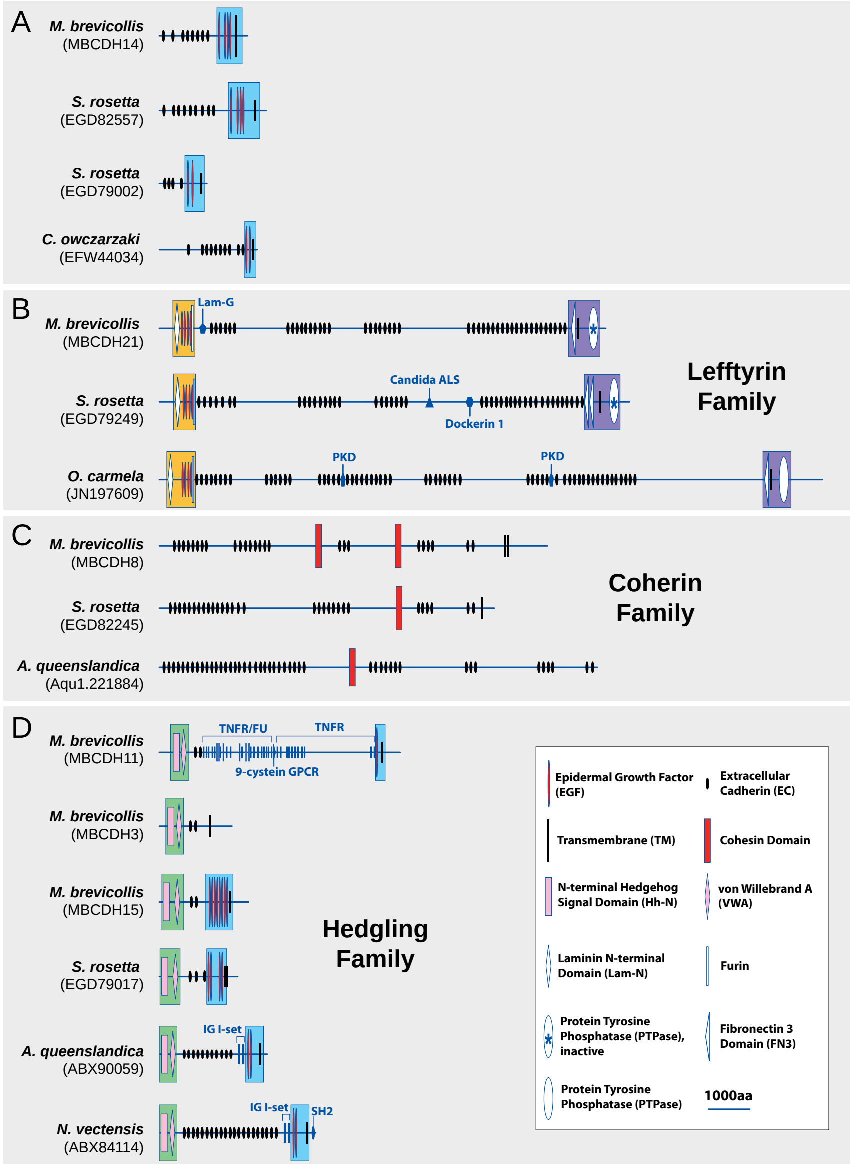
- 3 families of Cadherins in last common ancestor of choanoflagelates and Metazoa.

- Lefftyrin Family:
  LEF: Laminin N-terminal (Lam-N) domain, four EGF domains and a Furin domain

  FTY: Fibronectin 3 (FN3) domains, a TM domain and a cytoplasmic protein tyrosine phosphatase (PTPase) domain

- Coherin Family:
  Coherin domains (only found in *archea* and *bacteria*.

- Hedgling Family:
  Hh-N domain (secreted portion of Hh) and VWA domains.

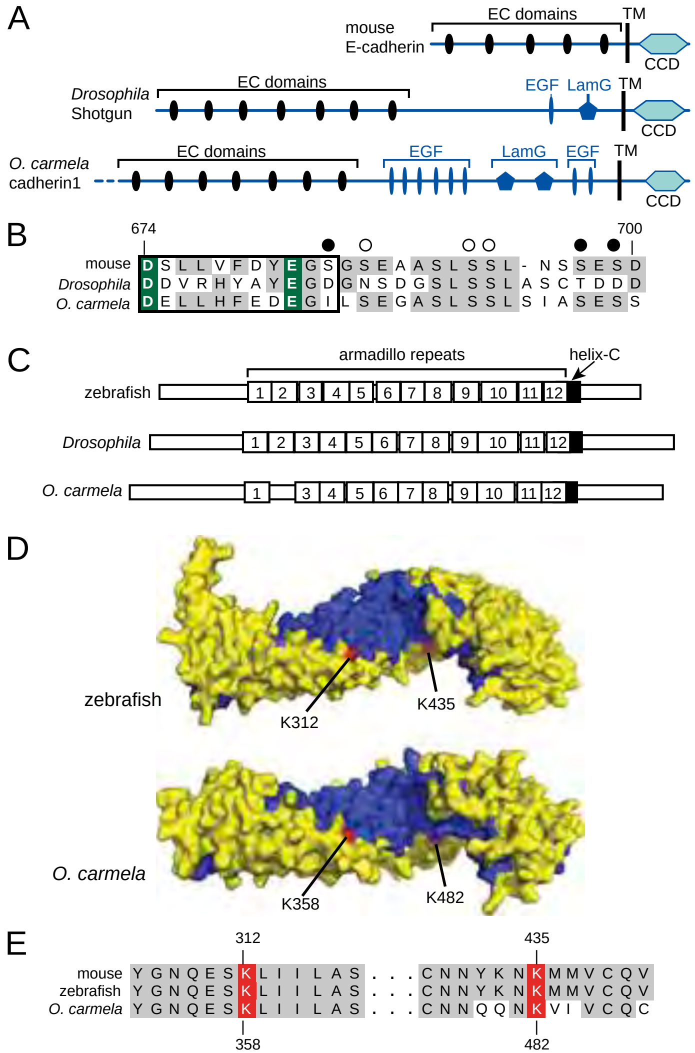


Nichols SA. et al, and King N. *PNAS*. 109:13046. 2012

Emergence of Classical Cadherins in Sponges

- Presence of classical Cadherin in the sponge *Oscarella carmela*
- Conservation of 2 amino acids (Glutamate and Aspartate) involved in ß-catenin binding

- ß-catenin ortholog in *O. carmela*: 11 Arm repeats and helix C domain
- Arm repeat structure of zebrafish and predicted structure in sponge shows similar positively charged groove with 2 conserved Lysines with similar orientation.

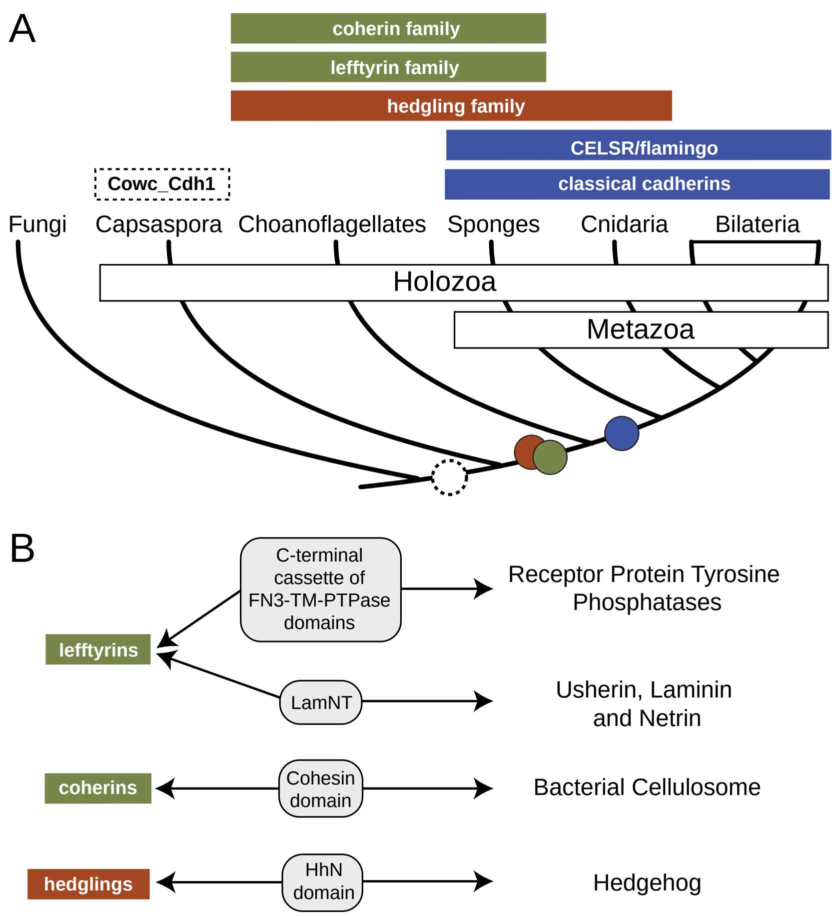


Nichols SA. et al, and King N. *PNAS*. 109:13046. 2012

Premetazoan ancestry of Cadherins

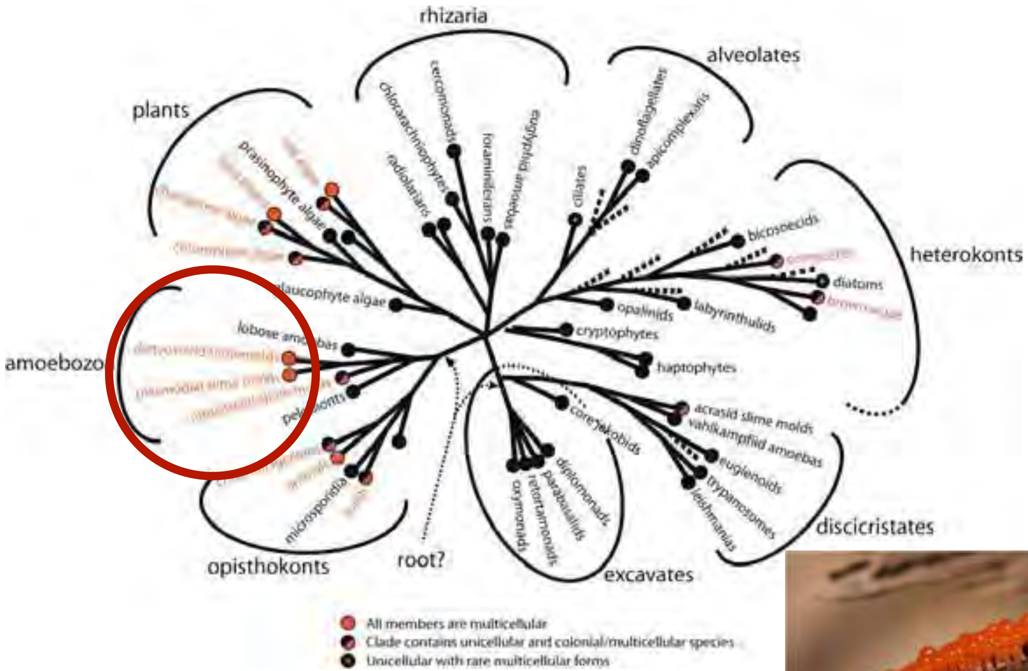
- Cadherins present in last common ancestor to choanflagelates and Metazoa had a signalling function

- The « invention » of a *bone fide* classical Cadherin with adhesion function and link to ß-catenin in common ancestor of Sponges, Cnidaria and Bilateria.



Nichols SA. et al, and King N. *PNAS*. 109:13046. 2012

Multicellularity in Slime Molds



Trichia decipens

Arcyria cinerea

Stemonitis

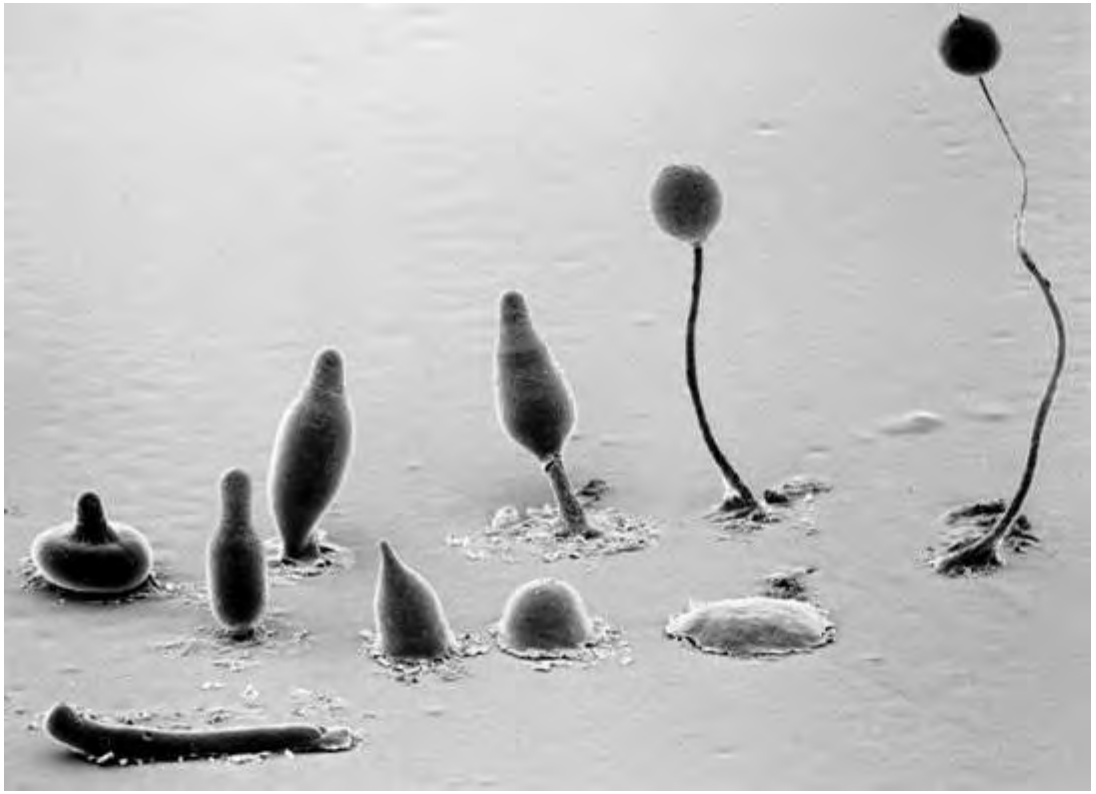
Physarum polycephalum

Ceratiomyxa fructiculosa

Metatrichia vesparium

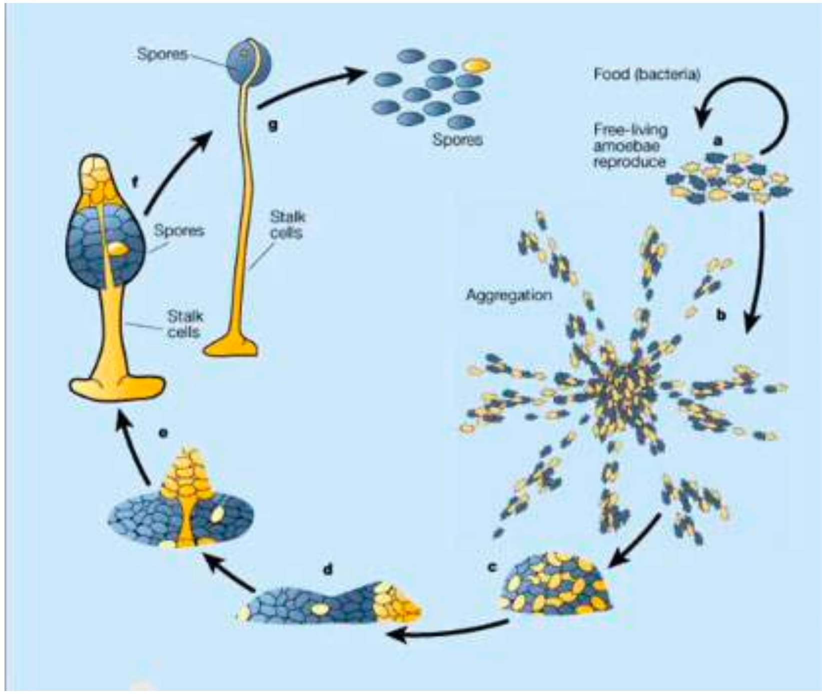
http://www.kuriositas.com/2012/05/slime-mold-alien-landscapes-on-earth.html

Multicellularity in Slime Molds



M.J. Grimson & R.L. Blanton.
Biological Sciences Electron Microscopy Laboratory, Texas Tech University

https://www.youtube.com/watch?v=vjRPla0BONA



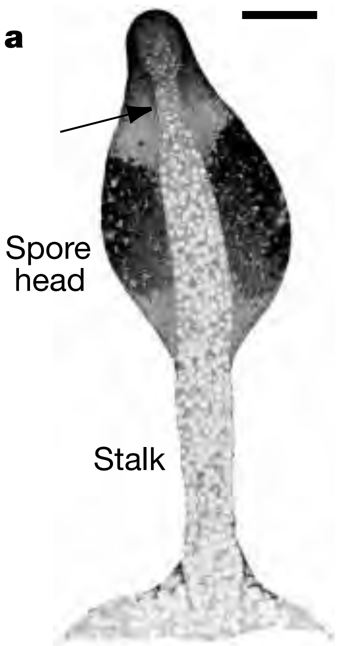
www.dictybase.org/ (Shaulsky)

Multicellularity in Slime Molds: Adherens junctions

Adherens junctions and β-catenin-mediated cell signalling in a non-metazoan organism

Mark J. Grimson*†, Juliet C. Coates†‡§, Jonathan P. Reynolds‡, Mark Shipman‡, Richard L. Blanton* & Adrian J. Harwood‡

NATURE | VOL 408 | 7 DECEMBER 2000 |



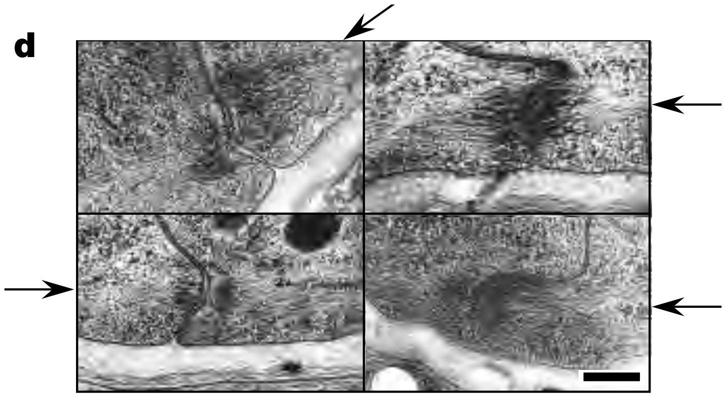


Figure 1 Identification of adherens junctions in the *Dictyostelium* fruiting body.

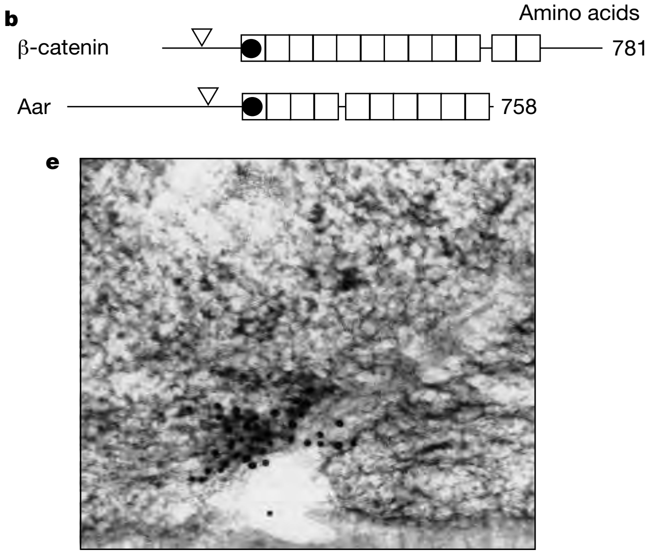


Figure 3 *aardvark* (*aar*) encodes a homologue of β-catenin.

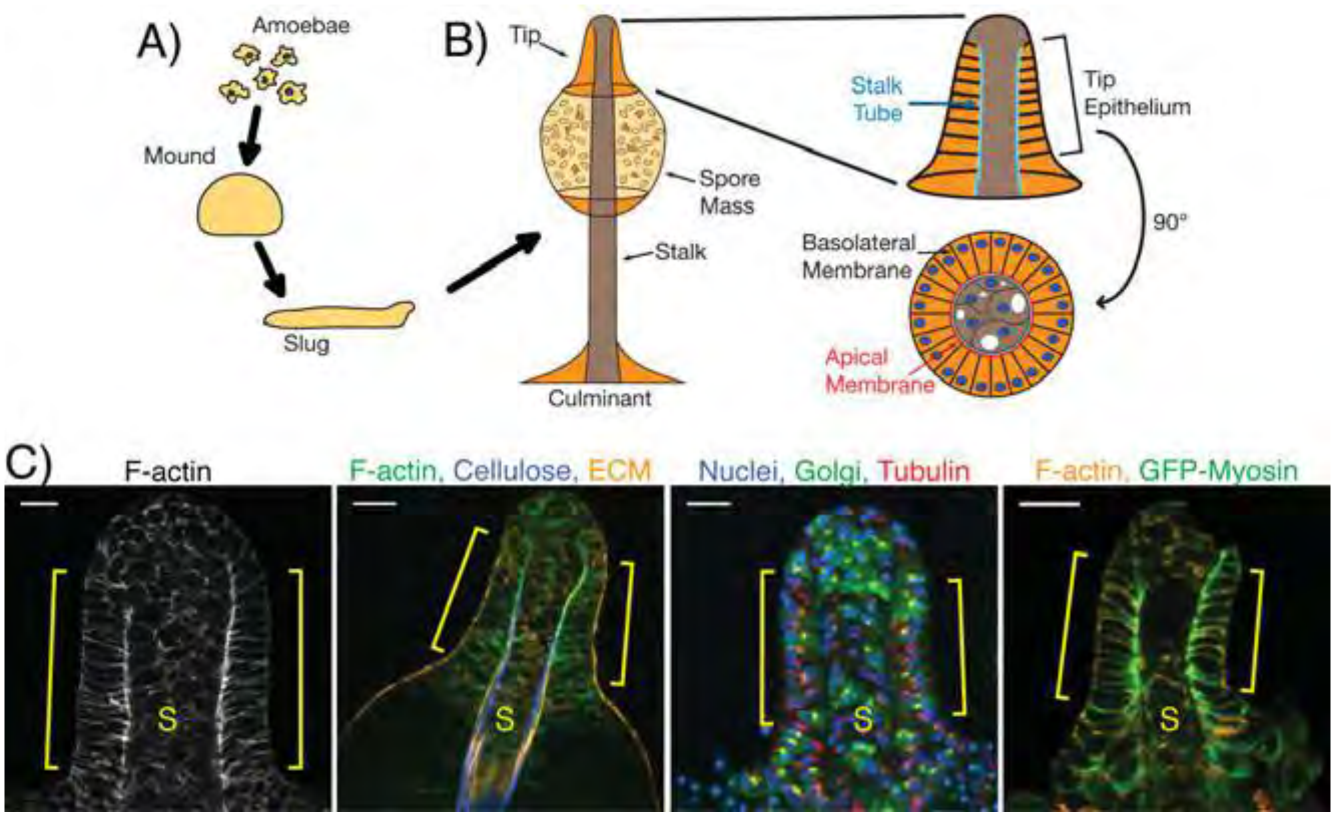
Grimson MJ et al, and Harwood AJ. *Nature*. 408:727. 2000

Multicellularity in Slime Molds: epithelium

A Polarized Epithelium Organized by β- and α-Catenin Predates Cadherin and Metazoan Origins

Daniel J. Dickinson,[1] W. James Nelson,[1,2,3]* William I. Weis[1,3,4]*

11 MARCH 2011 VOL 331 SCIENCE

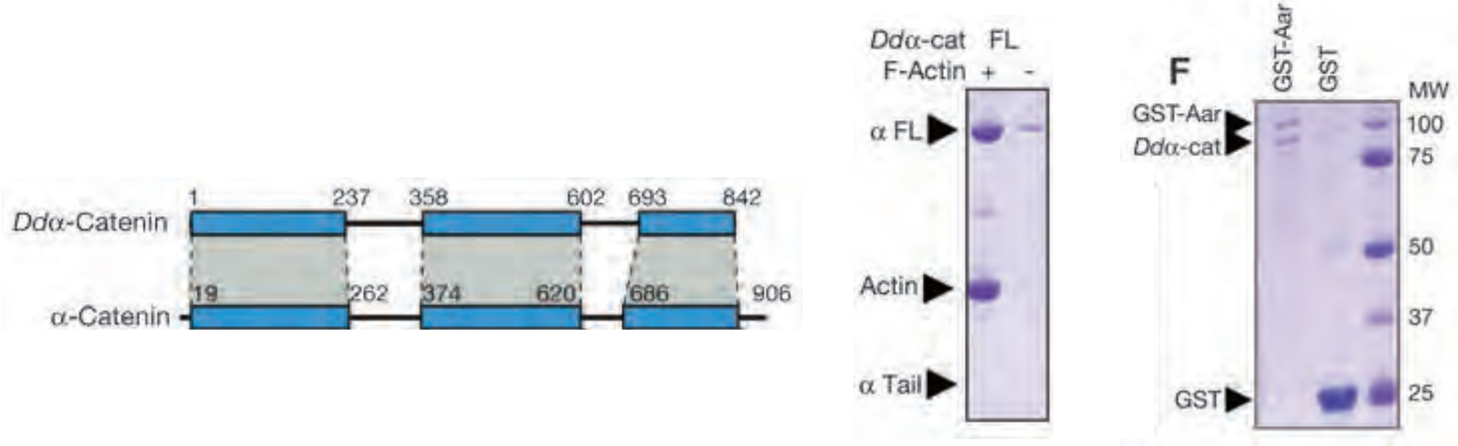


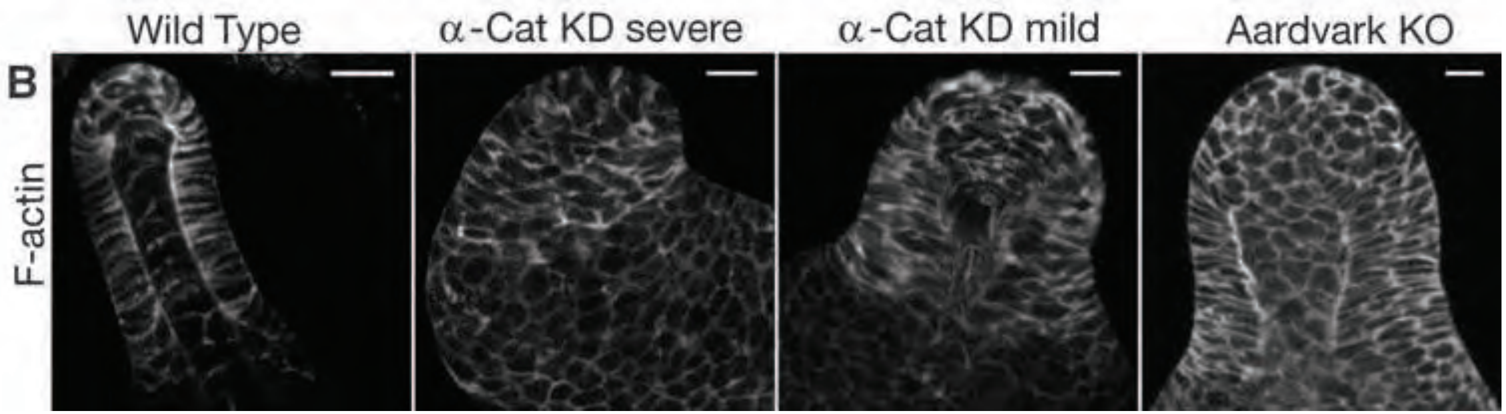
Dickinson DJ et al *Bioessays*, 34:833. 2012 (Review)

Dickinson DJ, Nelson WJ and Weiss W. *Science*. 331:1336. 2011

Multicellularity in Slime Molds: epithelium

α and ß-Catenin form a complex
and are required for columnar organisation





Dickinson DJ, Nelson WJ and Weiss W. *Science*. 331:1336. 2011

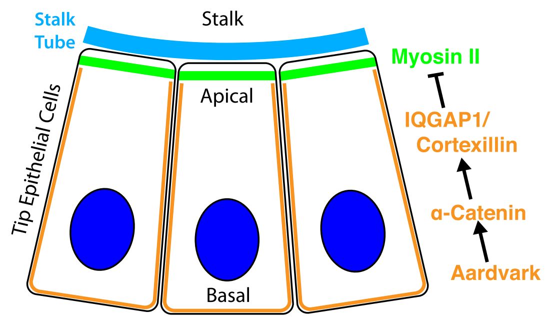
Multicellularity in Slime Molds: epithelium

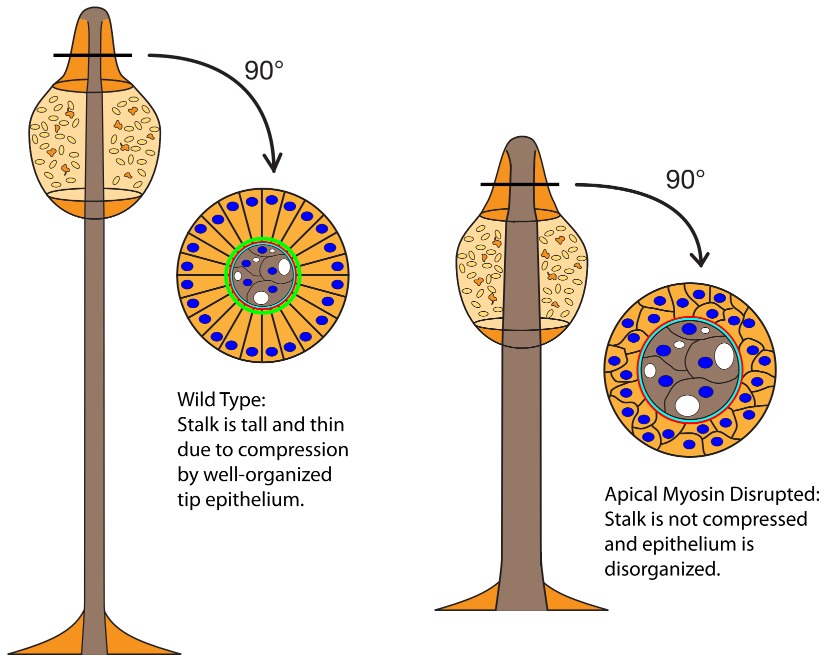
α-Catenin and IQGAP Regulate Myosin Localization to Control Epithelial Tube Morphogenesis in *Dictyostelium*

Daniel J. Dickinson,[1,6] Douglas N. Robinson,[5] W. James Nelson,[1,2,3,*] and William I. Weis[1,3,4,*]

Developmental Cell *23*, 533–546, September 11, 2012

Morphogenetic function
of catenins
without Cadherins

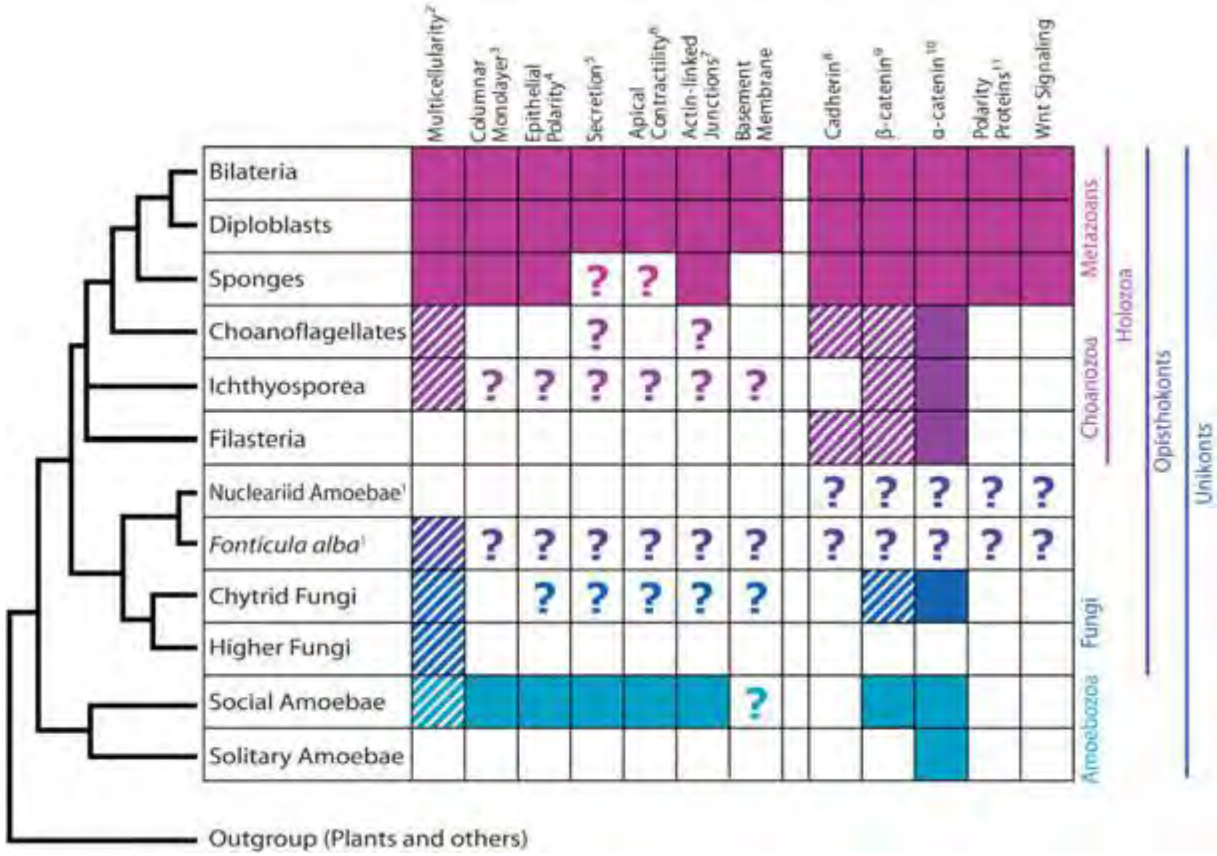




« Facultative multicellularity Hypothesis »

- The traditional view is that multicellularity evolved independently in metaoza and slime molds

- The « facultative multicellularity hypothesis » proposes that ancestors had a facultative epithelial organisation dependent on catenins that was subsequently lost, except in Metazoa



Dickinson DJ et al *Bioessays*, 34:833. 2012 (Review)

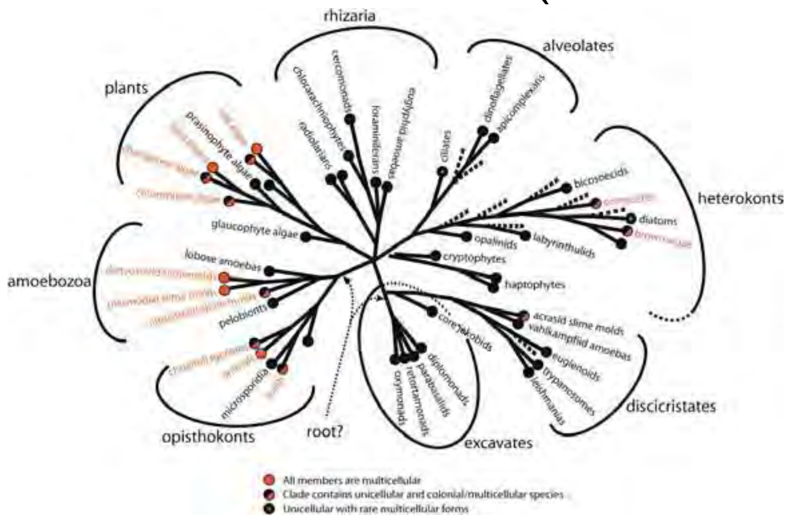
Summary

- **Cadherin based Adhesion** most likely evolved in 3 parallel steps:

1. **Emergence of Cadherins** involved in sensing external environment and signalling in organisms with facultative multicellularity (LCA to Metazoa and Choanoflafelates ?).

2. **Emergence of Catenins** and actin coupling involved in cell-cell interactions and epithelial organisation (possibly in LCA to slime molds, Metazoa, choanos etc ?)

3. **Functional coupling of Catenins and Cadherins** (LCA to Sponges and Bilateria ?)



Conclusions

Prochain cours: 14 Novembre 2017

5. Adhesion as an active mechanism

4.1. Clustering

4.2. Mechanosensation - Mechano-transduction

6. Adhesion and *dissipation*