

## RE-SOLVING THE CADHERIN-CATENIN-ACTIN CONUNDRUM

William I. Weis<sup>1,3</sup> and W. James Nelson<sup>2,3</sup>

From the Departments of Structural Biology<sup>1</sup>, Biological Sciences<sup>2</sup>, and Molecular and Cellular Physiology<sup>3</sup>, Stanford University, Stanford, CA 94305 USA

Running title: The cadherin-catenin-actin conundrum

Address correspondence to William I. Weis ([bill.weis@stanford.edu](mailto:bill.weis@stanford.edu)) or W. James Nelson ([wjnelson@stanford.edu](mailto:wjnelson@stanford.edu))

Cell-cell adhesion plays critical roles in establishing and maintaining tissue architecture and function (1,2). In these roles, cell-cell adhesion must be adaptable and, depending on the biological circumstance, weak, dynamic or strong. Different adhesion structures (adherens junctions, tight junctions, desmosomes) regulate cell-cell adhesion, and each comprises distinct membrane-bound adhesion proteins that interact with the cytoskeleton.

Of the proteins that form these adhesion structures, the  $\text{Ca}^{++}$ -dependent classical cadherins found in adherens junctions have critical roles in controlling the specificity, organization, and dynamics of cell-cell adhesions. Cadherins are required for the formation of the first overt forms of tissue differentiation in early vertebrate and invertebrate development (3,4). The specificity of adhesion amongst different cell types depends upon the strength of binding between, and surface concentration of cadherins (5,6).

During  $\text{Ca}^{++}$ -dependent cell-cell adhesion, cadherins rapidly concentrate at sites of cell-cell contact through an active process involving the actin cytoskeleton (7), which reorganizes as cell-cell contacts form (8,9). Actomyosin contractility may also play a role in cell-cell adhesion (10), and remodeling of cell and tissue structures in development (11,12).

### Potential Protein-Protein Linkages Between Cadherins and the Actin Cytoskeleton

Classical cadherins bind directly to several cytoplasmic proteins including  $\beta$ -catenin, plakoglobin (a close relative of  $\beta$ -catenin) and p120. p120 may regulate the cadherin-actin cytoskeleton nexus indirectly by locally

controlling the activity of the Rho inhibitor p190RhoGAP and thereby activation of Rho and Rac (13), and the rate of cadherin endocytosis (14). Plakoglobin and  $\beta$ -catenin play a more direct role by binding to  $\alpha$ -catenin (15), an actin filament binding/bundling protein that also binds other actin-binding proteins (16).

$\alpha$ -Catenin binds and bundles actin filaments (17), and has been shown to form binary interactions with several actin-binding proteins, including vinculin (18),  $\alpha$ -actinin (19), spectrin (20), ZO-1 (21), afadin (22), ajuba (23), and proteins that regulate actin assembly including formins (24). In some cases, these interactions were demonstrated directly by binding between purified recombinant proteins, whereas others were indicated by yeast two-hybrid assay, co-immunoprecipitation or subcellular colocalization. Based upon these data it is easy to build protein-protein interaction maps in which  $\alpha$ -catenin links the cadherin-catenin complex to actin (Fig. 1A).

Several cell lines that lack endogenous  $\alpha$ -catenin have been used to investigate  $\alpha$ -catenin functions. Surprisingly, these cells form cell-cell adhesions and aggregate in the presence of extracellular  $\text{Ca}^{++}$ , although not as quickly or irreversibly as cells “rescued” by expression of ectopic  $\alpha$ -catenin (25,26). Equally surprising, the most significant effects of genetic deletion of  $\alpha$ -catenin *in vivo* were increased cell migration, shortening of the cell cycle, increased proliferation (hyperplasia) and decreased apoptosis, rather than gross disruption of cell-cell adhesion (27,28). These effects are very different from those caused by genetic deletion of cadherin, which results in complete disruption of cell adhesion and tissue architecture (3,4).

### *A Direct Test of Protein Complexes Linking Cadherin to the Actin Cytoskeleton*

The ability of catenins to physically connect cadherins to actin was tested by direct binding studies with purified proteins, and measurement of protein dynamics in live cells (29,30). When E-cadherin,  $\beta$ -catenin and  $\alpha$ -catenin were mixed at concentrations that were both sufficient to form a ternary complex and 17x higher than the estimated  $K_D$  for the  $\alpha$ -catenin-actin interaction (17), a fraction of  $\alpha$ -catenin, but neither cadherin nor  $\beta$ -catenin, cosedimented with F-actin, implying that  $\alpha$ -catenin cannot bind to  $\beta$ -catenin and actin simultaneously (29) (Fig. 1B). Potentially, there are two concerns with this conclusion. First,  $\alpha$ -catenin can form homodimers that compete with  $\beta$ -catenin and lower the effective affinity of  $\alpha$ - $\beta$ -catenin interaction (see below). Therefore, a chimera comprising the  $\alpha$ -catenin binding site of  $\beta$ -catenin fused to  $\alpha$ -catenin was made to create a high effective concentration of the partners to insure that all  $\alpha$ -catenin is bound to  $\beta$ -catenin (31). This chimera did not sediment with F-actin, confirming that binding of  $\alpha$ -catenin to the E-cadherin/ $\beta$ -catenin complex and actin is mutually exclusive (30). Second, the bacterially-expressed proteins used in these experiments lacked post-translational modifications that might be required for binding to actin, or a required co-factor was missing. Therefore, binding studies were performed with phosphorylated proteins and on E-cadherin embedded in plasma membrane patches from MDCK cells in the presence of cytosol, to provide endogenous factors. Even under these conditions, the membrane-bound E-cadherin/ $\beta$ -catenin/ $\alpha$ -catenin complex did not bind F-actin (29). The lack of binding of the E-cadherin/catenin complex to actin was unanticipated and highlights the problem of extrapolating data from binary to higher-order interactions.

The allosteric behavior of  $\alpha$ -catenin, in which binding to one partner inhibits binding to the other, appears to be related to its oligomeric state as either a monomer or homodimer (30) (Fig. 1B). Structural data revealed that the sites for  $\alpha$ -catenin homodimerization and  $\beta$ -catenin binding overlap (31). This implies that  $\beta$ -catenin should

bind more strongly to  $\alpha$ -catenin monomer than to the homodimer, since the homodimer would have to dissociate in order to allow  $\beta$ -catenin to bind (31). Direct binding studies showed that  $\beta$ -catenin preferentially bound to  $\alpha$ -catenin monomer, whereas actin bound more strongly to  $\alpha$ -catenin homodimer (30). Moreover, because preparations of  $\alpha$ -catenin monomer are always contaminated with homodimer (30), the observed binding of  $\alpha$ -catenin “monomer” to actin is likely due to contaminating homodimer. These data, as well as differences in proteolytic sensitivity of the  $\alpha$ -catenin monomer, homodimer, and  $\beta$ / $\alpha$ -catenin chimera (the latter representing the  $\beta$ -catenin-bound form) (30), indicate that different molecular conformations are associated with the  $\beta$ -catenin-(monomer) and actin-(homodimer) binding states of  $\alpha$ -catenin.

If  $\alpha$ -catenin does not link the cadherin-catenin complex directly to actin, it is possible that one or more of the large number of  $\alpha$ -catenin binding partners is involved. Direct binding studies showed that neither vinculin nor  $\alpha$ -actinin, both of which are often cited as such linkers (18,19), could confer binding of the ternary cadherin/catenin complex to actin (29). It remains possible that one of the other  $\alpha$ -catenin partners (*e.g.*, afadin, ZO-1, Ajuba, formin) serves this role, but this has not been tested directly. Nonetheless, it is reasonable to assume that any protein forming a link between cadherins, catenins and actin should be present in these complexes at levels comparable to cadherins and catenins. However, a chemically cross-linked protein complex immunoprecipitated from  $^{35}\text{S}$ -methionine-labelled cells with an anti-cadherin antibody had amounts of  $\beta$ -catenin, plakoglobin and  $\alpha$ -catenin that were comparable to that of cadherin, but other co-immunoprecipitated proteins were considerably less abundant (32) and are therefore unlikely to be obligate parts of a linked structure. Finally, direct interactions between the cadherin complex and actin might occur under certain conditions not tested biochemically, for example tension on actin-bound  $\alpha$ -catenin might enable binding to  $\beta$ -catenin (33), but new assays will be needed to test these possibilities directly and rigorously.

If actin is bound directly to the cadherin/catenin complex it might be expected that the diffusion properties of these proteins are similar. Fluorescence recovery after photobleaching measurements in live cells demonstrated that E-cadherin,  $\beta$ -catenin, and  $\alpha$ -catenin had essentially identical recovery halftimes and immobile fractions, whereas actin had a much faster recovery and smaller immobile fraction (29). Importantly, deletion of either the cadherin cytoplasmic domain or the  $\alpha$ -catenin actin-binding domain, *i.e.*, breaking putative links between E-cadherin and  $\alpha$ -catenin to the cytoskeleton, had no effect on E-cadherin or  $\alpha$ -catenin dynamics. Blocking actin polymerization or stabilizing filaments also had no effect on the dynamics of the cadherin/catenin complex. Taken together, these results are incompatible with a stable linkage between the E-cadherin/catenin complex and actin, even one mediated by multiple weak interactions as suggested in a Velcro model (33).

### Reconciling the “old” with the “new”: what is the role of $\alpha$ -catenin?

Discussion about the significance of these new results (33,34) has revolved around studies of cadherin- $\alpha$ -catenin fusion proteins, which bypass  $\beta$ -catenin and assume a direct linkage from cadherin to actin. Using L-cells, which lack endogenous cadherin but express both  $\beta$ - and  $\alpha$ -catenin, Nagafuchi *et al.* (35) expressed chimeras of E-cadherin lacking its cytoplasmic domain fused to either full-length  $\alpha$ -catenin, the amino-terminal 508 residues of  $\alpha$ -catenin, or the C-terminal 400 residues  $\alpha$ -catenin that include the actin-binding domain. The cadherin/ $\alpha$ -catenin full-length and cadherin/ $\alpha$ -catenin actin-binding domain chimeras induced cell-cell adhesion (35), and had reduced diffusion in the plane of the membrane suggesting that they were anchored to the underlying cytoskeleton (36). Similarly, a chimera of E-cadherin linked to a fusion of the N-terminal domain of  $\alpha$ -catenin and the C-terminal actin-binding domain of vinculin induced cell-cell adhesion in cells that lacked endogenous vinculin and  $\alpha$ -catenin (25,26). These results have been interpreted as evidence that  $\alpha$ -catenin plays a

central role in cell-cell adhesion by linking the cadherin/ $\alpha$ -catenin complex to the actin cytoskeleton either directly or indirectly through vinculin or ZO-1. However, since  $\alpha$ -catenin cannot bind to  $\beta$ -catenin and actin simultaneously, chimeras that bypass  $\beta$ -catenin cannot represent the properties of the cadherin-catenin complex in a real adhesive contact.

Nonetheless, how can the results with chimeric E-cadherin/ $\alpha$ -catenin proteins be reconciled with direct evidence that  $\alpha$ -catenin does not bind simultaneously to the cadherin/ $\beta$ -catenin complex and actin? A simple explanation is that the chimeras enabled the delivery of sufficient amounts of cadherin to the cell surface to induce cell-cell adhesion; recall that the number and concentration of cadherin molecules at the surface can profoundly influence cell adhesiveness and sorting (6,37). Unfortunately, the level of surface-expressed cadherin was not quantified in these studies. In this context, it is noteworthy that the chimera of E-cadherin fused to the N-terminal region of  $\alpha$ -catenin had an abnormal subcellular distribution and did not induce cell-cell adhesion (35). Cadherin/ $\alpha$ -catenin chimeras also appear to restore the correct migratory behavior of follicle cells in *Drosophila* oogenesis (38). Again, these observations may be due in part to restoring cell-surface cadherin molecules to cells genetically deleted for E-cadherin.

Other published data do not support a linkage between actin and cadherin-bound  $\alpha$ -catenin. First, a chimera of E-cadherin fused to residues 508-643 of  $\alpha$ -catenin conferred adhesion to cells (26), despite the fact that this portion of  $\alpha$ -catenin does not include the binding sites for actin, which spans residues 671-906 (22), vinculin or ZO-1 (25,26), or the homodimerization site (31). Second, it has been reported that the cadherin complex is less soluble in buffers containing non-ionic detergents, which is taken to indicate incorporation into the detergent-insoluble cytoskeleton (39-41). However, E-cadherin,  $\beta$ -catenin and plakoglobin were found in a detergent-insoluble fraction of cells lacking  $\alpha$ -catenin (42), indicating that  $\alpha$ -catenin is not needed to confer resistance of E-cadherin to extraction with non-ionic detergents. Moreover, E-cadherin/ $\alpha$ -catenin chimeras lacking the  $\alpha$ -catenin actin-binding

domain showed a similar amount of resistance to detergent extractability compared to the full-length protein (26,35), calling into question the interpretation that detergent insolubility is a direct readout of specific cytoskeletal association.

Since the simple model in which  $\alpha$ -catenin physically connects the cadherin- $\beta$ -catenin complex to actin does not hold up to experimental scrutiny, alternative roles of  $\alpha$ -catenin in regulating actin dynamics were investigated. It was found that  $\alpha$ -catenin suppressed Arp2/3-mediated actin polymerization by directly competing with Arp2/3 for actin filaments (30) (Fig. 1B). Because this activity required actin binding, the  $\alpha$ -catenin homodimer was more potent than the monomer in suppressing Arp2/3 activity, with complete suppression observed at 5 $\mu$ M  $\alpha$ -catenin. Since the concentration of  $\alpha$ -catenin in MDCK cell cytosol is 0.6  $\mu$ M (30), the local concentration of  $\alpha$ -catenin would have to increase 10-fold to affect Arp2/3, a condition that could simply arise by clustering the cadherin complex at cell-cell contacts (see below).

What might be the physiological significance of the negative regulation of Arp2/3 complex by  $\alpha$ -catenin? During cell-cell adhesion actin undergoes a dramatic reorganization that could be mediated by changes in the local distribution and concentration of  $\alpha$ -catenin (Fig. 1B). Cells form transient contacts mediated by cadherins present on highly dynamic lamellipodia (7) driven by Arp2/3-mediated polymerization of branched actin networks perpendicular to the membrane (43). As the contact matures, cadherins become concentrated on the opposed surfaces, and lamellipodial movements slow and eventually cease as a stable cell-cell contact forms (8,9). At the same time, actin filaments at mature adherens junctions are reorganized into linear, unbranched bundles parallel to the membrane (44) (Fig. 1B).

The newly uncovered properties of  $\alpha$ -catenin can be applied to a model that explains these changes in membrane dynamics and actin organization during formation of intercellular junctions (Fig. 1B). In non-adherent cells, cadherin and associated  $\beta$ -catenin, which binds strongly to cadherin and appears to be required for transport of cadherin to the cell surface (45), are

present on lamellipodial membranes (7,36). Monomeric  $\alpha$ -catenin, which appears to predominate in the cytosol (30), binds to the cadherin/ $\beta$ -catenin complex at the plasma membrane (46). As cadherins on opposing cell surfaces engage, the membranes are brought into close proximity, which favors more cadherin-cadherin interactions. This produces a local clustering of cadherins (36,47) and thereby increases the local concentration of  $\alpha$ -catenin bound in the E-cadherin/catenin complex. Since  $\alpha$ -catenin bound to the E-cadherin/catenin complex can exchange with cytosolic  $\alpha$ -catenin (30),  $\alpha$ -catenin that dissociates from the clustered E-cadherin/ $\beta$ -catenin complex will be at a high local concentration, favoring homodimer formation. As a consequence,  $\alpha$ -catenin homodimers locally inhibit the Arp2/3 complex, thereby reducing actin branching and lamellipodial activity, and induce filament bundling. It has been reported that  $\alpha$ -catenin can promote linear actin cable formation by formins, which would also induce actin remodeling locally (24), although this has not been tested with purified components.

Could this model explain some of the effects of the cadherin/ $\alpha$ -catenin chimeras described above? Unexplained phenotypes of the transfected L-cells were defects in cytokinesis and decreased cell motility (35). Since  $\beta$ -catenin is bypassed, the  $\alpha$ -catenin in the chimeras would retain actin-binding activity that suppresses Arp2/3 activity at the contact and prevent changes in actin organization needed for proper cytokinesis (35). Likewise, the decreased motility of these cells can be explained by constitutive suppression of Arp2/3 at the prospective leading edge of a migratory cell. Indeed, PC-9 lung carcinoma cells, which lack  $\alpha$ -catenin, are highly invasive and motile, properties reversed by expression of  $\alpha$ -catenin (48), again consistent with the ability of  $\alpha$ -catenin to suppress Arp2/3. Moreover, in both of the L-cell (35) and *Drosophila* oocyte (38) studies cited above, the cells expressed endogenous  $\alpha$ -catenin. For chimeric molecules containing the N-terminal region of  $\alpha$ -catenin, which harbors the homodimerization domain, structural data (31) predict that dimers between endogenous  $\alpha$ -catenin monomer and the fusion protein could occur and thereby provide a further increase in local  $\alpha$ -

catenin concentration. This could provide sufficient  $\alpha$ -catenin to regulate actin at the junction.

### What connects actin to the adherens junction?

Actin cables are associated with developing and mature adherens junctions. Furthermore, the movement of the adherens junction during cellularization of the *Drosophila* embryo, and other morphogenetic changes rely on actomyosin activity (12). It is not clear, however, whether actin always needs to be anchored to other adherens junction components except during periods of active constriction.

If the cadherin/catenin complex does not interact directly with actin, what anchors actin in the adherens junction? Several plausible candidates have been identified. First, the nectin adhesion molecules are also found in adherens junctions (49). The cytoplasmic domain of nectin binds to I-afadin, which binds to both actin and  $\alpha$ -catenin (22). The ability of afadin to form a quaternary complex with nectin,  $\alpha$ -catenin and actin has yet to be tested, however. Second, the C-terminus of  $\beta$ -catenin features a conserved PDZ

binding motif that interacts with the scaffold protein Lin7 (50), which in turn binds through CASK to other components of the actin cytoskeleton (51). Whether these interactions are important for cell adhesion is unclear since deletion of the  $\beta$ -catenin C-terminal region in *Drosophila* has no apparent effect on adherens junction function (52). Third, Shroom is another PDZ domain-containing actin-binding protein required for neural tube morphogenesis that localizes to adherens junctions (53). Fourth, Vezatin is a transmembrane protein of adherens junctions that links myosin to the cadherin-catenin complex (54). Finally, a recent report identified an interaction between the synaptotagmin-like protein bitesize found near the site of adherens junction formation and moesin, an actin-binding member of the ERM family of cytoskeletal proteins; significantly, *bitesize* mutants fail to establish proper actin organization at the adherens junctions during *Drosophila* cellularization (55). An essential step in understanding cell and tissue morphogenesis will be the development of rigorous assays to test the roles of these, and potentially other candidate proteins in linking actin to cell-cell adhesion structures.

### References

1. Takeichi, M. (1995) *Curr Opin Cell Biol* 7, 619-627
2. Gumbiner, B. M. (2005) *Nat Rev Mol Cell Biol* 6, 622-634
3. Larue, L., Antos, C., Butz, S., Huber, O., Delmas, V., Dominis, M., and Kemler, R. (1996) *Development* 122, 3185-3194
4. Wang, F., Dumstrei, K., Haag, T., and Hartenstein, V. (2004) *Dev Biol* 270, 350-363
5. Nose, A., Nagafuchi, A., and Takeichi, M. (1988) *Cell* 54, 993-1001
6. Foty, R. A., and Steinberg, M. S. (2005) *Dev Biol* 278, 255-263
7. Adams, C. L., and Nelson, W. J. (1998) *Curr Opin Cell Biol* 10, 572-577
8. Ehrlich, J. S., Hansen, M. D., and Nelson, W. J. (2002) *Dev Cell* 3, 259-270
9. Vaezi, A., Bauer, C., Vasioukhin, V., and Fuchs, E. (2002) *Dev Cell* 3, 367-381
10. Shewan, A. M., Maddugoda, M., Kraemer, A., Stehbens, S. J., Verma, S., Kovacs, E. M., and Yap, A. S. (2005) *Mol Biol Cell* 16, 4531-4542
11. Young, P. E., Pesacreta, T. C., and Kiehart, D. P. (1991) *Development* 111, 1-14
12. Dawes-Hoang, R. E., Parmar, K. M., Christiansen, A. E., Phelps, C. B., Brand, A. H., and Wieschaus, E. F. (2005) *Development* 132, 4165-4178
13. Anastasiadis, P. Z., and Reynolds, A. B. (2001) *Curr Opin Cell Biol* 13, 604-610
14. Davis, M. A., Ireton, R. C., and Reynolds, A. B. (2003) *J Cell Biol* 163, 525-534

15. Aberle, H., Butz, S., Stappert, J., Weissig, H., Kemler, R., and Hoschuetzky, H. (1994) *J Cell Sci* 107, 3655-3663
16. Kobiela, A., and Fuchs, E. (2004) *Nat Rev Mol Cell Biol* 5, 614-625
17. Rimm, D. L., Koslov, E. R., Kebriaei, P., Cianci, C. D., and Morrow, J. S. (1995) *Proc Natl Acad Sci U S A* 92, 8813-8817
18. Weiss, E. E., Kroemker, M., Rudiger, A. H., Jockusch, B. M., and Rudiger, M. (1998) *J Cell Biol* 141, 755-764
19. Knudsen, K. A., Soler, A. P., Johnson, K. R., and Wheelock, M. J. (1995) *J Cell Biol* 130, 67-77
20. Pradhan, D., Lombardo, C. R., Roe, S., Rimm, D. L., and Morrow, J. S. (2001) *J Biol Chem* 276, 4175-4181
21. Itoh, M., Nagafuchi, A., Moroi, S., and Tsukita, S. (1997) *J Cell Biol* 138, 181-192
22. Pokutta, S., Drees, F., Takai, Y., Nelson, W. J., and Weis, W. I. (2002) *J Biol Chem* 277, 18868-18874
23. Marie, H., Pratt, S. J., Betson, M., Epple, H., Kittler, J. T., Meek, L., Moss, S. J., Troyanovsky, S., Attwell, D., Longmore, G. D., and Braga, V. M. (2003) *J Biol Chem* 278, 1220-1228
24. Kobiela, A., Pasolli, H. A., and Fuchs, E. (2004) *Nat Cell Biol* 6, 21-30
25. Watabe-Uchida, M., Uchida, N., Imamura, Y., Nagafuchi, A., Fujimoto, K., Uemura, T., Vermeulen, S., van Roy, F., Adamson, E. D., and Takeichi, M. (1998) *J Cell Biol* 142, 847-857
26. Imamura, Y., Itoh, M., Maeno, Y., Tsukita, S., and Nagafuchi, A. (1999) *J Cell Biol* 144, 1311-1322
27. Vasioukhin, V., Bauer, C., Degenstein, L., Wise, B., and Fuchs, E. (2001) *Cell* 104, 605-617
28. Lien, W. H., Klezovitch, O., Fernandez, T. E., Delrow, J., and Vasioukhin, V. (2006) *Science* 311, 1609-1612
29. Yamada, S., Pokutta, S., Drees, F., Weis, W. I., and Nelson, W. J. (2005) *Cell* 123, 889-901
30. Drees, F., Pokutta, S., Yamada, S., Nelson, W. J., and Weis, W. I. (2005) *Cell* 123, 903-915
31. Pokutta, S., and Weis, W. I. (2000) *Mol Cell* 5, 533-543
32. Nathke, I. S., Hinck, L., Swedlow, J. R., Papkoff, J., and Nelson, W. J. (1994) *J Cell Biol* 125, 1341-1352
33. BurrIDGE, K. (2006) *Nature* 440, 38-39
34. Gates, J., and Peifer, M. (2005) *Cell* 123, 769-772
35. Nagafuchi, A., Ishihara, S., and Tsukita, S. (1994) *J Cell Biol* 127, 235-245
36. Sako, Y., Nagafuchi, A., Tsukita, S., Takeichi, M., and Kusumi, A. (1998) *J Cell Biol* 140, 1227-1240
37. Steinberg, M. S., and Takeichi, M. (1994) *Proc Natl Acad Sci U S A* 91, 206-209
38. Pacquelet, A., and Rorth, P. (2005) *J Cell Biol* 170, 803-812
39. McCrea, P. D., and Gumbiner, B. M. (1991) *J Biol Chem* 266, 4514-4520
40. Nagafuchi, A., and Takeichi, M. (1988) *EMBO J* 7, 3679-3684
41. Ozawa, M., Baribault, H., and Kemler, R. (1989) *EMBO J* 8, 1711-1717
42. van Hengel, J., Gohon, L., Bruyneel, E., Vermeulen, S., Cornelissen, M., Mareel, M., and von Roy, F. (1997) *J Cell Biol* 137, 1103-1116
43. Pollard, T. D., and Borisy, G. G. (2003) *Cell* 112, 453-465
44. Hirokawa, N., Keller, T. C., 3rd, Chasan, R., and Mooseker, M. S. (1983) *J Cell Biol* 96, 1325-1336
45. Chen, Y. T., Stewart, D. B., and Nelson, W. J. (1999) *J Cell Biol* 144, 687-699
46. Hinck, L., Nathke, I. S., Papkoff, J., and Nelson, W. J. (1994) *J Cell Biol* 125, 1327-1340
47. Chen, C. P., Posy, S., Ben-Shaul, A., Shapiro, L., and Honig, B. H. (2005) *Proc Natl Acad Sci U S A* 102, 8531-8536
48. Watabe, M., Nagafuchi, A., Tsukita, S., and Takeichi, M. (1994) *J Cell Biol* 127, 247-256
49. Takai, Y., and Nakanishi, H. (2003) *J Cell Sci* 116, 17-27
50. Perego, C., Vanoni, C., Massari, S., Longhi, R., and Pietrini, G. (2000) *EMBO J* 19, 3978-3989
51. Hsueh, Y. P. (2006) *Curr Med Chem* 13, 1915-1927

52. Cox, R. T., Kirkpatrick, C., and Peifer, M. (1996) *J Cell Biol* 134, 133-148
53. Hildebrand, J. D. (2005) *J Cell Sci* 118, 5191-5203
54. Kussel-Andermann, P., El-Amraoui, A., Safieddine, S., Nouaille, S., Perfettini, I., Lecuit, M., Cossart, P., Wolfrum, U., and Petit, C. (2000) *EMBO J* 19, 6020-6029
55. Pilot, F., Philippe, J. M., Lemmers, C., and Lecuit, T. (2006) *Nature* 442, 580-584



Footnotes

Work in the authors' laboratories is supported by grants GM56169 (W.I.W.) and GM35527 (W.J.N.) from the National Institutes of Health.

Key words: Cadherin, catenins, actin, cell-cell adhesion, cytoskeleton



**Figure 1. Models of how the cadherin-catenin complex is linked to, and regulates the actin cytoskeleton.**

- A. Model based upon the assumption that  $\alpha$ -catenin binds simultaneously to  $\beta$ -catenin and actin filaments.
- B. Model based upon data from Refs. (29) and (30) that  $\alpha$ -catenin monomers and dimers regulate binding to  $\beta$ -catenin and actin filaments, respectively, and that  $\alpha$ -catenin also inhibits Arp2/3-mediated actin branching and promotes actin bundling. See text for details.

**B**

