Published in final edited form as:

Nat Rev Mol Cell Biol. 2004 August ; 5(8): 614–625.

α-CATENIN: AT THE JUNCTION OF INTERCELLULAR ADHESION AND ACTIN DYNAMICS

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Abstract

α-catenin has often been considered to be a non-regulatory intercellular adhesion protein, in contrast to β-catenin, which has well-documented dual roles in cell–cell adhesion and signal transduction. Recently, however, α-catenin has been found to be important not only in connecting the E-cadherin–β-catenin complex to the actin cytoskeleton, but also in coordinating actin dynamics and inversely correlating cell adhesion with proliferation. As the number of α-catenin-interacting partners increases, intriguing new connections imply even more complex regulatory functions for this protein.

In multicellular organisms, cell–cell contacts that are mediated by CLASSIC CADHERINS are essential in many fundamental processes, including morphogenesis, maintenance of tissue integrity, wound healing and cell polarity. The prototype classic cadherin is the transmembrane protein E-cadherin. This protein uses its extracellular domain to bind Ca²⁺ and interact with E-cadherin on adjacent cells, thereby forming ADHERENS JUNCTIONS. To establish efficient cell–cell junctions, E-cadherin uses its cytoplasmic domain to couple to catenins and the actin cytoskeleton. This association sets the classic cadherins apart from DESMOSOMAL cadherins, which form complexes with the intracellular proteins plakoglobin and desmoplakin to form a more robust Ca²⁺-induced adhesive interaction — the desmosome — that links the INTERMEDIATE-FILAMENT cytoskeleton (see also the article by Lynne Chang and Robert Goldman in this issue). Many cells have both adherens junctions and desmosomes, which function coordinately in intercellular adhesion (FIG. 1).

CLASSIC CADHERINS, Cadherins are transmembrane molecules that mediate Ca²⁺-dependent cell–cell adhesion. Classic cadherins are typified by an extracellular segment that consists of five distinct Ca²⁺-binding domains and a conserved cytoplasmic domain, which binds β-catenin. The extracellular part interacts homotypically with cadherins on the surface of neighbouring cells to form adherens junctions. The cytoplasmic tail links the actin cytoskeleton to adherens junctions.; ADHERENS JUNCTION, A specialized

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Competing interests statement

The authors declare no competing financial interests.

DATABASES

The following terms in this article are linked online to:

Entrez Gene:

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CTNNA1 | *CTNNA2* | *CTNNA3* | *CTNNAL1* | *Fmn1* | *Grem1*

Swiss-Prot: <http://www.expasy.ch>

Ajuba | Armadillo | β-catenin | α-catenin | desmoplakin | DIA1 | E-cadherin | αE-catenin | FGF4 | FMN1 | gremlin | HMP1 | HMP-2 | HMR-1 | IQGAP1 | LEF1 | myosin VIIA | αN-catenin | p120 catenin | plakoglobin | SHH | VASP | vezatin | vinculin | ZO1

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intercellular junction of the plasma membrane, in which the cadherin molecules of adjacent cells interact in a Ca^{2+} -dependent manner. Actin filaments are linked to this structure through catenins that are located underneath the junction.; **DESMOSOMES**, Specialized junctional structures that form a tight connection between epithelial cells or cardiac myocytes. They consist of several transmembrane adhesive glycoproteins (desmogleins and desmocollins) and cytoplasmic plaque proteins (desmoplakins) that link to intermediate filaments.; **INTERMEDIATE FILAMENTS**, Proteins that acquired their name from the diameter of their polymeric structure, which is midway between the diameters of thin actin microfilaments and thick microtubules. Their ability to form very stable filaments enables them to confer mechanical strength on the cytoskeleton..

Desmosomes use their attachments to intermediate filaments to provide mechanical strength to intercellular connections¹⁻³. They are particularly important in tissues that are subjected to substantial physical stress, such as muscle and epidermis. By contrast, adherens junctions use their connections to the **ACTOMYOSIN NETWORK** to remodel cell–cell interactions and provide flexible dynamic adhesion during wound repair of adult tissues and embryonic development⁴⁻⁶. Whereas desmosomes and their associated intermediate filaments function as molecular clamps to reinforce intercellular junctions, actin dynamics and adherens-junction formation have been implicated in the initial steps of bringing membranes together and in the final steps of sealing membranes into epithelial sheets.

ACTOMYOSIN NETWORK, A complex of myosin and actin filaments that is responsible for a range of cellular movements in eukaryotic cells. Myosins can translocate vesicles or other cargo on actin filaments..

Dysregulation of cadherin-mediated junctions can lead to severe developmental defects. Mutations in desmosomal genes often result in degenerative disorders, and several excellent reviews have recently described the composition and function of these robust adhesive structures¹⁻³. Curiously, however, although mutations in adherens-junction proteins can sometimes cause tissue degeneration, in other cases they can contribute to carcinogenesis and metastasis⁴⁻⁶. With an increasing knowledge of the composition of adherens junctions, their assembly, and their relationship to other membrane junctions and receptors, new insights into some of these processes are beginning to unfold.

At the heart of the story lie the catenins, which associate with the cytoplasmic domain of cadherins to assemble a protein complex that can associate with the actin cytoskeleton, coordinate stable intercellular adhesion, and regulate indirect associations with desmosomes, **TIGHT JUNCTIONS**, growth-factor receptors and microtubules⁴. In addition, in response to WNT signalling, excess β -catenin that is not used in cell–cell junctions can accumulate and adopt a second function as a nuclear transcriptional co-activator for the lymphoid enhancer-binding factor-1 (LEF1)/T-cell-specific factor (TCF) family of DNA-binding proteins⁷⁻⁹. As sustained stabilization of β -catenin has been associated with a range of human cancers, this regulatory function has been the main focus of the cancer–cadherin link. The reader is referred to several elegant reviews that have covered, in depth, the role of β -catenin in signalling and cancer⁷⁻⁹. However, mutations in E-cadherin and α -catenin can also contribute to cancers¹⁰⁻¹⁷, and gene-targeting studies indicate that the proliferation that is sometimes associated with such mutations does not always result from the activity of nuclear β -catenin^{18,19}.

TIGHT JUNCTIONS, The most apical intercellular junctions, which function as selective (semi-permeable) diffusion barriers between individual cells. They are identified as a belt-like region in which two lipid-apposing membranes lie close together..

In this review, we focus on α -catenin, which is the protein that connects E-cadherin– β -catenin complexes with the actin cytoskeleton^{20,21}. Whereas all other catenins (β -catenin, plakoglobin and p120 catenin) share considerable sequence similarity and belong to the Armadillo family of proteins, α -catenin differs notably in both sequence and structural organization. Although it was previously considered to be solely a structural protein, new roles have begun to emerge for α -catenin in both assembling the cytoskeleton and regulating its dynamics at cell–cell junctions. In addition, recent studies imply that the interactions of α -catenin with E-cadherin– β -catenin complexes might control the accessibility of these complexes to other cellular proteins. In the past few years, various binding partners for α -catenin have surfaced, which have shed new light on the functions of α -catenin and its underlying mechanisms of action (FIG. 2).

α -catenins in development and differentiation

α -catenin is conserved across the eukaryotic kingdom, where it functions broadly in intercellular adhesion during development and differentiation. In *Drosophila melanogaster*, cell adhesion is disrupted when α -catenin contains a mutation in the binding site for Armadillo, which is the *D. melanogaster* homologue of β -catenin²². Adherens junctions are also present in the nematode *Caenorhabditis elegans*, which expresses the homologues HMR-1 (cadherin), HMP-1 (α -catenin) and HMP-2 (β -catenin)²³.

In mice, there are three α -catenins and one close relative, which all share substantial amino-acid sequence identity (TABLE 1): α E-catenin is most prevalent in epithelial tissues²⁴; α N-catenin is restricted to neural tissues^{25,26}; α T-catenin is expressed primarily in heart tissue²⁷; and α -catulin, which is an α -catenin-like protein, is ubiquitously expressed^{28,29}. A more distant relative is vinculin, which is ubiquitously expressed and localizes to both FOCAL ADHESIONS and adherens junctions³⁰ (TABLE 2).

FOCAL ADHESIONS, A cell-to-substrate adhesion structure that anchors the ends of actin microfilaments (stress fibres) and mediates strong attachment to substrates..

α E-catenin

Formerly known as cadherin-associated protein (CAP)-102, α E-catenin is the founding member of the α -catenin family^{31,32}. Localized on chromosome 18q11.0 (REF. ³³), the murine gene encodes the 102-kDa α E-catenin^{32,34}. The human α E-catenin gene (*CTNNA1*) localizes to chromosome 5q31 and consists of 16 coding exons (906 amino acids; 102 kDa) and at least one 5' non-coding exon³⁵. Human and mouse α E-catenin proteins are exceptionally highly conserved, sharing 99.2% identity. This evolutionary conservation might reflect the diversity of the interacting protein partners and functions of α E-catenin³⁶.

α E-catenin was initially identified on the basis of its ability to associate with E-cadherin^{24,34}. It also interacts with other classic cadherins, such as neuronal (N) and placental (P) cadherin²⁴. When kidney epithelial cells are cultured in medium that contains Ca^{2+} at levels that induce the formation of adherens junctions, E-cadherin and catenins shift from the soluble to the cytoskeletal fraction (if the cells are lysed and fractionated) concomitant with the formation of stable adherens junctions^{37,38}. Gene-targeting studies in mice indicate that α E-catenin is required to mediate the formation of adherens junctions in epithelial cells^{18,34,39}. In addition, cancer cell lines that lack α E-catenin do not show proper cell–cell adhesion¹⁰ unless the wild-type gene is reintroduced and adherens-junction formation is restored^{14,25,40}.

A ^{GENE-TRAP}-induced mouse mutation of the α E-catenin gene, which specifically deletes the region that encodes the carboxy-terminal third of the protein, results in an embryonic-lethal phenotype that is similar to that of the *E-cadherin*-null-mutant mouse⁴¹. In both cases, the proteins are required at the ^{BLASTOCYST STAGE} and, without α E-catenin, the outer epithelial covering (trophectoderm) of the developing embryo lacks integrity^{41,42}.

GENE TRAP, A methodology that is used to characterize new genes and analyse their importance in biological phenomena. The technique involves the use of mouse embryonic stem cells and reporter vectors that are designed to randomly integrate into the genome, tag an insertion site and generate a mutation.; BLASTOCYST STAGE, The stage during embryonic development that is characterized by the formation of two cell types: the embryoblast (the inner cell mass on the inside of the blastocoel) and the trophoblast (the cells on the outside of the blastocoel)..

To examine the functional importance of α E-catenin in other epithelial tissues, Vasioukhin and colleagues engineered a conditional α E-catenin-mutant mouse¹⁸. When α E-catenin expression was ablated from the developing skin around embryonic day 15, hair-follicle development was impaired and the architecture of the epidermal tissue was markedly altered. In the epidermis, the formation of adherens junctions seemed to be compromised, even though E-cadherin and β -catenin complexes still localized to cell–cell borders. Desmosomes loosely held the skin epithelium together, but partial defects in epithelial polarity arose, including suprabasal mitoses (mitosis is usually observed only in the basal layer of the epidermis). Perhaps most intriguing was the presence of epidermal hyperproliferation and multinucleate cells, which were accompanied by epithelial invaginations that resembled the precancerous lesions that are known as squamous-cell carcinomas *in situ*.

Although null mutations in α E-catenin have been associated with epithelial cancers¹⁰⁻¹⁴, it has usually been assumed that perturbations in cell–cell adhesion are late, rather than early, steps in carcinogenesis, and that they are preceded by mutations in cell-cycle-regulated genes that lead to uncontrolled growth. In the mice that lacked α E-catenin, however, the skin epithelium uniformly showed epidermal hyperproliferation shortly after α E-catenin-gene ablation, which prompted researchers to investigate alternative molecular explanations. *In vitro* and *in vivo* studies uncovered a sustained activation of the Ras–ERK/MAPK (extracellular signal-regulated kinase/mitogen-activated protein kinase) pathway, which seemed to involve the insulin–insulin-like-growth-factor signal-transduction pathway¹⁸. Curiously, these perturbations seemed to occur independently of the effects on intercellular adhesion and of β -catenin–LEF1/TCF-mediated gene transcription. Although the precise mechanism remains elusive, these findings indicate that when α E-catenin is absent, E-cadherin– β -catenin complexes might interact in new ways with components of signal-transduction pathways that are involved in cell-cycle regulation. Such a mechanism could be important for understanding the inverse link between α E-catenin mutations and tumorigenesis. In a ‘natural’ setting, the mechanism might be relevant to processes such as wound healing, in which proliferation is transiently enhanced and cell–cell adhesion is reduced during the epithelial regeneration. In this model, although α E-catenin would not be mutated, it might be transiently inactivated, perhaps through post-translational modification or associations with other proteins.

α N-catenin

α N-catenin (encoded by *CTNNA2*) or cadherin-associated-protein related (CAPR) was first characterized by Claverie and colleagues as a human cDNA encoding a protein that was 80% identical to α E-catenin (CAP102) but that contained a 48-residue insert²⁶. The *CTNNA2* gene maps to human chromosome 2p12–p11.1, which is homologous to the B3-D region of mouse chromosome 6 (34.2).

α N-catenin localizes to adherens junctions that border ACTIVE ZONES in developing and mature synapses throughout the developing and postnatal brain^{43,44}. The expression of specific cadherin subtypes delineates specific neuronal circuits, which indicates that cadherin–catenin complexes mediate adhesion between pre- and postsynaptic membranes^{45–47}. Interestingly, the classic mouse mutation cerebellar deficient folia (*cdf*) results from a deletion in the α N-catenin gene, and *cdf* mice show ataxia, cerebellar hypoplasia and abnormal cerebellar lobulation⁴⁸. Approximately 40% of the PURKINJE CELLS in these animals are located ectopically in the white matter and inner granule-cell layer (FIG. 3). Transgenic re-expression of the α N-catenin transgene in these mice restored normal cerebellar morphology. Taken together, these findings underline a role for α N-catenin in stabilizing N-cadherin-mediated synapse formation during the development of the central nervous system⁴⁸.

ACTIVE ZONES, The sites along nerve terminals where synaptic vesicles dock and undergo Ca^{2+} -dependent exocytosis during synaptic transmission.; **PURKINJE CELLS**, Large neurons with extensive dendritic projections that form a layer near to the surface of the cerebellum..

α T-catenin

α T-catenin (encoded by *CTNNA3*) is predominantly expressed in the heart and testis²⁷. The human and mouse *CTNNA3* genes contain 18 exons, the boundaries of which are identical to those in the human *CTNNA2* gene⁴⁹. α T-catenin seems to be functionally equivalent to α E-catenin on the basis of its ability to restore cell–cell adhesion in a colon-cancer cell line in which the *CTNNA1* gene is mutated²⁷. Because of its chromosomal position (10q21) and its high level of expression in the heart, *CTNNA3* has been deemed to be a candidate for a form of DILATED CARDIOMYOPATHY that has been linked to human chromosome 10q21–q23 (CMD1C). However, mutation screening of all 18 exons of the *CTNNA3* gene in one family that is affected by this disease failed to uncover any mutations⁴⁹.

DILATED CARDIOMYOPATHY, Also known as ‘congestive cardiomyopathy’, this is the most common form of myocardial disease, which causes decreased systolic function and increased ventricular volume..

α -catulin

Catenin α -like-1 — or α -catulin (encoded by *CTNNAL1*) — was first characterized as a 2.45-kb transcript that was downregulated in human pancreatic cancer cells²⁸. *In vitro* transcription and translation of the cloned transcript yielded an 82-kDa protein that shares 24.8% identity with α E-catenin. The human *CTNNAL1* gene maps to chromosome 9q22–q32 (mouse chromosome 4 band C1)²⁸. α -catulin mRNA is expressed ubiquitously, although the levels are lower in neural tissues. At 734 amino acids, the predicted α -catulin polypeptide is smaller than α N- and α E-catenin; it lacks the central 110-residue region and has a shorter carboxyl terminus. It is not yet known whether α -catulin localizes to cell–cell borders or is a component of adherens junctions. However, the amino-terminal AMPHIPATHIC HELICES of α -catenin that are thought to ensure an interaction with β -catenin are also present in α -catulin. Furthermore, amphipathic helices in the carboxy-terminal part of vinculin and α -catenin, which allow these proteins to bind to the actin cytoskeleton, are also present in α -catulin²⁹. So, sequence homology between α -catulin and α -catenin or vinculin implies that α -catulin might have the potential to bind to β -catenin and the actin cytoskeleton.

AMPHIPATHIC HELICES, Helical structures that consist of hydrophobic non-polar residues on one side of the helical cylinder, and hydrophilic and polar residues on the other side..

YEAST TWO-HYBRID ANALYSES have uncovered the lymphoid blast crisis oncogene (LBC) Rho **GUANINE NUCLEOTIDE-EXCHANGE FACTOR** (LBC Rho-GEF) as a partner for α -catulin but not for α E-catenin, which indicates that α -catulin might have a new role in modulating signalling by the Rho pathway²⁹. It will be interesting to see how the functions and associations of α -catulin differ from those of the 'classic' α -catenins.

YEAST TWO-HYBRID ANALYSIS, A technique that is used to study protein–protein interactions *in vivo* in yeast cells.; **GUANINE NUCLEOTIDE-EXCHANGE FACTOR**, A protein that facilitates the exchange of guanine diphosphate (GDP) for guanine triphosphate (GTP) in the nucleotide-binding pocket of a GTP-binding protein..

α E-catenin structure

Sequence similarities and structural relationships

Because of three extended regions of sequence similarity that are shared by α E-catenin and its distant cousin vinculin (known as the vinculin-homology (VH) domains VH1–VH3), α E-catenin has been described as a relative of vinculin^{24,34,50,51} (FIGS 4–5). Although the degree of identity is not high, these homologies are regarded as biologically meaningful, not only because both molecules anchor actin filaments to the plasma membrane, but also because some ligand-binding sites map to the regions that are more highly conserved between the proteins. Actin and α -actinin are well-characterized binding partners of both proteins^{52–56}, and there is substantial evidence of a direct interaction between vinculin and β -catenin *in vivo*⁵⁷.

The actin-binding domains in both vinculin (which contains a bipartite actin-binding site) and α E-catenin are localized in their carboxy-terminal segments (residues 893–985/1016–1066 and 697–906, respectively; FIG. 4)^{58–60}. Vinculin is interesting in that its head and tail segments can interact with each other to provide a conformational state that precludes its ability to associate with focal-complex proteins and with the actin cytoskeleton^{61,62}. On signal-transduction-mediated activation of focal-complex assembly, however, activated phospholipids can change the conformation of vinculin associated with its partners talin (an actin-binding protein that binds directly to integrins) and actin (reviewed in ^{REFS} 63,64). *A priori*, it might be tempting to speculate that the similarity of α E-catenin to vinculin means that it too can undergo autoregulation. However, the head-to-tail interactions of vinculin have been strongly detected by yeast two-hybrid analyses, whereas corresponding α E-catenin interactions have not been found (^{REF.} 50 and A.K. *et al.*, unpublished data). One possibility is that the lack of a proline-rich hinge region in α E-catenin, which is present in vinculin, yields a less flexible structure, which might prevent the head-to-tail interaction⁶⁵.

Despite sequence and structural differences that result in different modes of regulation and only partially overlapping binding partners, both vinculin and α E-catenin participate in coordinating actin dynamics at their respective adhesive junctions. Vinculin seems to be more important at integrin-mediated junctions, whereas α E-catenin seems to be exclusive for adherens junctions. Despite these differences, the association of α E-catenin with E-cadherin– β -catenin complexes and actin must be intricately regulated in a manner that seems conceptually, if not mechanistically, analogous to the coordinated association of vinculin with talin and actin. Whether α E-catenin changes its ligand-binding ability through post-translational modification, localized activation of phospholipids or dynamic interactions with other proteins remains an important question for the future.

Three-dimensional structure of the M-fragment of α E-catenin

To define the segments of α E-catenin that are necessary for mediating intercellular adhesion, sequences that encode the extracellular and transmembrane domains of E-cadherin were fused to various segments of α E-catenin cDNA, and the trans-genes were tested for the ability of their encoded fusion proteins to induce the rapid aggregation of mouse L CELLS⁶⁶. This led to the identification of the intercellular adhesion modulation (M) domain (residues 509–643, which partially includes the VH2 domain) of α E-catenin. In this assay, weak intercellular adhesion was facilitated by an E-cadherin–M-domain fusion protein, whereas a fusion protein containing E-cadherin and the full-length α E-catenin conferred considerably stronger adhesion. Although other explanations are possible, the underlying difference is likely to reside, at least in part, in the need for not only the M-domain but also the domain that is involved in actin-based cytoskeletal interactions, which are known to be required for stable intercellular adhesion^{37, 66}.

L CELLS, Cells of a mouse fibroblast line that is derived from connective tissue and does not express classic cadherin molecules..

Crystallographic analysis of the so-called M-fragment (residues 377–633), which includes the M-domain, detected a tandem repeat of a four- α -helix bundle. This is structurally related to the vinculin tail⁶⁷ (FIG. 5). Overall, these findings indicate that α E-catenin probably comprises a series of repeating antiparallel α -helical domains.

In solution, the M-fragment can form relatively low-affinity dimers⁶⁷. On the basis of the findings of Imamura and colleagues⁶⁶, it seems likely that, through weak dimerization of the M-domain of α E-catenin, the lateral dimerization of E-cadherin molecules in the plasma membrane might be enhanced and/or stabilized, thereby promoting and/or strengthening cell–cell adhesion^{68,69}.

Dimerization and β -catenin-binding domains of α E-catenin

In vitro binding assays indicate that classic cadherins, β -catenin and α E-catenin assemble into a complex with a 1:1:1 stoichiometry⁷⁰. α E-catenin forms a homodimer in solution at micromolar concentrations^{56,62}; however, in the presence of β -catenin or plakoglobin, the homodimer dissociates and a 1:1 heterodimer of α E-catenin and β -catenin/plakoglobin is observed^{62,71}. Indeed, the two processes seem to be mutually exclusive, as judged by the fact that the site on α E-catenin for β -catenin binding (residues 54–148)^{62,71–74} overlaps with that for homodimerization (residues 82–279)^{62,71}. The crystal structure of this domain indicates that α E-catenin dimerizes through the formation of a four-helix bundle in which two antiparallel helices are contributed by each protomer. The precise role of homodimerization in adherens-junction assembly remains unclear. One attractive possibility is that the transition between homo- and heterodimer occurs at the cell membrane, which enables a β -catenin-induced conformational change to influence the association of α E-catenin with other partners — for example, actin filaments and/or their polymerizing machinery. It is not clear how this relates to the potential dimerization of α E-catenin through the M-domain or the possible enhancement of E-cadherin lateral dimerization.

α E-catenin and the actin cytoskeleton

Proteins that link α E-catenin to actin

Studies of KERATINOCYTES in which the α E-catenin gene (*CTNNA1*) has been conditionally inactivated have uncovered a role for α E-catenin in the formation of the radial actin cables that are necessary for stabilizing adherens junctions, sealing membranes and assembling epithelial sheets^{18,39}. During the initial steps of epithelial-sheet formation, linear radial actin cables

assemble at nascent intercellular adherens junctions; this process requires α E-catenin and actin polymerization.

KERATINOCYTES, Differentiated epithelial cells of the skin..

α E-catenin was postulated to interact directly with filamentous (F)-actin⁷⁵, and a direct interaction was confirmed by Rimm and co-workers⁵⁶. Biochemical and genetic approaches have uncovered domains in α E-catenin that mediate further interactions with actin-binding proteins (FIG. 6), which have provided new insights into the importance of α E-catenin in actin dynamics (reviewed in ^{REFS} 50,76). α -actinin and vinculin were among the first binding partners of α E-catenin to be described^{60,66,73,77}; both interact with similar residues in α E-catenin and can bind actin directly. The carboxy-terminal 280 residues of α E-catenin interact with the zonula occludens-1 (ZO1) protein, which is also able to bind actin directly⁶⁶.

Another binding partner of α E-catenin is afadin, which is known to bind to F-actin and might recruit it to sites of nascent adherens junctions. Afadin also associates with the protein nectin, which forms the transmembrane core of another intercellular adhesion system^{78,79}. Other associates of α E-catenin include vasodilator-stimulated phosphoprotein (VASP) and Enabled (Ena), which localize to adherens junctions in an α E-catenin-dependent fashion³⁹. Whether these interactions are direct or indirect is not yet clear, as α E-catenin also associates directly with members of the zyxin family, which can also bind actin and/or recruit members of the Ena/VASP families⁵². Irrespective of how VASP gets to the adherens junctions, both Ena and VASP can bind to the actin-monomer-binding protein profilin, which promotes the addition of ATP-actin monomers to actin filaments. VASP has recently been shown to compete with capping protein for the BARBED END of pre-existing actin filaments, which provides a mechanism for how VASP promotes the extension of actin polymers (reviewed in ^{REF.} 4).

BARBED END, The fast-polymerizing end of an actin filament, which is defined by the arrowhead-shaped decoration of actin filaments with myosin fragments..

Although the presence of Ena/VASP proteins is sufficient to explain the addition of actin subunits to preexisting actin filaments, it might not be sufficient to account for *de novo* actin polymerization. Recently, however, we identified isoforms of formin-1 (FMN1), the founding member of the ^{FORMIN FAMILY}, as binding partners for α E-catenin and as candidates for generating the radial actin cables that assemble at nascent adherens junctions⁸⁰. Using yeast two-hybrid and *in vitro* analyses, a region in the amino-terminal segment of several isoforms of FMN1 was shown to interact specifically with residues ~300–500 of α E-catenin. The conserved formin homology (FH) domains in the carboxy-terminal portion of FMN1 contain sites for the nucleation of actin polymerization (reviewed in ^{REF.} 81). The carboxy-terminal segment of FMN1 can nucleate the polymerization of unbranched actin filaments *in vitro* and function in transfected cells in an α E-catenin-dependent fashion to promote the polymerization of radial actin filaments⁸⁰. When transiently expressed, the carboxy-terminal portion of another formin, diaphanous protein homologue-1 (Dia1) also localizes to adherens junctions (reviewed in ^{REF.} 81). Because the FMN1 domain that associates with α E-catenin does not seem to be conserved in Dia1, it remains unclear how this carboxy-terminal segment of Dia1 is recruited to junctions. However, recent *in vitro* studies indicate that Dia1 might also nucleate actin polymerization⁸², and then associate with, and move processively along, the growing end of actin filaments in cells⁸³.

FORMIN FAMILY, A family of multidomain scaffold proteins that are involved in actin-dependent morphogenetic events. They are conserved from fungi to humans and are

characterized by the presence of two conserved carboxy-terminal regions: the formin homology (FH) domains FH1 and FH2.

Although FMN1 and Dia1 have surfaced as good candidates to initiate the formation of linear actin cables at sites of nascent adherens junctions, it remains to be determined whether these, or any other formins in their native state, are functional at these sites, and, if so, how they are regulated to control actin polymerization. Given the complexity and possible redundancy within the mammalian formin family, resolving formin functions might be best addressed in lower eukaryotic systems. Irrespective of mechanism, once they are assembled at nascent junctions, actin filaments seem to bundle into linear cables. α -actinin is a candidate for this bundling, as it is known to form antiparallel dumbbell-like structures and thereby place an F-actin-binding site at each pole of an α -actinin dimer. Radial actin cables at junctions seem to function with myosins and generate tension across a growing epithelial sheet⁸⁴. In searching for a binding partner for myosin VIIA, Kussel-Andermann and colleagues⁸⁵ have identified another protein that links adherens junctions and the actomyosin-based contractile system³⁷. Known as vezatin, this protein interacts with myosin VIIA and the carboxy-terminal region of α E-catenin. This interaction has prompted speculation that myosin VIIA, when anchored by vezatin to the adherens junctions, might use the actin cytoskeleton to generate tension, thereby strengthening cell–cell adhesion.

Finally, α E-catenin interacts directly with spectrin, which is an important component of the skeleton that underlies and reinforces the plasma membrane. The binding of spectrin to adherens-junction complexes might stabilize intercellular adhesion by integrating the complexes into this macromolecular membrane structure⁸⁶.

Why so many connections?

Given the nature of the many associates of α E-catenin, it seems likely that this protein is a central player in nucleating the assembly of a multiprotein complex that links E-cadherin– β -catenin complexes to F-actin. Certainly, the *CTNNA1*-null keratinocytes described above illustrate the importance of this process not only for stabilizing intercellular junctions, but also for coordinating actin dynamics at these sites^{18,39} (FIG. 7). But why are there so many different ways to connect α E-catenin with actin dynamics?

One factor that might help to explain the diversity in potential binding surfaces for actin at adherens junctions is the range of cytoskeletal changes that must occur in epithelial cells for them to establish stable cell–cell contacts and assemble into epithelial sheets. Some insights into these dynamics stem from video-microscopy studies of cells that express actin or cadherin bound to green fluorescent protein (GFP) while Ca^{2+} levels are raised and epithelial sheets form^{37,84,87}.

During the initial steps of establishing cell–cell contacts, activated Cdc42 and Rac, which are members of the Rho family of small GTPases, stimulate the extension of FILOPODIA and LAMELLIPODIA, respectively^{5,37,39,84,88}. The Arp2/3 PROTEIN COMPLEX has been implicated in nucleating actin polymerization and producing the extensive branched cortical meshwork of F-actin that develops beneath the membrane at Rac-stimulated lamellipodia (reviewed in REF. ⁸⁹). Lamellipodial extensions generate large dynamic contacts between the surfaces of apposing cells. By contrast, filopodia-like extensions involve the polymerization of linear actin filaments and seem to be much more rapidly formed. Filopodia have been implicated in the generation of homophilic interactions between two opposing E-cadherin– β -catenin complexes at the tips of the cell–cell contact sites.

FILOPODIA, Thin, transient actin protrusions that extend out from the cell surface and are formed by the elongation of bundled actin filaments in its core.; LAMELLIPODIA, Cellular

protrusions that contain extensively branched arrays of actin filaments, which are orientated with their plus (barbed) ends toward the plasma membrane.; Arp2/3 PROTEIN COMPLEX, A complex that consists of two actin-related proteins, Arp2 and Arp3, along with five smaller proteins. When activated, the Arp2/3 complex binds to the side of an existing actin filament and nucleates the assembly of a new actin filament. The resulting branch structure is Y-shaped..

Once nascent adherens junctions (known as puncta) have assembled from clusters of transmembrane E-cadherin molecules and their cytoplasmic associates (β -catenin and α E-catenin), the contacts are stabilized by a second step that involves the attachment and/or *de novo* assembly of a linear radial actin cable at the tip of each punctum^{38,39,90}. Proteins of the VASP and mammalian orthologue of Ena (MENA) families localize to these sites, and studies using a dominant-negative form of VASP imply that VASP might have a role in mediating intercellular adhesion in both cultured cells and transgenic mice³⁹. As outlined above, functional studies support a role for these proteins in the elongation of pre-existing actin filaments⁸⁹, and there are numerous ways in which developing adherens-junction complexes can bind to actin and potentially help to recruit F-actin.

The findings that imply a role for formins at adherens junctions are also intriguing, particularly given the broad role of formin-family members in stimulating *de novo* polymerization of linear radial actin cables (for reviews, see ^{REFS} 81,91). As outlined above, if native formins localize to cell–cell junctions and participate in regulating the formation of linear actin cables, then an interesting issue to address will be whether different formin-family members have redundant or distinct roles in intercellular adhesion. Equally important will be whether Ena/VASP and formin-family members work together to assemble radial actin cables, or whether these proteins function independently, perhaps in response to different cellular cues.

α E-catenin binding to E-cadherin– β -catenin

Many events in organized epithelia, such as cytokinesis and cell migration, require dynamic remodelling of adhesive contacts. Once again, α E-catenin seems to be intricately involved in these processes. Whereas newly synthesized E-cadherin associates with β -catenin in the endoplasmic reticulum, α E-catenin seems to join the E-cadherin– β -catenin complex only after it has reached the plasma membrane⁹². Conversely, detachment of α E-catenin and actin from the E-cadherin– β -catenin complex has been observed during the disassembly of adherens junctions⁹³.

Although it is not yet clear precisely how the association of α E-catenin with E-cadherin– β -catenin complexes is regulated, the Armadillo subfamily of catenins (β -catenin, plakoglobin and p120 catenin) seems to be involved. On signalling from tyrosine-kinase growth-factor receptors, or in response to overexpression of non-receptor tyrosine kinases, β -catenin is phosphorylated — an event that is accompanied by a decrease in adhesion^{4,94} and a loss of cytoskeletal anchorage to cell–cell junctions⁹⁵. Moreover, in cells that are treated with pervanadate, which is an inhibitor of phosphotyrosine phosphatases, tyrosine phosphorylation of β -catenin and plakoglobin correlates with the dissociation of α E-catenin from the E-cadherin– β -catenin complex⁹⁶.

Rho-family GTPases also participate in regulating cadherin-mediated cell adhesion (reviewed in ^{REF} 97). Although several mechanisms are possible and, in fact, are likely to account for this, it is known that IQGAP1, which is a target of activated Cdc42 and Rac1 GTPases, binds to β -catenin and induces the dissociation of α E-catenin from the E-cadherin– β -catenin complex⁹⁸. On the basis of these data, the association of α E-catenin with the E-cadherin– β -catenin complex seems a probable target for the functional modulation of this complex.

α E-catenin and tumour formation

Several studies imply that the disruption of cadherin-based adhesion is a main step in the progression of human epithelial cancers. Reduced levels of E-cadherin and α E-catenin proteins seem to be characteristic of many different human cancers, including malignant tumours of the breast, colon, stomach, oesophagus, bladder and liver^{13,15-17,99-101}. The proportion of such tumours that fail to express one or both of these proteins has been reported to be as high as 80%, and the loss of E-cadherin or α E-catenin often correlates with the degree of tumour differentiation and metastasis^{13,102-104}. The loss of α E-catenin seems to be the more common event, and also correlates better than the loss of E-cadherin with the level of invasiveness of a tumour and with its degree of differentiation^{13,102}. α E-catenin is absent or markedly depleted in several human cancer cell lines, including the lung cancer cell line PC9 (REF. 10) and the prostate adenocarcinoma cell line PC3 (REFS 11,12). If α E-catenin is artificially reintroduced into PC3 cells, E-cadherin-dependent adhesion is restored and the invasive phenotype is suppressed¹¹. In this respect, α E-catenin seems to function as a tumour suppressor, similar to several of the classic cadherins.

The seminal work of Shimoyama and co-workers associated a loss of α E-catenin-gene function with human cancer by showing downregulation of the expression of α E-catenin in PC9 cells following homozygous deletion of part of the α E-catenin gene¹⁰. Bullions and colleagues, however, have taken the connection one step further by identifying a mutation in the α E-catenin gene in cells that are derived from an ovarian carcinoma¹⁴. The *Ov2008* α E-catenin mutation results in an amino-terminally truncated form of the protein that localizes to the cytoplasm and does not bind β -catenin efficiently. Again, restoration of wild-type α E-catenin expression restricted the uncontrolled growth of the cells and restored a normal adhesive morphology.

As mentioned above, mutations in E-cadherin have also been found in human cancers and E-cadherin has been shown to have growth-suppressor activity. On the basis of cell-culture studies, some of the tumour-suppressor effects of E-cadherin might be adhesion independent. As E-cadherin binds to β -catenin, cells that have appreciable soluble pools of β -catenin might respond to elevated E-cadherin levels by suppressing the transcription of LEF1/TCF-regulated genes¹⁰⁵. Conversely, a loss of E-cadherin expression might, in certain instances, resemble sustained activation of Wingless/WNT-related (WNT) signalling, which has a well-established link to some types of human cancer.

The ability of E-cadherin to compete with transcription factors for β -catenin raises the question of whether the loss of α E-catenin might also affect the status of WNT signalling — perhaps by negatively affecting the stability of E-cadherin- β -catenin complexes and increasing the soluble pool of β -catenin. Although this is theoretically possible, the gene-targeting studies that have been carried out so far do not support this idea; for example, when mice in which α E-catenin was conditionally deleted in the developing skin were mated with WNT-reporter-expressing mice, no increase in the activity of β -catenin-transcription-factor complexes was detected, despite the increase in epidermal-cell proliferation¹⁸. So, although α E-catenin expression clearly restores the normal phenotype to α E-catenin-mutant cancer cells, the mechanisms by which α E-catenin loss influences tumorigenesis might be distinct from those caused by either E-cadherin loss or β -catenin overactivation. The sustained activation of the Ras-ERK/MAPK pathway in skin epidermis that lacks α E-catenin expression provides one possible mechanism, which goes beyond a simple loss of cell-cell adhesion.

Potential nuclear partners for α E-catenin

The discovery that β -catenin can associate with and activate transcription factors in response to WNT signalling has been followed by more than a decade of research linking intercellular

adhesion to transcriptional regulation and cancer⁷⁻⁹. Other interactions between cell-junction proteins and nuclear factors have since been detected¹⁰⁶, and α E-catenin seems to be no exception.

Ajuba, which is a member of the zyxin family of proteins, has been shown to interact directly with α E-catenin¹⁰⁷. Interestingly, whereas zyxin localizes to focal adhesions, which can be considered to be cell–substratum junctions, Ajuba localizes to cell–cell junctions. Through its dual association with the amino-terminal segment of α E-catenin and with F-actin, Ajuba might contribute to the coupling of adherens junctions to the actin cytoskeleton. Like zyxin, however, Ajuba has also been detected in the nucleus, and so has the intriguing potential to coordinate the regulation of transcription and cell adhesion¹⁰⁸. Although further studies will be necessary to assess whether this hypothesis is correct, Ajuba joins β -catenin as a protein that localizes to both the nucleus and adherens junctions.

Another potentially interesting α E-catenin associate that is worth mentioning in this context is FMN1. *Fmn1* was first identified as the gene that was mutated in mouse embryos that were homozygous for the limb deformity (*ld*) mutation¹⁰⁹. FMN1 is the founding member of the formin family, and it has only more recently become apparent that a mutation in a formin gene leads to a disruption in the establishment of the Sonic hedgehog (SHH)–FGF4–BMP (where FGF stands for fibroblast growth factor and BMP is bone morphogenetic protein) feedback loop that is necessary for the formation of the apical ectodermal ridge (the layer of surface ectodermal cells at the apex of the embryonic limb bud). Interestingly, expression of Gremlin, which is a BMP-inhibitory protein, is lost in the *ld*-mutant mouse and grafting Gremlin-expressing cells into *ld*-mutant limb buds restores the feedback loop¹¹⁰. Recent studies imply that mutations in the *Grem1* gene are sufficient to cause the *ld* phenotype without apparent consequence to *Fmn1* expression¹¹¹. As the *Grem1* mutation fails to complement the *ld* mutation, it has been suggested that the *ld* phenotype might reflect defects in *Grem1*-gene transcription, rather than unveiling a role for FMN1 *per se*¹¹¹. Although this reveals a functional role for Gremlin, it leaves open the functional importance of FMN1. Further studies, removing redundancies among formin-family members, will probably be required to address this intriguing issue.

Conclusions and perspectives

Although it has not been as extensively studied as its prominent partner β -catenin, α E-catenin has come into its own in recent years as an essential component of adherens junctions that can also integrate adhesion with other essential cellular events. It is well established that α E-catenin is a central protein not only in linking the actin cytoskeleton to E-cadherin– β -catenin complexes, but also in recruiting a range of other important proteins to developing intercellular junctions. Some of these proteins, such as members of the Ena/VASP and formin families, seem to be important in regulating actin polymerization at developing junctions. Others, such as vezatin and α -actinin, probably participate in generating force or tension at the interface between actin and adherens junctions. Others still, such as spectrin, might integrate the adherens junctions with the underlying cortical network, whereas Ajuba might generate crosstalk between junctions and the transcriptional state of the cell.

Studies of many of these connections are still in their infancy. In the future, it will be important to establish what conformational changes or protein modifications are involved in the selective recruitment of α E-catenin to E-cadherin– β -catenin complexes at the plasma membrane. What are the main molecular steps that are involved in regulating how α E-catenin selectively associates with and activates the actin-polymerizing/organizing machinery? Do formins have overlapping functions, particularly in epithelial-sheet formation? It is also possible that individual formins or formin isoforms might have distinct functions.

In addition, the precise roles of the Rho-family GTPases and the Ena/VASP-family members in regulating cadherin-mediated junction formation remain to be discovered. It is not known how broadly used these mechanisms are, or how they are involved in the functions of specific α -catenin-family members. Does α E-catenin strictly regulate actin-cytoskeletal dynamics at adherens junctions, or does it also have a role in polarizing the microtubule cytoskeleton? It is not clear whether Ajuba or other α E-catenin-associated proteins function as integrators of cell adhesion and transcriptional regulation, and, if so, under what circumstances this might occur. Finally, what mechanisms are involved in cadherin and α E-catenin dysregulation, which occurs during tumorigenesis and metastasis?

Finding the answers to these questions will keep investigators in the α -catenin and associated actin-dynamics fields occupied for the coming decade. However, as these answers unfold, we will be in a considerably better position to determine the extent to which α -catenin fits the role of the gatekeeper at the crossroads of adherens junctions, cytoskeletal dynamics and gene expression.

Acknowledgements

We are grateful to D. Barford and D. R. Critchley for providing us with images. E.F. is an investigator at the Howard Hughes Medical Institute, New York, USA. A.K. is a research associate supported by the US National Institutes of Health.

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Figure 1. Intercellular junctions in skin

The electron micrograph and corresponding schematic depict the main types of intercellular junction in epithelial cells. Tight junctions are composed of transmembrane proteins that link to the actin cytoskeleton and prevent the leakage of small molecules through intercellular spaces. Adherens junctions are formed by homophilic interactions between E-cadherin molecules, and are connected to the actin network through β - and α -catenins. They function to coordinate the actin cytoskeleton across an epithelial sheet. Desmosomes are composed of desmosomal cadherins that are linked to intermediate filaments and integrate the intermediate-filament network across the epithelial sheet. Electron micrograph courtesy of H. Amalia Pasolli, Rockefeller University, New York, USA.

Figure 2. A multiprotein complex at adherens junctions

The extracellular region of E-cadherin, which contains extracellular cadherin (EC) domains, undergoes a Ca^{2+} -dependent conformational change that allows it to homodimerize at the membrane. Through extracellular interactions with E-cadherins on a neighbouring cell, opposing cadherin dimers can integrate the actin cytoskeletons. Stabilization of intercellular adhesion requires the cytoplasmic domain of E-cadherin, which binds to β -catenin. β -catenin, in turn, binds α -catenin, which is central in recruiting a number of cytoskeletal proteins, including the filamentous (F)-actin-nucleating formin proteins (Fmn), and the actin-binding proteins vinculin, Ajuba, myosin VIIa, vezatin, α -actinin and members of the vasodilator-stimulated phosphoprotein (VASP) family of F-actin-elongating proteins. At least some of these interactions are essential in polymerizing and organizing actin into cables that help to seal membranes and integrate the actin cytoskeleton across the epithelial sheet. By contrast, p120 catenin (p120), which is related to β -catenin, binds to E-cadherin through a juxtamembrane domain and seems to function in cadherin turnover, perhaps by regulating

cadherin trafficking. An emerging intercellular adhesion system (not shown), consisting of nectin and afadin, also has roles in the organization of a range of intercellular junctions. Nectin is a Ca^{2+} -independent, immunoglobulin-like, intercellular adhesion molecule, and afadin is a nectin- and actin-filament-binding protein that connects nectin to the actin cytoskeleton^{78, 79}.

Figure 3. Abnormal cerebellar development in α N-catenin-mutant mice

Mutations in the α N-catenin gene underlie the genetic defect in the ataxic cerebellar deficient folia (*cdf*)-mutant mice. The cerebella of *cdf/cdf*-mutant mice show hypoplasia and abnormal lobulation. **a** | A schematic representation of the midline sagittal sections from wild-type and *cdf/cdf*-mutant mouse brain cerebella shows scattered Purkinje cells in the more central white matter and abnormal lobulation (blue stars). The magnified region (**b**) shows the structure of the cerebellar cortex (the grey matter), which includes the cell bodies and dendrites of the Purkinje cells; the axons of the granule cells; and the cell bodies, dendrites and axons of the basket cells.

Figure 4. Sequence similarities between vinculin and α E-catenin

The coloured areas represent regions of similarity between the two proteins. The degrees of amino-acid identity are indicated as percentages. The magenta region in vinculin represents the proline-rich hinge segment. Actin-binding domains are marked as the red open boxes (amino acids 697–906 for α E-catenin and 893–985/1016–1066 for vinculin). The intercellular adhesion modulation (M) domain (residues 509–643) of α E-catenin is marked as the blue open box. The numbers correspond to amino acids of the protein sequence. VH, vinculin-homology domain.

Figure 5. Comparison of the crystal structures of the α E-catenin M-fragment and vinculin tail
 The crucial functions of α E-catenin and vinculin are to mediate protein–protein and protein–phospholipid interactions. Proteins composed of tandemly repeated α -helical bundles provide a structural framework for the assembly of multiprotein complexes. **a** | View of the α E-catenin M-fragment structure with two four-helix domains (domains 1 and 2) coloured from the amino terminus (blue) to the carboxyl terminus (red). Letter labels for each of the helices are shown. **b** | The crystal structure of the carboxy-terminal part of vinculin comprises five helices (H0–H4). **c** | A comparison of the α E-catenin M-fragment domain 1 (red/orange; left) and domain 2 (green; middle) with the vinculin-tail domain (dark/light blue; right). Parts **a** and **c** courtesy of D. Barford and reproduced with permission from REF.⁶⁷ © (2001) Macmillan Magazines Ltd; part **b** courtesy of D. R. Critchley, Biochemistry Department, University of Leicester, UK and reproduced with permission from REF.¹¹³ © (1999) Elsevier.

Figure 6. Functionally important regions of αE-catenin

This schematic of αE-catenin illustrates its three vinculin homology (VH) domains (VH1–VH3). The direct binding partners for αE-catenin are listed on the right, and the corresponding domain diagrams denote the regions and encompassing amino-acid residues of αE-catenin that have been identified as biochemically essential for the interaction. αE-catenin interacts with E-cadherin–β-catenin complexes through its amino-terminal β-catenin-binding domain. In solution, αE-catenin forms a homodimer through its dimerization domain. When αE-catenin associates with E-cadherin–β-catenin complexes, however, the αE-catenin homodimer dissociates, and heterodimers of α- and β-catenin are formed. The intercellular adhesion modulation (M) domain, which partially includes the VH2 domain of αE-catenin, defines the segments of αE-catenin that are necessary for mediating intercellular adhesion. The carboxy-terminal region, which includes the VH3 domain of αE-catenin, overlaps with the filamentous (F)-actin-binding domain. The vinculin-, α-actinin- and formin-1-binding domains on αE-catenin facilitate organization of the F-actin cytoskeleton and the regulation of actin dynamics during the formation of stable intercellular adhesions.

Figure 7. Model of adherens-junction formation in keratinocytes

a | Initial cell–cell contacts are formed by opposing E-cadherin– β -catenin complexes at the tips of filopodia or lamellipodia. These initial contacts are nascent adherens junctions and are termed puncta. **b** | In the presence of α E-catenin, formin and other proteins such as VASP (vasodilator-stimulated phosphoprotein) that bind to α E-catenin and/or the actin cytoskeleton, bundles of radial actin cables assemble on each side of the puncta and form anchors to the underlying cortical actin ring. **c** | As a consequence of actin reorganization, mature adherens junctions are formed.

Table 1
Amino-acid sequence identities (and similarities) between mouse α -catenins/vinculin*

	α E-catenin	α N-catenin	α T-catenin	α -catulin	Vinculin
α E-catenin	100%	76.5% (83.1%)	56.1% (73.7%)	24.8% (33.9%)	22.5% (31.0%)
α N-catenin	—	100%	58.5% (69.6%)	25.6% (32.8%)	22.3% (30.0%)
α T-catenin	—	—	100%	19.7% (32.1%)	17.3% (30.3%)
α -catulin	—	—	—	100%	18.6% (23.7%)
Vinculin	—	—	—	—	100%

* Data are from REF. 7.

Table 2Members of the α -catenin/vinculin family and their functions

Family member	Chromosome localization (human/mouse)	Cellular localization	Phenotype
α E-catenin	5q31/18q11.0	Adherens junctions	Lethal at the blastocyst stage
α N-catenin	2p12–p11.1/6-B3D	Adherens junctions	Cerebellar deficient folia
α T-catenin	10q21–q23	Adherens junctions	ND
α -catulin	9q22–q32/4-C1	ND	ND
Vinculin	10q21–q23/14-A2	Focal contacts and adherens junctions	Lethal by embryonic day 10

The α -catenin/vinculin-family members are crucial for the formation of proper adherens junctions during development, as judged by the phenotypes of the knockout animals. α E-catenin is required at the blastocyst stage and without this protein, the outer epithelial covering (trophectoderm) of the developing embryo lacks integrity. Loss of α N-catenin results in the cerebellar deficient folia (*cdf*) phenotype with ataxia, cerebellar hypoplasia and abnormal cerebellar lobulation. Vinculin knockout results in heart and brain defects during embryonic development. Vinculin-mutant embryos are also 30–40% smaller, growth of their somites and limbs are retarded, and their ectodermal tissues are sparse and fragile¹¹². ND, not determined.