REGULATION OF CADHERIN-MEDIATED ADHESION IN MORPHOGENESIS

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Abstract | Cadherin cell-adhesion proteins mediate many facets of tissue morphogenesis. The dynamic regulation of cadherins in response to various extracellular signals controls cell sorting, cell rearrangements and cell movements. Cadherins are regulated at the cell surface by an inside-out signalling mechanism that is analogous to the integrins in platelets and leukocytes. Signal-transduction pathways impinge on the catenins (cytoplasmic cadherin-associated proteins), which transduce changes across the membrane to alter the state of the cadherin adhesive bond.

ADHERENS JUNCTION
Close cell–cell contacts that are observed by electron microscopy and that are often associated with actin filaments at the cytoplasmic surface.

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The regulation of adhesive contacts between cells underlies many morphogenetic processes during both the development of new tissues and the controlled growth and turnover of adult tissues[1]. Various types of cell adhesion molecules and cell junctions control the physical interactions between cells. However, a family of adhesion molecules — the cadherins — is particularly important for the dynamic regulation of adhesive contacts that is associated with diverse morphogenetic processes (FIG. 1). In embryonic development, cadherins control the separation of distinct tissue layers or the fusion of tissue masses[2], the formation of tissue boundaries[3,4], changes in the shapes of tissues owing to cell rearrangements[5,6], the conversions between histological cell states (such as epithelia versus mesenchyme)[1,7,8], the long-range migration of cells and neuronal processes[9,10], and the formation of synapses between neurons[11].

In adult tissues, cadherins are involved in the orderly turnover of rapidly growing tissues such as the lining of the gut and the epidermis[12–14], the plasticity and regulation of neuronal synapses[15,16], the physiological regulation of epithelial and endothelial cell junctions to allow controlled passage of solutes, water and lymphoid cells across the cell layer[17,18], and the maintenance of stable tissue organization to prevent the dissociation and spread of tumour cells[8,19].

Given the diversity of biological processes that are mediated by cadherins, it is not surprising that many different cellular mechanisms have been found to regulate cell adhesion and cell junction formation. E-cadherin (epithelial cadherin), the most commonly studied cadherin, forms the ADHERENS JUNCTION in epithelial cells and facilitates the formation of the entire epithelial junctional complex[20] (FIG. 2a).

Alterations in the assembly or disassembly of adherens junctions occur in association with major changes in the state of cell differentiation, which take place during the epithelial–mesenchymal transition, when tightly adherent and polarized epithelial cells dissociate from each other and migrate away to form other structures. One such example is the formation of the neural crest from the neural tube, which goes on to form a diverse set of structures at different locations in the embryo. Such transitions probably affect the state of assembly of cell junctions both directly and indirectly, and involve numerous changes in gene expression as well as post-translational processes[7,8,21]. Moreover, the normal assembly and turnover of cadherin-based junctions in cells under steady-state conditions must be regulated, as the biogenesis of junctions is a complex multi-step process that, similar to the formation of all subcellular organelles and compartments, is subject to complex cellular control

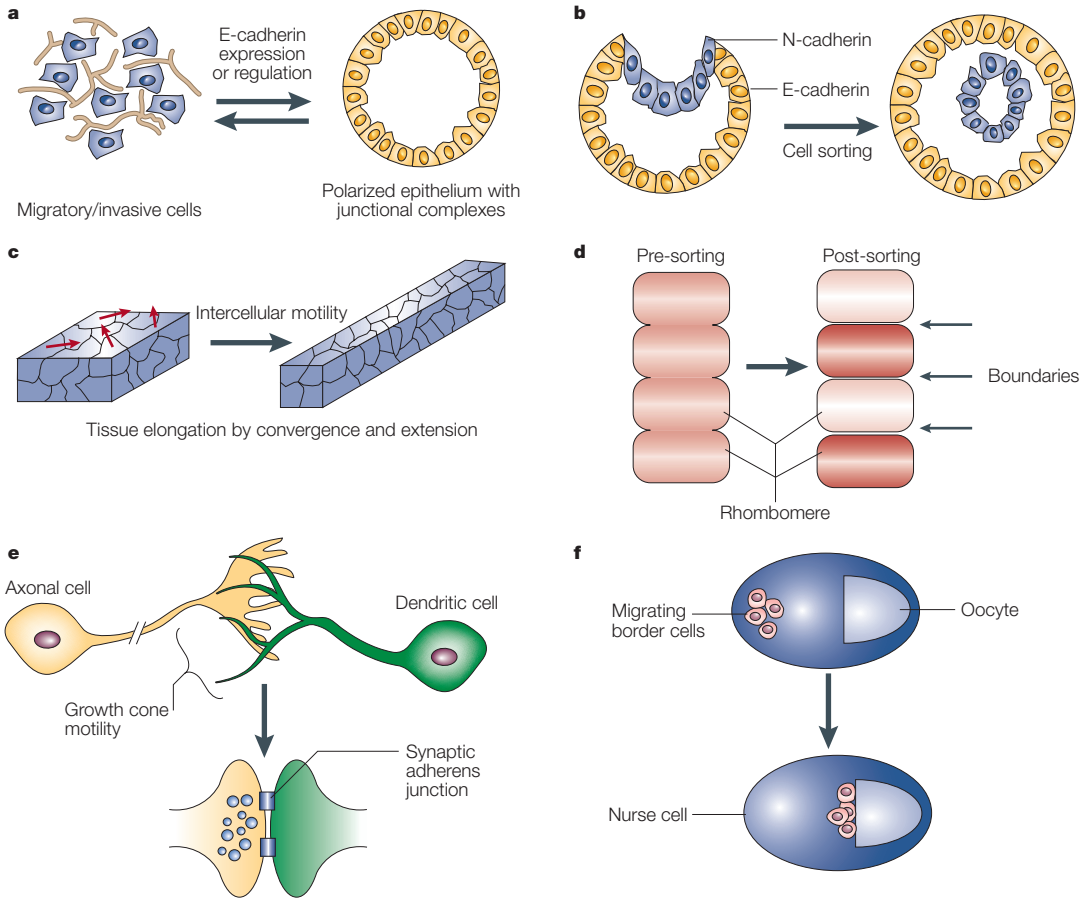


Figure 1 | **Cadherin regulation in tissue morphogenesis. a** | The epithelial–mesenchymal transition (EMT) and its reverse — the mesenchymal–epithelial transition[7,8]. E-cadherin (epithelial cadherin) mediates the adhesion of cells, the transition of cells from organization in a loose mesenchymal network — in which they lack polarity and have migratory and invasive potential — to their tight apposition in a polarized epithelial barrier, and the formation of tight junctional complexes. Loss of E-cadherin expression is associated with the EMT and its loss or dysregulation plays a part in tumour cell invasion and metastasis. The yellow cells express E-cadherin, in contrast to the blue cells that do not. **b** | Cell sorting owing to differential expression of cadherins drives tissue separation during embryonic development[2,53]. Expression of N-cadherin (neural cadherin; blue) in the presumptive neural epithelium allows it to separate from the E-cadherin-expressing ectoderm (yellow). **c** | Cell rearrangements[5,6,64]. The dynamic breaking and reforming of cadherin adhesive bonds is required for cells to change neighbours despite being held together in the tissue. In the example shown, called convergence and extension[5], cells rearrange in such a way as to cause the tissue to narrow and elongate. **d** | Formation of compartment boundaries[3,4,55–57]. Selective adhesion, which is accomplished through regulation of adhesive strength, creates boundaries between developmental compartments in a tissue, as in the formation of rhombomeres in the developing vertebrate hindbrain. **e** | Growth cone motility and synapse formation. N-cadherin (and other cadherins) can mediate growth cone motility along cells that express N-cadherin[9]. Cadherins also form adherens-type junctions as part of the synaptic junction[11], which is important for synaptic specificity, regulation of synaptic plasticity and dendrite morphogenesis[15,16]. **f** | Cell migration. In contrast to its role in stabilizing epithelial junctions, E-cadherin also mediates the long-range migration of cells through tissues; for example, the migration of border cells (pink) in the *Drosophila melanogaster* egg chamber[10]. The border cells migrate from one end of the egg chamber between the nurse cells until they reach the oocyte.

mechanisms that involve the cytoskeleton, membrane dynamics and signalling events[22–26].

By contrast, during certain developmental and physiological processes, cell adhesion is modulated rapidly in response to growth factors or other signals, sometimes without gross changes in the presence of adhesive complexes or junctions at cell contacts[1,6,10,27–31]. This direct response to cellular signals is analogous to the rapid regulation of integrin function, called 'inside-out signalling', that occurs in leukocytes and platelets[32,33].

The dynamic physiological regulation of the adhesive functions of cadherins at the cell surface is especially important for many morphogenetic processes, such as cell sorting, cell rearrangements and cell movements. Although seemingly more subtle, as it involves adhesive changes without overt dissociation of cells, dynamic physiological regulation is crucial for morphogenesis, and is therefore the main focus of this review. Here, I first introduce the cadherins and discuss the roles of cadherin regulation in morphogenesis. To describe the mechanism of cadherin regulation, I discuss different

models for the cadherin homophilic bond, consider the roles of the catenins and the cytoskeleton in cadherin function, and present evidence that dynamic regulation involves inside-out signalling across the membrane to alter the state of the homophilic adhesive bond.

The cadherins

The cadherins constitute a large superfamily of cell–cell adhesion molecules[34,35] that show various patterns of expression associated with morphogenetic processes (TABLE 1). Most is known about the classic cadherins, which are Ca^{2+}-dependent, homophilic, cell-adhesion molecules that are expressed in almost all solid tissues[2]. Many classic cadherins are often associated with various forms of adherens junctions (FIG. 2a). The classic cadherins were originally named for the tissue in which they are most prominently expressed, but it has become clear that these expression patterns are not exclusive, and most cadherins can be expressed in many different tissues. E-cadherin (epithelial cadherin) is expressed primarily in epithelial cells and is associated with the zonula adherens of the epithelial junctional complex (FIG. 2a). E-cadherin and the zonula adherens help the cells form a tight, polarized cell layer that can perform barrier and transport functions[20].

N-cadherin and R-cadherin (neural and retinal cadherins) are widely expressed in the nervous system, and are associated with small adherens-type junctions at synapses, as well as at GROWTH CONES and other parts of the neuron[9,11]. Many types of cadherins are expressed in the mammalian nervous system, presumably owing to the many different cell interactions that take place there[34,36]. VE-cadherin (vascular-endothelial cadherin) is expressed in endothelial cells that line the vasculature and, similar to E-cadherin, it is associated with the adherens junctions that help these cells to form transport barriers[18,37]. Other classic cadherins are often named by number (for example, cadherin-11) because of their varied patterns of expression.

Another subfamily of cadherins are the desmosomal cadherins, which are exclusively expressed in the desmosomes (adhesive junctions that associate with the intermediate filaments of the cytoskeleton) of epithelial cells and cardiac muscle cells[38,39].

A large and poorly understood subfamily of cadherins is the proto-cadherin family, which are only expressed in vertebrates[34,35]. Most attention has focussed on the expression of proto-cadherins in the nervous system, but proto-cadherins can also be expressed elsewhere. Although the extracellular domains of proto-cadherins contain cadherin-type repeats (see below), they are different from classic cadherins and their cytoplasmic domains do not interact with the catenins, but instead interact with other proteins, such as Fyn-kinase and probably other as-yet-unknown proteins.

Another group of cadherin-like proteins contains various molecules (such as FAT, Daschous and Flamingo) that do not fall into a distinct subfamily[34,35]. They are identified as cadherins solely by the presence of a variable number of cadherin-type repeats in their extracellular domains.

GROWTH CONE
Motile tip of the axon or dendrite of a growing nerve cell, which spreads out into a large cone-shaped appendage.

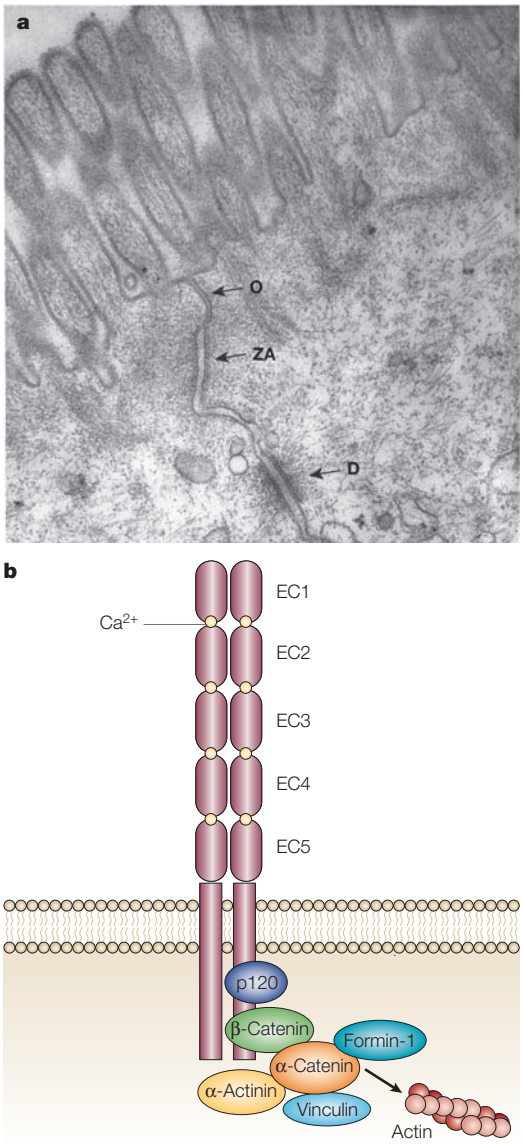


Figure 2 | **The adherens junction and the classic cadherin–catenin complex. a** | Electron micrograph of a zonula adherens (ZA) junction of epithelia. The ZA junction completely encircles the apex of the epithelial cell, but only a section through the junction is shown. The membranes of the two cells align tightly at the junction with an extracellular gap of ~250Å. The cytoplasmic surface of the junction appears as a dense 'plaque', presumably of cytoskeletal proteins, which associates with actin filaments. A tight junction (also known as a zonula occludens junction) is shown (O). D, desmosome. **b** | The cadherin–catenin protein complex. The cadherin is a parallel or *cis* homodimer. The extracellular region of classic cadherins consists of five cadherin-type repeats (EC domains; extracellular cadherin domains) that are bound together by Ca^{2+} ions (yellow circles) to form stiff, rod-like proteins. The core universal-catenin complex consists of p120 catenin, bound to the juxtamembrane region, and β-catenin, bound to the distal region, which in turn binds α-catenin. In a less well understood way, α-catenin binds to actin and actin-binding proteins, such as vinculin, α-actinin or formin-1. Cadherins and catenins have also been found to interact with many other proteins, especially signalling proteins, in various cell types or circumstances. Other cadherin-associated proteins include nectin, afadin, receptor tyrosine kinases and receptor tyrosine phosphatases.

Table 1 | **Members of the cadherin superfamily**

Subtype	Examples	Common features
Classic cadherins	Type I: E-cadherin, N-cadherin, R-cadherin Type II: VE-cadherin	Well established Ca^{2+}-dependent homophilic adhesion function Cytoplasmic domains interact with β-catenin, α-catenin and p120 Linked to the actin cytoskeleton Associated with adherens junctions
Desmosomal cadherins	Desmocollins, Desmosgleins	Adhesion proteins of desmosomal junctions Similar in structure to classic cadherins, but have distinct structural differences Cytoplasmic domains interact with plakoglobin (γ-catenin) and desmoplakin Linked to intermediate filament cytoskeleton
Atypical cadherins	T-cadherin, LI-cadherin	Function as homophilic adhesion proteins without interaction with catenins or link to actin cytoskeleton
Proto-cadherins	CNRs (α-Pcdhs), β- Pcdhs, γ-Pcdhs, PAPC, AXPC	Variable EC domains Many proto-cadherin genes (such as α-, β-, γ-pcdhs) often present in large gene clusters with complex splicing Others, such as PAPC and AXPC, are present as single genes Highly expressed in nervous system Cytoplasmic domains do not interact with catenins — some interact with Fyn-kinase, other interactions unknown
Cadherin-related signalling proteins	FAT, Daschous,Flamingo (seven membrane spanning), RET tyrosine kinase	Variable number of cadherin-type repeats in extracellular domains Roles in tumour suppression, embryonic patterning and establishment of cell polarity (especially in *Drosophila melanogaster*) Not known if these proteins function as homophilic adhesion molecules

The principle feature common to all cadherins is the presence of extracellular cadherin repeats (EC domains) in the extracellular region of a membrane protein. Data from REFS 34,35. AXPC, axial proto-cadherin; CNRs, cadherin-related neuronal receptors; E-cadherin, epithelial cadherin; LI-cadherin, liver-intestine cadherin; N-cadherin, neural cadherin; PAPC, paraxial proto-cadherin; pcdhs, proto-cadherins; T-cadherin, truncated-cadherin; VE-cadherin, vascular-endothelial cadherin.

Classic cadherins are single-pass transmembrane proteins that interact with a number of different cytoplasmic proteins to carry out their functions, which include cell–cell adhesion, cytoskeletal anchoring and signalling[2,30,34]. Classic cadherins form a core protein complex that consists of a parallel (*cis*) cadherin dimer and the catenin polypeptides (FIG. 2b). α-Catenin interacts, through β-catenin, with the distal part of the cadherin cytoplasmic domain, and p120 catenin interacts with a more proximal region of the cytoplasmic domain[40–42]. These cadherin proteins are universally present in all cadherin complexes (BOX 1). α-Catenin can mediate physical links to the actin cytoskeleton, either by directly binding actin filaments[43] or indirectly through other actin-binding proteins such as vinculin, α-actinin, and ZO1 (REFS 14,44–46). p120 catenin seems to influence cadherin function in several ways (see below).

The extracellular domain of the classic cadherin molecule consists of five cadherin-type repeats, called EC (extracellular cadherin) domains that are bound together by Ca^{2+} in a rod-like structure[47,48]. The extracellular-domain dimer mediates the adhesive binding function that is regulated by catenins and the cytoplasmic domain.

The cadherins and tissue morphogenesis

The cadherins and cell sorting. The expression of different types of cadherins mediates selective cell recognition events that are responsible for the sorting of different groups of cells in developing tissues, and the formation of selective connections between neurons in the developing nervous system[2,11,36]. The phenomenon of selective cell recognition and cell sorting is controlled by several different parameters. Cell sorting seems to be due in part to the HOMOPHILIC BINDING specificity of the extracellular domain, as the identity of the EC1 domain determines cell-sorting specificity when experimentally transferred from one cadherin to another[49]. However, different cadherins can be promiscuous with regards to their adhesive binding properties, with evidence for heterophilic adhesion between different classic cadherins[50,51]. The level of cadherin expression, and presumably therefore the overall strength of adhesion, has also been found to strongly influence cell-sorting behaviour, independently of the type of cadherin expressed[51,52]. Furthermore, it is important to realize that many cell types express several different cadherins, but the combinatorial property of cadherin expression that controls cell-sorting behaviour has not yet been identified. For example, during the development of the spinal cord, spinal motor-neuron cell bodies express several classic cadherins and sort into different functional groups. Each group of neuronal cell bodies expresses a different set of four cadherins, but the expression of one particular cadherin was found to dominate sorting behaviour for each group[53]. These findings indicate that homophilic binding specificity can contribute to cell-sorting behaviour. However, other factors, such as cadherin-mediated signalling events, quantitative differences in adhesion, or other cellular consequences of adhesion that are mediated by different cadherins (for example, cytoskeletal organization), can determine overall cell-sorting behaviour.

HOMOPHILIC BINDING
The binding of a molecule (for example, an adhesion molecule) in one cell to an identical molecule that is usually on another cell.

Box 1 | **The catenins**

'Catenin' is greek for link, and the catenins were named as such because of their initially proposed roles of linking cadherins to the actin cytoskeleton. It has, however, become clear that catenins have many other functions. Structurally, β-catenin is a so-called armadillo-repeat protein, named after its homologue in *Drosophila melanogaster*, Armadillo. The armadillo repeats form a central rod-like domain that serves as a binding site for most of its numerous binding partners. The N and C termini are regulatory domains that control its degradation, binding and signalling activities.

β-Catenin is also an intracellular signal transduction molecule that mediates signalling in the WNT growth factor pathway[97]. Normally, in the absence of an extracellular Wnt ligand, the cytosolic (non-cadherin bound) levels of β-catenin are low because it is targeted for degradation by a complex of proteins. Wnt signalling through its receptor (Frizzled-LRP) inhibits the targeting of β-catenin for degradation, which allows it to accumulate in the cytosol. It enters the nucleus, interacts with the transcription factor T-cell factor (TCF) or leukocyte enhancing factor (LEF), and activates the expression of target genes.

Plakoglobin, also known as γ-catenin, is an armadillo-repeat protein that is similar to β-catenin and that can bind to the β-catenin-binding region of cadherins. It is highly enriched in desmosomes where it helps to mediate a link to the intermediate filament cytoskeleton, but can also be found at adherens junctions. It does not seem to have the same Wnt-pathway signalling function as β-catenin, but could be involved in other signalling pathways.

α-Catenin is a cytoskeletal protein that generates extensive flattening between neighbouring cell surfaces[14]. It binds to actin and several other actin-binding proteins, as well as to the N-terminal region of β-catenin (it does not interact directly with cadherins). It binds to signalling proteins, such as formin-1, which regulate the actin cytoskeleton. It also seems to have a signalling role that regulates cell proliferation.

p120-Catenin is another armadillo-repeat-containing protein that was initially discovered as a substrate for the Src protein kinase. It binds to a different region of the cadherin cytoplasmic domain from β-catenin, and both proteins can bind cadherin simultaneously. The role of p120-catenin in cadherin function is probably regulatory rather than structural. There are also p120-like catenins; δ-catenin and ARVCF. Although less well studied, they seem to bind in a similar way to cadherins and have similar functions to p120 catenin.

WNT
A family of highly conserved, secreted signalling molecules that regulate inductive interactions during embryogenesis as well as stem cell growth in adult tissues.

FIBRONECTIN
An extracellular-matrix protein that functions to support strong cell adhesion and motility through the cell-surface receptor integrin $\alpha_5\beta_1$ — an adhesion receptor that also causes intracellular signalling.

INTEGRINS
A large family of heterodimeric transmembrane proteins that function as receptors for cell-adhesion molecules.

IMAGINAL DISC
A single-cell-layer epithelial structure of the *Drosophila melanogaster* larva that gives rise to wings, legs and other appendages.

HEDGEHOG
A family of secreted signalling molecules that mediates inductive interactions in embryos.

RHOMBOMERE
Neuroepithelial segments that are found transiently in the embryonic hindbrain and that adopt distinct molecular and cellular properties, restrictions in cell mixing, and ordered domains of gene expression.

Cell signalling, cadherin regulation and cell sorting. The physiological regulation of the adhesive function of a cadherin at the cell surface can also mediate cell sorting, and is probably a common mechanism that underlies the formation of tissue boundaries and the rearrangement of cells in development. In early *Xenopus laevis* embryos, the adhesive properties of C-cadherin (type I classic cadherin) are downregulated during gastrulation by transforming growth factor β (TGFβ) growth factors (such as activin and nodal)[6,28] and by the binding of FIBRONECTIN to INTEGRINS[27]. Nodal is involved in the induction of mesodermal cell fate and also induces the newly determined mesodermal tissue to undergo morphogenetic movements. Integrins also regulate morphogenetic movements in gastrulation by providing traction on the extracellular matrix and by sensing regional boundaries set by the matrix[27]. Regulation of C-cadherin-mediated adhesion by these factors controls cell-sorting behaviour and the formation of boundaries between tissue layers[27,54].

The dynamic regulation of adhesion might also explain cell sorting that occurs in developing tissues in which there are no known differences in the expression of cadherins. During *Drosophila melanogaster* development, the wing IMAGINAL DISC is divided into anterior and posterior compartments that express different sets of genes. A distinct boundary forms between these two compartments, which the cells normally do not cross, although a continuous epithelium is formed across the compartment boundary. Adhesive sorting of cells with respect to the anterior–posterior axis of the imaginal disc is required to keep cells in their correct compartments and to form the distinct boundary between them[55]. This occurs despite the fact that these epithelial cells all express high levels of E-cadherin and show no known differences in their expression of other adhesive proteins. Importantly, adhesive sorting along the anterior–posterior axis occurs in response to signalling by the growth factor HEDGEHOG, which is expressed by the cells in the posterior compartment[55]. This raises the possibility that the regulation of existing adhesion molecules such as E-cadherin, rather than the expression of different adhesion proteins, is responsible for cell-sorting behaviour.

Adhesive sorting is also known to underlie the formation of RHOMBOMERE boundaries in the vertebrate embryonic nervous system and the patterning of tissue types along the proximal–distal axis in the developing limb bud[56–59]. Rhombomere cell sorting is driven by the pattern of expression of ephrins and Eph receptors[60], which function by both repulsive and adhesive sorting mechanisms[61], rather than by the pattern of cadherin expression. Both ephrins and cadherins have been implicated in cell sorting in the developing limb bud[58,62]. Signalling by the Eph receptor Pagliaccio has been shown to downregulate C-cadherin-mediated adhesion in *X. laevis* embryos[31], which indicates that ephrins and Eph receptor signalling could affect cell-sorting behaviour by regulating cadherin adhesive activity.

The cadherins and cell movement. Although cadherins are often thought to mediate stable cell interactions, such as in the adherens junctions and the desmosomes of epithelial cells, they also have dynamic roles in mediating cell rearrangements and cell migration. For example, the regulation of C-cadherin-mediated

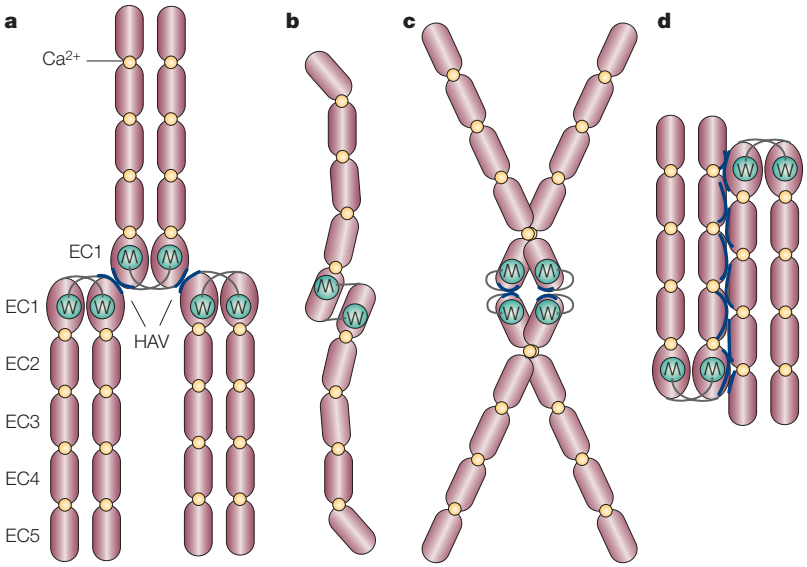


Figure 3 | **Various models of the cadherin homophilic bond. a** | Linear zipper model composed of interdigitating Trp-mediated *cis* dimers[66]. The *cis*-strand dimer results from the reciprocal insertion of the Trp2 residue (W) in the EC1 domain of one subunit into a hydrophobic pocket (green) of the extracellular cadherin (EC)1 domain of the other subunit. The homophilic-binding (or *trans* interaction) occurs at a different site (shown in blue), that surrounds the HAV sequence. **b** | Revised Trp-dimer model, in which Trp2 mediates the *trans*-homophilic bond rather than the *cis* dimer[48]. As in the linear zipper model (**a**), there is still a reciprocal insertion of the Trp2 residue into the hydrophobic pocket (green) between subunits. However, the two cadherin subunits extend in opposite directions. In the crystal structure, the cadherin seems to form *cis* interactions through domains EC2 and EC3 (not shown). **c** | Model that invokes a Ca^{2+}-dependent *cis* dimer, and intramolecular Trp2 binding to activate the adhesive binding interface[77]. In this model, *cis* dimerization is mediated by the Ca^{2+}-binding sites that are located at the interface between the EC1 and EC2 domains. Insertion of the Trp2 residue into the hydrophobic pocket on EC1 (green) is intramolecular and, rather than mediating dimerization, this insertion changes the conformation of the surface of EC1 (blue), which activates the cadherin to engage in a *trans*-homophilic bond. **d** | A model that invokes extensive overlap between Trp-mediated dimers. This model implicates the other EC domains as well as EC1 in the formation of the homophilic bond[78–80]. Here, Trp2 mediates *cis* dimerization as in model **a**. However, the homophilic binding interface (blue) involves many of the EC domains. Ca^{2+} ions are indicated by yellow circles.

adhesion in response to growth factors and fibronectin in gastrulating *X. laevis* embryos is required for the convergence and extension tissue movements that underlie the elongation of the body axis[6,27]. Convergence and extension movements are driven by local rearrangements of cells with respect to adjoining cells[5], and require the continuous breaking and reforming of C-cadherin adhesive bonds. Similarly, N-cadherin is known to mediate growth cone motility[9,63], and even E-cadherin, which is usually thought to form stable epithelial junctions, mediates the long-range migration of BORDER CELLS in the developing *D. melanogaster* ovary[10]. Less is known about the dynamics of adhesion in adult tissues that undergo ordered movements and turnover, but E-cadherin certainly has an important role in the homeostasis and turnover of tissues such as the intestinal lining and the epidermis[12,13]. At a minimum, therefore, dynamic regulation of adhesion is required so that moving or migrating cells can continually break and remake adhesive bonds to change cell neighbours. The dynamic regulation of cadherin adhesions might also drive cell movements. This process, called 'intercellular motility', is analogous to the role of integrins in the migration of cells on the extracellular matrix[1,64].

BORDER CELLS
Four to eight epithelial follicle cells in the developing *Drosophila melanogaster* ovary. These cells are recruited by two non-migratory polar cells and migrate towards the anterior border of the oocyte.

CIS DIMER
A dimer on the same membrane. A *trans* dimer is a dimer on the facing membrane.

The cadherin homophilic bond

Structure. Ultimately, to understand how adhesion is regulated, it is necessary to understand the molecular nature of the adhesive bond itself. So far, the structure has been analyzed primarily by *in vitro* studies of purified recombinant protein fragments, which include analysis of the crystal structures of several cadherin extracellular domains, and many biochemical and biophysical studies on the binding properties of cadherins. Several models for the cadherin homophilic bond have been proposed[65] (FIG. 3). The 'linear zipper' model is based on the crystal structure of the N-cadherin N-terminal EC1 domain[66] (FIG. 3a). Two dimerization interfaces in EC1 were observed; one was thought to mediate *cis* dimerization, in which the Trp2 residue of each subunit inserts into a hydrophobic pocket on the other EC1 subunit; the second putative adhesion dimer interface is a flat surface that surrounds the conserved HAV sequence. The existence of the Trp2-mediated *cis*-strand dimer has been supported by a large amount of experimental evidence[67–73]. However, the participation of the putative adhesion dimer interface that surrounds the HAV sequence has not been supported by mutagenesis studies[74–76] and probably arose from crystal packing interactions — artefactual interfaces that result from crystallization.

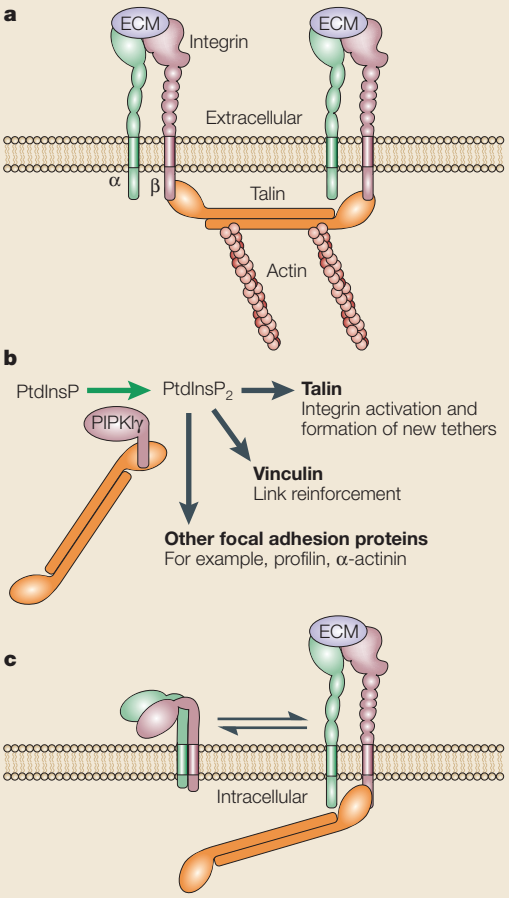
A revised model has been proposed from a recent crystal structure of the C-cadherin ectodomain, in which the Trp2-mediated strand dimer has been proposed to be the homophilic adhesive binding interface instead of the *CIS* DIMER interface[48] (FIG. 3b). It might be possible to reconcile this model with the evidence for a Trp2-mediated *cis* lateral dimer on the cell surface by invoking a model in which the Trp2 dimer interaction switches between *cis* and *trans* interactions during the formation of the adhesive bond[71]. The *trans* Trp2-homophilic bond model has also been proposed for the desmosomal glycoproteins as a result of an electron microscopic study of desmosomes[39].

An alternative model for the *cis* dimer and homophilic bond has also been proposed on the basis of the crystal structure of EC1–EC2 of E-cadherin and electron microscopy studies of artificially multimerized cadherins[77]. In this model (FIG. 3c), *cis* dimerization occurs at the Ca^{2+}-binding site between EC1 and EC2, and the Trp2 residue inserts intramolecularly into its own pocket to activate adhesive binding at another surface of EC1. Another model, based on biophysical and biochemical studies that measure the adhesive binding properties of the C-cadherin ectodomain, has been proposed[78–80]. This model entails a much more extensive overlap between ectodomains and indicates important roles for the other EC domains in the adhesive binding interface (FIG. 3d). Further support for this model comes from a study of L-CAM (chicken E-cadherin), which showed that EC1 is not essential for adhesive binding[76]. Further work is needed to decipher which of these models best explains

Box 2 | **Inside-out integrin signalling**

Inside-out integrin regulation results from either affinity modulation or avidity modulation[83,126]. The integrin extracellular domains can undergo conformational changes that affect adhesive binding[2,127]. The recent integrin crystal structures reveal different conformations, and several studies have shown that these conformations correspond to different functional binding states[32,128]. The conformation of the extracellular domains seems to be controlled by changes in the association between cytoplasmic and transmembrane domains, and the cytoskeletal protein talin seems to have an important regulatory role[33,129–131]. Changes in the oligomerization state of the integrin α- and β-chains have also been found to occur in association with the conformational changes that mediate inside-out regulation[84]. An important concept about the regulation of integrins is that they function as transmembrane ALLOSTERIC SWITCHES**, and that conformational changes that occur on the extracellular side to mediate inside-out regulation are coupled to changes in the cytoplasmic domains that mediate outside-in signalling[32].**

As shown in the figure, talin contributes to integrin function in three ways[33]. The integrins consist of heterodimers of α- and β-subunits. The subunits each have a globular head region, which together form the main binding site for extracellular matrix (ECM) proteins, such as fibronectin, fibrinogen and collagen. The short cytoplasmic domain of the β-subunit interacts with talin. As shown in part a of the figure, talin directly links to actin. Talin forms anti-parallel homodimers, and each subunit has an N-terminal globular head domain, which contains the major integrin binding site, and a C-terminal rod domain, which contains actin-binding sites that physically link the integrins to the actin cytoskeleton and that might also contribute to integrin clustering. As part b shows, during signalling to the cytoskeleton, talin binds and activates phosphatidylinositol phosphate kinase Iγ (PIPKIγ), which results in increased phosphatidylinositol bisphosphate ($PtdInsP_2$) production. This, in turn, regulates talin, vinculin and other focal adhesion proteins, which results in integrin activation, reinforcement of cytoskeletal links and focal adhesion formation. Part c of the figure shows regulation of integrin affinity by talin. The binding of talin to integrin tails induces conformational changes in the integrin extracellular domains, which increases their affinity for the ECM ligands, such as fibronectin, fibrinogen and collagen. The figure is reproduced, with permission, from *Nature Cell Biology* (REF. 33) © (2003) Macmillan Magazines Ltd.



the structure of the homophilic bond, but an intriguing possibility is that some of the different models represent different conformational states that are important for the regulation of adhesion.

Regulation. To understand the mechanism of the physiological regulation of the cadherins, it is essential to understand how cytoplasmic signals elicit molecular changes that result in alterations in the adhesive homophilic binding properties of the extracellular domain. This is analogous to the well studied inside-out signalling that regulates the integrins, where the binding of the integrin extracellular domain to ligands in the extracellular matrix is regulated by cytoplasmic signalling events (BOX 2). Although inside-out signalling by the cadherins is not as well studied as the integrins, there are reasons to believe that it occurs in an analogous way.

Even without a final consensus on the structure of the cadherin homophilic bond, there is evidence that cadherins, similar to integrins, undergo some sort of change in physical organization or conformation associated with their state of activation. Downregulation of the adhesive activity of C-cadherin in the *X. laevis* embryo in response to the TGFβ-like growth factor activin occurs rapidly without any changes in the amount of C-cadherin on the cell surface or in its association with cytoplasmic catenins[28]. However, the binding of cells to anti-C-cadherin antibodies is altered, and this change in accessibility probably reflects a change in the conformation or organizational state of the protein on the cell surface[6]. Moreover, binding of a monoclonal antibody to the EC5 domain of C-cadherin promotes an activated state of C-cadherin, which reverses the downregulation of adhesion that is triggered by activin. Unfortunately, the physical changes in C-cadherin that were detected or stimulated by these antibodies are not yet known.

For integrins such as the platelet-specific integrin $\alpha_{IIb}\beta_3$, a measurable change in its affinity for the ligand fibrinogen, known as affinity modulation, is the best evidence for a change in binding properties that are associated with inside-out regulation. By contrast, there is no evidence for changes in the affinity of an individual cadherin homophilic bond at the cell surface. However, biophysical measurements indicate that the affinity of the cadherin bond is low[79,81,82], which indicates that multivalent binding events are more relevant to the understanding of cadherin-mediated adhesion. Clustering and/or oligomerization of integrins is also associated with inside-out regulation of binding activity, a process called avidity modulation[83,84]. Cadherins have also been observed to undergo ligand-dependent clustering at the cell surface[42], and experimental induction

ALLOSTERIC SWITCHES
Switches that function by causing a conformational change in a protein.

of cadherin clustering has been shown to increase the strength of adhesion[85]. Changes in the state of cadherin *cis* dimerization at the cell surface have also been proposed to be involved in the regulation of adhesion[69,70,72]. Mutations in the cytoplasmic tail have been shown to affect the extent of dimerization[68,70], which raises the possibility that inside-out signalling could influence dimerization and therefore adhesion. So far, however, there is no direct evidence that the extent of *cis* dimerization or clustering changes as a result of regulation by physiological signals, or that regulation of dimerization or clustering controls the strength of cell adhesion under normal physiological circumstances.

The actin cytoskeleton and cadherin function. The actin cytoskeleton is closely associated with cadherin-mediated cell adhesion, especially at the adherens junction, similar to the linkage of integrins to actin at focal adhesions[23,86,87]. It is important to consider the roles of the actin cytoskeleton and the adherens junctions in cadherin-mediated adhesion, and how they contribute to the physiological regulation of adhesion. Attachment to the actin cytoskeleton and the formation of adherens junctions are probably not essential for the formation of the basic adhesive bond itself. Instead, the actin cytoskeleton might be coupled to sites of adhesion at the adherens junctions to produce force to generate changes in cell shape (for example, flattening) and/or cell movements, to help in the organization of cell structure and to establish cell polarity. Although these processes are unquestionably coupled to the formation of adhesions in the cell, they might be separable to some degree.

Cadherins are known to link to the actin cytoskeleton through the catenins (FIG. 4a). But there are situations in which the linkage to the actin cytoskeleton is not required for the basic adhesive interaction. Two naturally occurring cadherins, T-cadherin and LI (liver-intestine)-cadherin, lack the typical cadherin cytoplasmic domains, but are effective cell adhesion molecules[88,89]. T-cadherin is GPI-LINKED and so has no cytoplasmic domain or binding partners. LI-cadherin has a very short cytoplasmic tail and mediates adhesion that is independent of observable cytoskeletal interactions. Moreover, mutational analysis of several classic cadherins revealed that the catenin-mediated linkage to the cytoskeleton is not absolutely required for them to mediate basic cell adhesion. Mouse E-cadherin that has a deletion of the entire cytoplasmic domain has been shown to mediate effective cell aggregation[68,90], and C-cadherin that lacks the β-catenin binding domain continues to mediate cell adhesion[42]. Indeed, C-cadherin could mediate cell adhesion even when its entire cytoplasmic domain was replaced by a protein oligomerization domain[85], which indicates that oligomerization is sufficient for basic adhesive function, independent of a link to the cytoskeleton.

Cadherins, especially E-cadherin, are often concentrated in adherens junctions, which are rich in actin filaments and actin-binding proteins[23,86]. However, cadherins can function as effective adhesion molecules even when they are not localized in obvious junctions, particulary in non-epithelial cell types such as neuronal processes and embryonic mesodermal cells[9,91]. If these cadherins form junctions of similar molecular architecture they would have to be numerous, highly dispersed and too small to be resolved or detected by microscopy. More probably, these dispersed cadherins function without the full cytoskeletal linkage that is typical of adherens junctions. Even E-cadherin, which is often enriched in the adherens junctions of epithelial cells, is also often present in non-junctional regions of cell–cell contact[92,93]. A different adhesion protein of the immunoglobulin superfamily, nectin, has been found to be more highly localized to adherens junctions than E-cadherin[94]. Nectin and its cytoplasmic binding partner, afadin, interact with the E-cadherin–catenin complex and are thought to facilitate E-cadherin-mediated adhesion, either by its direct interaction or as a result of nectin-triggered signalling events[95,96]. Together, these findings indicate that adherens junctions represent a specialized form of cadherin-mediated cell adhesion that is important for cytoskeletal attachment, epithelial cell organization and cell polarity.

The catenins and cadherin regulation

Regulatory roles of α- and β-catenin. α- and β-catenin (BOX 1) have other roles in cadherin-mediated adhesion in addition to the direct physical linkage of cadherins to the actin cytoskeleton at the adherens junctions. There is the well known role of β-catenin as a signal transduction molecule that mediates signalling in the Wnt signalling pathway[97] , an aspect of catenin function that is outside the scope of this review. The catenins interact, both directly and indirectly, with other signalling molecules that influence the state of the actin cytoskeleton[14,86] (FIG. 4b). For example, E-cadherin has been shown to regulate actin polymerization by signalling to the Arp2/3 complex through phosphatidylinositol 3-kinase (PI3K) and the GTPase Rac[98,99]. Although the mechanism of this activation is not well understood, Rac activation depends on the p120-catenin binding domain of E-cadherin[99], and there is evidence that β-catenin interacts, either directly or indirectly, with PI3K[37,100]. Formin-1 is a FORMIN PROTEIN that is known to nucleate actin polymerization in response to Rho, Rac and Cdc42 in many cell types. Formin-1 interacts with α-catenin and regulates actin polymerization at adherens junctions to mediate tight sealing of the epithelial sheet[101].

Importantly, the catenins probably also directly influence the adhesive state of the cadherin extracellular domain, and possibly even inside-out regulation of its functional conformation (FIG. 4c). Although the mechanisms by which catenins influence the cadherin extracellular domain are not well explored, there is evidence that catenin binding to the cadherin cytoplasmic domain regulates the dimerization state and/or clustering of cadherins independently of binding to the cytoskeleton, as well as regulating the ability of the cadherin to engage in a homophilic bond[42,70,85,102]. For example, although deletion of the entire cytoplasmic domain from mouse E-cadherin does not significantly inhibit its adhesive function, the juxtamembrane region of

GPI-LINKED
A post-translational modification that attaches proteins to the exoplasmic leaflet of membranes by a lipid moiety.

FORMIN PROTEINS
A family of proteins that contain a formin homology-2 domain and that can promote actin assembly.

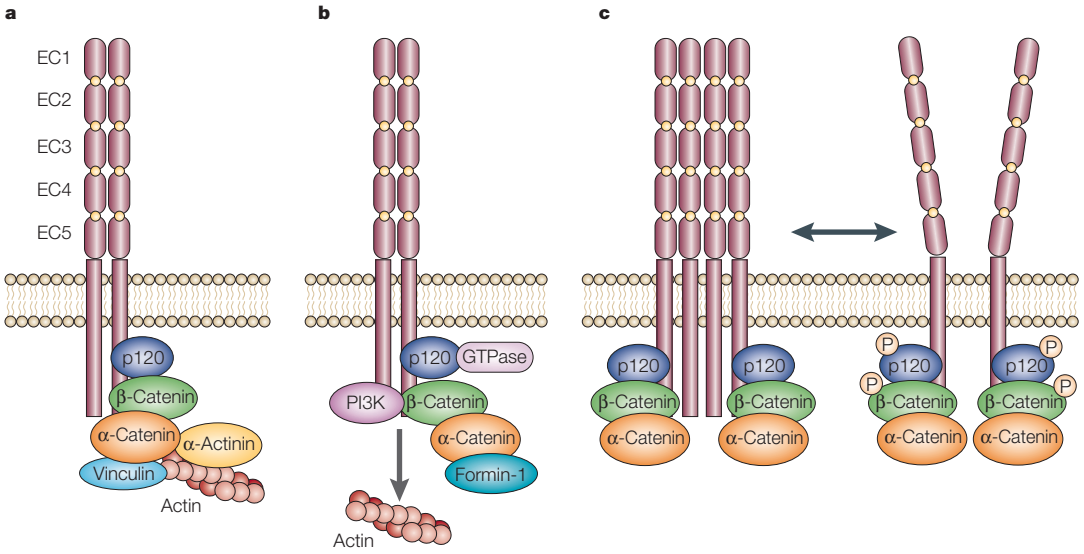


Figure 4 | **Three ways in which catenins contribute to cadherin function.** The contribution of catenins to cadherin function can be compared to the involvement of talin in integrin function (BOX 2). **a** | Direct physical links to the actin cytoskeleton. α-Catenin binds to actin filaments directly[43], but also interacts with two actin-binding proteins, α-actinin and vinculin[45,46], which probably also mediate the link to actin filaments. **b** | Signalling to the cytoskeleton. Although so far not as well understood as for the integrins, there are many ways in which the cadherins, through the catenins, produce signals that influence the cytoskeleton[14]. For example, p120-catenin can regulate the GTPases Rho and Rac; formin-1 interacts with α-catenin and regulates assembly of linear actin filaments; and PI3K (phosphatidylinositol 3-kinase) has been found to interact with β-catenin[100] and to be activated by cadherins[37,99]. **c** | Regulation of the homophilic binding properties of cadherins. Although also poorly understood compared with the integrins, regulation of the conformation or organization of the cadherin extracellular domain is probably involved in adhesion regulation. A hypothetical example is shown, in which the *cis* Trp2-mediated dimerization and higher-order clustering are controlled by the phosphorylation status of the catenins. As proposed in this example, phosphorylation of the catenins could lead to a disruption of the *cis* dimerization and reduced clustering of the cadherin molecules at the cell surface, resulting in an inactive or less active adhesive conformation. Ca^{2+} ions are indicated by yellow circles. EC, extracellular cadherin.

the cytoplasmic domain seems to have inhibitory activity, as deletion of the distal β-catenin-binding region inactivates E-cadherin adhesion[68,90]. Although the inhibitory activity of the juxtamembrane region is specific to E-cadherin, this indicates that the catenins can function by relieving the inhibition imposed on the cadherins by other factors. The inhibitory activity of the juxtamembrane region is also independent of p120-catenin binding, which indicates that there remain unknown interactions and possible new binding factors for the cytoplasmic domain.

The role of p120 catenin. The exact role of p120 catenin in cadherin-mediated adhesion is not certain, and several different roles have been proposed. In contrast to α- and β-catenin, there is no evidence that p120 mediates a direct link to the actin cytoskeleton. In studies of mammalian tissue culture cells, selective mutation of the p120 binding domain, as well as expression of mutant p120 proteins, can have profound effects on cadherin-mediated adhesion[102,103]. Surprisingly, however, mutation of the p120 gene in *D. melanogaster* or *Caenorhabditis elegans*, or mutation of the p120 binding domain of *D. melanogaster* E-cadherin, do not have significant effects on embryonic development[104–106]. p120 mutations in *D. melanogaster* do, however, enhance the adhesion defects that are produced by mutations in other adhesion-related genes, indicating that p120 has some role in adhesion that can be compensated for by another protein or pathway.

Recently, p120 binding to cadherins has been found to regulate cadherin stability; loss of p120 expression leads to significantly reduced levels of E-cadherin in epithelia[107]. Nonetheless, p120 must have other roles in cadherin function, as it can affect adhesion independently of the levels of cadherin expression[102,103]. The juxtamembrane domain, to which p120 binds, has been found to influence strongly the adhesive state and/or clustering of the cadherin independently of the β-catenin binding domain[42,68,102]. Whether this is due to a direct effect on the conformation or adhesive binding function of the cadherin, or results from an indirect effect through a regulatory signalling pathway, is not yet known. p120 can also regulate the activities of SMALL GTPASES, inhibiting Rho and activating Rac or Cdc42 (REFS 99,108,109), but whether these effects occur in association with cadherins is uncertain. Rho has been found to interact with *D. melanogaster* p120 and α-catenin[110], indicating that p120 might have a role in recruiting Rho to the cadherin complex. There is also evidence that p120 binds to kinesin to facilitate transport of cadherin complexes along microtubules[26], but it is not yet known whether this

SMALL GTPASES
GDP/GTP-regulated binary switches that regulate signal-transduction. The GDP-bound form of the GTPase is usually inactive, whereas the GTP-bound form is active and activates downstream signalling pathways that control actin organization.

interaction plays a part in the regulation of cadherin adhesive function. Elucidating how p120 and the juxtamembrane region of the cadherin cytoplasmic domain cooperate with α- and β-catenin binding at the distal cadherin cytoplasmic region remains an important problem in this field.

Three roles for catenins in cadherin function. In summary, catenins seem to have at least three distinct roles in cadherin function (FIG. 4): direct physical linkage to actin, the control of signalling molecules that regulate the actin cytoskeleton, and direct control of the adhesive state of the cadherin extracellular binding domain. These are the same important functions that have been attributed to the integrin-associated linker protein talin[33]: a direct link to actin filaments, direct regulation of the conformational state of the integrin extracellular domain and control of cytoskeletal assembly through the activation of phosphatidylinositol phosphate kinase (PIPK) (FIG. 4 and related text in BOX 2). Perhaps cadherins and integrins share similar mechanisms of adhesion regulation and junction formation even though the specific proteins are different.

Cadherin regulation by signalling

Many different signalling pathways have been found to negatively regulate cadherin-mediated adhesion. The most extensively studied in cell-culture models are those triggered by receptor tyrosine kinases, such as the epidermal growth factor receptor (EGFR), hepatocyte growth factor (HGF)/scatter factor receptor (met), Eph receptors, or receptors functioning through non-tyrosine kinases, such as Src or Abl[29,31,63,111–115]. Similarly, several tyrosine phosphatases, both receptor and non-receptor forms, have been implicated in increasing adhesion[116–118], presumably by dephosphorylating the substrates that are phosphorylated by the tyrosine kinases that inhibit adhesion. Other signalling pathways, which include those mediated by serine kinases (TGFβ/activin) and integrins, have also been found to regulate cadherins[6,27,28].

The role of catenin phosphorylation. The activation of tyrosine kinases in cultured cells usually causes tyrosine phosphorylation of β-catenin, which led to the prevailing hypothesis that β-catenin tyrosine phosphorylation is a common mechanism that underlies cadherin regulation. However, β-catenin might not be the only or even the key substrate for tyrosine kinases that is important for cadherin regulation. E-cadherin is strongly inactivated by expression of Src, but a cadherin–α-catenin fusion chimaera that bypasses β-catenin but retains adhesive function, is still regulated by Src[113]. This indicates that other targets of tyrosine kinases might also be important regulators of cadherin-mediated adhesion.

The mechanisms by which biochemical modifications of catenins affect adhesive function are so far not well understood. One simple hypothesis is that they disrupt the cadherin–catenin complex, thereby breaking the linkage of cadherins to the actin cytoskeleton[115]. For example, N-cadherin-mediated adhesion in cultured neurons was found to be inhibited by the activation of the neuronal guidance receptor Robo[63]. When activated by its ligand Slit, Robo recruited the Abl tyrosine kinase to the cadherin–catenin complex through its cytoplasmic domain, and the resultant tyrosine phosphorylation of β-catenin caused its dissociation from the cadherin. However, β-catenin dissociation from the cadherin complex cannot be a universal mechanism for regulation of adhesion by tyrosine kinases. When β-catenin tyrosine phosphorylation is associated with regulation of adhesion — for example, by activation of EGFR, Src or Met — no obvious dissociation of the complex has been observed[29,40,41,111]. The complex does not dissociate when adhesion is physiologically regulated in *X. laevis* embryos in response to activin, a TGFβ receptor ligand[28]. Given that cadherins can mediate basic cell adhesion independently of their physical links to the cytoskeleton (as discussed above), it is probable that intracellular signalling events, including catenin phosphorylation, affect the adhesive function of cadherins in other ways.

I suggest that the phosphorylation of β-catenin regulates other aspects of its function in addition to the direct link of cadherins to the cytoskeleton. The X-ray crystal structure of β-catenin in complex with the cadherin cytoplasmic domain reveals that there is an extended region of contact between them, which involves multiple, potentially independent binding regions[119]. Although biochemical studies indicate that the phosphorylation of β-catenin at certain sites (or phosphorylation of the cadherin cytoplasmic domain) can alter the apparent binding affinity of β-catenin for the cadherin[112,115], the extent or structure of their interaction might also be altered. It is therefore possible that phosphorylation could alter this interaction so that it leads to a different functional conformation of the cadherin, such as a change in *cis* dimerization or higher-order clustering (FIG. 4c). Alternatively, tyrosine phosphorylation could trigger the recruitment of other signalling proteins to β-catenin — a common mechanism that is used for regulating signalling interactions in other systems — which could in turn affect the cadherin or the cytoskeleton (FIG. 4b). Although there is little direct experimental support for these mechanisms, I suggest that cytoplasmic signalling events and catenin modifications induce changes in the structure of the homophilic bond that is responsible for adhesion regulation.

The p120 catenin is also a substrate for tyrosine and serine kinases[40,41], and p120-catenin phosphorylation might have an important role in the regulation of adhesion. In studies of mammalian tissue culture cells, modification of p120 catenin is correlated with adhesion regulation[102]. As described above, the exact role of p120 catenin in cadherin-mediated adhesion, as well as its requirement for adhesion *in vivo*, is still being investigated. The role of p120-catenin phosphorylation will have to be explored in the overall context of the function of p120 catenin.

Small GTPases and the regulation of cadherins. A large amount of work using cultured cells and *D. melanogaster* and *C. elegans* embryos has demonstrated important roles for small GTPases in the establishment of cadherin-mediated adhesion and in the assembly of adherens junctions[21,86,120–123]. These include the Rho subfamily (Rac, Rho and Cdc42) as well as Arf GTPases and Rap1, a Ras subfamily member (a detailed summary of these findings is beyond the scope of this review). These GTPases have powerful and diverse effects at many levels of cell function, which include influencing membrane trafficking and the turnover of cadherins, altering the state of assembly of the actin cytoskeleton, and controlling the process of cell polarization, all of which can affect the process of adherens junction formation. The GTPases also participate in transducing signals from the cadherin–catenin complex to the actin cytoskeleton, thereby mediating an indirect connection to the cytoskeleton[99,108]. In many cases, the GTPases are important for mediating major changes in cell structure that are associated with changes in the state of differentiation, such as the epithelial–mesenchymal transition or the formation of epithelia. There is also some evidence that GTPases might have a more direct role in the dynamic inside-out regulation of cadherin adhesive function.

Rap1 is known to regulate integrin-mediated adhesion[124], and recently has been found to regulate the adhesive activity of E-cadherin at the cell surface[122] and the positioning of adherens junctions in *D. melanogaster*[123]. Cdc42 has been reported to regulate the association of catenins with E-cadherin through the effector protein IQGAP[125]. IQGAP binds to β-catenin and causes the dissociation of α-catenin from the complex, and is therefore thought to disengage the cadherin from the actin cytoskeleton. However, α-catenin dissociation from the cadherin complex is not observed in most cases of physiological regulation of cadherins. In general, dissecting out a specific role for GTPases in the direct regulation of cadherin adhesive function has been difficult, because the GTPases affect such diverse cellular processes, all of which — especially the state of the actin cytoskeleton — are important for the process of adhesion and intercellular junction formation.

Concluding remarks

The dynamic regulation of cadherin adhesion activity in response to developmental or physiological signalling pathways has a key role in tissue morphogenesis. The mechanism of cadherin regulation has features that are similar to the inside-out signalling that is mediated by the integrins. Signalling pathways that impinge on the catenins can elicit changes in the cadherin across the cell membrane to alter the functional state of the homophilic adhesive binding domain. Similar to the cytoplasmic regulators of integrins, the catenins have many roles in cadherin function — not only to mediate a direct physical link to the actin cytoskeleton, but also to regulate the state of the adhesive bond on the outside of the cell and to indirectly regulate the state of the cytoskeleton through activation of signalling pathways. Understanding how all these processes are integrated to control the dynamic process of cell adhesion in developing tissues remains an exciting challenge for the future.

Many different cellular and biochemical mechanisms have been suggested to control cadherin-mediated adhesion, but it will be important to distinguish the process of dynamic developmental and physiological regulation from the various cellular processes that are more generally involved in the formation, maintenance and turnover of adhesive junctions. This will require a greater emphasis on the study of regulation, either in model organisms or in intact developing tissue explants, rather than relying solely on cells in culture. Although cultured cells provide advantages for investigating molecular mechanisms, they are typically studied out of the context of the normal biological processes of tissue development. And, although changes in adhesion in cultured cells that result from the application of known growth factors might mimic processes that occur in developing tissues, the intracellular pathways that affect cadherins are often studied without appreciating the overall signalling pathway or biological process of which they might be a part. Therefore, details of molecular mechanisms that are derived from the study of cultured cells need to be integrated with studies on developing tissues.

Elucidating the mechanisms that underlie the dynamic regulation of cadherins will also require a fuller understanding of the basic mechanisms of cadherin-mediated adhesion. Although much progress has been made in determining the structure of the extracellular cadherin adhesive binding domain *in vitro*, there are several different models for the nature of the homophilic bond. This is due, in part, to the ambiguity that arises from a protein that forms both *cis* and *trans* dimers, and is also due to the probable multivalent nature of the adhesive bond. It is therefore crucial to find better ways to study the higher-order assembly of multiple cadherin dimers when they form functional adhesive complexes. Moreover, we need to learn more about how the catenins influence the structure and adhesive state of the cadherin dimer beyond the simple notion of their roles in mediating a direct physical link to the actin cytoskeleton. It will be important to learn how modifications of catenins in response to signalling pathways exert their effects on cadherin. Similarly, it will be important to learn more about how cadherins interact with signalling molecules through the catenins and transduce signals to the cytoskeleton to affect cell junctions, cell organization and cell motility. In the near future, it should be possible to understand how these molecular aspects of cadherin function operate in the context of dynamic regulation in the developing organism.

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Competing interests statement

The author declares no competing financial interests.

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