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Regulation of cell–cell adhesion by the cadherin–catenin complex

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Abstract

Ca^{2+}-dependent cell–cell adhesion is regulated by the cadherin family of cell adhesion proteins. Cadherins form *trans*-interactions on opposing cell surfaces which result in weak cell–cell adhesion. Stronger cell–cell adhesion occurs by clustering of cadherins and through changes in the organization of the actin cytoskeleton. Although cadherins were thought to bind directly to the actin cytoskeleton through cytoplasmic proteins, termed α- and β-catenin, recent studies with purified proteins indicate that the interaction is not direct, and instead an allosteric switch in α-catenin may mediate actin cytoskeleton reorganization. Organization and function of the cadherin–catenin complex are additionally regulated by phosphorylation and endocytosis. Direct studies of cell–cell adhesion has revealed that the cadherin–catenin complex and the underlying actin cytoskeleton undergo a series of reorganizations that are controlled by the Rho GTPases, Rac1 and RhoA, that result in the expansion and completion of cell–cell adhesion. In the present article, *in vitro* protein assembly studies and live-cell studies of *de novo* cell–cell adhesion are discussed in the context of how the cadherin–catenin complex and the actin cytoskeleton regulate cell-cell adhesion.

Keywords

actin; cadherin; catenin; cell–cell adhesion; cytoskeleton; Rho GTPase

Overview

Cell–cell adhesion is involved in all aspects of tissue morphogenesis in multicellular organisms, including regulating cell shape, movement and sorting into complex organizations in tissues and organs [1,2]. In addition to dynamic changes in cell–cell contacts, tissue morphogenesis requires remodelling of the actin cytoskeleton to effect changes in cell shape and dynamics. Thus insight into mechanisms that regulate cellular dynamics during tissue morphogenesis requires not only an understanding of cell–cell adhesion, but also an understanding of how the actin cytoskeleton is remodelled.

Epithelial cell–cell adhesion is mediated by a variety of membrane proteins, including classical cadherins, claudins/ occludin, nectin and desmosomal cadherins [1-4]. Classical cadherins are required to initiate cell–cell contacts, and other adhesion protein complexes subsequently assemble, including the tight junction, which controls paracellular diffusion [5], and desmosomes, which maintain the structural continuum of the epithelium [6].

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Cadherins are single-membrane-spanning proteins with a divergent extracellular domain of five repeats and a conserved cytoplasmic domain [7]. Binding between extracellular domains, which requires Ca^{2+} for protein conformation [8], is thought to involve multiple *cis*-dimers of cadherin [9] that form *trans*-oligomers between cadherins on opposing cell surfaces [10]. Binding between cadherin extracellular domains is weak [10], but strong cell–cell adhesion develops during lateral clustering of cadherins (see below). Clustering of cadherins was thought to depend on linkage through cytoplasmic catenins to the actin cytoskeleton since β-catenin binds directly to both the cadherin cytoplasmic domain [11] and to the actin-binding protein α-catenin [12], and it was assumed, but had not been shown directly, that α-catenin simply linked the E-cadherin–β-catenin complex to the actin cytoskeleton [13,14]. However, recent studies have shown that interactions between the cadherin–catenin complex and the actin cytoskeleton are more complex and dynamic [15] (Figure 1).

In addition to roles in cell–cell adhesion, the actin cytoskeleton plays important roles in regulating plasma membrane dynamics, cell migration and cell shape through the local activation of nucleators of actin polymerization such as the Arp2/3 (actin-related protein 2/3) complex [16]. The actin cytoskeleton has different organizations during cell migration (branched actin arrays [16]) and at cell–cell contacts (parallel actin bundles [17]), but it is unclear how actin polymerization and organization are regulated when migratory cells form cadherin-mediated cell–cell adhesion and become quiescent. A reversal of these phenotypes also occurs during development and wound healing, and in diseases such as cancer when dynamic cell movement is (re-)initiated as stationary contacting cells are induced to become migratory. Several mechanisms may be involved in regulating cell–cell adhesion, including changes in strengths of interactions within the cadherin–catenin complex through phosphorylation, endocytosis of cadherins and by local regulation of the actin cytoskeleton by α-catenin. These regulatory mechanisms are summarized and placed in the context of recent studies of *de novo* adhesion between pairs of epithelial cells.

Regulation of the cadherin–catenin complex by phosphorylation and endocytosis

The structural integrity of the cadherin–catenin complex is positively and negatively regulated by kinases that are often up-regulated during dynamic cell movements in development and in cancer. Three serine residues in the cadherin cytoplasmic domain (Ser^{684}, Ser^{686} and Ser^{692}) are phosphorylated by the protein kinases CK2 and GSK3β (glycogen synthase kinase 3β), which creates additional interactions with β-catenin resulting in a large increase in the affinity of the interaction (picomolar affinity [11]). In contrast, tyrosine phosphorylation of β-catenin at Tyr^{489} or Tyr^{654} disrupts binding to cadherin, and at Tyr^{142} disrupts binding to α-catenin [18]. Src phosphorylates β-catenin at Tyr^{654} [19]. Other tyrosine kinases phosphorylate β-catenin at Tyr^{489} (Abl [20]), Tyr^{654} {EGFR (epidermal growth factor receptor) [21]} and Tyr^{142} (Fer [22]) (Figure 1).

Tyrosine kinase phosphorylation of β-catenin is balanced by protein tyrosine phosphatases that bind β-catenin and cadherin. The non-receptor protein tyrosine phosphatase PTP1B (protein tyrosine phosphatase 1B) regulates cadherin-based adhesion by binding directly to the cadherin cytoplasmic domain and dephosphorylating β-catenin at Tyr^{654} [23]. Phosphorylation of PTP1B at Tyr^{152} is required for the interaction with cadherin [20]. The tyrosine kinase Fer appears to be responsible for phosphorylating PTP1B. Fer binds to the cadherin-binding protein p120, which would promote binding of PTP1B to cadherin and dephosphorylation of β-catenin at Tyr^{654}. Inhibiting the p120–Fer interaction prevents dephosphorylation of β-catenin at Tyr^{654} and disrupts the cadherin–catenin complex [24].

Although a considerable amount is known about sites of phosphorylation in the cadherin–catenin complex and about activated kinases such as Src perturbing cell–cell adhesion (for example, see [25]), little is known about how specific kinases are activated or target the complex during cell–cell adhesion. Recent studies of the inactivation of N-cadherin following binding of the secreted axon guidance cue Slit to its receptor, Robo, have shown a regulatory role of β-catenin phosphorylation on cell–cell adhesion [26]. In this case, a complex of Slit-bound Robo, Abl tyrosine kinase and N-cadherin-associated β-catenin is formed; Abl-mediated phosphorylation of β-catenin at Tyr^{489} results in uncoupling of the β-catenin-N-cadherin complex. The result of β-catenin phosphorylation is the loss of N-cadherin function, and targeting of phospho-Tyr^{489}-β-catenin to the nucleus where it activates gene expression [26]. Further studies, however, are needed to examine changes in the phosphorylation status of the cadherin–catenin complex during initiation and loss of cell–cell adhesion in other cell types, particularly epithelial cells.

In addition to β-catenin, another related protein termed p120-catenin binds to the juxtamembrane region of the cytoplasmic domain of classical cadherins [27]. Like β-catenin, p120-catenin binding to cadherin is regulated by phosphorylation. Phosphorylation of p120-catenin increases binding affinity to E-cadherin [22]. Association of p120-catenin with E-cadherin has been proposed to stabilize E-cadherin at the plasma membrane during the formation of cell–cell contacts [28]. siRNA (small interfering RNA)-mediated knockdown of p120-catenin [29] and competitive expression of other cadherins [30] suggest that p120-catenin increases the retention of the cadherin complex at the plasma membrane and prevents cadherin internalization and degradation.

One mechanism of targeting cadherin for degradation involves Hakai, an E3-ubiquitin ligase, which binds E-cadherin in a Src phosphorylation-dependent manner [31]. Expression of Hakai increased both the ubiquitination and rate of E-cadherin endocytosis [31], but it is not known whether p120-catenin binding is involved in this degradation pathway. It is important to note, however, that loss of p120-catenin in an E-cadherin-null background has also been shown to increase cell–cell adhesion, raising the possibility that p120-catenin plays additional roles in modulating cell–cell adhesion [32].

In vitro analysis of cadherin, catenin and actin interactions

Although the cadherin–catenin complex includes the actin-binding protein α-catenin [13], it had not been shown whether the complex bound directly to the actin cytoskeleton, as had been generally assumed [14]. This model has now been tested directly with purified proteins [33,34]. The results of this analysis showed that the association of the cadherin–catenin complex with the actin cytoskeleton is more complex than previously thought (reviewed in [15]). Although a 1:1:1 stoichiometric complex of cadherin (cytoplasmic domain), β-catenin and α-catenin could be reconstituted *in vitro*, as reported previously [12], an interaction of the complex with actin filaments could not be demonstrated. Furthermore, direct comparison of the dynamics of the cadherin–catenin complex with those of actin in whole epithelial cells using FRAP (fluorescence recovery after photobleaching) showed that, although E-cadherin, β-catenin and α-catenin had similar recovery profiles and mobile fractions, actin immediately adjacent to cell–cell contacts was much more dynamic [34]. These results appeared to be in conflict with a previous study showing that α-catenin is just an actin-binding and -bundling protein bound to cadhenin [13]. However, a resolution of these apparently disparate results was the finding that α-catenin exists as either a monomer or a homodimer, and that the homodimer has a higher affinity for actin filaments than the monomer; conversely, the α-catenin monomer has a higher affinity for β-cadherin bound to cadherin than the homodimer [33] (Figure 1). Two key experiments underscored these conclusions: (i) a chimaeric monomeric protein comprising the α-catenin-binding domain of

β-catenin fused to α-catenin, which folds to form an intermolecular complex similar to that of the β-catenin-α-catenin heterodimer, did not bind actin filaments; and (ii) when a preassembled purified ternary complex of cadherin (cytoplasmic domain), β-catenin and α-catenin was incubated with actin filaments, only α-catenin, but not the remaining cadherin–catenin complex, pelleted with actin filaments; under these experimental conditions, the source of the actin-binding fraction of α-catenin must have been the pre-assembled cadherin–catenin complex, indicating that α-catenin can dissociate from the complex, presumably homodimerize and bind actin filaments [33].

In addition to the fact that α-catenin homodimers bind (and bundle) actin filaments, additional studies revealed that α-catenin homodimers suppress Arp2/3-mediated actin polymerization by competing directly with the Arp2/3 complex for binding to actin filaments [33]; recall that actin bundles are associated with strong cell–cell contacts [17], whereas Arp2/3-mediated actin polymerization is required for dynamic membrane organization (lamellipodia) and cell migration [16]. These results suggest new roles for α-catenin in local regulation of actin assembly and organization at sites of cell–cell adhesion (see below and Figure 2).

Dynamics of the cadherin–catenin complex and actin cytoskeleton during *de novo* cell–cell adhesion

High-resolution live-cell imaging of normal MDCK (Madin–Darby canine kidney) epithelial cells showed that functional E-cadherin–GFP (green fluorescent protein) and associated catenins are immediately recruited to initial cell–cell contacts where they become progressively immobilized into puncta, more of which are added as the contact expands laterally [35]. In a model in which actin filaments are associated directly with the cadherin–catenin complex, it would be expected that actin filaments would become concentrated and reorganized around cadherin–catenin puncta as the cell–cell contact expanded. Indeed, actin cables have been observed to impinge on cadherin puncta during formation of cell–cell adhesion by keratinocytes [36], a stratified epithelium, although these actin cables were present during cell migration before cell–cell adhesion and appeared to coalesce and sharpen further upon retraction of lamellae along the cell–cell contact [37]. Analysis of sites of actin filament assembly indicated that new assembly was occurring at the tips of filaments that appeared to be closely associated with cadherin puncta [36].

On the other hand, studies of simple epithelia, such as MDCK cells, revealed that the cortical bundle of actin associated with the periphery of migrating cells initially frayed and then dissociated beneath sites of cell–cell contact [38,39]. This resulted in relatively few actin filaments associated directly with sites of cell–cell adhesion; those that remained appeared to be mostly associated with dynamic lamellipodia [38,39] that were generally localized to the periphery of the expanding cell–cell contact ([38], see also [40]) and contained Arp3–GFP [39]. The ends of the cortical actin bundle localized to the edges of the expanding MDCK cell–cell contact and eventually relocated to the periphery of the adhering cells. Analysis of sites of actin filament assembly in MDCK cell–cell contacts revealed little if any new assembly within the established cell–cell contact that contained the cadherin–catenin complex, but new assembly occurred at the periphery of the contact where the ends of the cortical actin bundle are located and integrin-based cell adhesion complexes are also concentrated [39]; it would be interesting to determine whether the sites of actin assembly at cadherin puncta in adhering keratinocytes (see above) were also associated with integrin-based adhesions. It remains unclear whether differences in the location of actin filaments and sites of actin assembly between stratified epithelial keratinocytes and simple epithelial MDCK cells are due to cell-type difference, perhaps associated with different functions of

the cells; clearly, further work is needed to identify where actin assembly occurs and how actin assembly is regulated locally and excluded from other sites.

Analysis of the expansion of cell–cell contacts in MDCK cells indicated diverse roles for the actin cytoskeleton in cell–cell adhesion, including localized lamellipodia activity involved in initiating contact between adjacent cells, and actomyosin contraction in later stages of cell–cell adhesion (compaction) [39]. Lamellipodia activity is mediated by Rac1 control of actin dynamics by locally regulating the activity of actin nucleators, such as the Arp2/3 complex [16]. Rac1 is activated upon E-cadherin adhesion [41,42] and Rac1 protein co-localizes with E-cadherin during initial cell–cell adhesion [38,42]. Direct analysis of subcellular sites of Rac1 activity, using FRET (fluorescence resonance energy transfer), revealed that Rac1 activity is restricted to regions of newly forming cell–cell contacts, but was suppressed in regions of established cell–cell contacts, resulting in a zone of Rac1 activity at the edges of the expanding cell–cell contact [39]. Diminished Rac1 activity, and hence membrane dynamics, in the newly formed cell–cell contact might allow weak *trans*-interactions between E-cadherin on opposing membranes to be maintained. At present, it is not known how Rac1 is localized to, and selectively activated at, new cell–cell adhesions. Rac1 activation may be mediated directly by local activation of PI3K (phosphoinositide 3-kinase) [43] and accumulation of phosphoinositides that recruit guanine-exchange factors [43,44]; indeed, Rac1 distribution at the edge of expanding MDCK cell–cell contacts is similar to that of PH (pleckstrin homology)-Akt-GFP, a readout for phosphoinositides [38] (Figure 3). However, PI3K activity is not required for either Rac1 or E-cadherin accumulation at cell–cell contacts [38,45] suggesting that Rac1 recruitment and activation might also involve interactions with protein complexes associated with cell–cell adhesion [46].

If the cadherin–catenin complex is not bound directly to the actin cytoskeleton as indicated by *in vitro* studies with purified proteins (see above), how might the actin-binding/bundling protein α-catenin regulate these local changes in actin organization during initial cell–cell adhesion? It has been suggested that changes in actin organization are due to the formation and local concentration of α-catenin dimers [15,33] (Figure 2). Clustering of the cadherin–catenin complex upon cell–cell adhesion, perhaps by diffusion-mediated trapping [47], would result in an increase in the local concentration of α-catenin sufficient for dimerization of α-catenin, from monomer dissociating from the cadherin–catenin complex [33] and in the cytoplasm. α-Catenin homodimers could then locally inhibit Arp2/3-mediated actin polymerization [33], which would result in local changes in the branched organization of the actin cytoskeleton, and decreases in actin polymerization [39] and membrane (lamellipodia) dynamics [38] (Figure 2). Although analyses of MDCK cell–cell adhesion are consistent with these ideas of α-catenin functions, further studies are needed to test whether α-catenin dimers indeed form at cell–cell contacts, and whether α-catenin dimers are involved directly in the decrease in actin polymerization and membrane activity observed in live cells.

Observations of simple epithelial MDCK cell–cell adhesion showed that the latter stages of contact formation appeared to require an active process involving actomyosin contraction. Previous studies have reported that activated (phospho-) myosin II localized to cell–cell contacts and that disruption of regulatory pathways controlling myosin II activation affected the maintenance and reformation of disrupted cell–cell contacts in confluent cell monolayers [48-50]. However, more recent studies analysed the spatiotemporal regulation of RhoA activity using FRET and actomyosin contractility during *de novo* cell–cell adhesion between pairs of cells [39]. These studies revealed that active RhoA and phosphomyosin II were excluded from the centre of the contact and restricted to the cortical actin bundle in a zone at the outside edges of cell–cell contacts, where G-actin was also incorporated (see above and Figure 3). To define the directionality of actomyosin contractility, low concentrations of latrunculin D were used to cap the barbed ends of actin filaments and then the distribution of

actin filaments was observed; these studies revealed that actomyosin contractile forces were directed outwards and backwards from the cell–cell contact [39]. This direction of actomyosin contraction would have the effect of pulling the edges of the contacting membranes outwards to fully expand the contact to the width of the cells; in the opposite direction to that assumed to occur during resealing of cell–cell contacts in cell monolayers [48,49,51], indicating that different contractile mechanisms are involved during formation of *de novo* cell–cell adhesion and reformation of cell–cell contacts between cells in established monolayers. At present, it is not clear how the barbed ends of the cortical actin bundle are anchored at the edges of the contact during *de novo* cell–cell adhesion, although high-resolution TIRF (total internal reflection fluorescence) microscopy indicates that they are closely localized with cadherin–catenin complexes and integrin-based focal adhesions [39]. Since the cadherin–catenin complex does not bind actin directly [33,34] it is possible that, at these sites, actin may be anchored by integrin-based focal adhesions [52], but further studies on actin linkages to integrins and cross-talk with the cadherin–catenin complex are required to resolve the mechanism(s) involved.

At present it is unclear how RhoA activity is localized to the outer edges of the expanding cell–cell contact. RhoA activation and actomyosin contraction could be induced by local clustering of integrin-mediated adhesions at the edge of the cell–cell contact [52]. Alternatively, or in combination, RhoA activity could be suppressed in the centre of the expanding contact by p120-catenin localized with cadherin along the contact [53]; however, further studies will be needed to test these possibilities directly.

Future perspectives

Previous studies of the structural and functional organization of the cadherin–catenin complex have revealed that the cadherin–catenin complex is not simply linked directly to the actin cytoskeleton, but may, through newly uncovered roles for α-catenin, locally regulate actin cytoskeleton organization and polymerization by the Arp2/3 complex [33,34]. Live-cell analysis of MDCK cell–cell adhesion has begun to test these new properties of the cadherin–catenin complex. These studies indicate that the actin cytoskeleton does not directly associate with, or polymerize around the cadherin–catenin complex, but instead undergoes dramatic reorganization as the contact expands [34,54]. In MDCK cells, the reorganization of the actin cytoskeleton coincides with decreases in actin polymerization and membrane dynamics at stabilized cell–cell contacts, which are consistent with decreased Arp2/3 complex activity in regions of high concentrations of the cadherin–catenin complex [39]; further studies are required, however, to test whether α-catenin dimers are involved directly in regulating Arp2/3 and membrane activity. Localized and transient up-regulation of membrane dynamics by Rac1, and actomyosin contraction by RhoA, appears to initialize further cell–cell contacts and maximally expand the contact respectively. Despite these new insights, much remains unknown, including: definitive evidence of α-catenin dimerization from clustered cadherin–catenin complexes; roles for α-catenin homodimers in locally regulating actin and membrane dynamics; and mechanisms locally up-regulating and then suppressing Rho family GTPases. In addition, it is unclear how changes in cadherin–catenin phosphorylation or endocytosis are regulated under normal conditions of cell–cell adhesion, or how these processes might affect protein dynamics and functions of the cadherin–catenin complex. Further studies of protein dynamics in live cells, and manipulation of different pools of α-catenin may provide further molecular insights into functions of the cadherin–catenin complex in regulating cell–cell adhesion.

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Abbreviations used

Arp2/3	actin-related protein 2/3
EGFR	epidermal growth factor receptor
FRET	fluorescence resonance energy transfer
GFP	green fluorescent protein
GSK3β	glycogen synthase kinase 3β
MDCK	Madin-Darby canine kidney
PI3K	phosphoinositide 3-kinase
PTP1B	protein tyrosine phosphatase 1B.

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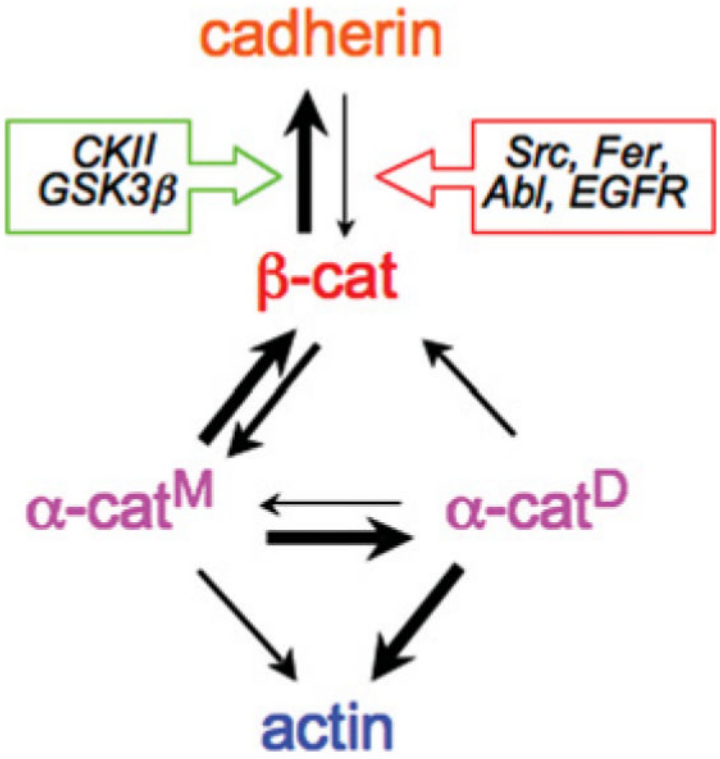

Figure 1. Protein-protein interactions between cadherins, catenins and the actin cytoskeleton

Protein interactions formed between cadherin, β-catenin (β-cat), α-catenin monomers (α-cat^{M}), α-catenin dimers (α-cat^{D}) and actin. Differences in the thickness of the arrows represent strengths of protein-protein interactions (i.e. increased thickness shows increased binding). The interaction between cadherin and β-catenin is regulated by kinases that increase (green box: CK2 and GSK3β) or decrease (red box: Src, Fer, Abl and EGFR) the binding affinity.

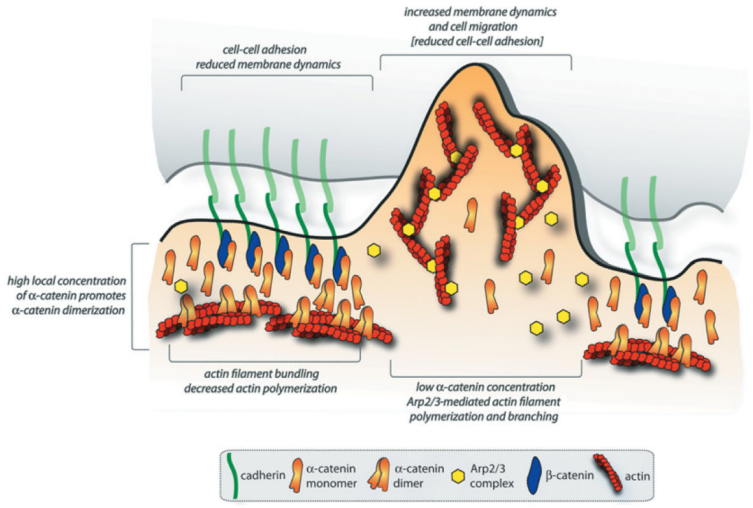

Figure 2. A model for regulation of cytoskeleton and membrane dynamics by the cadherin–catenin complex

See the text for details.

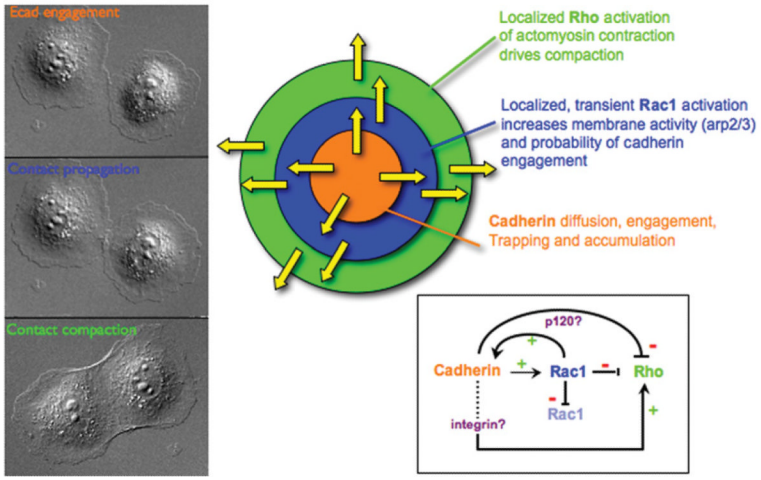

Figure 3. A model for propagation of cell–cell adhesion in which two zones of Rho family GTPase activity are restricted to the edges of the cell–cell contact as it expands laterally

Left: cell–cell adhesion between pairs of MDCK cells involves initial E-cadherin engagement, followed by propagation and finally compaction of the contact. Upper-right: the initial zone comprises a zone of cadherin engagement (orange); a zone of active Rac1 and its downstream effectors, the Arp2/3 complex and lamellipodia, localized to *de novo* contacts between cells at the edges of the zone of cadherin engagement (blue); and the zone of RhoA and its downstream effector actomyosin contractility, restricted to the edges of the contact and is required to drive expansion and completion of cell–cell adhesion (green). The activity zone of Rac1 is transient and rapidly diminishes as cadherin accumulates, but a new round of activation occurs at the periphery of the contacting membranes that would push the membranes together to initiate new E-cadherin adhesion. These sequential signalling zones comprising E-cadherin accumulation, Rac1-induced lamellipodia and RhoA-induced actomyosin contraction co-ordinate the induction, propagation and expansion of the cell–cell contact. Lower-right: a model representing regulatory interactions between cadherin, p120-catenin, Rho GTPases and integrins (-, negative regulation; +, positive regulation) (see the text for details).