Integrins and cadherins join forces to form adhesive networks

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Summary
Cell–cell and cell–extracellular-matrix (cell–ECM) adhesions have much in common, including shared cytoskeletal linkages, signaling molecules and adaptor proteins that serve to regulate multiple cellular functions. The term ‘adhesive crosstalk’ is widely used to indicate the presumed functional communication between distinct adhesive specializations in the cell. However, this distinction is largely a simplification on the basis of the non-overlapping subcellular distribution of molecules that are involved in adhesion and adhesion-dependent signaling at points of cell–cell and cell–substrate contact. The purpose of this Commentary is to highlight data that demonstrate the coordination and interdependence of cadherin and integrin adhesions. We describe the convergence of adhesive inputs on cell signaling pathways and cytoskeletal assemblies involved in regulating cell polarity, migration, proliferation and survival, differentiation and morphogenesis. Cell–cell and cell–ECM adhesions represent highly integrated networks of protein interactions that are crucial for tissue homeostasis and the responses of individual cells to their adhesive environments. We argue that the machinery of adhesion in multicellular tissues comprises an interdependent network of cell–cell and cell–ECM interactions and signaling responses, and not merely crosstalk between spatially and functionally distinct adhesive specializations within cells.

Key words: Adhesion, Cadherin, Crosstalk, Integrin, Mechanotransduction

Introduction
Knowledge of cell adhesion proteins and the molecules that associate with them has grown rapidly in recent years. Cadherins and integrins are involved in both bidirectional cell signaling events, and the physical linkages of cells to each other and to the extracellular matrix (ECM). Physical adhesive linkages are crucial for the maintenance of tissue architecture and can also serve instructive roles by enabling cells to sense and respond to changes in their environments. In some cases, this occurs through translation of mechanical inputs into intracellular signals, a process known as mechanotransduction. A simple survey of adhesion-dependent cell signaling pathways reveals that many of the molecular components and functional outputs are common to several different types of adhesion. This leads to questions of how and where these signaling pathways intersect, and what functional consequences result from these interactions? Although other adhesion molecules are likely to be involved and can be viewed as additional nodes in an overall cellular adhesive network, this review focuses on integrin-based cell–ECM interactions and cadherin-dependent cell–cell contacts because a more coherent picture of interactions between these functionally important adhesions is now emerging.

Adhesive crosstalk – re-evaluation of concepts and the case for adhesive networks
The term crosstalk is typically used to represent an interaction(s) between two or more independently initiated signaling pathways, the outcomes of which include the amplification or attenuation of individual pathways, or the initiation of new signals. In the context of signals transduced through integrins and cadherins these pathways intersect in ways that resemble more closely an integrated network rather than distinct cascades (see Box 1). Integrins and cadherins are both transmembrane adhesion receptors, have many signaling effector molecules in common, link to common scaffolding and cytoskeletal elements, and share the ability to influence crucial downstream functions, such as cell growth, survival and transcriptional activity. Owing to these common features and molecular associations, cell signaling pathways that depend on cadherins and integrins are likely to interact on multiple levels, and these interactions occur over varying time and length scales. We can distinguish such networks on the basis of both short- and long-range physical associations and cell signaling events. By these criteria we define three general modes of adhesive interactions (Fig. 1).

In the most-indirect or -remote mode of adhesive interactions, signals that originate from one type of adhesion lead to a change in the functional activity of other adhesive contacts elsewhere in the cell (Fig. 1A). We term this ‘long-range input–output’ signaling. For example, cell adhesion to specific ECM proteins or to neighboring cells might lead to changes in gene expression, which could include alterations in levels of adhesion molecules or other proteins involved in regulating adhesion (Onodera et al., 2010). Alternatively, engagement or disengagement of one type of adhesion might modify the functional activities of another by effecting changes in membrane trafficking, cytoskeletal association and/or avidity or binding affinity (Avizienyte et al., 2002).

Another type of interaction between adhesions involves the convergence of independently initiated cell signaling events, often involving downstream effectors that are common to both integrin and cadherin adhesions (Fig. 1B). These shared effectors include non-receptor tyrosine kinases, adaptor and scaffolding proteins, and small GTPases. In addition, cell–cell and cell–matrix adhesions are also linked to the common structural elements that comprise the cytoskeleton. Actin, microtubules and intermediate filaments form distinct, but often spatially overlapping, macromolecular...
Box 1. Adhesive networks

The term ‘adhesive crosstalk’ is used widely to highlight presumed functional interactions between two distinct types of adhesion (e.g. integrin and cadherin adhesions; see Figure A, blue and green dots, respectively). Although often spatially distinct, integrin and cadherin adhesions activate many of the same signaling pathways and elicit similar cellular functions, supporting the notion that they should instead be considered as interdependent functional nodes in a larger adhesive network (see Figure B). In some cellular contexts, cadherins and integrins are best perceived as functionally equivalent (teal nodes) with respect to output and network response. Modulation of one node influences adhesive function and signaling activities of adhesive nodes throughout the network, symbolized by the simple graphic representation.

![Figure A: Simple crosstalk](image1.png)

![Figure B: Integrated network](image2.png)

-assemblies. These cytoskeletal networks provide physical scaffolds that connect adhesion complexes not only proximally but also at a distance across cells and cell junctions.

The lateral coupling of adhesion receptors can be viewed as a third form of interaction, which involves more short-range associations within the plane of the membrane (Fig. 1C). In this instance, however, the proximal interactions of integrin and cadherin do not necessarily involve shared cytoskeletal linkages, or even cell–cell or cell–ECM engagement. Adaptor proteins, such as tetraspanins or growth factor receptors – e.g. the insulin-like growth factor 1 receptor (IGF1R) – can facilitate lateral associations of integrins and cadherins (Chattopadhyay et al., 2003; Canonici et al., 2008). One result of this type of interaction is that integrins promote stability of cell–cell adhesions (Chattopadhyay et al., 2003). Although lateral integrin–cadherin associations are known to occur, their physiological significance remains unclear.

Each of these three modes of adhesive interaction can also converge on a common pathway(s), resulting in a complex feedback loop that, in turn, modulates the functions of one or more of the initiating signals (Fig. 1D). For example, RhoGTPases act as both points of convergent signaling downstream of adhesions as well as upstream modifiers of functions of individual adhesion molecules. In the following sections we consider examples of adhesive networking in the context of the three types of general mechanism that are illustrated in Fig. 1A–C and Table 1.

Mechanisms for integrating adhesive signals RhoGTPases

RhoGTPases are central to cell signaling pathways both upstream and downstream of cadherin and integrin adhesions (Huveneers and Danen, 2009; Watanabe et al., 2009), making them prime candidates for mediating integration of adhesion-dependent signals. They are known to modulate a wide range of cellular behaviors including cytoskeletal organization, cell polarity, cell proliferation, and the formation and maturation of adhesive junctions (Etienne-Manneville and Hall, 2002). RhoGTPases have a primary role in regulating the assembly of integrin-based focal adhesions (Hall, 1998). Similarly, the assembly of cadherin-based adherens junctions requires the activity of Rho, Rac and Cdc42 (Van Aelst and Symons, 2002). Rho GTPases must be tightly regulated in the cell given that a certain degree of Rho activity is required for cell–cell adhesion but increased levels of Rho activity disrupt cadherin adhesions (Zhong et al., 1997).

Adhesion through classical cadherins results in increased Rac1 activity upon engagement but inhibits RhoA activity over the course of a few hours (Noren et al., 2001). The effects of cadherin adhesion on RhoGTPases are known to require the cytoplasmic domain of cadherin, but the mechanism of signal transduction remains to be established (Noren et al., 2001; Watanabe et al., 2009). A number of proteins bind the cytoplasmic tails of cadherins and some of these have been shown to regulate RhoGTPase activity. p120 catenin binds to the juxtamembrane region of the cadherin tail and, when overexpressed, can decrease Rho activity while increasing Rac and Cdc42 activity (Braga and Yap, 2005). Another study suggested that p120 catenin interacts with p190 Rho GTPase activating protein (RhoGAP), locally inhibiting Rho in response to
Table 1. Examples of interactions between cadherins and integrins

| Cadherin  | Integrin  | Effector intermediate | Type of signaling interaction | Cell or tissue type | Cellular or physiological condition | Citation |
|-----------|-----------|-----------------------|-------------------------------|---------------------|------------------------------------|----------|
| E-cadherin | β1-integrin | Rac1, cyclin D1 | Convergent | MCF10A mammary epithelial cells | Proliferation | (Fournier et al., 2008) |
| N-cadherin | β1-integrin | PTP1B | Convergent | PC12, chick neural retina explants | Neurite outgrowth | (Pathre et al., 2001) |
| DE-cadherin | β-integrin | Rac, JNK | Convergent, input–output | Drosophila border cells | Collective cell migration | (Llense and Martin-Blanco, 2008; Wang et al., 2010) |
| N-cadherin | β1-integrin | Fer | Convergent, input–output | Chick neural retina explants | Neurite outgrowth | (Arregui et al., 2000) |
| E-cadherin | αβ1-integrin | Btbd7 | Input–output | Salivary gland | Branching morphogenesis | (Sakai et al., 2003; Onodera et al., 2010) |
| E-cadherin | αv or α5β1-integrin | Src, ROCK or MLCK | Input–output | L fibroblasts, S180 mouse sarcoma, SCC13 squamous cell carcinoma | Cell–cell adhesion | (Martinez-Rico et al., 2010) |
| E-cadherin | β1-integrin | FAK | Input–output | Human colon carcinoma | Epithelial–mesenchymal transition | (Wang et al., 2004) |
| E-cadherin | Collagen receptor | Matrix metalloproteinase | Input–output | Ovarian carcinoma cells | Epithelial–mesenchymal transition | (Symowicz et al., 2007) |
| E-cadherin | Fibronectin receptor | Rapi | Input–output | Fisher rat thyroid (FRT) cells | Cell–matrix adhesion | (Balazc et al., 2005) |
| E-cadherin | Laminin receptor | Rac1b, PI3 kinase | Input–output | HT-29 human colon adenocarcinoma | Cell–cell adhesion | (Charrier et al., 2006) |
| N-cadherin | β1- and β3-integrin | Ca²⁺ | Input–output | Neural crest cells | Cell migration | (Monier-Gavelle and Duband, 1997; Theveneau et al., 2010) |
| N-cadherin | Fibronectin receptor | Rac1 | Input–output | Human mesenchymal stem cells | Myogenesis | (Gao et al., 2010) |
| VE-cadherin | αβ3-integrin | VEGFR2, She | Input–output | Bovine aortic endothelial cells | Inflammation | (Tzima et al., 2005; Liu et al., 2008) |
| E-cadherin | αβ3-integrin | CD151 | Lateral coupling | Immortalized mouse kidney epithelia | | (Chattopadhyay et al., 2003) |
| E-cadherin | αv-integrin | IGF-1R, α-catelin | Lateral coupling | Human colon adenocarcinoma | Cell migration | (Canonic et al., 2008) |

Rac activation (Wildenberg et al., 2006). p190 RhoGAP is activated by integrin adhesion and is thought to be a convergence point for signaling by integrins and syndecans (Bass et al., 2008). In epithelia and endothelia, in which both cell–cell and cell–matrix adhesions are required, p190 RhoGAP is likely to be a point of convergent signaling between integrins and cadherins.

Rho is transiently activated by the formation of new integrin adhesions (Ren et al., 1999; Bhardiraju et al., 2007), and this activation can have consequences for the adhesive functions of cadherins. There are several examples of RhoGTPases that act as signaling intermediaries between integrins and cadherins. The activities of Rho and Rac downstream of integrin signaling are thought to regulate the formation of adherens junctions in epithelial cells (Playford et al., 2008). Integrin signaling in colon cancer cells promotes cell–cell junction formation through activation of phosphatidylinositol 3-kinase (PI 3-kinase) and Rac1B (Chartier et al., 2006). In addition to these input–output pathways, RhoGTPases are also implicated in convergent signaling. For example, both integrin and cadherin adhesions have been shown to enhance cell proliferation by promoting the expression of cyclin D1 in a redundant manner through Rac (Fig. 2) (Fournier et al., 2008).

Rho activation is a node in the convergent signaling network initiated by cadherins and integrins that can exert varied effects on adhesions depending on the downstream effectors involved (Fig. 2). Rho signaling through diaphamous Dia reorganizes the actin cytoskeleton to stabilize adherens junctions, whereas Rho-kinase (ROCK) is thought to disrupt cell–cell junctions by activating actomyosin contractility to excess (Sahai and Marshall, 2002). RhoA-mediated activation of the effector ROCK is regulated by cell–matrix adhesion, cell shape and cytoskeletal tension. In fact, tension generated by cell spreading is required for activation of ROCK by RhoA (Bhardiraju et al., 2007). This suggests the existence of a positive feedback loop, in which tension generated by cell–matrix adhesion stimulates activation of ROCK, which in turn enhances the formation and maturation of integrin-based adhesions. Regulation of cytoskeletal tension is also crucial for the accumulation of E-cadherin at cell–cell contacts. ROCK regulates the activity of the motor protein nonmuscle myosin II downstream of initial E-cadherin ligation in order to stabilize newly formed cell–cell junctions (Shewan et al., 2005). Cdc42 limits Rho signaling to achieve the crucial tension levels that are required to maintain cell–cell junctions, preventing excess tension that would probably lead to the dissociation of these adhesions (Warner and Longmore, 2009).

Owing to the complex spatiotemporal regulation of RhoGTPases, it is difficult to separate their roles in the initial establishment of adhesions from those in the signaling events downstream of cadherin and integrin engagement. Furthermore, because these proteins are involved in so many pathways, localization and timing become extremely important in dictating cellular responses to a given stimulus. Rac1 is localized to sites of cell–cell contact where it might have a role in mediating rapid changes in actin organization concurrent with the formation of new cell–cell junctions (Ehrlich et al., 2002). More recent work has shown that localization of both Rac and Rho to cell–cell contacts is essential for the formation and expansion of cadherin adhesions. The spatiotemporal localization...
Fig. 2. Molecular mechanisms for integration of adhesive signals. Activation of Rac by both cadherins (dark blue) and integrins (light green) upregulates proliferation in an additive manner through an increase in the expression of cyclin D1 (orange arrows). Cyclic strain induces cadherin-dependent activation of Rac and cyclin D1, but it has not yet been established how sensitive integrin-mediated promotion of proliferation is to cyclic strain. Cadherins and integrins antagonistically influence the activity of Rho GTPase and thus of Rho (purple arrows). Active Rho has dramatically different effects on cell adhesion depending on the downstream effector it binds. Rho signaling through Dia produces reorganization of actin in a manner that strengthens cell–cell adhesion, whereas signaling through ROCK enhances actin contractility, which in turn promotes cell–cell and cell–matrix adhesion. However, a high level of Rho- and ROCK-mediated actin contractility is antagonistic to cell–cell junctions. Fer kinase is activated by cadherin and integrin adhesions, and activated Fer phosphorylates (P) the actin-organizing protein cortactin (blue arrows). Reorganization of the actin cytoskeleton by cortactin can enhance either cell–cell adhesion or migration. Shear stress across endothelial cells leads to inflammation (green arrows). Shear stress induces the assembly of a VEGFR–VE-cadherin–Shc complex (VEGFR in purple) and the phosphorylation of Shc, which then leads to activation of ERK1/2 and, subsequently, to inflammation. Phosphorylated Shc associates with integrins in a cadherin dependent manner and activates the NF-κB pathway, also resulting in inflammation. Solid lines represent direct interactions or effects, dashed lines indicate an indirect or unknown mechanism. The extracellular matrix is shown beneath the cells in blue and the actin cytoskeleton is represented by the pink lines.

of both the GTPases and their effectors suggests specific roles in adhesion formation, with Rac facilitating actin remodeling and Rho stimulating actomyosin contractility (Yamada and Nelson, 2007). The downstream effects of RhoGTPase activation can differ dramatically depending on the site of activation. Rac is required for epithelial wound healing and promotes cell migration when activated at cell–matrix contact sites, but promotes cell–cell adhesion and formation of adherens junctions when activated at cell–cell junctions (Van Aelst and Symons, 2002; Liu et al., 2010). Network complexity increases when we consider the functions of other GTPases, such as the Ras family member Rap1, which has been implicated in regulation of integrin activity downstream of cadherins (see Box 2). Clearly, signaling through GTPases is a much-used mechanism for intracellular communication, and is influenced by both cell–cell and cell–ECM adhesions. Only recently were suitable tools developed that enable GTPase activities to be visualized in time and space, thus revealing specific activation events that mediate interactions between adhesions (Yamada and Nelson, 2007; Wang et al., 2010).

Tyrosine kinases
A number of tyrosine kinases are localized to cell–cell and cell–matrix adhesions (Giammone and Sheetz, 2006; McLachlan et al., 2007) where they function as prominent nodes in the adhesive network. Activation of Src family kinases frequently accompanies the formation of both cell–cell and cell–ECM adhesions. Src is recruited and activated upon E-cadherin ligation and this provides a positive feedback loop that signals through PI 3-kinase to promote the stability of cell–cell contacts (McLachlan et al., 2007). However, Src levels at cell–cell adhesions must be tightly regulated, because constitutively active Src disrupts cell–cell contacts and alters cell morphology (Behrens et al., 1993). Integrin ligation also leads to Src activation and this has divergent downstream consequences, often involving RhoGTPases (Huveneers and Danen, 2009). In epithelial cells, constitutively active Src at sites of integrin–matrix adhesion leads to peripheral accumulation of activated myosin, which is disruptive to cell–cell junctions (Avizienyte et al., 2004). However, moderate Src activation and regulation of actomyosin contractility by ROCK or myosin light-chain kinase (MLCK) are necessary for the integrin-mediated strengthening of E-cadherin adhesions (Martinez-Rico et al., 2010). Although cytoskeletal tension is important for the formation of both cell–cell and cell–matrix adhesions, excessive tension might serve to rip junctions apart or induce changes in protein conformation that lead to junctional instability.

The focal adhesion kinase (Fak, also known as PTK2) is another non-receptor tyrosine kinase, which as a primary signaling partner of Src is implicated in many of the same signaling pathways (Playford and Schaller, 2004). Unlike Src, however, Fak contains a focal adhesion targeting (FAT) sequence, consistent with its role as a downstream effector of integrin adhesion and signaling. For example, transforming growth factor-β (TGF-β) inhibits epithelial-to-mesenchymal transition (EMT) in at least some colon cancer cells, and stimulates increased expression of ECM leading to
Box 2. Rap1 is poised between cadherins and integrins

Rac, Rho and Cdc42 are not the only GTPases functioning in the signaling networks that connect integrins and cadherins. Rap1, a member of the RasGTPase family has also been implicated in the transmission of signals between cell–cell and cell–matrix adhesions (Retta et al., 2006). It is known to activate integrins in various cell types, demonstrating a role for Rap1 in inside-out integrin signaling (Retta et al., 2006). Rap1 was also shown to be important for the formation and maintenance of cadherin adhesions (Watanabe et al., 2009). These findings place Rap1 upstream of both adhesion types, but more recent work has demonstrated the regulation of Rap1 activity by E-cadherin adhesion (Balzac et al., 2005). Disruption of E-cadherin adhesions results in a dramatic increase in Rap1 activity, which can then be downregulated by re-forming cell–cell junctions. Although this finding suggests that Rap1 functions both upstream and downstream of cadherins, the same is not true for integrins. Rap1 activity is not dependent on the substrate onto which the cells are plated, indicating that Rap1 is not regulated by integrin adhesions. Dissolution of cell–cell junctions does result in an increase in focal adhesions, and this is abrogated by inhibition of Rap1 activity. This places Rap1 neatly between cadherin and integrin adhesions. It is not yet clear how Rap1 activity is affected by endogenous disruption of cadherin adhesion, such as through increased actomyosin-mediated tension. Additional data suggest that internalization and endocytic trafficking of cadherins is required for Rap1 activation, although the precise mechanism of Rap1 regulation by cadherins is unknown.

integrin engagement and activation of Fak (Wang et al., 2004). Fak then promotes E-cadherin expression and cell cohesion (Wang et al., 2004), but the mechanism by which this occurs remains unclear. Nonetheless, this is consistent with Fak knockdown studies, which report stimulation of EMT and inhibition of cadherin adhesion (Yano et al., 2004). Because Fak is normally associated with integrin adhesions there is much speculation about its role in cell–cell junctions. Regulation of RasGTPases is one possible mechanism of action because Fak can inhibit the activity of Rho, and constitutively active Rho mutants can phenocopy Fak loss-of-function (Playford et al., 2008). Interestingly, Fak has also been shown to localize to cell–cell contacts, although the significance – if any – of its localization at cell–cell adhesions is unclear (Crawford et al., 2003; Playford et al., 2008).

The non-receptor tyrosine kinase Fer is also reported to be involved in communication between cell–cell and cell–ECM adhesive contacts (Arregui et al., 2000). Fer can be activated upon engagement of either cadherins or integrins (El Sayegh et al., 2005; Sangrar et al., 2007). The association of Fer with the actin-organizing protein cortactin might help coordinate cellular responses to various adhesive inputs. Cortactin is required for cell spreading on fibronectin, and the activation of cortactin by Fer promotes cell motility (Illes et al., 2006; Sangrar et al., 2007). Phosphorylation of cortactin by Src and/or Fer downstream of E-cadherin ligation enhances cell–cell adhesion (El Sayegh et al., 2005; Ren et al., 2009). This suggests that Fer signaling feeds back to cell–cell and cell–matrix adhesions by promoting cortactin-dependent reorganization of actin (Fig. 2).

Several growth factor receptor tyrosine kinases are reported to regulate cadherin and integrin adhesive functions. For instance, vascular endothelial growth factor (VEGF) signalling through the VEGF receptor 2 (VEGFR2, also known as KDR) both increases integrin-dependent migration and decreases stability of vascular endothelial (VE)–cadherin adhesions (Carmeliet et al., 1999; Byzova et al., 2000). Receptor tyrosine kinases can also enable lateral molecular associations between different types of adhesion. IGF1R forms a ternary complex with E-cadherin and αv-integrins at cell–cell contacts. Binding of the ligand IGF1 causes the relocalization of αv-integrin to focal contacts and an increase in cell migration (Canonici et al., 2008). Thus, IGF1R might sequester integrins at cell–cell contacts and inhibit migration in the absence of growth factor signaling.

Phosphatases

Given the central importance of kinases to many adhesion-dependent cell signaling pathways, it is crucial to also consider the role of phosphatases in the regulation of adhesive networks. There are a number of protein tyrosine phosphatases (PTPs) that associate with cell–cell and cell–ECM adhesions – such as PTP1B, which localizes to the cytoplasmic tail of cadherins and also to focal adhesions (Stoker, 2005; Burridge et al., 2006; Sallee et al., 2006). The catalytic activity of PTP1B is required for dephosphorylation of β-catenin and association of N-cadherin with the actin cytoskeleton, both of which are crucial for the stability of cell–cell junctions (Sallee et al., 2006). PTP1B is also involved in signaling from integrin adhesions, probably through dephosphorylation of the inhibitory tyrosine residue of Src, which leads to activation of Fak (Arregui et al., 1998). Outgrowth of neurites depends on both cell–cell and cell–matrix interactions, and PTP1B has been shown to be required for this process, probably also through regulation of Src activity (Pathre et al., 2001). PTPμ is another member of the PTP family that is necessary for maintaining the integrity of cell–cell adhesions. In addition to its role in stabilizing cell–cell junctions through dephosphorylation of functional components, PTPμ might also recruit regulatory proteins to sites of cell–cell adhesion (Sallee et al., 2006). Expression of PTPμ in kidney epithelial cells is dependent on a complex between αβ1-integrin and tetraspanin that associates with E-cadherin on the lateral membranes of cells. An interesting feature of this lateral complex coupling is that a specific subset of unligated integrins appears to associate with and promote stability of cell–cell adhesions, and that these are distinct from the subset of integrins involved in matrix adhesion (Chattopadhayay et al., 2003).

Scaffold and adaptor proteins

The consequences of cadherin and integrin engagement can vary greatly depending upon the specific intracellular environment at the site of signal initiation. Scaffold and adaptor proteins are crucial elements of adhesion-dependent signaling cascades. They facilitate the localization of key downstream effectors, thereby increasing the probability of interactions between activated signaling components. Receptor for activated C kinase-1 (RACK1, also known as GNB2L1) is a scaffolding protein that binds the cytoplasmic tails of integrins and interacts with intracellular signaling components such as protein kinase C (PKC) (Besson et al., 2002). RACK1 is a crucial component of the E-cadherin and αβ1-integrin–tetraspanin lateral signaling complex described above (Chattopadhayay et al., 2003). Binding to PTPμ might recruit RACK1 to cell–cell adhesions, serving to localize activated PKC or other effectors (Mourton et al., 2001). PKC has numerous roles in promoting cell–cell and cell–matrix adhesions (Larsson, 2006). Localization of active PKC by RACK1 might be key to specifying the types of adhesion that are affected by PKC signaling.
In general, adaptor proteins link signaling components but lack intrinsic enzymatic or kinase activities. Motifs such as the phosphotyrosine-binding Src homology 2 (SH2) domain allow adaptors to bring signaling proteins together and propagate signaling cascades initiated by a diverse array of stimuli. The SH2 domain-containing (Shc) adaptor protein forms a complex with growth factor receptor-bound protein 2 (GRB2) and the Son of Sevenless (SOS) family of guanine nucleotide exchange factors to activate Ras and, subsequently, mitogen-activated protein (MAP) kinases, the pathway of which is activated through many inputs including integrin signaling and mechanical force (Ravichandran, 2001). Shc has recently been shown to associate with both cell–cell and cell–matrix adhesions in response to fluid flow across vascular endothelial cells (Liu et al., 2008). Phosphorylated Shc is recruited to cell–cell junctions at the onset of fluid flow, particularly in areas of tissue where fluid-flow shear stresses are high and result in inflammation. Previous work demonstrated the assembly of a VEGFR2–VE-cadherin complex in response to shear stress and it is now apparent that Shc interacts with components of this complex (Shay-Salit et al., 2002; Liu et al., 2008). Shc is also recruited to integrin adhesions in response to fluid flow, a process that requires the presence of Shc-cadherin. Phosphorylation of the MAPK family members ERK1/2 and activation of NF-κB are increased by fluid flow in a Shc-dependent manner. Interestingly the activation of NF-κB, but not the activation of ERK1/2, is dependent on ECM composition (Liu et al., 2008). These data suggest that Shc is a central mediator of fluid flow-induced signaling events that include cadherin-dependent activation of signaling at cell–matrix junctions (Fig. 2).

There are several other classes of protein that can act as adaptors even though they are not traditionally thought of as such. One example is the catenin family of proteins, of which some are involved in both cell–cell adhesion and cell signaling. Catenins are crucial for connecting cadherins to the cytoskeleton, although not necessarily through a direct physical link (Nelson, 2008). Catenins are required for the initiation of many signaling pathways downstream of cadherin adhesion, including those that regulate RhoGTPase activities, actomyosin organization and contractility, and stability of cell–cell junctions (Perez-Moreno and Fuchs, 2006).

Plakoglobin (Pkg, also known as JUP or γ-catenin), associates with both desmosomes and adherens junctions where it helps maintain tissue integrity through interactions with α-catenin or desmoplakin (Zhurinsky et al., 2000; Acehan et al., 2008). By serving as a link between cadherin and either α-catenin or desmoplakin, Pkg connects cadherins to actin or intermediate filament networks, respectively. Pkg is reported to suppress motility of cell sheets and single keratinocytes on collagen (Yin et al., 2005). Although the mechanism for regulation of cell motility by Pkg is not clear, there is some evidence that Pkg works through long-range mechanisms to promote fibronectin expression and inhibit Src function (Yin et al., 2005; Todorovic et al., 2010). Pkg is a known target of Src kinase activity, thus it is possible that the presence of Pkg at cell–cell junctions sequesters Src away from cell–matrix adhesions where it typically promotes cell migration (Webb et al., 2004; Lee et al., 2010).

Cytoskeleton

One consequence of the signalling events and mechanical linkages that are initiated by both cell–cell and cell–matrix adhesions is the assembly and reorganization of cytoskeletal networks. Thus the regulation of cytoskeletal dynamics might be considered a consequence of convergent signaling. In turn, the cytoskeleton mediates both short-range and long-range physical interactions between adhesions throughout the cell. Linkage to the cytoskeleton provides structural integrity to adhesions and allows for cellular movement, maintenance of cell and tissue shape, and remodeling of the extracellular environment. Moreover, by coupling to molecular motors the cytoskeleton can exert forces that are then applied externally to the ECM and neighbouring cells.

Actin filaments provide integral support to the cell by linking adhesive contacts on the cell surface to the interior. Actin is tethered by macromolecular complexes at points of integrin contact with ECM, and this association can be visualized in vitro on planar substrates as focal adhesions. Cadherin adhesions direct the assembly of actin filaments near the cell cortex where they provide strength to lateral contacts between adjacent cells. We refer the reader to a recent review article (Maruthamuthu et al., 2010), which details and summarizes a plethora of reported connections between cell adhesion molecules and the actin cytoskeleton. The overall emerging picture is that – by acting as a force-bearing scaffold between sites of integrin and cadherin adhesion – the actin cytoskeleton provides a direct physical basis for adhesive network interactions.

Microtubule dynamic instability provides another mechanism for integrating the cytoskeleton with signaling pathways that are initiated by both cell–ECM and cell–cell adhesions. Microtubules are in a state of constant flux through processes of assembly and disassembly. Extension of microtubule plus ends into focal contacts promotes the dissolution of these adhesions (Ezratty et al., 2005). Association of microtubules with focal contacts promotes phosphorylation of kinases, including Fak, within the focal adhesion complex, inducing destabilization of protein–protein associations and resulting in the release of actin filaments from these contacts. Moreover, cadherins are reported to affect microtubule dynamics. In highly migratory and undifferentiated cells, the minus ends of microtubules are typically anchored in centrosomes. In terminally differentiated cells such as polarized epithelia, however, the minus ends of microtubules are instead stabilized by association with cadherin adhesions (Chausovsky et al., 2000; Meng et al., 2008). Likewise, plus ends of microtubules in these cells are stabilized by a linkage to the basal cortex through integrin adhesions (Hotta et al., 2010). Thus, microtubules that are capable of regulating cell–ECM adhesions are also anchored and regulated by cadherins, providing another potential cytoskeleton-based mechanism for adhesive networking.

Mitotic spindle orientation is a major determinant of the axis and symmetry of cell division (Bringmann and Hyman, 2005), which is established by the positioning of distally located microtubule minus-end anchors, the centrosomes (Heald et al., 1997). In epithelial cells, centrosomes are localized to adherens junctions during mitosis allowing symmetrical cell division within the plane of the tissue (Lu et al., 2001; den Elzen et al., 2009). In other cell types – such as, for example, neural stem cells – cadherin and integrin adhesions are hypothesized to compete for microtubule association with centrosomes (Loulier et al., 2009). Because of this competition, mitotic spindle orientation and cell division occur on an oblique axis. The result is an asymmetric cell division that leaves the neural stem cell in its niche while creating a daughter cell that moves into more differentiated regions of the central nervous system (Kosodo et al., 2004). Although the precise mechanisms remain unclear, coordinated positioning of the spindle by the adhesion receptor network appears to have broad insignificance.
to adult stem cell niche maintenance (Marthiens et al., 2010), organ development (Baena-Lopez et al., 2005), and early embryonic morphogenesis (Gong et al., 2004).

Intermediate filaments also associate directly with both integrin and cadherin adhesions. In contrast to actin filaments, intermediate filaments exhibit high tensile strength, extensibility, elasticity and flexibility (Fudge et al., 2003). Nonetheless, intermediate filaments are highly dynamic and capable of depolymerization and polymerization anywhere along an existing filament (Godsel et al., 2008; Colakoglu and Brown, 2009). Although most studies of intermediate filaments have focused on their association with highly stable adhesive junctions, such as desmosomes and hemidesmosomes, they are also found in association with more dynamic adhesions that involve classical cadherins (Kowalczyk et al., 1998; Leonard et al., 2008) and non-hemidesmosomal integrins (Tsuruta and Jones, 2003; Bhattacharya et al., 2009). Intermediate filaments lack filament polarity, and the distinct ‘hubs’ of filament organization and polymerization (Godsel et al., 2008) that are characteristic of the actin and microtubule cytoskeletons. Intermediate filament networks have yet to be implicated directly in functionally connecting different adhesions; however, their role in anchoring and stabilizing adhesive junctions suggests that they are important, particularly in cases where adhesive networks are subject to mechanical forces.

Different types of cytoskeletal networks are further integrated through direct crosslinking by cytoskeletal scaffold proteins such as plectins, which contain binding sites for actin, microtubules and intermediate filaments (Sonnenberg and Liem, 2007). Moreover, motor proteins, such as myosin, kinesin and dynein, can be thought of as mobile crosslinkers that generate forces within and between cytoskeletal networks (Chang and Goldman, 2004). As a consequence of these varied molecular crosslinks, cadherin and integrin adhesions are able to form and maintain physical connections that are not necessarily limited to a single cytoskeletal network.

**Adhesive networks in mechanotransduction and multicellular processes**

As signaling through adhesive networks proceeds, the impact on cellular functions is substantial. Many of the pathways discussed above were elucidated using immortalized tumorigenic cell lines, so the functional implications for normal tissues are not immediately apparent. However, other studies that focused on a variety of tissues, developmental systems and primary cells have provided considerable insight into the physiological roles of adhesive interactions. Nearly all major cellular functions are reported to be influenced by a combination of integrin and cadherin signaling events, including proliferation, migration, differentiation (Box 3) and apoptosis (Fouquet et al., 2004; Kang et al., 2007). Moreover, the coordinated initiation, strengthening and dissolution of cell–cell and cell–matrix adhesions are crucial for morphogenesis and, thus, the directing of both form and function.

**Migration**

In cancer metastasis and EMT, integrin and cadherin adhesions display an antagonistic relationship that determines whether cells maintain associations with their neighbors or uncouple and initiate migration (Avizienyte et al., 2002; Guarino, 2007). For example, in ovarian carcinoma cells, downregulation of E-cadherin through matrix metalloproteinase (MMP)-mediated proteolysis is initiated by integrin ligation to collagen (Symowicz et al., 2007). This decreased cadherin-mediated cohesion allows the cells to disperse and migrate independently.

Although this scenario might best reflect the behavior of metastatic cancer cells and other instances of EMT, it is important to consider that normal, intact tissues also undergo migratory processes. In collective cell migration, substrate traction is finely balanced with cell cohesion to maintain organization of the migratory tissue (Fig. 3A). In fact, cadherin adhesions in normal tissues provide instructive signals that regulate the polarity of cells and, as a result, the direction of migration. As cells come in contact with one another, cadherin adhesions are formed, Cdc42 signaling is activated, and the centrosome reorients anteriorly relative to the cell nucleus (Desai et al., 2009; Dupin et al., 2009), indicating that a broad repolarization has occurred throughout the cell. Protrusive activity is suppressed locally near cadherin adhesions, and increased on opposing sides of the cell at sites of integrin–ECM adhesion (Desai et al., 2009; Borghi et al., 2010). Even highly migratory tissues, such as some cranial neural crest, maintain cell–cell

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**Box 3. Adhesive interactions in differentiation and morphogenesis**

**Cell differentiation**

Differentiation of cells is influenced by cell adhesion receptors, which integrate several different adhesive inputs, including ECM composition, cell density and cell shape (McBeath et al., 2004; Messina et al., 2005; Engler et al., 2006; Rozario and DeSimone, 2010). Actomyosin-generated tension is applied through integrin adhesions and provides an instructive signal for the differentiation of mesenchymal stem cells into myoblasts (Engler et al., 2006; Gao et al., 2010). Integrin-mediated activation of Rac impacts cell–cell adhesions through increasing N-cadherin expression, a process necessary for myogenesis (Gao et al., 2010). In myogenesis, cell–matrix adhesion signaling enhances cell–cell adhesions, but in some other cell types cadherins and integrins antagonize each other to carry out a differentiation program. For example, in terminally differentiating keratinocytes, cadherins are required for tissue stratification, expression of keratinocyte-specific genes and downregulation of integrins – all crucial steps in the keratinocyte differentiation program (Hodivala and Watt, 1994; Watt, 2002). These types of coordinated interaction between cadherins and integrins after cell signaling, and change tissue architecture to promote the differentiated phenotype.

**Branching morphogenesis**

Branching morphogenesis is a crucial developmental process and responsible for the formation and functional organization of lung, kidney and most glandular tissues. During branching morphogenesis, fibronectin engagement by integrins results in localized decrease of cadherin expression at sites of cleft formation (Sakai et al., 2003). This is an example of long-range input–output interactions (Fig. 1A), by which – in this case integrin – signaling increases the expression of Btbd7. How Btbd7 operates is not known, but its presence leads to changes in gene expression that include suppression of E-cadherin and induction of the cell-scattering snail homolog 2 (Snai2) gene (Onodera et al., 2010). Although localized suppression of E-cadherin expression promotes the cleft formation that precedes new branching, E-cadherin is more broadly required throughout the tissue to support columnar morphology, bud outgrowth and luminal structure (Walker et al., 2008). For branching morphogenesis, localized downregulation of cadherins by integrin–matrix engagement is a way of designating distinct areas of tissue to undergo morphogenetic growth.
adhesions while they move, although these adhesions are dynamic and cell contacts transient. N-cadherin adhesions in neural crest cells are required for the subcellular localization of activated RhoGTPases in response to chemoattractants. Without N-cadherin the cells fail to migrate directionally or collectively (Theveneau et al., 2010). Expression of N-cadherin at the cell surface is regulated locally through signaling pathways that are initiated by β1- and β3-integrins (Monier-Gavelle and Duband, 1997). In border cells of Drosophila melanogaster, asymmetric protrusions initiated by localized Rac activation in a single border cell can alter migratory direction of an entire cluster of border cells (Wang et al., 2010). Cohesion of border cells is stabilized by both β-integrin and Rac signaling through the MAPK Jun N-terminal kinase (JNK), and these signaling proteins are required for normal collective cell migration (Llense and Martin-Blanco, 2008; Wang et al., 2010).

Migration of whole tissues is a recurring feature of development and morphogenesis, and wound healing. Collectively migrating tissues use a mechanism of distributed traction, whereby both leading edge cells and those that follow polarize and migrate in a directional manner (Davidson et al., 2002; Farooqui and Fenteany, 2005). Substrate traction forces and intercellular tissue tension are developed as an intact tissue translocates. Trepap and co-workers reported that, although leading cells generate the highest substrate traction, intercellular tension increases progressively as a function of distance from the leading edge (Trepap et al., 2009). Moreover, tension on cadherin adhesions recruits scaffolding proteins, such as vinculin and α-catenin, which mediate cytoskeletal reinforcement of the adhesions and the resultant strain-stiffening response (Chu et al., 2004; le Duc et al., 2010; Yonemura et al., 2010). However, an important question remains when tying these observations together: does tension on cadherin adhesions have ramifications for protrusive activity and polarity of the cell? We speculate that, because cadherins are responsive to mechanical force, changes in the physical linkage of cadherins to cytoskeletal networks and the association with scaffolding proteins have an important role in the polarization of migratory cells and tissues.

**Early embryonic morphogenesis**

Several examples of adhesive networks can be illustrated by using early-embryonic models of tissue morphogenesis. During convergent extension, mesodermal cells mediolaterally intercalate to form the notochord and drive axial elongation of the embryo (Fig. 3B). The cells are not able to complete this process in the absence of fibronectin, when α5β1-integrin is inhibited, or when cadherin adhesion is altered (Marsden and DeSimone, 2003; Davidson et al., 2006). Moreover, adhesion and signaling of α5β1-integrin can modulate cadherin adhesion, which is required for cell intercalation and cell-sorting behaviors (Marsden and DeSimone, 2003), although the mechanism of signaling between these adhesions remains unclear. Communication between adhesion receptors in this system is also bidirectional. Tension on cadherin adhesions induces integrin-dependent assembly of fibronectin fibrils (Fig. 3C) (Dzamba et al., 2009). Fibronectin fibril assembly is, in turn, required for normal morphogenetic movements in early embryogenesis, such as epiboly and mesendodermal migration (Rozario et al., 2009). Activation of the planar cell polarity pathway (PCP) – a non-canonical Wnt signaling cascade – is required for convergence and extension movements, and also promotes the assembly of the fibronectin matrix by regulating cadherin adhesion and tissue tension (Dzamba et al., 2009). Thus, PCP signaling is...
probably an important signaling pathway that links cadherin and integrin functions in the early embryo.

Endothelial cell biology

Vascular endothelial cells comprise the inner layer of blood vessels and are exposed to three major types of mechanical stress: shear stress, cyclic strain and hydrostatic pressure (Fig. 3D). These cells are in tight cohesion with one another and with the underlying matrix, forming a semipermeable barrier against the pressurized bloodstream. Mechanical stress on this tissue is sensed and transduced, at least in part, by adhesion complexes. Shear stress induces alignment and elongation of cells in the direction of fluid flow, as well as expression of genes that result in an inflammatory response. VE-cadherin, platelet endothelial cell adhesion molecule (PECAM) and VEGFR2 form a complex in response to flow, and this complex signals through Src to activate the integrin response to shear (Fig. 2) (Tzima et al., 2005; Liu et al., 2008). Cyclic strain induces proliferation in endothelial cells through a VE-cadherin—Rac1-mediated pathway (Liu et al., 2007). Integrin signaling has been demonstrated to increase cyclin D1 in endothelial cells to promote proliferation (Schwartz and Assoian, 2001), and cell strain induces proliferation in some cell types through integrin signaling (Wilson et al., 1995). It remains to be determined, however, whether the proliferative effects of cyclic strain are mediated entirely by VE-cadherin or whether strain induction of endothelial proliferation also requires integrin-mediated cyclin D1 expression.

Proliferation can also be stimulated by signaling through αv-integrins in endothelial cells under hydrostatic pressure (Fig. 2) (Schwartz et al., 1999). However, the signal to proliferate is negatively balanced by the presence of VE-cadherin-mediated cell contacts (Ohashi et al., 2007), which are stabilized by physiological hydrostatic pressures (Muller-Marschhausen et al., 2008). The point at which VE-cadherin and αv-integrin signals converge to regulate proliferation induced through hydrostatic pressure is unknown. Furthermore, it is not clear how VE-cadherins negatively regulate proliferation in this context yet promote proliferation that is induced by cyclic strain. Clearly, different types of stress on cadherin adhesions stimulate unique signaling pathways that differentially affect integrin signaling. Endothelial cells in vivo are exposed to multiple stresses simultaneously. The mechanism by which cells integrate these disparate inputs and orchestrate a cellular response is an important question for future research.

Conclusions

In this commentary we have presented an overview of emerging mechanisms through which cadherin- and integrin-dependent adhesion and signaling functions intersect and interact. Although cell–cell and cell–ECM adhesive complexes have variable compositions and mediate interactions at often topologically distinct positions in the cell, they share many structural similarities and signaling functions. Cadherins and integrins each coordinate responses to changes in the adhesive state through altered physical linkages with the cytoskeleton and by participating in bidirectional cell signaling events. Rather than thinking of cell–cell and cell–matrix adhesions in individual cells and tissues as operating largely in isolation, we argue that these complexes are part of a larger adhesive network wherein multiple types of cell adhesion necessarily interact. Much future effort in this area will continue to focus on elucidating the remaining signaling molecules, scaffolding and adapter proteins that comprise adhesive networks.

However, the larger challenge is to understand how cell–cell and cell–ECM adhesion and signaling inputs are integrated to affect the responses of cells within contextually appropriate and dynamic microenvironments, such as those found within embryos, normal tissues and tumors.

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