The Cross-Rho’s of Cell-Cell Adhesion*

In vivo, cells live, proliferate, move, and die in a densely populated neighborhood surrounded by a lush forest of tissue and stromal components. Few, if any, cellular processes are not affected by a cell's adhesive interactions with its neighbors and with the surrounding matrix. Consequently, changes in a cell's adhesive properties accompany the misregulations in other cell functions that cause and/or result from various pathological conditions such as cancer progression. During the transition from a benign to a metastatic state, there is a breakdown of adhesive bonds between neighboring cells. At the same time, the renegade metastatic cells assume the ability to interact with, migrate over, and invade foreign tissues.

Most human tumors are of epithelial origin; however, as carcinomas become invasive, they undergo a switch from their differentiated epithelial state to a fibroblastic mesenchymal state (epithelial-mesenchymal transition, EMT1) (1). This dedifferentiated epithelial state to a fibroblastic mesenchymal state is accompanied by, and perhaps even caused by, a breakdown in the integrity of intercellular junctions. Although junctional integrity can be compromised in a number of ways, misregulation of E-cadherin-mediated adhesion is a key factor in most epithelial cancers (2, 3).

Cell-Cell Adhesion and RhoGTPases

Cadherin-mediated adherens junctions (AJs) are the most thoroughly studied cell-cell adhesion structures. Classical cadherins include E-cadherin, which is expressed in epithelial cells, N-cadherin, which is predominantly expressed in neural tissues and fibroblasts, and VE-cadherin, which is expressed in endothelial cells (4). These cadherins are single span transmembrane proteins that establish Ca2⁺-dependent cell-cell contacts. Homophilic interactions between the extracellular domains of cadherins on neighboring cells are integral to the establishment of AJs. The intracellular regions of cadherins interact with various partners, most notably, the catenins, p120catenin (p120) and β-catenin, which then interacts with α-catenin, linking the cadherin complex to the actin cytoskeleton and strengthening the adhesion.

Several signaling pathways regulate cadherin adhesion, and in turn, the adhesive complexes influence a number of pathways. We limit our discussion to the effects of Rho signaling on cell adhesion and its relevance to EMT. Although we focus on cadherin-mediated adhesion, processes regulating cell-cell adhesion are intimately coupled to those regulating adhesion to the extracellular matrix.

The Rho proteins, Cdc42, Rac1, and RhoA, are best known as master regulators of the actin cytoskeleton and promote the formation of filopodia, lamellipodia, and stress fibers, respectively. However, it has become clear that the functions of these proteins extend far beyond remodeling actin, including regulating motility, polarity, microtubule dynamics, trafficking, and cell adhesion (5).

Work from several laboratories indicates that cadherin ligation activates Cdc42 and Rac1 and inhibits RhoA, although the mechanisms involved are not yet clear (6–8 and references therein). The exchange factor, Tiam1, appears to be one important mediator. In NIH3T3 cells, Tiam1-induced Rac1 activation coupled with RhoA inhibition results in increased cadherin adhesion and an epithelial phenotype. Conversely, in Ras-transformed MDCK cells, Tiam1 is transcriptionally down-regulated, Rac1 activity decreases, RhoA activity increases, cadherin adhesion decreases, and EMT is favored. In VE-cadherin-null endothelial cells, transfection of VE-cadherin cDNA resulted in increased Tiam1 expression, its localization to cell-cell junctions, and a concomitant increase in Rac1 activity and decrease in RhoA activity (9). Interestingly, the molecular events triggered by VE-cadherin expression were accompanied by a morphological transition from a fibroblastoid to an endothelial phenotype, reminiscent of the behavior of MDCK and NIH3T3 cells.

These examples suggest that the balance between Rac1 and RhoA activities is crucial. This balance is subject to antagonistic signaling between Rac1 and RhoA pathways. Rac1 signaling, via the production of reactive oxygen species, inhibits low molecular weight tyrosine phosphatase, the target of which is the RhoA inhibitor p190RhoGAP (10). Consequently, phosphorylation and activation of p190RhoGAP is favored, and RhoA is inhibited. Phosphorylation of p190RhoGAP is mediated by Src family kinases, which are activated following cadherin ligation (11). Thus, during adhesion signaling, RhoA inhibition may be mediated by two complementary steps: phosphorylation of p190RhoGAP and Rac1-mediated inhibition of low molecular weight tyrosine phosphatase. As p190RhoGAP has been shown to localize to protrusive structures, it has been suggested that the inhibition of RhoA may be required to decrease tension and contractility, thereby facilitating AJ formation (11).

Other work in the literature points to the importance of Rho-GTPases in facilitating the establishment of cadherin adhesion. In MDCK cells, Rac1 and lamellipodia localized only transiently to newly forming cell-cell contact sites and were removed as contacts stabilized and became older (12). Because E-cadherin remains present even at older contact sites, the mere presence of E-cadherin was not sufficient for Rac1 localization to AJs. Thus, the authors suggested that lamellipodia formation is the initial driver for cell-cell adhesion and Rac1 functions in the initiation of cell-cell contacts, not in their stabilization (12).

Cdc42-driven filopodia are thought to precede the formation of lamellipodia. In endothelial cells, even non-junctional VE-cadherin was found to activate Cdc42 (13). Because VE-cadherin is non-junctional in wounded cells, filopodia resulting from Cdc42 activation may be involved in the initiation of cell-cell contacts. Indeed, in keratinocytes, filopodia extension appears to be the initial trigger for AJ formation (14). Interestingly, ligation of the tetraspanin CD151 resulted in Cdc42-mediated filopodia formation in different epithelial cell lines, and overexpression of CD151 promoted the formation of E-cadherin puncta (15). The filopodia extension occurred even in E-cadherin-deficient cells, strengthening the view that filopodia formation is the first step in AJ formation.

Whether Cdc42-driven filopodia or Rac1-driven lamellipodia is the initial step in AJ formation might depend on experimental variables. Alternatively, it is possible that cells extend filopodia independent of cadherin ligation. Once a contact is formed, cadherins activate Rac1, which then facilitates recruitment of other complex components and polymerization of actin to strengthen nascent contacts leading to maturation of AJs.

RhoA also participates in AJ formation, most likely via its effector Dia and Rho kinase (ROCK) (16). Dia is known to promote actin polymerization and microtubule organization, whereas ROCK functions to enhance contractile force. Inhibition of RhoA by C3 exoenzyme disrupted AJs in different epithelial cell lines in a Dia-dependent manner. On the other hand, overexpression of activated RhoA also disrupted AJs and caused (non-apoptotic) membrane blebbing, which further destabilized adhesions. These activ-
with calmodulin directly affects its role linking RhoGTPases to Cdc42 with the cytoskeleton. Because calmodulin binding also pre-
termination increases, IQGAP1 preferentially binds calmodulin and dis-
interaction of IQGAP1 with Cdc42 or Rac1 enhances E-cadherin cell
for actin accumulation at E-cadherin contact sites (21). Thus, the
Furthermore, it has recently been shown that Rac1 requires IQGAP1
toskeleton, and the actin cross-linking ability of IQGAP1 is enhanced. Consequently, Cdc42 is brought to the cy-
E-cadherin-mediated adhesion differently, depending on its binding
localization, and effectors all affect the outcome of RhofGPTase signaling. RhofGPTases have many effectors with varied functions.
Here we discuss a few signaling partners that are particularly relevant in pathways regulating cell-cell adhesion.

**Rho Effectors in Adhesion Regulation**

IQGAP1— IQGAP1 localizes to sites of cell-cell contact and affects E-cadherin-mediated adhesion differently, depending on its binding partners. IQGAP1 binds to β-catenin, displacing α-catenin from the cadherin complex (18). Consequently, the AJ components are dissociated from the actin cytoskeleton, and adhesion is compromised. Because active Rac1 and Cdc42 associate with IQGAP1, they prevent its interaction with β-catenin (19) and prevent AJ weakening.

IQGAP1 interacts with numerous proteins and its interaction with calmodulin directly affects its role linking RhoGTPases to cadherin (20). When intracellular Ca2+ is low, IQGAP1 binds to active Cdc42 and actin. Consequently, Cdc42 is brought to the cytoskeleton, and the actin cross-linking ability of IQGAP1 is enhanced.

Recently, it has been shown that Rac1 requires IQGAP1 for its activation in epithelial cells (21). This interaction of IQGAP1 with Cdc42 or Rac1 enhances E-cadherin cell adhesion on two levels: by preventing dissociation of α-catenin and by promoting actin polymerization. When the intracellular Ca2+ concentration increases, IQGAP1 preferentially binds calmodulin and dissociates from both Cdc42 and actin, dissolving the connection of Cdc42 with the cytoskeleton. Because calmodulin binding also prevents IQGAP1 from binding to β-catenin, there is probably a very fine-tuned regulation of the binding preferences of IQGAP1, depending on intracellular Ca2+ concentration and active Cdc42 and Rac1, and consequent effects on intercellular adhesion.

In an *in vitro* model for EMT and cancer cell dispersal, hepatocyte growth factor (HGF) induces cell-cell dissociation and scattering. HGF treatment results in loss of α-catenin from cell-cell contact sites, followed by loss of E-cadherin, prior to cell dispersal (22). Expression of activated Cdc42 or Rac1 in MDCK cells prevents both the HGF-induced disappearance of α-catenin from contact sites and the subsequent cell dissociation and scattering. HGF treatment decreases active Rac1, reducing the IQGAP1-Rac1 association. Freed IQGAP1 then interacts with β-catenin, displacing α-catenin, with subsequent cell-cell dissociation and dispersal (22) (Fig. 1A). In some gastric tumors, a correlation was found between increased membrane localization of IQGAP1, decreased membrane localization of α-catenin and E-cadherin, and dysfunction of E-
cadherin-mediated adhesion (23). Stated in a different way, the IQGAP1-Rac1 association is increased in cancers with dedifferentiated, diffused, invasive tumors rather than those that were differentiated, demonstrating the physiological relevance of this signaling module during EMT of tumor progression.

In migrating MCF-7 cells, IQGAP1 localizes to the leading edge. Overexpression of IQGAP1 in these and other epithelial cells increased their motility in a Cdc42- and Rac1-dependent manner (24). IQGAP1 expression also increased the invasiveness of MCF7 cells. siRNA-mediated reduction in IQGAP1 expression resulted in decreased motility and invasiveness (24). Further more, knockdown of IQGAP1 decreased Cdc42-induced invasiveness of T47D cells (24). Thus, IQGAP1 appears to function both upstream and downstream relative to active Cdc42 and Rac1 and is potentially involved in multiple steps of EMT.

**Merlin**—The product of the Nf2 tumor and metastasis suppressor gene, Merlin, is closely related to the ezrin/radixin/moesin proteins, which provide links between several membrane proteins and the cytoskeleton (25–27). Merlin alternates between folded and unfolded conformations, depending on its phosphorylation state. The conformationally closed form of Merlin is the active growth suppressor and is inactivated by phosphorylation at Ser-518 (28–30). Recently, a number of reports point to reciprocal interactions between Merlin and Rac1 signaling. In its active state, Merlin inhibits Rac1-mediated signaling and prevents activation of the Rac effector, p21-activated kinase (Pak) (28, 31). It is therefore possible that Merlin’s inhibition of Rac1 and Pak is a mechanism for growth suppression (Fig. 2A). However, active Rac1 stimulates Pak, which phosphorylates Merlin at Ser-518 and thus inactivates it (29, 30). Because active Merlin inhibits Rac1 signaling, its phosphorylation by Pak would be expected to potentiate Rac1 signaling. The interaction between Merlin and Pak was shown to be dynamic: the association was enhanced in cells at high density (abundant intercell-cell contact) and in cells detached from substrate (lack of cell-matrix contact) (31). Interestingly, Pak activation by Rac1 has been found to be compromised in non-adherent cells (32). Thus, Merlin may inhibit growth signaling in cells detached from substrate.

The phosphorylation status and activity of Merlin is regulated by cell confluence (33). At low cell density, Merlin is phosphorylated and growth-permissive, whereas at high cell density, Merlin becomes dephosphorylated and activated as a growth inhibitor. These results are consistent with a role for Merlin as a mediator of contact-dependent growth inhibition. In fact, Merlin-deficient cells are impaired and high densities are also defective in establishing stable cadherin AJs although AJ components are expressed and localized to the membrane, but diffusely. Because Merlin localizes to AJ’s in wild type cells, its presence may be required to stabilize cell-cell adhesion. As mentioned previously, Rac1 has been reported to be recruited to nascent AJs and to be removed as AJs mature (12). It has been suggested that Rac1 is transiently recruited to AJs to inhibit Merlin and facilitate AJ weakening (34). In keratinocytes, Merlin inactivation results in diffuse distribution of active Rac1 (35). However, ARNO was found to elevate Rac1 activity (35). It is thus conceivable that GIT/PKL bring Arf6 in proximity to the PIX complex and thereby facilitate Rac1 activation. But, it is interesting that ArfGAPs (GIT and PKL) localize at focal adhesion sites (36). Thus, Arf6 regulates endosomal-plasma membrane trafficking and also affects cell morphology and motility via Rac1 signaling.

In MDCK cells, expression of ARNO, an Arf6GEF, activates Arf6, induces lamellipodia formation, and stimulates migration (36). Interestingly, the effect was only observed in cells at the periphery of a group or at the leading edge of a wound. This indicates that the absence of cell-cell adhesion is required for the ARNO-induced effect. The induction of lamellipodia and motility was found to coincide with ARNO-induced increases in the activities of Rac1 and phospholipase D, both of which were necessary for the increased motility (36). It is not yet clear how Arf6 activates Rac1. But, it is interesting that ArfGAPs (GIT and PKL) localize to focal contact sites via multimolecular complexes including PIX, a Rac1GEF (35). It is thus conceivable that GIT/PKL bring Arf6 in proximity to the PIX complex and thereby facilitate Rac1 activation. But, it is interesting that ArfGAPs (GIT and PKL) localize at focal contact sites via multimolecular complexes including PIX, a Rac1GEF (35). It is thus conceivable that GIT/PKL bring Arf6 in proximity to the PIX complex and thereby facilitate Rac1 activation.
Interacts with active Rac1 and Cdc42 decrease; IQGAP1 sites. Upon HGF stimulation, amounts of p120 are found at cadherin contacts and activate Rac1, promoting actin polymerization at contact sites. Upon HGF stimulation, Arf6 is activated and recruits Nm23-H1, and E-cadherin is endocytosed. Also, Nm23-H1 interacts with Tiam1, preventing Rac1 activation. As a consequence of both steps, AJs are disrupted.

High level p120 overexpression was shown to induce a branched, dendritic morphology (41, 42) whereas lower amounts induce the formation of filopodia and lamellipodia while inhibiting stress fibers and focal adhesions (42, 43). Correspondingly, p120 overexpression inhibited RhoA but stimulated Cdc42 and Rac1 activation (41–43). Furthermore, p120 overexpression also enhanced basal cell motility in several cell types (42, 43) and enhanced HGF-induced scattering of MDCK cells (44).

The mechanisms by which p120 regulates RhoGTPases are not yet clear. Purified p120 interacts with RhoA in vitro and inhibits its exchange of GDP for GTP, suggesting that p120 may act as a guanine nucleotide dissociation inhibitor for RhoA (41). Vav2 (a GEF for Rho family GTPases) has also been shown to interact with p120 and could mediate the activation of Cdc42 and Rac1 (42). Another group provided evidence that the N terminus of p120 is necessary for its ability to induce motility and influence GTPase activity (44). However, in this report, p120 overexpression was found to activate RhoA without affecting the activities of Cdc42 and Rac1.

Overexpressed p120 is mostly cytoplasmic, and its effects on the RhoGTPases and morphology are inhibited upon its binding to cadherins (41–43). These results support a model in which p120 shuttles between cadherin-bound and cytoplasmic pools (45). When p120 interacts with cadherins, it relieves RhoA inhibition and, simultaneously, brings RhoA to the membrane, where it can be activated and both p120 and RhoA can strengthen adhesion by promoting cadherin clustering. When p120 is cytoplasmic, it inhibits RhoA and activates Cdc42 and Rac1, promoting motility. Subconfluent MDCK cells contain a substantial pool of cytoplasmic p120. As cells become confluent, the majority of p120 was found at cell-cell junctions associated with cadherins (43). These findings suggest a simple means by which p120 acts as a regulator of contact-dependent inhibition of cell motility (Fig. 2B). Furthermore, because cadherins may inhibit cell motility by sequestering p120, loss of E-cadherin adhesion during EMT may translate into increased cytoplasmic p120 and increased motility.

p120 also appears to play a role in stabilizing cell surface cadherin. Sw48 cells, which bear an inactivating mutation in the p120 gene, exhibit impaired cadherin-mediated adhesion and are unable to establish normal epithelial morphology. Phenotypic rescue by restoring p120 expression was associated with an increase in the half-life of E-cadherin, indicating that p120 may stabilize E-cadherin (46). Using siRNA, two other studies have also implicated p120 in maintaining cadherin. Knockdown of p120 in multiple cell lines (expressing different cadherin subtypes) resulted in decreased steady-state cadherin amounts and compromised cell-cell adhesion (47). The decrease resulted from cadherin internalization, not alterations in synthesis or delivery to the membrane (47).

Concluding Remarks

Clearly, many proteins participate in pathways that regulate cell-cell adhesion and maintain the integrity of the cellular neighborhood. These regulators also participate in pathways that induce the breakdown of the neighborhood. RhoGTPases and their signaling partners lie at the crossroads of many of these pathways, implicated in the formation and disruption of cell-cell adhesion and in the maintenance and destruction of epithelial morphology.
Hence, the regulation of RhoGTPase activity and signaling specificity is integral to the fate of cell-cell adhesions.

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