REVIEW

Rap1: A turnabout for the crosstalk between cadherins and integrins

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Abstract

The coordinate modulation of the cellular functions of cadherins and integrins plays an essential role in fundamental physiological and pathological processes, including morphogenesis, tissue differentiation and renewal, wound healing, immune surveillance, inflammatory response, tumour progression, and metastasis. However, the molecular mechanisms underlying the fine-balanced relationship between cadherin and integrin functions are still elusive. This review focuses on recent findings on the involvement of the small GTPase Rap1 in the regulation of cadherin- and integrin-dependent cell adhesion and signal transduction. In particular, it highlights some of the novel results recently obtained that raise the possibility of a pivotal role for Rap1 in the functional crosstalk between cadherins and integrins, suggesting interesting new regulatory mechanisms.

Keywords: Cadherins; Integrins; Rap1; Molecular crosstalk; Endosome signalling; Vesicle trafficking

Contents

Introduction ............................................................................................................................................... 283
Rap1 and integrins ................................................................................................................................. 284
Rap1 and cadherins ............................................................................................................................... 285
Rap1 as a turnabout for endosome signalling pathways connecting cadherins to integrins. ............... 287
Conclusions and future directions ....................................................................................................... 288
Acknowledgements ............................................................................................................................ 290
References ............................................................................................................................................ 290

Introduction

Cadherins and integrins are the major cell–cell and cell–extracellular matrix (ECM) adhesion receptors, respectively, and represent critical determinants of tissue architecture and function both in developing and adult organisms (Hynes, 2002; Wheelock and Johnson, 2003). Cadherins are single-pass transmembrane glycoproteins that support calcium-dependent, homophilic cell–cell adhesion. Together with their cytoplasmic domain interactors, such as β-catenin and p120ctn, they constitute the core components of adherens junctions (AJs). These specialised adhesive structures link the cadherin homophilic adhesion to the actin cytoskeleton, and are required for formation and maintenance of stable
cell–cell adhesion and differentiated phenotype in all solid tissues (Peifer and Yap, 2003; Wheelock and Johnson, 2003).

Integrins are heterodimeric transmembrane glycoproteins composed of noncovalently linked α and β subunits, which are endowed with both structural and regulatory functions. They link the ECM to several distinct cytoplasmic proteins and the actin cytoskeleton at focal adhesion sites. There they provide both outside-in and inside-out transmission of signals across the plasma membrane that control a number of critical cellular processes, including adhesion, migration, proliferation, differentiation, apoptosis, and gene expression (Hynes, 2002).

The postulate that the activity of these two fundamental cell–cell and cell–matrix adhesion receptors must be temporally and spatially coordinated for the proper development and maintenance of tissue architecture, as well as the evidence that coordinate disruption of cadherin-dependent intercellular junctions and induction of integrin-dependent cell motility take place during the epithelial–mesenchymal transition of most malignant tumours (Frame, 2002; Thiery, 2002), suggest that a fine-tuned molecular crosstalk must exist between integrins and cadherins. However, although evidence is growing that there is indeed crosstalk between members of these two adhesive receptor families (Avizienyte et al., 2002; Gimond et al., 1999; Hintermann et al., 2005; Hodivala and Watt, 1994; Huttenlocher et al., 1998; Lu et al., 1998; Monier-Gavelle and Duband, 1997; Nelson et al., 2004; Retta et al., 2001; Schreider et al., 2002; von Schlippe et al., 2000), the molecules and molecular mechanisms involved in such interesting phenomenon are still very little defined. To clarify how this crosstalk is regulated remains therefore a fundamental challenge for basic and translational research, including research on tumour progression and other pathologic disorders associated with either cadherin or integrin dysfunctions.

Among the molecules that might act as a “traffic light” at the crossroad between cadherin and integrin signalling pathways, Rap1, a member of the Ras subfamily of small GTPases, is emerging as a major candidate. Like other small GTPases, Rap1 cycles between an inactive GDP-bound and an active GTP-bound conformation that allows interactions with effectors, thus triggering cellular responses. This cycle is tightly regulated, both spatially and temporally, by several and markedly distinct guanine nucleotide exchange factors (GEFs) and GT-Pase-activating proteins (GAPs), which show unique expression profiles and subcellular localisation in different cells (Bos et al., 2001; Caron, 2003; Ohba et al., 2003). Recent biochemical, cellular and developmental evidence has unambiguously revealed that Rap1 plays a crucial role in fundamental physiological and pathological processes through the control of major integrin and cadherin adhesion-related cellular functions (Bos, 2005; Caron, 2003; Hattori and Minato, 2003; Wittechen et al., 2005), and may be indeed involved in transmitting information from cadherins to integrins (Bulzac et al., 2005).

In this review, we will discuss the most recent advances on the role of Rap1 in outside-in and inside-out signalling implicating cadherins and integrins, and propose a new model where Rap1 functions as a turnabout for endocytic and exocytic protein trafficking pathways that coordinate cadherin and integrin functions in a temporally and spatially precise manner.

Rap1 and integrins

Rap1 has been shown to be activated in response to various growth factors, cytokines, and chemokines that act on receptor tyrosine kinases (RTKs) or G-protein-coupled receptors, and implicated in a wide range of biochemical pathways in all eukaryotic cells through a number of distinct effectors (Bos et al., 2001; Caron, 2003). Since its original identification as a suppressor of Ras transformation (Kitayama et al., 1989), Rap1 has mainly been shown to either compete or cooperate with Ras in the regulation of the mitogen-activated protein kinase (MAPK) pathway (Cook et al., 1993; Mochizuki et al., 1999; Vossler et al., 1997; York et al., 1998). However, subsequent studies have indicated that the MAPK-related signalling pathways controlled by Ras and Rap1 may be functionally and spatially separated (Mochizuki et al., 2001; Ohba et al., 2003; Zhu et al., 2002). On the other hand, a number of recent studies have unambiguously revealed that Rap1 plays a major role in various integrin-dependent biological processes, such as immunological synapse formation, macrophage phagocytosis, chemokine-induced adhesion and transmigration of leukocytes, lymphocyte and dendritic cell homing to peripheral organs, platelet adhesion and aggregation, as well as adhesion of several distinct cell lines to various ECM proteins, including fibronectin, fibrinogen, collagen, and laminin (reviewed in Bos, 2005; Bos et al., 2001, 2003; Caron, 2003). Combined, these studies have firmly established that Rap1 regulates the inside-out activation of integrins. Integrin activity is regulated through various mechanisms, including recruitment to the plasma membrane from intracellular stores (change in number), redistribution and clustering at sites of cell adhesion (change in avidity) and conformational changes (change in affinity). Much evidence has been accumulated that Rap1 may regulate both recycling, avidity, and affinity of integrins that are associated with the actin cytoskeleton, including α5β1, α4β1, α5β1, αLβ2, αMβ2, and αMβ3 (Bos, 2005; Bos et al., 2003; Caron, 2003; Dustin et al., 2004), suggesting that Rap1 controls integrin-mediated cellular functions by
modulating a common inside-out activation process. However, the molecular mechanisms underlying the inside-out activation of integrins by Rap1 are not clearly defined yet, although some intriguing models have been recently proposed. These suggest that Rap1 may regulate integrin activation either directly, through their polarised spatial redistribution and stabilisation in an active conformation, or indirectly, through an effect on actin cytoskeleton dynamics (Bertoni et al., 2002; Bivona et al., 2004; Bos, 2005; Caron, 2003; Dustin et al., 2004; Katagiri et al., 2003).

Conversely, the role of Rap1 in the outside-in signalling from engaged integrins has been controversial, as previous studies came to somewhat contradictory conclusions (Bos et al., 2003). In particular, major ambiguities have resulted from reports showing either an increase or a decrease of GTP-loaded Rap1 during cell–matrix adhesion (Buensuceso and O’Toole, 2000; Posern et al., 1998), as well as from studies showing that the direct activation of integrins induced by activating monoclonal antibody and/or Mn^{2+} treatments either did or did not lead to activation of Rap1 (de Bruyn et al., 2002; Franke et al., 2000). Recently, this question has been carefully addressed (Balzac et al., 2005). In particular, using various adherent cell lines and different experimental tools, it has been clearly shown that a marked increase in the GTP loading of Rap1 occurs during cell detachment from the substratum, but mainly because of cell–cell contact disruption. Conversely, a progressive downregulation of Rap1 activity occurs during cell adhesion as a consequence of cell–cell contact formation (Balzac et al., 2005). Importantly, the outcomes of this work have unambiguously excluded a direct involvement of integrin outside-in signalling in the modulation of Rap1 activity that occurs during cell adhesion/de-adhesion processes, pointing instead to a major role for the dynamics of cell–cell contacts in the regulation of Rap1 activity. These results have suggested that Rap1 is not directly involved in the transmission of signals downstream of integrins, allowing to postulate that the role of this small GTPase in integrin functions is uni-directional and uniquely related to the control of integrin activation by inside-out signalling (Balzac et al., 2005).

**Rap1 and cadherins**

An early suggestion that Rap1 can also play an important role in the regulation of cadherin adhesive functions came from a study in *Drosophila melanogaster* showing that Rap1 regulates morphogenetic processes through the control of cadherin repositioning for proper AJ formation and distribution subsequent to cytokinesis (Knox and Brown, 2002). Consistent with this finding, the knockout of a Rap1GEF, C3G, in mice resulted in embryonic lethality due to aberrant epithelial cell adhesion in developing tissues (Ohba et al., 2001). Since these milestones, much evidence has been rapidly accumulated that defective Rap1 activation is associated with loss of AJs and cell scattering, and, conversely, that Rap1 activation may promote the formation of cadherin-mediated cell–cell contacts (Fukuyama et al., 2005; Hogan et al., 2004; Price et al., 2004; Yajnik et al., 2003), suggesting that Rap1 plays a major role in the inside-out regulation of cadherin adhesive functions. These results have been recently corroborated and extended by data in endothelial cells that have implicated Rap1 in the control of endothelial barrier function through the regulation of the formation and tightening of VE-cadherin-mediated cell–cell adhesion (Cullere et al., 2005; Fukuhara et al., 2005). However, whether the Rap1-dependent formation of cadherin-based cell–cell contacts is due to the stimulation of cadherin recruitment to the cell surface, the relocation of cadherin at the plasma membrane, or a reorganisation of the cortical actin cytoskeleton is still a debated question.

On the other hand, recent evidence has demonstrated that Rap1 activity is influenced by the dynamics of cell–cell contacts, and that Rap1 can be indeed a target for E-cadherin-mediated outside-in signalling (Balzac et al., 2005). In particular, it has been shown that in epithelial cells a strong activation of Rap1 occurs upon AJ disassembly and is triggered by E-cadherin internalisation and endocytic trafficking to the perinuclear recycling endosome compartment. This E-cadherin endocytosis-dependent activation of Rap1 is associated with and controlled by an increased Src kinase activity. Moreover, it correlates with the colocalisation of Rap1 and E-cadherin at the perinuclear recycling endosome compartment, and the association of Rap1 with a subset of E-cadherin–catenin complexes that do not contain p120^catenin. Conversely, a downregulation of Rap1 activity occurs upon the formation of E-cadherin-dependent cell–cell junctions as a consequence of the recycling of E-cadherin to the plasma membrane. These results suggest that cadherins play a major role in the outside-in modulation of Rap1 activity during cell adhesion through a regulatory mechanism based on endosome signalling and vesicular trafficking (Balzac et al., 2005).

Among the GEFs for Rap1 that could be implicated in such mechanism, C3G is a likely candidate, as it has been very recently identified as a new binding protein for the cytoplasmic domain of E-cadherin, and shown to interact with E-cadherin when cell–cell contacts are weak or lost (Hogan et al., 2004), which is compatible with the hypothesis that this interaction occurs during the disassembly of AJs (Balzac et al., 2005) (Fig. 1). Moreover, C3G is the only Rap1GEF that has been linked definitively to tyrosine kinase signalling pathways (Ohba et al., 2001), and is also an
established downstream effector of Src (Ling et al., 2003; Schmitt and Stork, 2002; Weissman et al., 2004). On the other hand, the reversibility of Rap1 activation that accompanies the formation of cadherin-dependent intercellular junctions implicates the recruitment and/or activation of GAPS for Rap1 at sites of cell–cell junctions. Consistently, recent kinetic estimates of GAP activity at various locations in living cells show that Rap1GAP activity is high at the plasma membrane and low at endomembranes (Ohba et al., 2003). Moreover, it has been reported that afadin (AF-6), an adaptor protein that binds to nectins in nascent AJs (Fukuyama et al., 2005), may negatively regulate Rap1 through the recruitment of the Rap1GAP Spa1 (Su et al., 2003). In this context, it is worth noting that internalisation and recycling of cadherins has recently emerged as a major mechanism that controls AJ formation, remodelling, and maintenance (Le et al., 1999; Mary et al., 2002; Palacios et al., 2001; Pecce and Gutkind, 2002). There is also compelling evidence that Rap1 is activated mainly on endosomal compartments (Mochizuki et al., 2001; Ohba et al., 2003; York et al., 2000), and implicated in the control of vesicular trafficking (Bivona et al., 2004; Maillet et al., 2003; Ozaki et al., 2000; Zhu et al., 2002), and cell polarity (Schwamborn and Puschel, 2004). On this basis it is tempting to speculate that activated Rap1 may function to direct vesicular traffic for correct delivery of recycling cadherins to pre-existent or nascent sites of cell–cell adhesion, where Rap1GAPs may serve as a signal terminator to ensure an appropriate positioning of AJ assembling sites (Fig. 1). In turn, this process may represent a prerequisite for polarizing the downstream cascade of events involving the ordered recruitment of structural and regulatory components which governs AJ organisation and function. Accordingly, in budding yeasts, Bud2, a GAP for the Rap1 orthologue Bud1, first recognises a presumptive positional landmark on the plasma membrane for proper bud site selection and then directs polarity establishment through the recruitment of Bud1. This in turn brings proteins that direct the cytoskeleton and secretory apparatus toward the bud site, thereby restricting bud site assembly at the proper location (Gulli and Peter, 2001; Park et al., 1999; Pryune and Bretscher, 2000). In this context, it can be also postulated that the basal activity of Rap1 in confluent cells (Balzac et al., 2005) is required for the constitutive recycling of cadherins (Le et al., 1999). Moreover, the enhanced Rap1 activation associated with the remodelling or disruption of cell–cell junctions could provide a negative feedback mechanism necessary for counterbalancing the increased endocytosis of cadherins, as well as for allowing the rapid redistribution of cadherins to the plasma membrane once cell–cell adhesion can be reformed. Importantly, the finding that Rap1 and p120ctn form distinct complexes with E-cadherin (Balzac et al., 2005) indicates that these two proteins likely serve distinct functions in cadherin turnover. Indeed, the binding of p120ctn to the cadherin juxtamembrane domain has been previously shown to promote cadherin clustering (Yap et al., 1997), whereas recent evidence consistently indicates that a core function of p120ctn in cadherin complexes is to regulate cadherin stability at the cell surface (Peifer and Yap, 2003). Noteworthy, in p120ctn-deficient cells, cadherins traffic normally to the cell surface, but are then rapidly turned over and removed (Davis et al., 2003; Xiao et al., 2003). Thus, it is tempting to speculate that Rap1 and p120ctn play complementary roles in cadherin turnover. In particular, whereas Rap1 could regulate the balance between endocytosis and exocytosis of E-cadherin, this balance might be shifted to accumulate either more or less E-cadherin on the plasma membrane depending on the functional state of stabilizing factors, such as p120ctn (Fig. 1).

Rap1 as a turnabout for endosome signalling pathways connecting cadherins to integrins

The finding that E-cadherin plays a major role in the outside-in regulation of Rap1 activity during cell adhesion (Balzac et al., 2005), combined with the well established pivotal role of Rap1 in the inside-out regulation of integrin adhesive functions (Bos et al.,

Fig. 1. Hypothetical model for the Rap1-mediated crosstalk between cadherins and integrins. In confluent epithelial cells both Src kinase and Rap1 activity are reduced to basal levels. Rap1 is diffusely distributed in the cytoplasm, where it associates with endosomal compartments, while AJs are stabilised by p120ctn binding to the E-cadherin juxtamembrane domain. Upon stimuli that induce the weakening of cell–cell adhesion, Src kinase activity is enhanced and may in turn activate the endocytic machinery underlying E-cadherin internalisation. Major known targets for Src tyrosine kinase activity in response to stimuli that weaken AJs are E-cadherin itself and p120ctn. On the other hand, C3G, a Rap1GEF which is known to be regulated by tyrosine phosphorylation and has been reported to bind to the E-cadherin cytoplasmic domain, might also be activated upon cell–cell adhesion weakening. Internalised E-cadherin must proceed through the endocytic pathway in order to induce Rap1 activation, which likely occurs upon E-cadherin transit from early to recycling endosomes where a protein complex containing E-cadherin and Rap1 may form. Activated Rap1 may in turn control the polarised redistribution to presumptive adhesion sites of either integrins and/or integrin regulators, leading to the formation of enhanced integrin-mediated cell–matrix adhesions, or recycling cadherins, leading to the reformation of AJs (modified from Balzac et al., 2005). $x = \alpha$-catenin; $\beta = \beta$-catenin; GEF = Rap1GEF; GAP = Rap1GAP.
has raised the possibility that Rap1 could be placed at the crossroad between both signalling pathways. Indeed, using GFP-zyxin as a marker for the transition of integrin-mediated adhesions from weak focal complexes to stable focal adhesions (Rottner et al., 2001; Zaidel-Bar et al., 2004), and time-lapse video microscopy analyses, it has been recently demonstrated that in epithelial cells the activation of Rap1 triggered by disruption of cell–cell junctions and E-cadherin endocytosis is associated with and required for the formation of integrin-mediated adhesive structures corresponding to mature focal adhesions. This implies changes in local adhesive strength of integrins, and suggests the existence of an inverse relationship between the assembly/disassembly of cadherin- and integrin-dependent adhesive structures (Balzac et al., 2005).

Importantly, these findings have also suggested a major role for Rap1 in transmitting information from cadherin-based to integrin-based adhesive structures to couple cadherin inhibition to integrin activation during the remodelling of epithelial tissues (Balzac et al., 2005). Consistently, it has been postulated that in physiological conditions AJ disassembly needs to be associated with integrin activation and increased cell adhesion to the ECM in order to prevent uncontrolled cell dissemination. Indeed, an increased migration has been associated with a reduced strength of cell adhesion to the ECM (Lynch et al., 2005), whereas there is compelling evidence for a “tug-of-war” between cell–cell and cell–matrix adhesions (Avizienyte et al., 2002; Gimond et al., 1999; Nelson et al., 2004; Ryan et al., 2001).

On the other hand, there is accumulating evidence that, like cadherins, also integrins undergo recycling from endosomal storage compartments to the plasma membrane (Ng et al., 1999; Pierini et al., 2000; Powelka et al., 2004). Moreover, active Rap1 has been also implicated in the regulation of trafficking pathways for integrins and integrin function regulators (Katagiri et al., 2003; Tohyama et al., 2003). Furthermore, Rap1 regulation of integrin-mediated cell adhesion has been recently shown to be sensitive to agents that block endosome recycling (Bivona et al., 2004). In this context, the finding that the E-cadherin endocytosis-dependent activation of Rap1 is coupled to and required for the enhanced assembly of focal adhesions (Balzac et al., 2005), suggests that Rap1 might mediate the crosstalk between cadherins and integrins by linking E-cadherin endocytosis to the oriented delivery of integrin and/or integrin regulators to cell–matrix adhesion sites (Fig. 1). Consistently, there is growing evidence that vesicular transport is important in spatial and temporal regulation of signal transduction through the compartmentalisation and restricted delivery of specialised signalling complexes (York et al., 2000; Sorkin and von Zastrow, 2002; Hoeller et al., 2005). In addition, direct connections between the endocytic and exocytic machinery have been previously suggested for cell polarity development and maintenance (Drees et al., 2001).

Conclusions and future directions

Over the past few years, it has clearly emerged that, in addition to their structural roles, both integrins and cadherins can provide bi-directional transmission of signals across topographically discrete regions of the plasma membrane. In particular, besides the well established role of integrins in a number of outside-in and inside-out signalling events (Hynes, 2002; Miranti and Brugge, 2002), a consistent signal regulating property related to the adhesive and tumour suppressor functions of cadherins have been recently recognised, including the modulation of the activation and signalling of diverse Rho family GTPases, RTKs, and MAPKs (Qian et al., 2004; Wheelock and Johnson, 2003; Yap and Kovacs, 2003; Laprise et al., 2004). However, integrin and cadherin signalling pathways are usually studied separately and, despite the growing number of studies and correlative data suggesting the existence of fine-tuned molecular crosstalks between distinct members of these adhesion receptor families, the functional crosstalk between cadherins and integrins has remained largely unexplained at the molecular level.

Recent evidence now indicates that the small GTPase Rap1 plays a major role in mediating this fundamental biological phenomenon, and suggests a novel regulatory mechanism (Balzac et al., 2005). In mammalian cells, Rap1 has been largely implicated in the regulation of both cadherin- and integrin-mediated cell adhesion (Bos, 2005), but also in endosome signalling (Mochizuki et al., 2001; York et al., 2000), control of endocytotic trafficking pathways (Bivona et al., 2004; Maillet et al., 2003; Ozaki et al., 2000; Zhu et al., 2002), and establishment and maintenance of cell polarity (Schwamborn and Puschel, 2004). Consistently, in budding yeasts, the Rap1 orthologue Bud1 shuttles between the cytosol and the bud site on the plasma membrane to bring proteins essential for polarity establishment and bud formation to the proper cortical site landmarks (Park et al., 1999; Gulli and Peter, 2001; Pruyne and Bretscher, 2000). On the other hand, endocytosis and recycling of both cadherins and integrins have recently emerged as major mechanisms that control cell adhesion formation and maintenance (Le et al., 1999; Pece and Gutkind, 2002; Powelka et al., 2004; Tohyama et al., 2003). Combined with these observations, the recent findings of Balzac et al. (2005) point to a model where Rap1 acts as a turnabout for endosome signalling and membrane trafficking pathways to orchestrate the delivery of either cadherins or integrins to specific cell–cell and cell–matrix landmarks.
at the plasma membrane. Through its pivotal role at the crossing of these pathways, Rap1 may ultimately execute a fine-tuned, temporal and spatially coordinated control of the functional crosstalk between cadherins and integrins for proper, ready responses to environmental cues (Fig. 2). Furthermore, the Rap1-dependent recruitment of cadherins or integrins to nascent, target adhesion sites by transport vesicles might in turn initiate a positive feedback loop, involving Rho GTPases, capable of recruiting other structural and regulatory proteins to presumptive cell–cell and cell–matrix adhesion sites at the plasma membrane. This delivering process then triggers subsequent signalling pathways, involving Rho GTPases, that transduce the Rap1 signal to bring about polarisation of the spatial distribution of cytoskeletal proteins, the secretory apparatus, and other cellular constituents. Eventually, this regulated traffic allows the ordered assembly of macromolecular complexes to determine a temporally and spatially coordinated formation and regulation of integrin- and cadherin-mediated adhesive structures.
components of AJs or focal adhesions, respectively, and driving the specific remodelling of the cytoskeleton for proper establishment and maintenance of cell adhesion and polarity. The unifying theme we like to propose is therefore that Rap1 serves as a crucial determinant of establishment and maintenance of cell polarisation and tissue architecture through the coordinated control of cadherin and integrin distribution and adhesive functions. Accordingly, both integrin- and cadherin-mediated adhesion is required to determine a functional polarisation of many, if not all, cell types (Nelson et al., 2004; Schreider et al., 2002).

Future challenges in the field include further characterisation of the putative molecular complex (signalosome) that can mediate the E-cadherin endocytosis-dependent activation of Rap1 (Balzac et al., 2005) (Fig. 1), as well as further dissection of the pathways activated by Rap1 that regulate cell–matrix and cell–cell adhesion. Among the putative components of the signalosome that triggers Rap1 activation upon cell–cell junction disassembly, Src has been indicated as a crucial candidate (Balzac et al., 2005). Interestingly, Src activity has been consistently implicated in the destabilisation and turnover of epithelial cell–cell adhesions through the tyrosine phosphorylation of AJ components and/or the activation of the endocytic machinery (Frame, 2002; Fujita et al., 2002; Owens et al., 2000; Palovuori et al., 2003). Moreover, it has been suggested to cooperate with activated RTKs to couple the weakening of cell–cell adhesions with the formation of prominent integrin-mediated cell–matrix adhesions in normal epithelial cells (Avizienyte et al., 2002; Frame, 2002). Combining these observations with the growing evidence of cadherin/RTKs coendocytosis coupled to disruption of cell–cell adhesion (Kamei et al., 1999), and endosomal signalling of RTKs (Mochizuki et al., 2001; York et al., 2000; Hoeller et al., 2005), a potential regulatory mechanism emerges that will be of considerable interest for future studies. On the other hand, it would be interesting to define the potential roles of Rap1 effectors involved in the MAPK pathway. In fact, it has been reported that the MAP kinases ERK1 and ERK2 are pivotally positioned to control the balance between cadherin and integrin functions, enhancing cell–matrix interactions when active or cell–cell interactions when inactive (Lu et al., 1998). Intriguingly, this might bring the attention back to the original identification of Rap1 as a suppressor of Ras transformation through the modulation of ERK activity (Kitayama et al., 1989).

Further biochemical analyses, combined with video microscopy studies of the dynamics of E-cadherin, Rap1, and other candidate players tagged with fluorescent proteins should better pave new and old Rap1-mediated signalling routes for further understanding of the molecular mechanisms that orchestrate the crosstalk between cadherins and integrins over the next few years.

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References


