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Small GTPases and regulation of cadherin dependent cell–cell adhesion

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Abstract

Cadherins belong to a superfamily of cell–cell adhesion receptors that bind to the same type of molecules (homotypic interaction) in a calcium dependent manner. Different members of the family are found in a wide variety of cell types and cadherin adhesive function plays a role in cell fate, segregation, and differentiation, which ensures the higher order of organisation found in many tissues. This review will focus on the role that cadherin adhesiveness plays in the differentiation of epithelial cells, and how cadherin function can be regulated by proteins of the small GTPase family. In the text, readers are referred to recent reviews and other chapters covering important topics that are not discussed here because of space limitation.

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E-cadherin and P-cadherin are found in epithelia and their function is essential to establish and maintain the differentiated epithelial phenotype (reviewed by Gumbiner).[1] It is possible that the role of cadherin receptors during epithelial differentiation is purely mechanical: the close apposition of membranes may facilitate the formation of other junctional components and cytoskeletal rearrangement. Alternatively (or in conjunction with their mechano-adhesive function), adhesion mediated by cadherin receptors may effectively trigger signalling events. Evidence is now accumulating for the involvement of cadherin in the induction of gene expression, cellular differentiation, growth control, and the distribution of cytoplasmic proteins.[2–7]

During tumorigenesis in epithelial cells, E-cadherin adhesiveness is frequently reduced or abolished in a variety of different ways (reviewed by Christofori and Semb).[8] Loss of E-cadherin mediated adhesion results in increased dedifferentiation of tumour cells (transition from adenoma to carcinoma).[9] Interestingly, in some cases, the transformed cells switch on the expression of other types of cadherin receptors normally found in mesenchymal and fibroblast cells.[10 11] However, in contrast to E-cadherin,[8] expression of these receptors can neither restore the epithelial morphology nor prevent invasiveness. Thus, the reduction of metastatic potential by the expression of functional E-cadherin may be the sum of two factors: sticking cells together and influencing the differentiation status of tumour cells.[9]

Regulation of cadherin function

Formation of a cadherin mediated adhesive contact can be devided into three steps that have different requirements and use distinct receptor domains (for a recent review see Yap *et al*).[12] (1) Cadherins dimerise at the cell surface, and the extracellular domain alone is sufficent to induce dimerisation in the absence of calcium ions (fig 1A).[13–15] (2) Homophilic binding occurs as: the receptors interact with dimers on opposing cells in an antiparallel fashion. Formation of this cadherin adhesive unit requires the extracellular domain and calcium ions.[14–17] (3) Adhesive receptors cluster laterally at sites of cell–cell adhesion (fig 1A),[18] in a process in which interaction of the cadherin tail with intracellular proteins and the actin cytoskeleton are determinant factors.[15 19 20] These three steps yield an increase in the number of binding sites and in the adhesive strength of the receptors for each unit area of the membrane.[19 21 22] In addition, the interaction with the cytoskeleton keeps the clustered receptors together and provides a framework for the localisation of many different cytoskeletal and signalling proteins at intercellular junctions (see below; reviewed by Yamada and Geiger).[23]

Because of the important cellular functions in which cadherins participate, there is much interest in understanding how their function is regulated. The association of cadherins with actin filaments is mediated by proteins called catenins.[24–27] Cadherin interacts directly with β-catenin, and α-catenin links this complex to actin filaments.[28–34] The direct interaction of cadherin complexes with tyrosine kinases,[35] receptor tyrosine phosphatases,[36–38] and kinase substrates[39–41] suggests that the phosphorylation of the complex may be modulated. However, the functional importance of phosphorylation for cadherin adhesion is not clear.[42–45] Activation of many signalling pathways can perturb intercellular contacts, but neither their specificity, with respect to cadherin receptors, nor the mechanism involved have been established (reviewed by Yap *et al*).[12] Recently, key regulators of cadherin mediated adhesiveness were identified as proteins of the small GTPase family, and their role is discussed below.

Small GTPases

The Ras superfamily of small GTPases contains proteins whose function is dependent on the type of guanine nucleotide bound. The Ras

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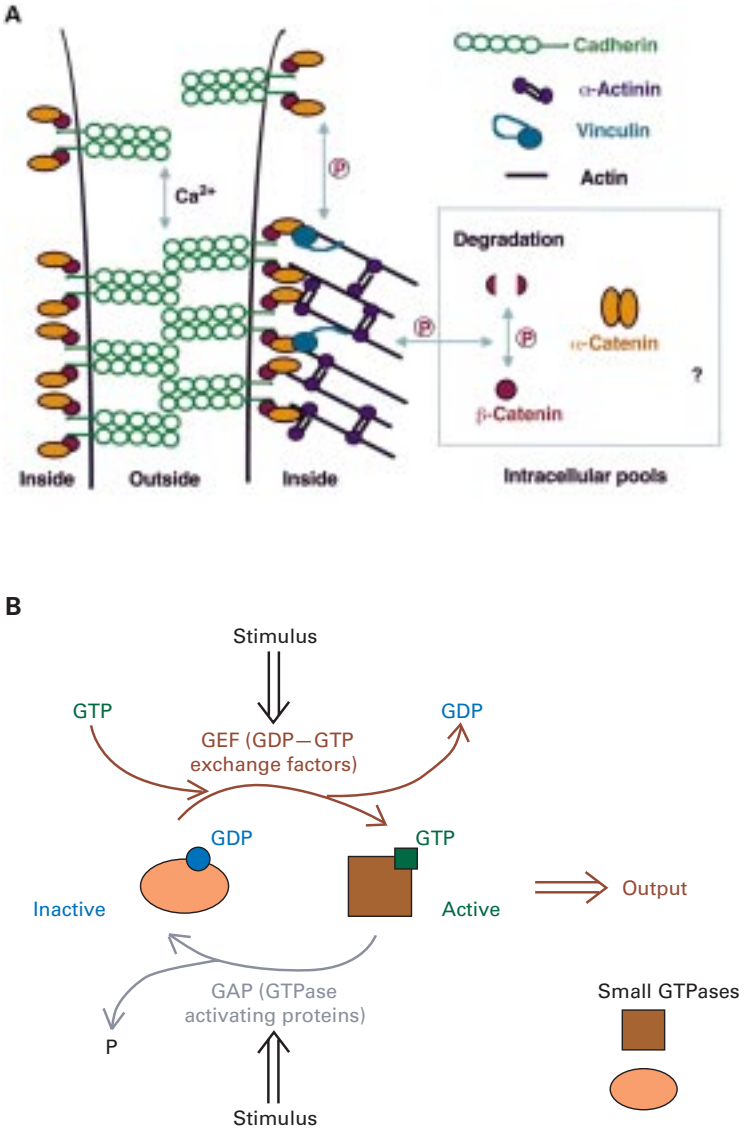

Figure 1 (A) Clustering of cadherins at sites of cell–cell contacts: cadherin receptors may exist as dimers at the cell surface, constitutively associated with cytoplasmic proteins called catenins. The receptors interact with the same type of molecules in neighbouring cells (homophilic binding). This interaction occurs in a antiparallel fashion and results in the lateral clustering or zipping up of cadherin complexes at sites of cell–cell contact. Functional adhesion requires calcium ions (to stabilise the extracellular domain) and association of the receptors with the actin cytoskeleton, which is indirectly mediated by the actin binding proteins α-catenin, vinculin, and α-actinin. The phosphorylation of the cadherin tail and/or the catenins might be involved in the clustering process, interaction with the cytoskeleton, or the shuttling of catenins from cytosolic pools to adhesive sites. The turnover of β-catenin cytoplasmic pools also involves phosphorylation events. (B) The GTPase cycle: most small GTPases are found associated with GDP, in an inactivated state. Replacing GDP with GTP activates the small GTPase, and this is the form competent for intracellular signalling. The hydrolysis of GTP to GDP occurs very rapidly and switches the molecule off. These two steps are tightly controlled by regulatory proteins: activation is mediated by guanine nucleotide exchange factors (GEFs), whereas GTP hydrolysis is facilitated by GTPase activating proteins (GAPs).

subfamily members are involved in growth control and differentiation. The Rho subfamily (Rho, Rac, and Cdc42) participates in cellular events involved primarily in cytoskeletal reorganisation, but these proteins can also activate kinase cascades, induce gene transcription, and induce DNA synthesis (reviewed by Van Aelst and D'Souza-Schorey[46] and Mackay and Hall[47]).

Inside the cell, members of the Ras family are normally found associated with GDP in an inactived state (fig 1B).[47] Activation is brought about by binding to GTP, a process that is tightly modulated by the GAP (GTPase activating protein) and GEF (guanine nucleotide exchange factor) regulatory proteins (fig 1B). The importance of appropriate control of the GTPase cycle is reflected by mutations that lock the molecule in an activated state. For example, activating mutations are frequently present in the Ras protein found in tumour cells (oncogenic form, H-Ras). Similar mutations in the Rho genes have not been found in tumours, even though activation of Rho proteins in tissue culture can induce transformation.[48–50] However, deletions have been identified in exchange factors specific for the Rho subfamily members that result in the activation of small GTPases (such as the oncogenes Lbc, Vav, and Dbl) (reviewed by Cerione and Zheng).[51]

The Rho subfamily

One of the first clues that the small GTPases might be involved in cell–cell adhesion came from work on drosophila.[52 53] In mammalian epithelial cells, the activity of endogenous Rho and Rac is required for the formation of cadherin dependent contacts, as well as for the cytoskeletal reorganisation that stabilises cadherin receptors in the plasma membrane (fig 2).[54] Inhibition of the small GTPases specifically removes cadherins from stable contacts, and this temporally precedes the release of other molecules involved in cell–cell adhesion.[55 56] Moreover, the regulation of cadherin function by Rho or Rac depends on the maturation status of the junctions and the cellular context (table 1).[57 58] The differential response of cadherin receptors to the small GTPases, which is dependent upon the cell type, is surprising because of the high homology among the members of the cadherin and small GTPase families. In addition to cadherin dependent contacts, in simple epithelial cells, Rho may also regulate the function of other adhesive structures, such as tight junctions.[59 60]

In Madin–Darby bovine kidney (MDCK) cells, exogenously expresssed Rac is found at cell–cell contacts, but both the activated and inactivated forms show the same staining pattern.[55 61] The functional importance of this is not clear but, in MDCK cells, proteins that can either activate (Tiam-1)[62] or inactivate (IQGAP)[63–65] the small GTPase Rac also localise to cell–cell contact sites.[64–66] Interestingly, IQGAP can bind directly to E-cadherin–β-catenin complexes, in an apparent competition with α-catenin.[67] The physiological importance of this association is not clear, but IQGAP can also bind and crosslink actin filaments and so could potentially replace α-catenin in the interaction of cadherin complexes with the cytoskeleton.[68] Although expression of the IQGAP gene does not remove E-cadherin from cell–cell contacts when cotransfected into fibroblasts, it is thought that the IQGAP–cadherin interaction renders the receptors less adhesive.[67] The latter is possibly the result of a weaker association of the complex with the actin cytoskeleton and/or an inactivation of the small GTPases at junctional structures.

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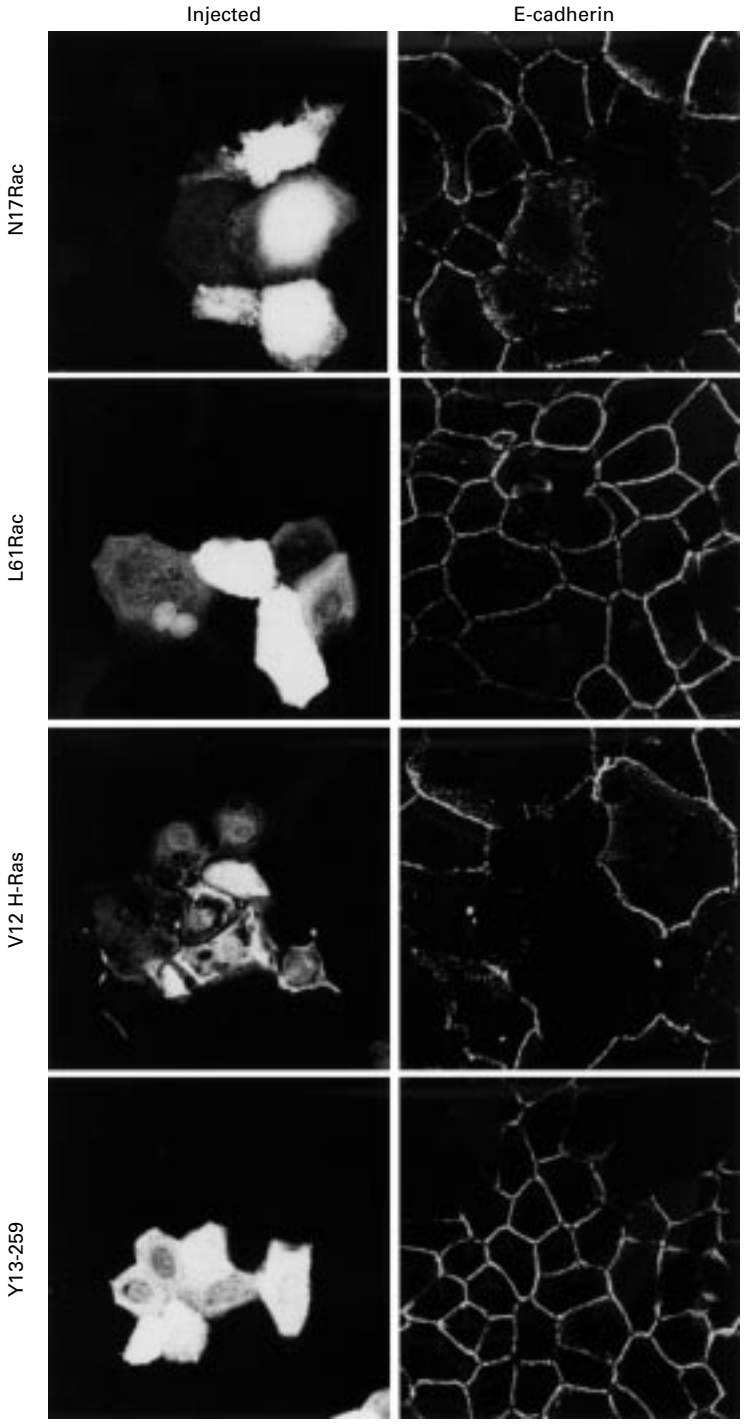

Figure 2 Effects of small GTPases in cadherin mediated adhesion. Keratinocytes grown in the absence of cell–cell contacts were microinjected with different recombinant proteins, and calcium dependent adhesion was induced. Cells were fixed and immunolabelled for E-cadherin to detect cadherin mediated adhesion (E-cadherin). Injected cells were identified by co-injection of fluorescent dextran (injected). Recombinant proteins microinjected were: dominant negative Rac (N17Rac); constitutively active Rac (L61Rac); constitutively active H-Ras (oncogenic form, V12 H-Ras), and Ras blocking functional antibody (Y13-259).

It appears that Rho and Rac are required in distinct pathways in the regulation of cell–cell adhesiveness,[54 55 61] as opposed to spreading on the substratum, in which a hierarchy among the small GTPases has been demonstrated.[69] In epithelial cells, actin recruitment to clustered cadherin receptors is dependent on the activity of Rac, but not of Rho.[54] It is conceivable that

Table 1 Summary of the effects of small GTPases in the regulation of cadherin dependent adhesion in different cadherin receptors and cell types

		Regulation by	
Receptor	*Cell type*	*Rho*	*Rac*
E-cadherin	Keratinocytes[54]	+	+
	MCDK (kidney epith.)[55]	+	+
	MCF10 (breast epith.)[56]	+	+
	L-cells (fibroblasts)[58]	+	−
	Small lung cells[57]	+	ND
P-cadherin	Keratinocytes[58]	+	+
VE-cadherin	Endothelial cells[58]	−	−
	CHO cells[58]	+	+

Cdc42 activity has no effect on E-cadherin adhesiveness.[55]
In small lung carcinoma cells, Rho inactivation leads to an enhanced aggregation of cells in suspension, as opposed to in the other adherent cell types, where Rho inactivation inhibits E-cadherin mediated adhesion.
CHO, Chinese hamster ovary cells; ND, not determined.

Rac can modulate cadherin function by regulating the association of the complexes with actin filaments, and this is in line with the reported role of Rac in actin polymerisation.[70 71] However, Rac function is necessary, but not sufficient, to promote accumulation of actin at the cell periphery because the presence of functional cadherin mediated adhesion is also required.[58]

On the other hand, transfection of activated Rac into MDCK cells results in an enhanced immunostaining of cadherin receptors and actin at sites of intercellular contacts, but its importance has not been established.[55 66] Although a strengthening of cadherin mediated adhesion by activated Rac is suggested by these results, it is not clear whether the augmented cadherin staining signal reflects an increase in the density of receptors at cell–cell contact sites.

The Ras subfamily

Another member of the superfamily, H-Ras, also interferes with cadherin adhesiveness (fig 2). Activating mutations in H-Ras are found frequently in human tumours, and are accompanied by loss of epithelial characteristics and increased migration. Oncogenic H-Ras can activate different intracellular pathways that contribute to Ras transformation[72 73]: phosphatidylinositol 3 (PI3) kinase, mitogen activated protein kinase (MAPK), and the small GTPases Rac and Ral (reviewed by Van Aelst and D'Souza-Schorey).[46] In addition, activation of each of these pathways individually is sufficient to promote morphological transformation in fibroblasts.[49 73–76]

Microinjection of activated H-Ras into MDCK cells promotes the disassembly of cadherin receptors from junctions (fig 2).[77] In epithelial cells, oncogenic Ras transfection leads to changes in both catenin phosphorylation and the association of the cadherin complex with the actin cytoskeleton.[78] In some cases, these changes do not necessarily result in the abrogation of cell–cell adhesion and epithelial morphology, but rather a weakening of intercellular contacts.[56 78] It is possible that different levels of expression of ras and the balance between the different activated pathways in distinct cell types can account for these discrepancies[79] (reviewed by Marshall).[80]

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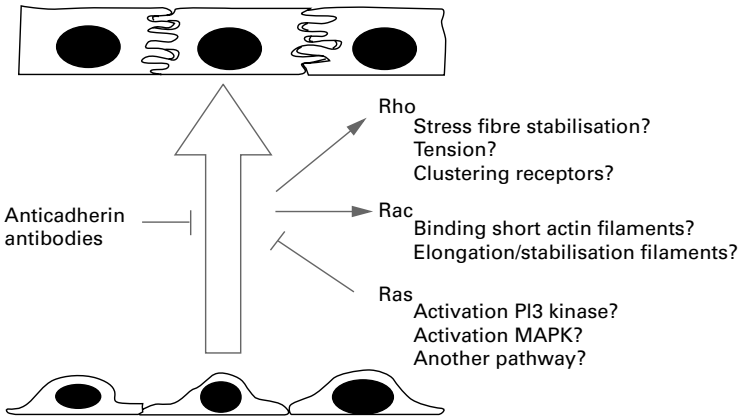

Figure 3 Possible roles of the small GTPases in the regulation of cadherin dependent adhesion. The activity of endogenous Rho and Rac is required for the establishment and maintenance of cadherin adhesiveness in different epithelial cells. Ras activation can abolish intercellular adhesion. The precise role of the GTPases is not known and a few possibilities are listed, based on their activity in epithelial and other cell types[54 55 58 61] (reviewed by Van Aelst and D'Souza-Schorey).[46] MAPK, mitogen activated kinase; P13, phosphatidylinositol kinase.

So far, the Ras pathway responsible for the specific perturbation of cadherin adhesiveness has not been identified. Inhibition of the MAPK and PI3 kinase pathways can prevent the destabilising effects of H-Ras on MDCK junctions.[77] Both MAPK and PI3 kinase are involved in the migration and invasiveness of epithelial cells after different stimuli, such as activation of small GTPase or growth factor treatment.[77 81–85] However, activation of either the MAPK or PI3 kinase pathway by itself is not sufficient to remove cadherin receptors from cell–cell contact sites.[77] Because of their known effects on cytoskeletal proteins, it is possible that activation of MAPK and PI3 kinase contributes to the Ras induced disorganisation of the cytoskeleton and hence destabilisation of junctions in epithelial cells.

In Ras transformed MDCKf3 cells, cadherin dependent adhesion, and polarised morphology can be restored by transfection of activated Rac or Tiam-1, an exchange factor for Rac.[66] Interestingly, the restoration of epithelial morphology by Rac in MDCKf3 cells is modulated by adhesion to different types of substrata because it is seen in cells plated on fibronectin, but not those plated on collagen.[84] Although the mechanism remains to be investigated, in MDCKf3 cells a crosstalk between cadherins and different extracellular matrix receptors might operate to influence the activation of distinct pathways by Ras. Similar crosstalk has been reported in other systems, suggesting an intracellular coordination of the regulation of cell–cell and cell–substratum adhesion.[86–92]

Future directions

Work from many laboratories now suggests that the small GTPases are key players in the regulation of intercellular adhesiveness, but the mechanism is far from elucidated (fig 3). The task now is to define whether cadherin adhesiveness can trigger the activation of the Rho family of small GTPases and to dissect further the pathway(s) activated by Rho and Rac that are important for cell–cell adhesion. Small GTPases are ideal candidates to participate in complex biological processes involving cell–cell and cell–matrix adhesion during epithelial morphogenesis, wound healing, and metastasis. Identification of the putative targets of the small GTPases that can modulate cadherin function will greatly enhance our understanding of the molecular mechanisms that operate in these important cellular processes.

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