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Classical cadherin adhesion molecules: coordinating cell adhesion, signaling and the cytoskeleton

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Summary

Classical cadherin adhesion molecules are fundamental determinants of tissue organization in both health and disease. Recent advances in understanding the molecular and cellular basis of cadherin function have revealed that these adhesion molecules serve as molecular couplers, linking cell surface adhesion and recognition to both the actin cytoskeleton and cell signalling pathways. We will review some of these developments, to provide an overview of progress in this rapidly-developing area of cell and developmental biology.

Introduction

The cadherins constitute a superfamily of cell surface glycoproteins, many of which participate in cell-cell adhesion and recognition. The founding members of the superfamily, commonly described as Classical (or Type 1) cadherins, occur in most solid tissues of the body (Tepass *et al.* 2000). Classical cadherins include proteins such as E-, N-, and VE-cadherin, which were named for the tissues in which they were first identified (in these cases, epithelial, neural and vascular endothelial cells, respectively). Molecular cloning of classical cadherins demonstrated that these were single-pass transmembrane glycoproteins whose extracellular regions comprised tandem repeats of a unique domain bearing negatively-charged amino acid sequences implicated in binding Ca^{2+} (Takeichi 1991). Homology with the cadherin domain was the basis for defining the cadherin superfamily, which contains a range of protein subfamilies that diverge significantly in sequence from the classical cadherins (Nollet *et al.* 2000). These include large families of protocadherins found principally in the CNS, the ret protooncogene, and cadherins with serpentine transmembrane domains (Yagi & Takeichi 2000). In this review we will confine our remarks to the classical cadherins, as these are the best-understood members of the cadherin superfamily. It is increasing clear, though, that other cadherin superfamily proteins exert profound effects on development and tissue organization, probably via molecular and cellular mechanisms quite distinct from those that classical cadherins utilize (Yagi & Takeichi 2000).

The cadherin molecular complex(es)

Classical cadherins function as membrane-spanning macromolecular complexes. Despite the presence of identifiable cadherin domains, the sequences of the ectodomains diverge significantly from one another. This likely reflects the requirement for these regions to mediate adhesive specificity. In contrast, the cytoplasmic tails are highly conserved amongst classical cadherins and serve to interact with a range of cytoplasmic proteins that link cadherins to the cell cytoskeleton and intracellular signalling pathways. The catenins were the first proteins to be identified in complex with cadherins (Ozawa *et al.* 1989) (Figure 1). These include β-catenin, which binds with high affinity to the distal cadherin cytoplasmic tail (McCrea & Gumbiner 1991) and, in turn, recruits α-catenin into the complex (Aberle *et al.* 1994). α-catenin binds actin filaments directly (Rimm *et al.* 1995) and can also associate with a range of other potential actin-binding proteins (Knudsen *et al.* 1995, Itoh *et al.* 1997). In contrast, p120-catenin (p120-ctn) binds directly to the membrane-proximal region of the cytoplasmic tail, independently of the other catenins (Daniel & Reynolds 1995).

Together this complex of four proteins is commonly regarded as the ''core'' cadherin-catenin complex. However, the complex is not static. Only β-catenin binds with high affinity to the cadherin cytoplasmic tail. Indeed, β-catenin co-translationally associates with the cadherin (Hinck *et al.* 1994) and it is not clear, under physiological circumstances, whether this association is broken during the lifetime of the cadherin. Both p120-ctn and α-catenin associate with the

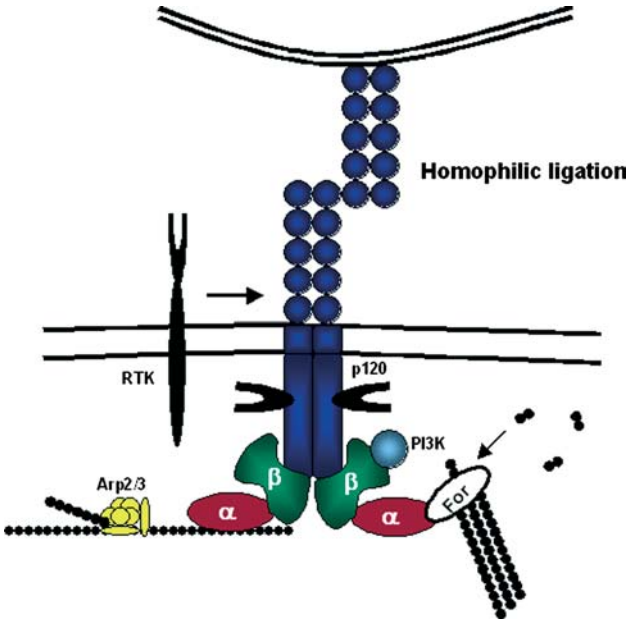

Figure 1. Schematic overview of the cadherin-catenin molecular complex. The "core" components of the classical cadherin molecular complex include the transmembrane cadherin molecule that associates with the cytoplasmic proteins β-catenin (β), α-catenin (α) and p120-catenin (p120). This core complex can further interact with a range of other cytoplasmic proteins. These latter interactions can mediate cadherin-actin cooperativity via mechanisms such as direct binding of α-catenin to actin filaments and recruitment of either formin-1 (For) and the Arp2/3 complex (Arp2/3). Classical cadherins can also interact, biochemically and functionally, with a range of signalling molecules, including receptor tyrosine kinases (RTK) and the lipid kinase, phosphoinositide 3-kinase.

cadherin complex through lower-affinity interactions. In contrast to β-catenin, α-catenin may not join the cadherin complex until the cadherin has been delivered to the basolateral membrane (Hinck *et al.* 1994). How α-catenin is targeted to the membrane is unknown but it is most likely subject to cellular regulation.

What determines binding of p120-ctn is also complicated. Recent metabolic labelling studies suggested that p120-ctn associates with N-cadherin in the biosynthetic pathway, before cleavage of the N-terminal prodomain to yield the mature form of the cadherin (Wahl *et al.* 2003). In contrast, independent studies using a minimal E-cadherin mutant that was mistargeted to the apical membrane of polarized epithelial cells showed that this mutant co-localized with β-catenin, but not with p120-ctn, implying that the local membrane environment might influence the steady-state incorporation of p120-ctn into the cadherin complex (Miranda *et al.* 2003). Clearly, the dynamic interactions of catenins with classical cadherins are complex and yet to be fully elucidated.

Moreover, it is now apparent that the catenins constitute just a small proportion of the increasing number of proteins that can associate with the classical cadherin-catenin complex. These include both transmembrane and cytoplasmic proteins, many of which participate in either cellular signalling (e.g. receptor tyrosine kinases and phosphatases, PI3-kinase, Shc; reviewed in (Yap & Kovacs 2003) or control of cytoskeletal dynamics (e.g. formin-1, Arp2/3, dynein (Ligon *et al.* 2001, Kovacs *et al.* 2002, Kobielak *et al.* 2004).It is thus probable that the "core" cadherin–catenin complex acts as a scaffold to support a range of molecular complexes that are regulated by cellular context and signalling. These diverse complexes likely serve quite distinct functions and ongoing efforts to define their regulation will be essential to understand their biological impact.

Cadherins are key determinants of tissue organisation

What then do classical cadherins do? A wealth of studies, both in whole organisms and cell culture models, have established cadherins as critical determinants of tissue organization (Tepass *et al.* 2000). Cadherins are necessary for tissue cohesion both in the embryo and in post-developmental life. For example, mice lacking N-cadherin die in utero and show dramatic dissociation of cardiac myocytes from one another, an adhesive defect that prevents the heart tube from developing normally (Radice *et al.* 1997). Moreover, cadherin dysfunction has pathologic impact. This is most evident in the case of E-cadherin, which exerts an invasion–suppressor function in epithelial cancers: loss of cadherin function promotes invasion and metastasis, the most clinically devastating stages in progression of tumors (Yap 1998, Christofori 2003). Indeed, expression of E-cadherin is inhibited by a range of transcriptional repressors, notably those of the snail/slug family, that participate in epithelial-to-mesenchymal transitions and may be upregulated in invasive cancers (Savagner 2001, Yang *et al.* 2004). Clearly, then, cadherins support the cell–cell adhesion necessary for cohesion of tissues and organs.

However, in addition to this cohesive function, cadherins also play central roles in patterning vertebrate and invertebrate organisms. One key developmental function of these proteins is to define cell populations with different developmental fates (Takeichi 1991). Such cell populations often express different complements of surface cadherins that facilitate tissue segregation (Figure 2). This is exemplified by embryonic neuroblasts, which switch from expressing E-cadherin to expressing N-cadherin as they segregate away from the neuroectoderm (Takeichi 1995). How do cadherins preserve cohesion within cell populations, yet allow different populations to segregate away from one another? The key lies in the ability of cadherins to support homophilic adhesive recognition, such that cells adhere productively to other cells that bear the same cadherin, but not to cells bearing different cadherins (Nose *et al.* 1988). This is exemplified experimentally

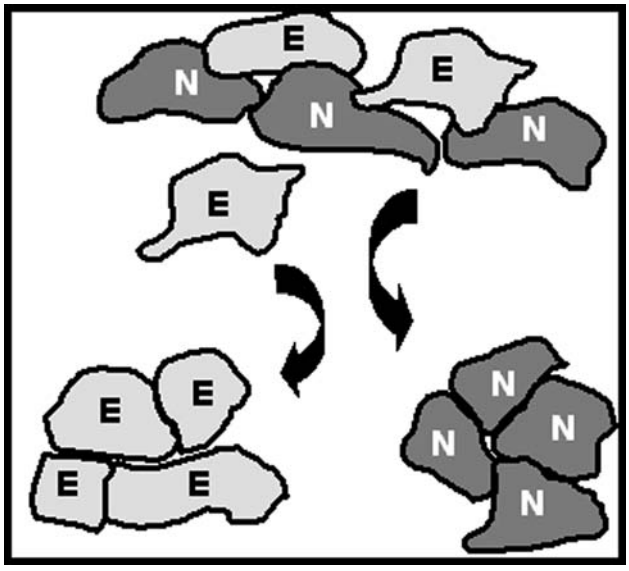

Figure 2. Classical cadherins mediate cell sorting, a key mode of cell–cell recognition. During tissue morphogenesis cadherins participate in segregating cells with different fates into distinct populations. One mechanism involves differences in either the complement of cadherins expressed (here illustrated by cells that express either E-cadherin or N-cadherin) or in the amount of cadherin expressed on the cell surface (not shown here). By either mechanism, cells cohere with other cells that express either the same cadherin (or same level of protein), leading to the segregation of cells into distinct populations.

by the ability of cultured cells bearing different cadherins to sort out from one another (Figure 2); such cell sorting is commonly regarded as the in vitro analog of tissue segregation during development (Nose *et al.* 1988). These adhesive interactions thus allow cells to discriminate like from un-like. Such specificity of adhesive recognition has commonly been attributed to the intrinsic binding properties of different cadherin ectodomains, although this may not be the whole answer (see below).

Cadherins also participate in the morphogenetic movements of cells upon one another that shape the early embryo and organs (Gumbiner 1992). This is clearly evidenced during vertebrate gastrulation where a variety of morphogenetic movements require regulated changes in cadherin function (Brieher & Gumbiner 1994). Similar forms of cell-upon-cell movement likely participate in remodelling post-developmental tissues, such as the gastrointestinal epithelium, that undergo regular turnover.

Clearly, then, cadherins can support functionally different forms of cell–cell interaction that include cell–cell cohesion, cell–cell discrimination, and cell-upon-cell locomotion. The (ongoing) challenge is to understand the molecular mechanisms responsible for these differences. An important advance is the increasing recognition that cadherins function as adhesion-activated cell signalling receptors (Yap & Kovacs 2003). In this model the productive engagement of cadherin ectodomains activates intracellular signals that regulate cell behaviour, especially cytoskeletal activity. Comprehensive development of this model will require us to integrate our emerging understanding of the cadherin ectodomain with ongoing efforts to understand the links between cadherins and both the cytoskeleton and cell signalling. In the remainder of this review, we will outline key elements of each of these areas.

The cadherin ectodomain

From first principles, surface adhesiveness and the specificity of adhesive interactions must be defined by the properties of the cadherin ectodomain. The realization that classical cadherins interact in a homophilic fashion implied that interdigitation of the ectodomains supported the adhesive interaction. Molecular characterization of the binding interaction, however, has led to conflicting results. A variety of quite different crystal and NMR structures have been generated, depending in part on the choice of ectodomain fragment studied (Boggon *et al.* 2002). Cryoelectron microscopy may provide a powerful alternative to defining the surface presentation of the extracellular domain in a native context (He *et al.* 2003). It should be noted, though, that these structural approaches can only provide static images of the binding interaction. Dynamic studies using purified proteins suggest that cadherins may engage in multiple, distinguishable interactions depending on the degree to which the ectodomains interdigitate (Sivasankar *et al.* 1999).

Of note, both quantitative and qualitative differences in cadherin expression support cell sorting. Tissue culture cells engineered to express differing levels of P-cadherin efficiently segregated away from one another (Steinberg & Takeichi 1994). Similarly, in the Drosophila egg chamber differences in the levels of DE cadherin expressed in the follicle and nurse cells determine positioning of the oocyte (Godt & Tepass 1998). Most commonly, though, cell sorting and segregation has been identified in the context of cell populations bearing different cadherins on their surfaces. The capacity for different cadherins to promote segregation of cell populations has been documented for many, but not all, classical cadherins (Takeichi 1995). This has commonly been attributed to specificity in the adhesive binding capacities of cadherin extracellular domains. In this model, strong binding between the ectodomains would cause cells expressing only, for example, N-cadherin, to cohere with one another. In contrast, weak (or absent) binding between the N-cadherin and E-cadherin ectodomains would prevent cells expressing these different cadherins from adhering to one another, leading ultimately to cell populations segregating into homogenous groups

expressing only E- or N-cadherin. However, recent studies have shown that purified recombinant cadherin ectodomains can robustly bind to different classical cadherins (Niessen & Gumbiner 2002). Therefore the ability of cadherins to direct cell sorting and segregation may not arise solely from the adhesive binding properties of their ectodomains.

One interesting paradox is that whereas the cadherin ectodomain determines surface adhesiveness, its intrinsic adhesive activity appears to be quite weak. This first emerged from the general observation that truncation of the cytoplasmic tail substantially reduced the adhesiveness of cadherin mutants expressed in cells (Takeichi 1991) and was substantiated by reports that studied the binding activity of recombinant cadherin ectodomains (Brieher *et al.* 1996). Instead, the lateral organization of extracellular regions appears to critically influence the macroscopic adhesiveness of cadherins presented on the cell surface. Lateral dimerisation appears to be minimally necessary for productive adhesion (Brieher *et al.* 1996) and the grouping of cadherins into larger-scale clusters further strengthens adhesion (Yap *et al.* 1998). It is tempting to speculate that the lateral oligomerization of intrinsically weak monomers may provide a mechanism for cells to rapidly regulate cadherin adhesive activity depending on biological context. Certainly, punctate concentrations of cadherin accumulate at sites of adhesion as epithelial cell–cell contacts assemble and mature (Adams *et al.* 1996). As lateral clustering requires the cadherin cytoplasmic tail (Yap *et al.* 1998), this provides one explanation for the functional contribution of the cadherin tail, and a potential mechanism to regulate adhesion in response to intracellular signalling. The molecular determinants of lateral clustering remain to be elucidated.

Cadherins and the actin cytoskeleton

It has long been recognized that classical cadherins function in intimate cooperation with the actin cytoskeleton. Early studies using drug inhibitors, such as cytochalasins, showed that actin integrity was essential for cadherins to act effectively (Jaffe *et al.* 1990). Since then it has become apparent that cadherins engage in several distinct functional and biochemical interactions with actin. Our more detailed understanding of this diverse interplay has been prompted, in significant part, by recent advances in characterizing the dynamic properties of the actin cytoskeleton.

Cadherins were initially envisaged to scaffold onto filaments of the cortical actin cytoskeleton. This was postulated to support adhesion by promoting cadherin clustering and/or stabilizing cadherins at the cell surface. Coupling of the cadherin–catenin complex to cortical microfilaments may involve several actin-binding proteins (Adams & Nelson 1998). The best-understood is α-catenin, which interacts directly with F-actin (Rimm *et al.* 1995) as well as with other cytoplasmic proteins (such as α-actinin and ZO-1 (Knudsen *et al.* 1995, Itoh *et al.* 1997) that can also bind microfilaments. The complement of actin-binding proteins involved in scaffolding cadherins is likely to be cell- and context-dependent, although the precise rules and signals which govern this are not understood. Moreover, rather than being static, cortical actin often moves laterally, parallel to the plane of the membrane (Lin *et al.* 1996). Coupling of cadherins to such cortical flow of actin may serve to provide traction at adhesive contacts or, indeed, participate in cell-upon-cell locomotion.

As well as binding passively to actin filaments, cadherins can also actively regulate the actin cytoskeleton, in two distinct ways (Figure 1). Firstly, cadherin ligation can recruit components of the Arp2/3 actin nucleator complex, thereby marking sites at the cell surface for assembly of actin filaments (Kovacs *et al.* 2002). Arp2/3-mediated actin assembly is a well-documented mechanism to generate force (Pollard & Borisy 2003). Arp2/3 appears to be preferentially recruited to newly-forming contacts or to contacts that are being remodelled. There it may serve to provide the force needed to efficiently bring cell surfaces together. Secondly, as cell–cell contacts mature, cadherin-based adherens junctions develop in concert with the assembly of prominent actin bundles (Adams *et al.* 1996, Vaezi *et al.* 2002). These perijunctional actin bundles are contractile and likely serve to couple cells together into mechanically-integrated sheets or populations. Actin bundling at cadherin contacts is a process that involves both Rho signalling (Vaezi *et al.* 2002) and the action of formin-1, a member of the Diaphanous/formin–homology protein family that can support actin assembly in bundles (Kobielak *et al.* 2004). Formin-1 is recruited into adhesive junctions by association with α-catenin. This suggests that as cell–cell contacts form and mature, cadherins may participate in progressively remodelling the actin cytoskeleton, firstly to promote efficient formation of contacts, and then to mechanically couple cells with one another into coherent sheets.

Cadherins and cell signalling

The inter-relationships between cadherins and cell signalling take two broad forms. Not only may signalling events regulate cadherin adhesive function, but cadherins themselves participate in transducing extracellular signals to the cell interior.

The capacity for cadherin function to be regulated by cell signalling was first raised by the observation that many proteins of the cadherin–catenin complex are subject to post-translational modification, especially

protein tyrosine phosphorylation (Daniel & Reynolds 1997). Indeed, p120-ctn was first identified as a Src kinase substrate and, like β-catenin, can be phosphorylated by a large number of receptor and non-receptor tyrosine kinases (Daniel & Reynolds 1997). Cadherin function can potentially be regulated by a diverse range of other cell signals (Gumbiner 2000). These include ubiquitination of the E-cadherin cytoplasmic tail (Fujita *et al*. 2002), which may regulate cadherin endocytosis, as well as signalling by small GTPases of the Rho family (Kaibuchi *et al*. 1999), which influence cadherin–actin cooperativity.

It should be noted, though, that the functional consequences of such signalling to cadherins are quite complex. For example, it is often suggested that tyrosine phosphorylation negatively regulates cadherin function, with biological consequences that include loss of cell–cell cohesion and epithelial-to-mesenchymal transformation (Nelson & Nusse 2004). However, many of these studies induced intense kinase activity, using agents such as v-Src or growth-factor stimulation of tumor cells that already over-express growth factor receptors (Daniel & Reynolds 1997). The precise role of tyrosine phosphorylation under physiological circumstances thus remains to be fully elucidated. In some cases, it may actually contribute positively to cadherin function (Calautti *et al*. 1998). Nor do we yet understand the precise molecular mechanisms that alter cadherin function in response to cell signalling.

As well as being targets for signal regulation, cadherins also participate in cell signalling to the cell interior. This may involve several potential scenarios (Figure 3), although it should be noted that β-catenin signalling (a key component of the canonical wnt signalling pathway) is not itself activated in response to cadherin ligation (Fagotto *et al*. 1996).

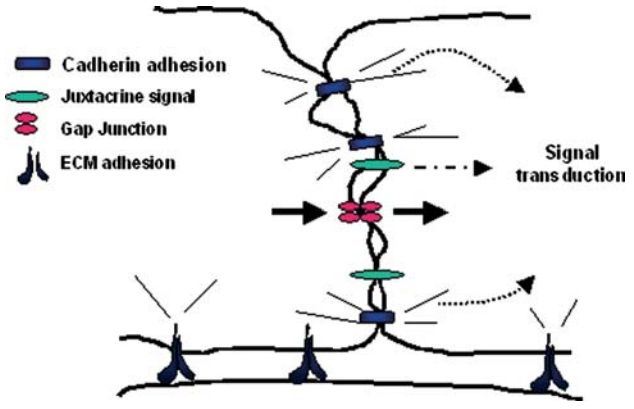

Figure 3. Classical cadherins and cell signalling. Cadherins may contribute to cell signalling by a number of mechanisms. These include activation of signals as immediate-early responses to cadherin ligation itself (''direct'' cadherin-activated cell signalling) and juxtacrine signalling. In the latter case, cadherin adhesion apposes cell surfaces, thus bringing surface-bound receptors into contact with their ligands (Juxtacrine signals) or allowing the assembly of gap junctions.

The simplest scenario entails activation of cell signalling pathways by cadherin ligation itself. Indeed, it has recently been demonstrated that cadherins can activate signalling by Rho family GTPases and PI3-kinase (Yap & Kovacs 2003). In a second model, classical cadherins may serve as part of signalling complexes, through lateral interactions with other membrane receptors, such as growth factor tyrosine kinases (Betson *et al*. 2002). E-cadherin can associate with the EGF receptor and may modulate its activity, perhaps even in the absence of EGF itself, by inducing co-clustering of receptors (Pece & Gutkind 2000). Finally, cadherins may support juxtacrine signalling by bringing together surface-bound signalling molecules that require cell membranes to be apposed. One example is gap junction communication, which requires cadherin adhesion for junctions to assemble (Gumbiner *et al*. 1988), although connexins appear not to interact with the cadherin-catenin complex itself.

Summary

All told, it is now apparent that the biological impact of classical cadherin receptors arises from their ability to coordinate surface adhesion and cell recognition with cytoskeletal activity and cell signalling. Ongoing efforts to elucidate the molecular basis for these mechanisms and test their physiological impact (particularly in whole organism models) will provide valuable insights into the role of these morphogenetic regulators in health and disease.

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