Published in final edited form as:

Subcell Biochem. 2012 ; 60: 171–196. doi:10.1007/978-94-007-4186-7_8.

Signaling from the Adherens Junction

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Abstract

The cadherin/catenin complex organizes to form a structural Velcro that joins the cytoskeletal networks of adjacent cells. Functional loss of this complex arrests the development of normal tissue organization, and years of research have gone into teasing out how the physical structure of adhesions conveys information to the cell interior. Evidence that most cadherin-binding partners also localize to the nucleus to regulate transcription supports the view that cadherins serve as simple stoichiometric inhibitors of nuclear signals. However, it is also clear that cadherin-based adhesion initiates a variety of molecular events that can ultimately impact nuclear signaling. This chapter discusses these two modes of cadherin signaling in the context of tissue growth and differentiation.

8.1 Introduction

To those new to the field of cell–cell adhesion, one only needs to watch a movie of a developing embryo or migrating monolayer of cells in culture to recognize the remarkably fluid yet coordinated nature of cell–cell adhesions. Indeed, observing such cell behaviors brings to mind two clear questions: How is cell–cell adhesion regulated and how is the state of cell contact communicated to the cell's interior? A central role for the cadherin/catenin adhesive complex in these cell behaviors was initially inferred from early studies showing that embryonic tissues fail to undergo normal morphogenesis in the presence of antibodies to the extracellular domain of E-cadherin (Gallin et al. 1986; Hirai et al. 1989). This result implied that cells fail to send morphogenetic signals when cadherin function is perturbed. In this chapter, we focus on the nature of these signals, particularly those that impact gene

expression. Other chapters in this volume address how cadherins signal more locally to alter the cortical actin cytoskeleton, which ultimately impacts the adhesive and mechanical properties of the cell (see Chaps. 6, 7 and 10).

Two models of cadherin signaling are presented, generally referred to as “transcriptional co-activator sequestration” versus “kinase inhibition” models (Fig. 8.1). For reasons that are largely historical in nature, the former mode is better appreciated since most cytoplasmic “peripheral” components of the cadherin complex (i.e., catenins) also localize to the nucleus to directly impact gene expression. Evidence that cadherins interact with transcriptional co-activators has long suggested a simple way to coordinate adhesion with changes in transcription, however there are problems with this model that merit deeper discussion. It is also clear that cadherin-based adhesion can strongly impact various growth factor receptor kinase signaling cascades, although clear molecular models for explaining these findings have yet to emerge. By discussing the differences between these two modes of cadherin signaling, we hope to build a conceptual framework for thinking about adhesion signaling.

8.2 β -Catenin is a Dual-Function Adhesion/Transcriptional Co-Activator Protein

The idea that cadherins might signal to the nucleus was first inspired by the discovery that β -catenin, originally identified as a stoichiometric co-precipitating partner of cadherins, was found to be highly homologous to Armadillo, a fly protein required for proper segmentation or “patterning” of the ventral epidermis (McCrea and Gumbiner 1991). At that time, Armadillo was one of a small number of components known to transduce a signal initiated by a secreted factor known as wingless (Wg), where a mutation in the fly β -catenin gene phenocopied the loss of a Wg signal (Peifer and Wieschaus 1990). Wg (and its vertebrate homologues, Wnts 1–19) are now widely appreciated as being used throughout embryonic development and adult tissue homeostasis to activate a repertoire of cell- and context-dependent genes that direct distinct cellular fates (Cadigan and Peifer 2009). The discovery that a cadherin-associated molecule also served an essential role in Wg/Wnt signal transduction led to one early hypothesis that plasma membrane-to-nuclear signaling occurred via β -catenin at the adherens junction. However, studies in both *Drosophila* and *Xenopus* systems later indicated that it was a cadherin-independent pool of β -catenin that was essential for transducing Wnt signals. For example, in the absence of a Wnt signal, most of the β -catenin is found associated with cadherins at cell contacts. In cells receiving a Wnt signal, however, a cytoplasmic/nuclear pool of β -catenin was also observed by immunofluorescence and biochemical fractionation methods (Funayama et al. 1995; Peifer et al. 1994; Schneider et al. 1996). Consistent with its nuclear localization, β -catenin was ultimately found to interact with LEF/TCF-type DNA-binding factors (Behrens et al. 1996; Molenaar et al. 1996), where β -catenin serves an essential co-activator function (Hecht et al. 1999) by recruiting components required for chromatin remodeling and RNA polymerase activation (reviewed in (Willert and Jones 2006)).

While formation of this binary transcription complex is the ultimate downstream step of Wnt signaling, it became clear that a large number of pathway components appear dedicated to generating a cadherin-free, nuclear signaling pool of β -catenin. Indeed, a convergence of

genetic epistasis, biochemical and human cancer studies led to a rapid ordering of receptor complex and midstream players in this pathway (reviewed in (van Amerongen and Nusse 2009); Fig. 8.2). We now appreciate that a secreted Wg/Wnt acts through cell surface receptors of the Frizzled (Fz) and Low-density lipoprotein (LDL) Receptor Related Protein (LRP) families. Fz receptors are seven-pass transmembrane proteins that topologically (and to some degree, functionally) resemble G-protein coupled receptors (Wang et al. 2006). The ultimate consequence of Frizzled/LRP5/6 co-receptor activation is the inhibition of a multi-protein kinase/scaffold complex that controls the phosphorylation-dependent destruction of β -catenin not otherwise bound with high affinity to cadherins (MacDonald et al. 2009).

8.3 Cadherins as Stoichiometric Inhibitors of β -Catenin Signaling

The existence of two compositionally distinct pools of β -catenin in the cell, one associated with the plasma membrane as an integral part of the cadherin core complex, and the other a cytoplasmic/nuclear pool that serves to transduce a membrane-to-nuclear signal, raises intriguing questions as to whether or not adhesion and Wnt signaling are coordinated through use of this common component, β -catenin. Indeed, experimental manipulations have revealed that cadherin expression and β -catenin signaling are interrelated. For example, forced expression of the cadherin can antagonize β -catenin signaling activity in a number of systems (Fagotto et al. 1996; Heasman et al. 1994; Orsulic et al. 1999; Sanson et al. 1996). Conversely, reductions in cadherin protein levels can enhance β -catenin signaling in certain contexts (Ciruna and Rossant 2001; Cox et al. 1996). Since cadherin can bind β -catenin directly (Jou et al. 1995), it is generally appreciated that cadherins inhibit β -catenin by sequestering the cytosolic signaling pool to membranes, preventing its access to the nuclear compartment. Indeed, biochemical and crystallographic evidence that β -catenin binds cadherins or TCFs through an overlapping binding interface (Graham et al. 2000; Huber and Weis 2001) rationalizes how cadherins can function as stoichiometric inhibitors of β -catenin/TCF signaling (Gottardi and Gumbiner 2001). It is important to recognize, however, that the ability of a cadherin to impact β -catenin signaling requires a baseline of active Wnt signaling. For example, introduction of E-cadherin in L929 cadherin-negative fibroblasts that are not receiving a Wnt signal shows that E-cadherin-mediated adhesion has little effect on gene expression (Kuphal and Behrens 2006), despite the well appreciated phenomenon that cadherins robustly upregulate and associate with β -catenin in this system (Ozawa et al. 1990). Moreover, epithelial cancers that have lost E-cadherin expression by various means fail to show a concomitant upregulation in β -catenin signaling (Caca et al. 1999; Herzig et al. 2007; van de Wetering et al. 2001). In some cell culture models, targeted loss of E-cadherin is associated with loss or down-regulation of β -catenin (Hendriksen et al. 2008), presumably because there are no other β -catenin-binding cadherins in these systems (e.g., N-cadherin or P-cadherin), and loss of this major high affinity β -catenin-binding partner leads to β -catenin elimination by the phospho-destruction complex. Indeed, isothermal calorimetry affinity measurements can rationalize this observation, as β -catenin binds the cadherin with anywhere from 28- to 190-fold higher affinity than to components of the destruction complex, APC and Axin (Choi et al. 2006). Thus taken altogether, the ability of a cadherin to limit β -catenin signaling is contextual and occurs only when cells are actively engaged in Wnt signaling.

The aforementioned studies combined with evidence that the affinity of β -catenin for the phospho-form of cadherin likely present in cells is ~ 570 -fold over the estimated β -catenin/TCF binding affinity (Choi et al. 2006) suggest that the cadherin might serve as an effective “sink” for β -catenin, so that β -catenin levels would have to rise beyond a threshold of cadherin expression in order to signal. However outside of the gain- and loss-of-function perturbation experiments discussed above, evidence that cadherin levels are modulated *in vivo* to set thresholds for Wnt signals is formally lacking. Quantitative microarray studies of Wnt-activated cells expressing different levels of cadherin, for example, might be informative for testing this principle. Alternatively, one might predict some cell types to be more sensitive to Wnt signals than others due to differences in cadherin abundance. Studies from our group, however, indicate this is not the case for primary lung fibroblasts and alveolar epithelial cells, which show similar levels of cadherin-bound β -catenin despite differences in expression of cadherin subtypes (Flozak and Gottardi, unpublished observation). Given that immune cell differentiation is known to be controlled by Wnt/ β -catenin signaling (e.g., TCF (T-cell factor) was originally shown to be important in T cell development (Verbeek et al. 1995)), and that immune cells lack robust cadherin expression, one wonders whether immune cells might be most sensitive to Wnt signals.

Mathematical modeling studies indicate that changes in the *rate* of cadherin protein synthesis, rather than its turnover, are expected to have the most direct consequence on Wnt signaling (van Leeuwen et al. 2007). While there are a few signals that have been shown to increase E-cadherin transcription in both cell culture (e.g., Wnt7a, (Ohira et al. 2003); WT-1, (Hosono et al. 2000)) and developmental models (Montell et al. 1992; Niewiadomska et al. 1999; Shimamura and Takeichi 1992), it is unclear whether these increases in cadherin synthesis are used to dampen endogenous Wnt/ β -catenin signals, in addition to providing enhanced cell–cell adhesiveness required for certain morphogenetic events. Interestingly, TCF-binding sites have been identified in the E-cadherin promoter (Huber et al. 1996), raising the possibility of a negative feedback mechanism where β -catenin nuclear signaling could activate E-cadherin transcription, which would in turn inhibit β -catenin signaling through sequestration. While activation of β -catenin signaling has been associated with the upregulation of E-cadherin in mouse intestine (Wong et al. 1998) and a *Drosophila* cell line (Yanagawa et al. 1997), the universality of this feedback mechanism is unclear. For example, it is also appreciated that the presence of TCF sites in promoters are not always associated with transcriptional upregulation (Blauwkamp et al. 2008). Indeed, one study showed that a Lef/TCF site in the E-cadherin promoter could interact with other factors to inhibit E-cadherin transcription during hair follicle development (Jamora et al. 2003).

If there are few instances where E-cadherin levels are elevated above its baseline for differentiative and morphogenetic purposes, there is clear evidence that E-cadherin is subject to potent negative regulation by transcriptional repressors that drive epithelial-mesenchymal transitions (EMT) during development and disease, such as Snail/Slug family zinc-finger transcription factors (Nieto 2002), the basic helix-loop-helix (bHLH) transcription factor, Twist (Yang et al. 2004) and ZEB1&2 (Korpala et al. 2008). Since these transcriptional regulators respond to a range of growth factor signaling pathways, including transforming growth factor beta (TGF β) -1 and -2, bone morphogenetic proteins (BMPs),

and fibroblast growth factors (FGFs) (reviewed in (Christofori 2006; Thiery et al. 2009)), it is easy to see how a number of signaling pathways could sensitize cells to Wnt signals by repressing a major negative regulator of β -catenin, E-cadherin. However, it is important to bear in mind that a phenomenon known as “cadherin-switching” typically accompanies EMTs, where the epithelial-specific E-cadherin (Epithelial-cadherin) is downregulated and replaced by the mesenchymal-specific N-cadherin (Neural-cadherin) (Wheelock et al. 2008). While N-cadherin and E-cadherin contribute to distinct adhesive activities (e.g., N-cadherin promotes while E-cadherin antagonizes cell motility and invasion (Chen et al. 1997; Fedor-Chaiken et al. 2003b; Kim et al. 2000; Nieman et al. 1999)), their abilities to bind β -catenin and antagonize Wnt signals appear identical (Gottardi et al. 2001; Sadot et al. 1998). Thus if E-cadherin downregulation during EMT is indeed a way to sensitize cells to Wnt signals, the upregulation of N-cadherin would have to be delayed for a sufficient temporal window so that Wnt signals are not buffered by another β -catenin-binding cadherin.

8.4 Evidence for β -Catenin “Release” from the Junction and Nuclear Signaling?

While the aforementioned studies present compelling evidence that changes in *cadherin biosynthesis* impact β -catenin nuclear signaling function, there has remained much interest in whether the cadherin-associated pool of β -catenin is ever “released” for the purposes of nuclear signaling (e.g., (Kam and Quaranta 2009)). Indeed it is quite appealing to imagine that changes in cadherin-engagement, junctional organization or some other aspect of adhesion might be communicated from the extracellular to cytoplasmic domain of the cadherin, resulting in molecular changes that lead to the release of β -catenin into the cytosol. There are many reasons this idea is attractive. For starters, it is worth noting that the precise contribution of β -catenin to adhesion has always been less apparent than its role as a transcriptional co-activator of Wnt signals. This may be in part because β -catenin is an essential component for Wnt signal transduction, while β -catenin adhesive function can be compensated by the highly homologous desmosomal component, Plakoglobin (Bierkamp et al. 1996; Haegel et al. 1995; Huber et al. 1997; Huelsken et al. 2000; Nieset et al. 1997). In addition, β -catenin’s role in adhesion has always been over-shadowed by cadherin and α -catenin, which provide essential homophilic recognition and actin-binding functions to the cadherin/catenin adhesive complex. The appeal of this release model is also driven by evidence that phosphorylations that impact the β -catenin/cadherin binding interface can substantially impact the affinity of these two proteins *in vitro* (reviewed in (Daugherty and Gottardi 2007)), raising the possibility that kinases and phosphatases could modulate β -catenin release. Lastly, evidence that the cadherin bound pool of β -catenin is generally much more abundant than the cytosolic fraction stabilized by Wnts further contributes to the notion that cadherins harbor a pool of β -catenin used for signaling. Given estimates that the N-terminally unphosphorylated signaling forms of β -catenin may be small, even relative to the stabilized pool (Hendriksen et al. 2008; Maher et al. 2010), it is possible to rationalize that a small level of β -catenin release from the cadherin (which might be difficult to detect using standard and typically inefficient co-immunoprecipitation analysis) could be freed into the signaling pool. However it is important to bear in mind that one mechanistic point seems inescapable for the “release model” to be true, and that is that β -catenin must be diverted

from the pathway that constitutively destroys the cadherin-free pool. In other words, mechanisms that promote β -catenin release from cadherin would either need to be coupled with a Wnt, or Wnt-like signal that inhibits the GSK3-dependent destruction of β -catenin. Alternatively, β -catenin would need to be released from the membrane in a form that would be protected from degradation, such as associated with the cadherin cytoplasmic domain (Simcha et al. 2001). This latter model will be discussed further in the context of cadherin ectodomain shedding and cytoplasmic domain processing below.

It should be noted that evidence that β -catenin signaling is sensitive to the protein synthesis inhibitor, cycloheximide, has long been interpreted to imply that only a *newly synthesized* form of β -catenin (i.e., rather than a previously synthesized pool coming from, for example, the cadherin complex) contributes to signaling (Willert et al. 2002). However, data from a cell-free *Xenopus* extract system that contains nuclei capable of responding to Wnt signals came to an opposite conclusion, finding that β -catenin signaling activity could in fact be recruited from a pre-existing (cycloheximide-insensitive) pool (Nelson and Gumbiner 1999). This finding has been recently supported in a cell culture-based study (Howard et al. 2011). Since interpretation of cycloheximide-based experiments can be problematic (Hanna et al. 2003; Liu et al. 2008), newer methods and insights may be required. Thus, to the extent that there remains debate over the source of the β -catenin signaling pool, the debate centers on whether β -catenin comes directly from the ribosome or via other multi-protein complexes (e.g., β -catenin/cadherin, β -catenin/APC, or β -catenin/Axin).

8.5 Cadherin-Based Adhesion can Limit β -Catenin Signaling Catalytically

If there is indeed a preexisting pool of β -catenin poised to signal, data from our lab and others suggest that the β -catenin phospho-destruction complex may be where to look (Faux et al. 2010; Harris and Nelson 2010; Hendriksen et al. 2008; Maher et al. 2010). For example, our lab has found that N-terminal phospho-forms of β -catenin (required for inhibition and degradation of β -catenin, (Liu et al. 2002)) can accumulate and co-localize with Axin and APC at cell–cell contacts, in a complex that is largely excluded from the cadherin/catenin complex (Maher et al. 2009). The implications of detecting these β -catenin phospho-forms at cell junctions are manifold. First, the ability to readily detect N-terminally phosphorylated β -catenin, when prevailing models suggest these phospho-forms are short-lived species, indicates that these forms are not as tightly coupled with degradation as previously expected, and raises the possibility that competing, N-terminal de-phosphorylation events could effectively “release” β -catenin for signaling. Second, evidence that N-terminal phospho-forms co-localize with Axin/APC at cadherin contacts, but are not obviously associated with the cadherin complex, raises the possibility that cadherin-based membrane dynamics might impact β -catenin signaling *indirectly* through modulating the activity of the β -catenin phospho-destruction complex. Indeed hints for such a model were already supported by studies in flies, where a single point mutation in APC that impacts its localization to adherens junctions was sufficient to compromise APC’s ability to promote β -catenin degradation (Jarrett et al. 2001; McCartney et al. 1999; Yu et al. 1999). Using a cell line that allowed us to more robustly capture phospho-forms of β -catenin that were considered transient intermediates, we learned that cadherins can promote the N-terminal “inhibitory” phosphorylation of β -catenin. In normal cells, we also found that cadherin-

based adhesion itself, rather than changes in cadherin abundance, can limit the accumulation of β -catenin induced by Wnts through enhancing the rate of β -catenin destruction (Maher et al. 2009) (Fig. 8.3).

How the phospho-destruction complex is localized to cell contacts, and how cadherins promote β -catenin N-terminal phosphorylation within this complex are not understood, but some recent studies are shedding molecular light on this area (Hay et al. 2009; Tanneberger et al. 2011). Indeed, it is worth noting that a wide variety of molecular components have been shown to affect β -catenin signaling. For example, a *Drosophila* genetic screen for enhancers of β -catenin signaling revealed that loss of proteins necessary for the establishment and maintenance of epithelial polarity, such as the Fat cadherin, Stardust and Dlg, could enhance β -catenin signaling (Greaves et al. 1999). More recently, components required for primary cilium structure/function and machineries that control planar polarity and convergence/extension movements have been shown to antagonize β -catenin signaling at the level of Disheveled (Corbit et al. 2008; Schwarz-Romond et al. 2002). We reason that a simple framework for explaining these effects is to recognize that the β -catenin phospho-destruction complex is “tunable,” and subject to a number of signaling inputs that ultimately control the rate at which β -catenin is consumed by the destruction complex. Cadherin-based adhesion may be the upstream “master cue” that polarity components and non-canonical Wnt signaling inputs depend upon for inhibition of β -catenin signaling via the destruction complex.

Overall, it appears that cadherins can inhibit β -catenin signaling in two ways: one as a stoichiometric binding partner that sequesters β -catenin from the nucleus, the other through a catalytic mechanism that impacts the rate at which β -catenin is consumed by the phospho-destruction complex (Figs. 8.3 and 8.4). Why might the cell need two modes for inhibiting β -catenin signaling by cadherins? Perhaps each mode is responsible for different degrees of inhibition. Whereas changes in cadherin biosynthesis that accompany EMT allow for robust β -catenin signals that alter cell fate, changes in cadherin-based adhesion associated with epithelial sheet wound closure may allow for a more modest regulation that impacts cell behaviors like motility and proliferation.

8.6 Cadherin Tail Clipping and Nuclear Signaling: The Notch Paradigm

Notch is a transmembrane protein that engages another transmembrane “ligand” on an adjacent cell (Delta) and Notch/Delta pairing is required for activating genes that impact neurogenesis (Louvi and Artavanis-Tsakonas 2006). In contrast to other ways that nuclear signals are conveyed from the plasma membrane, such as growth factor receptor signaling, which typically involves a cascade of kinase activation events and numerous intermediates, or the examples described above for cadherin signaling via β -catenin, the Notch cytoplasmic domain *directly* activates gene targets in the nucleus (Fortini 2002; Schroeter et al. 1998; Struhl and Adachi 1998). Specifically, the Notch cytodomain gains access to the nuclear compartment through a regulated intra-membrane cleavage event that liberates the cytodomain from the plasma membrane. Sequences within Notch favor its nuclear targeting and localization to Notch-regulated promoters required to inhibit neurogenesis (Bray 2006). Consistent with this Notch signaling paradigm, there is clear evidence that E-cadherin is

subject to both matrix metalloprotease (MMP)-mediated ectodomain and gamma secretase intra-membrane cleavage events (Lochter et al. 1997; Marambaud et al. 2002; Maretzky et al. 2005). One consequence of cadherin cytodomain cleavage has been demonstrated for N-cadherin, where the cytodomain inhibits numerous transcriptional targets by binding CREB-binding protein (CBP) and targeting it for proteosomal destruction (Marambaud et al. 2002). A second consequence of E-cadherin cytodomain cleavage appears to be an increase in β -catenin signaling (Maretzky et al. 2005), although the extent to which the signaling pool of β -catenin is liberated from a cleaved, cadherin cytodomain, or generated by a parallel Wnt signal that inhibits the destruction of newly synthesized β -catenin is not clear. Given evidence that the cadherin cytodomain is a potent inhibitor of β -catenin turnover by the phospho-destruction complex (Simcha et al. 2001) (through binding residues in β -catenin that overlap with those that engage phospho-destruction components, APC and Axin, (Ha et al. 2004; Xing et al. 2003, 2004)), it is easy to see how cadherin cytodomain clipping could potentially liberate a substantial pool of β -catenin/cadherin complexes into the cytosol. However, it is unclear how efficiently β -catenin can be displaced from the cadherin cytodomain given affinity measurements for the two proteins in the picomolar range (Choi et al. 2006), along with evidence that cadherin cytoplasmic domain-stabilized β -catenin shows no obvious signaling in reporter assays (Carien Niessen, personal communication). Thus if cadherin cytodomain clipping emerges as a way to generate a β -catenin nuclear signal, future mechanistic studies will be required to distinguish between β -catenin being released from the cadherin tail versus being stabilized by a Wnt or Wnt-like signal. It is also worth noting that a clipped cadherin cytodomain may have consequences for one of the other dual-localization catenins, p120-catenin (p120ctn) (Ferber et al. 2008).

8.7 Armadillo-Repeat Catenin Proteins in Adhesion and Transcription

While β -catenin is the best-known example of a dual-function adhesion-nuclear signaling protein, it is important to recognize that other catenins appear to follow the same paradigm. For example, Plakoglobin (also known as γ -catenin), which is highly homologous to β -catenin and typically associated with desmosomal cadherins, can interact with E-cadherin under conditions where β -catenin is limiting (Huelsenken et al. 2000). Like β -catenin, Plakoglobin can also interact with TCF family DNA binding proteins and impact gene expression (Kolligs et al. 1999; Simcha et al. 1998; Zhurinsky et al. 2000), although Plakoglobin appears to bind a distinct region on TCF that may differentially impact target gene expression (Miravet et al. 2002; Solanas et al. 2004). p120ctn, in addition to binding and stabilizing E-cadherin at the cell surface (see Chap. 9), can also independently interact with Kaiso (Daniel and Reynolds 1999), a DNA binding factor of the POZ family. Kaiso functions as a transcriptional repressor, and p120ctn appears to either promote Kaiso release or prevent its recruitment to DNA binding sites (Kelly et al. 2004; Kim et al. 2004; Ruzov et al. 2004). Interestingly, the *proximity* of p120ctn and β -catenin binding regions within the cadherin cytoplasmic domain is shared by some Wnt-regulated promoters, which can be co-regulated by proximal TCF- and Kaiso-binding elements (Park et al. 2006). These data imply that changes in the rate of cadherin synthesis or adhesion could doubly impact the expression of gene targets co-regulated by β -catenin (or Plakoglobin)/TCF and p120ctn/Kaiso. Like β -catenin, both p120ctn and Plakoglobin also contain a similar N-terminal

GSK3-sequence that controls the level of cadherin-free Plakoglobin/p120ctn in cells and allows their modest stabilization by Wnts (Hong et al. 2010). Thus Wnt signals may stabilize a family of catenin proteins that can impact gene expression, and cadherin-based adhesion may limit their signaling through both stoichiometric sequestration and catalytic phospho-destruction models (Fig. 8.4).

Is there a way to rationalize the observation that three distinct catenin proteins, β -catenin, p120ctn and Plakoglobin, play dual roles in transcription and cadherin-based adhesion? One theme in the organization of signal transduction pathways is that different pathways tend to rely on distinct protein-protein binding mechanisms in the service of transducing membrane to nuclear signals. For example, receptor tyrosine kinase signaling uses src-homology 2 (SH2) and phospho-tyrosine binding interactions, while the Hippo/Warts pathway uses WW and PPxY domain interactions at multiple levels of the pathway to transduce signals (Salah and Aqeilan 2011). In this light, it is important to recognize that β -catenin, Plakoglobin and p120ctn are all armadillo-repeat proteins. The armadillo repeat is a 42 amino acid motif that forms a triplet of alpha helices. When multiple repeats are brought together, as in the catenins, these triple helices stack to form a superhelix of helices that forms a groove into which nearly all arm-repeat protein ligands fit. Interestingly, the core nuclear import machinery proteins, Importins α and β , contain armadillo repeats, and the structurally related HEAT repeats, respectively (Andrade et al. 2001). These repeating-units form versatile protein-protein binding interfaces that allow importins to drive the recognition and nuclear accumulation of a seemingly diverse set of ligands (Coates 2003). Given that β -catenin is imported into the nucleus independently of a classic nuclear localization signal or the known importins, and interacts directly with the nuclear pore (Fagotto et al. 1998; Suh and Gumbiner 2003), it seems likely that p120ctn and Plakoglobin (and other junction-localized armadillo-repeat proteins localized to desmosomal cadherins, such as plakophilins) interact similarly with the nuclear pore complex to mediate their own nuclear/cytoplasmic shuttling (Henderson 2000; Karnovsky and Klymkowsky 1995; Krieghoff et al. 2006; Mertens et al. 1996). In light of this apparent structural conservation (Andrade et al. 2001), it has been reasoned that these armadillo repeat junction/nuclear proteins and the nuclear importins evolved from a common ancestor. Given evidence that catenin-binding cadherins are only found in metazoans ((Hulpiau and van Roy 2011); Chap. 2), it appears that cell-cell adhesive cadherins evolved to co-opt these nuclear signaling proteins for both structural and signaling purposes.

8.8 E-cadherin Mutations in Human Tumors and Implications for Critical Functions

An understanding of the relationship between cadherin protein expression, cell-cell adhesion and β -catenin signaling has been aided by studies that have sought to tease out how these factors contribute to E-cadherin tumor suppressor function. Numerous studies have reported loss of, or mutation within, the E-cadherin/catenin complex across a wide variety of epithelial cancers (reviewed by (Berx and van Roy 2009)). In most cases, E-cadherin loss correlates with the invasive component of a given tumor, suggesting that E-cadherin loss of function might promote tumor progression, local invasion and metastasis (Birchmeier et al.

1996; Vleminckx et al. 1991). Indeed in a well-defined mouse model of pancreatic islet cell cancer (Perl et al. 1998), E-cadherin is lost as tumors progress from adenoma to carcinoma, and forced expression of E-cadherin holds tumors at the adenoma stage compared with control mice. Conversely, forced down regulation of endogenous E-cadherin expression increases the number of metastases and tumors detected at the carcinoma stage, indicating that the down regulation of E-cadherin constitutes a key rate-limiting step in tumor progression. Germline mutations in E-cadherin have been found to be associated with a familial form of gastric cancer (Hereditary diffuse gastric carcinoma, HDGC), underscoring its importance as a true tumor suppressor gene (Berx et al. 1998). With regards to molecular mechanisms, it was long reasoned that the tumor/invasion suppressor activities of E-cadherin would be mediated through maintaining cell–cell adhesion. However, evidence that β -catenin is an oncogene, and that constitutive signaling is associated with numerous cancers (Giles et al. 2003; Howe and Brown 2004; Polakis 2000; Takigawa and Brown 2008) raises the possibility that an equally important role for E-cadherin in tumor suppression might be through antagonizing the nuclear signaling activity of β -catenin. Interestingly, restoring cadherin-negative epithelial cancer lines with forms of the cadherin that can rescue cell–cell adhesion independently of binding β -catenin, versus a form of the cadherin that can associate with β -catenin but not mediate adhesion reveals that an ability to bind β -catenin is most critical to E-cadherin's function as a growth or invasion suppressor (Gottardi et al. 2001; Wong and Gumbiner 2003). Remarkably, rescuing adhesive function with a well-studied E-cadherin- α -catenin fusion construct is not sufficient to mediate growth or invasion suppression. Interestingly, the requirement for β -catenin binding is not dependent on whether cells are receiving a Wnt signal (Wong and Gumbiner 2003), indicating that a form of E-cadherin that binds β -catenin is critical to its tumor suppressor function *regardless* of whether tumor cells rely on Wnt/ β -catenin signaling.

While such domain analyses indicate that E-cadherin binding to β -catenin is most critical to its tumor suppressive and invasive activities *in vitro* (Wong and Gumbiner 2003), mutations in E-cadherin associated with breast and gastric cancers *in vivo* do not reveal the β -catenin binding domain as a mutational hotspot, as has been found for other factors that bind and inhibit β -catenin signaling like APC and Axin (Berx et al. 1998). Instead, the E-cadherin mutations that are widely distributed in breast cancer are truncations that occur in the extracellular domain, while gastric cancer reveals a mutational hotspot in the third cadherin repeat in the extracellular domain. Remarkably, mutations that delete the β -catenin binding domain are rare. This broad distribution of E-cadherin mutations along the entire coding sequence strongly suggests that cadherin signaling cannot be all about the inhibition of β -catenin signaling. As will be discussed below, cadherins are required for epithelial polarity and impact a number of growth-factor receptor signaling pathways, functions that depend on the entire full-length protein.

8.9 Transmitting Diverse Signals from Cadherin-Based Contacts

If we expand the view of cadherin signaling beyond the core complex and the nuclear functions of armadillo repeat proteins, β -catenin, Plakoglobin and p120 ctn, what emerges is a view of cadherin signaling that ultimately encompasses what it means to be a multicellular tissue. As the major cell adhesion system in epithelia, the E-cadherin/catenin complex is

essential for establishing the close cell contacts that so many other junction and juxtacrine signaling molecules depend upon, from tight and gap junctions to membrane anchored signaling pairs like Notch/Delta or Ephrins and Eph-receptors (Fagotto and Gumbiner 1996; Ferreira et al. 2011; Zantek et al. 1999). Indeed as a master regulator of epithelial cell polarization (Nejsum and Nelson 2007, 2009), which entails the formation of distinct apical and basolateral membrane domains, one can readily see how most cell contact-dependent functions ultimately depend on E-cadherin, which formally places the cadherin “upstream” of, and responsible for, the transmission of numerous and diverse signals (Fig. 8.5). Because of this, the following sections aim to focus on the more proximal or direct targets of E-cadherin signaling.

The two phenomena most often examined in the context of cadherin signaling are contact inhibition of cell movement and contact inhibition of proliferation (reviewed in (Takai et al. 2008)). The former is readily observed when single epithelial cells join and become immobilized within a pre-existing colony of cells. This phenomenon is thought to depend on membrane-proximal cadherin-signals, which coordinate Rho-family GTPases and their regulators and effectors to change the dynamic organization of actin between adjacent cells (Mayor and Carmona-Fontaine 2010), and is discussed in detail in Chaps. 6 and 10. In contrast, contact inhibition of proliferation involves membrane-proximal events that ultimately lead to changes in gene expression and nuclear events required for mitosis. While these two phenomena almost certainly share similar molecular underpinnings, it is important to recognize that the time courses for these two phenomena are quite different. For example, contact inhibition of cell movement occurs in minutes, while inhibition of proliferation takes days and depends on cell density more than formal cell “contact” (Takai et al. 2008), indicating that these processes are molecularly distinct. Because cell proliferation depends on growth factors, and the time course of contact-dependent inhibition of proliferation strongly correlates with the inhibition of growth factor receptor tyrosine kinase activity (Takahashi and Suzuki 1996), there has been a longstanding interest in the relationship between E-cadherin and growth factor receptor tyrosine kinases, in particular, Epidermal growth factor receptor (EGFR). Indeed, while early studies showed that EGFR can colocalized with E-cadherin at apically-localized adherens junctions (Chen et al. 2002) and co-associate in immunoprecipitation assays (e.g., (Hoschuetzky et al. 1994)), a more intimate relationship between these two proteins was supported by evidence that EGFR-activation could promote the phosphorylation of tyrosine residues in cadherin-associated catenins (Daniel and Reynolds 1997; Hoschuetzky et al. 1994), suggesting that the cadherin/catenin complex may be a proximal target of EGFR signaling. Consistent with this idea, EGFR and E-cadherin genetically interact during eye development in flies, where loss of EGFR function can phenocopy E-cadherin overexpression, while a constitutively active form of EGFR worsens a weak mutant allele of E-cadherin (Dumstrei et al. 2002). Altogether, these data indicate that E-cadherin is both a downstream target *and* an upstream inhibitor of EGFR signaling.

8.10 E-Cadherin-Dependent Inhibition of Growth Factor Receptor Signaling

Currently, there are a few models that can explain how E-cadherin inhibits EGFR signaling. One study presents evidence that dense epithelial cell cultures preferentially restrict EGF

binding to high but not low affinity sites on the EGFR (Qian et al. 2004). Since the extracellular domain of E-cadherin is sufficient to interact with the EGFR by co-immunoprecipitation analysis (Qian et al. 2004), one possibility is that E-cadherin in dense epithelial cultures sterically hinders EGF binding to EGFR. However, more recent data indicate that E-cadherin can inhibit EGFR signaling at a step that is more downstream of receptor binding and activation by EGF (Curto et al. 2007; Perrais et al. 2007). For example, E-cadherin expressing cells treated with inert beads coated purely with E-cadherin-ectodomains show reduced proliferation and EGFR signaling despite robust EGFR phospho-activation (Perrais et al. 2007). While this E-cadherin-dependent inhibition of EGFR signaling requires the cytoplasmic, β -catenin-binding domain of E-cadherin and associated catenins (Perrais et al. 2007), molecular details of this inhibition remain unclear.

Some mechanistic hints may be provided by studies of the neurofibromatosis 2 (Nf2) tumor suppressor protein, also known as Merlin. Merlin is a member of the ezrin radixin and moesin (ERM) family of membrane/cytoskeleton linking proteins (reviewed in (Fehon et al. 2010)), and loss of Merlin results in a loss of density-dependent inhibition of cell proliferation in numerous cell types (Curto et al. 2007; Lallemand et al. 2003). Interestingly, Merlin can block the endocytosis of ligand-bound EGFR specifically in dense cell cultures, where EGFR internalization is known to be required for a full signaling response (Sorkin and von Zastrow 2009). Merlin can also be found to co-immunoprecipitate with both E-cadherin/catenin and EGFR complexes in dense but not sparse cultures, through making a direct interaction with α -catenin and an indirect interaction with EGFR through NHERF-1 (Curto et al. 2007; Gladden et al. 2010). Thus the E-cadherin/catenin complex can work with Merlin to shut-down EGFR signaling by preventing its internalization into an endocytic compartment from which it signals. Curiously, while E-cadherin can inhibit different classes of receptor tyrosine kinases (RTKs) (e.g., IGF-1R, c-Met receptor, ErbB2-4; (Qian et al. 2004; Vermeer et al. 2003), Merlin is selective for the EGFR (Curto et al. 2007), raising the possibility that the cadherin/catenin complex uses molecules functionally analogous to Merlin to limit signaling from distinct RTKs.

Alternatively, E-cadherin's general role in the establishment of a junctional barrier (Fig. 8.5) might limit access of apically localized growth factors, such as Heregulin α , from their basolaterally-localized ErbB2-4 receptors (Vermeer et al. 2003). Not all receptor complexes are regulated by density or cadherin expression, such as heterotrimeric G protein-coupled, lysophosphatidic acid (LPA) and muscarinic receptors (Qian et al. 2004), indicating that there is some specificity with regards to density-dependent downregulation of receptor signaling. It is also important to recognize that initial stages of cell contact formation are actually accompanied by an increase in EGFR activity (Fedor-Chaiken et al. 2003a; Pece and Gutkind 2000) and activation of other kinases/signaling events that promote proliferation and survival (Cadigan and Liu 2006; Goodwin et al. 2003; Nelson and Chen 2003), while only later stage "dense" contacts are associated with down-regulation of these same signals (reviewed in (Brunton et al. 2004)). Lastly, cadherin-subtypes can impact RTKs differentially. For example, while N-cadherin sustains FGF-receptor signals by preventing their endocytosis-mediated downregulation (Suyama et al. 2002), VE-cadherin attenuates some but not all effectors of VEGFR2 signaling (Carmeliet et al. 1999; Grazia Lampugnani et al. 2003; Rahimi and Kazlauskas 1999). Taken altogether, it is clear that the

relationship between cadherins, cell contact and signaling from diverse growth factor receptors is complex and depends on the type and maturity of the contact (Fig. 8.6).

8.11 The Cadherin/Catenin Complex as a Key Regulator of the Hippo/Warts Signaling Pathway

Historically, there has been concern that the density-dependent inhibition of proliferation observed *in vitro* (and examined in most of the aforementioned studies) is an artifact of cell culture. *In vivo*, most growth factors and their receptors interact at the basolateral surfaces of epithelial cells, however *in vitro* studies typically use cells grown on plastic dishes (as opposed to porous membrane filter supports), where the establishment of junctional polarity effectively “seals-off” the growth factor-rich apical media from the basolaterally-localized receptors. Fortunately, recent data indicate that the phenomenon of density-dependent inhibition of proliferation observed in culture involves the same molecular pathway recently appreciated to control organ size during normal tissue development. The Hippo signaling pathway is an evolutionarily conserved pathway that senses local cell densities to control tissue growth through a kinase cascade that ultimately phosphorylates and inhibits the transcriptional co-activator, Yes-associated protein (YAP) and its paralogs (Beausoleil et al. 2004). Similar to the β -catenin/TCF paradigm described above, YAP binding to TEAD/TEF family DNA-binding factors forms a binary transcription complex that activates genes that promote proliferation or inhibit apoptosis (Cho et al. 2006). Activation of the Hippo kinase phospho-activates the Warts kinase, which phosphorylates and inhibits the nuclear accumulation of YAP.

While key upstream activators of Hippo have been identified in the fly (Grusche et al. 2010), three recent studies indicate that the cadherin/catenin complex is a key regulator of the Hippo pathway in mammals. For example, forced expression of E-cadherin in cancer cells that previously silenced the E-cadherin gene restores the density-dependent exclusion of YAP from the nucleus (Kim et al. 2011). More important, the ability of E-cadherin ectodomain-coated beads to inhibit epithelial cell proliferation is lost upon knock-down of Hippo pathway signaling components or overexpression by YAP (Kim et al. 2011). How cadherin engagement limits the nuclear accumulation of YAP is not well understood, but two independent studies suggest that α -catenin functionally and physically participates in a complex that restrains the nuclear accumulation of YAP (Schlegelmilch et al. 2011; Silvis et al. 2011). Curiously, since YAP is generally not observed to accumulate at dense cell–cell contacts, and the vast majority of cytosolic α -catenin behaves as a monomer by gel filtration chromatography (Drees et al. 2005), suggesting that most of this pool of α -catenin is largely not associated with another protein, it may be more likely that α -catenin participates in the transmission of a signal that ultimately impacts the activity of central kinases in the Hippo/Warts signaling cassette, rather than serving as a stoichiometric inhibitor of YAP. Regardless of this issue, it is clear that the cadherin/catenin complex can convey growth inhibitory signals from dense contacts, through seemingly close physical interactions with both EGFR and Hippo pathway components (Fig. 8.6).

8.12 Summary and Perspectives

When we consider the various signals generated from cadherin-based adhesion receptors, the challenge has not been in appreciating the link between adhesion and signaling, but rather in understanding how an adhesive structure that lacks core enzymatic activity conveys information to the cell's interior. Evidence that most cadherin-binding partners belong to the armadillo family of proteins, many of which also associate with DNA binding factors in the nucleus, reveals a seemingly simple way to coordinate changes in gene expression with changes in the abundance of adhesive structures. Through this mode, cadherins can be viewed as simple stoichiometric inhibitors of catenin nuclear signals. However, it is also clear that cadherin-based adhesion in dense cell arrangements can impact a number of distinct molecular pathways required for tissue growth and proliferation. Mechanistically, the contribution of cadherin-based adhesion to these signals is less clear but appears to depend less on cadherin/catenin protein levels (which don't substantively change with cell density) than an organization that broadly impacts the activity of kinases involved in proliferation (e.g., growth factor receptor tyrosine kinases and Hippo/Warts signaling). Through this mode, cadherins can be viewed as inhibitors of kinase signaling cascades. The question is, "What is the arrangement or organization of a cadherin/catenin complex that broadly shuts down the activities of diverse kinases?" While a common mechanism may be unlikely, we speculate that the organization of cadherin-based adhesions into higher order junctional arrangements may be an important feature of this mode cadherin signaling (Niessen and Gottardi 2008). We look forward to future studies that aim to better define the organization of the cadherin/catenin complex into junctions, and how this organization conveys nuclear signals.

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Fig. 8.1.

General models of cadherin signaling to the nucleus. Cadherins interact with dual-localization proteins (e.g., β -catenin, Plakoglobin and p120 ctn) that functionally link cadherins to the cortical cytoskeleton and also control the activation of DNA-binding factors in the nucleus. The model presented in **a** and **b** reflects evidence that cells with greater cadherin abundance (*black bar, b*) can sequester, and thereby inhibit, the transcriptional co-activator function of these dual-localization proteins (shown as *purple color*) better than cells with fewer cadherins (*black bar, a*). The model presented in **c** and **d** reflects evidence that E-cadherin in densely packed epithelial monolayers can inhibit signaling from diverse growth factor receptor kinases (**d**) better than cells with less mature contacts (**c**)

Fig. 8.2.

Wnt signaling pathway. In the absence of Wnt (*left*), cytosolic β -catenin is continually phosphorylated by casein kinase 1 α (CK1) and glycogen synthase kinase 3 β (GSK3 β) within an Axin1 scaffold complex. This phosphorylation allows β -catenin to be recognized by a specific E3 ligase (β TrCP, not shown), which catalyzes the ubiquitylation and rapid degradation of β -catenin. The adenomatous polyposis coli (APC) tumor suppressor participates in the phospho-destruction of β -catenin by antagonizing β -catenin de-phosphorylation by phosphatases. During Wnt activation (*right*), GSK3 β activity is inhibited directly by Lrp5/6, which allows β -catenin to accumulate, enter the nucleus, interact with LEF/TCF family members and promote transcription

Fig. 8.3.

Density-dependent turnover of cytosolic β -catenin. In densely confluent cells, cadherins promote a faster turnover of β -catenin than in less adhesive (sub-confluent) cells. This may explain why cells migrating adjacent to a wound appear sensitized to Wnt signals. (Figure adapted from Maher et al. 2009)

Fig. 8.4.

Armadillo family proteins in cadherin-based adhesion and nuclear signaling. The cadherin cytoplasmic domain binds directly to three distinct armadillo-repeat proteins, β -catenin, Plakoglobin and p120ctn. These proteins play an obligate role in cadherin-based adhesion (*Left*). To varying degrees, cytoplasmic and nuclear pools of these catenins are generated by Wnt signals, which favors catenin activation of transcription. Cadherins appear to antagonize nuclear catenin functions via both stoichiometric sequestration (*left*) and catalytic destruction models (*right*)

Fig. 8.5.

E-cadherin is a master initiator of cell–cell contact, junction formation and epithelial polarity. E-cadherin-based adhesion is required for the establishment of diverse cell–cell junctions (e.g., tight junction, zonula adherens junction, desmosomes, gap junctions), as well as signals that require membrane-anchored ligand/receptor interactions (e.g., Notch/Delta, Ephrin/EphR). From this more global viewpoint, “E-cadherin signaling” encompasses signals coming from all of these complexes

Fig. 8.6.

E-cadherin and density-dependent inhibition of proliferation. E-cadherin in densely packed epithelial monolayers can inhibit access of EGF to the EGFR as well as downstream signaling from the EGFR (1) compared with less mature contacts (2) E-cadherin engagement can also limit the nuclear accumulation of YAP through a poorly defined mechanism that requires α-catenin (3 and 4)