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Catenins: Keeping Cells from Getting Their Signals Crossed

Review

Mirna Perez-Moreno[1] and Elaine Fuchs[1,*]
[1] Howard Hughes Medical Institute
Laboratory of Mammalian Cell Biology
and Development
The Rockefeller University
New York, New York 10021

Adherens junctions have been traditionally viewed as building blocks of tissue architecture. The foundations for this view began to change with the discovery that a central component of AJs, β-catenin, can also function as a transcriptional cofactor in Wnt signaling. In recent years, conventional views have similarly been shaken about the other two major AJ catenins, α-catenin and p120-catenin. Catenins have emerged as molecular sensors that integrate cell-cell junctions and cytoskeletal dynamics with signaling pathways that govern morphogenesis, tissue homeostasis, and even intercellular communication between different cell types within a tissue. These findings reveal novel aspects of AJ function in normal tissues and offer insights into how changes in AJs and their associated proteins and cytoskeletal dynamics impact wound-repair and cancer.

Introduction

The formation of tissues and organs during embryogenesis depends largely upon close interactions between neighboring cells. These connections orchestrate the assembly of different cell types into organized patterns toward the establishment of a higher organism. This also allows adult tissues to perform their unique functions, preserve their architectural integrity, and coordinate the precision with which cells are able to remodel their tissues during normal homeostasis and repair them in response to injury. By sensing signals through adhesion receptors, cells can respond and elicit the spatially coordinated events needed to maintain tissue homeostasis.

Cells embrace through an assortment of transmembrane glycoproteins, which interface with the underlying cytoskeleton to keep cells together within a living tissue. In both simple and stratified epithelia, these interactions are largely mediated by three junctional complexes: adherens junctions (AJs), tight junctions (TJs), and desmosomes (Farquhar and Palade, 1963; Matter et al., 2005; Perez-Moreno et al., 2003; Yin and Green, 2004).

Without diminishing the importance of other cellular junctions (Matter et al., 2005; Tsukita et al., 2001; Yin and Green, 2004), cadherin-mediated AJs are particularly important in controlling the specificity, formation, and maintenance of intercellular adhesion (Gumbiner et al., 1988; Lewis et al., 1994; Takeichi, 1990). In addition, they direct coordinated cellular organization and movements within epithelia and transmit information from the environment to the interior of cells (Brembeck et al., 2006; Gumbiner, 2000; Nelson and Nusse, 2004).

*Correspondence: fuchslb@rockefeller.edu

E-cadherin is the prototypic member of the subfamily of classical cadherins and is expressed in most epithelial tissues. It physically links neighboring cells together through its single-pass extracellular domain (Patel et al., 2003). This domain has five "extracellular cadherin" domains (ECs), EC1–5, which promote the calcium-dependent homotypic interactions and enable a cadherin to distinguish itself from other members (Patel et al., 2003). The cytoplasmic tail of a cadherin also lends specificity. Both desmosomal and classical cadherins interact with conserved members of the armadillo repeat family of catenins, but desmosomes associate with plakoglobin and plakophilins, while classical cadherins preferentially associate with p120-catenin and β-catenin (Perez-Moreno et al., 2003; Yin and Green, 2004). Under conditions where β-catenin is limiting and/or modified, plakoglobin can act as a substitute (Lewis et al., 1997; Miravet et al., 2003).

Despite their sequence similarities, p120-catenin and β-catenin bind to distinct sites on the cadherin tail. p120-catenin interacts with the membrane-proximal or juxtamembrane domain (JMD) involved in regulating the lateral clustering and stabilization of cadherins at the membrane (Davis et al., 2003; Ireton et al., 2002; Yap et al., 1998). By contrast, β-catenin interacts with the distal part of the cytoplasmic tail and with α-catenin, an unrelated catenin that can bind directly to filamentous (F)-actin (Pokutta et al., 2002; Rimm et al., 1995) as well as to several actin-binding proteins (Kobielak and Fuchs, 2004). We will return to these issues later.

Conceptually, the life of a cadherin-mediated AJ can be separated into three stages: formation, maintenance, and disassembly. The formation of cadherin contacts can be further subdivided into distinct phases: (1) an initial step involving the establishment of primordial contacts (puncta formation), (2) more rapid appearance of additional nascent contacts lateral to the initial puncta, and (3) maturation/expansion of nascent contacts through clustering of cadherins. Perturbations in the assembly, stability, and/or disassembly can alter the functional activity of cadherin-mediated AJs, which in turn can broadly destabilize intercellular adhesion and tissue integrity.

In addition to the roles of cadherin-mediated AJs in intercellular adhesion, it is becoming increasingly clear that cadherin-catenin molecules coordinate a dazzling array of cellular processes. Understanding how cadherin-catenin complexes modulate the intrinsic behavior of cells within a tissue and elucidating how they receive and transmit extrinsic cues provided by the microenvironment have now surfaced as major challenges for cell biologists. For the past 10 years, scientists have focused mainly on β-catenin, which is now a prominent example of a protein that functions dually as an AJ adhesion protein and as an essential mediator of the Wnt signal transduction pathway (Bienz, 2005; Nelson and Nusse, 2004). In this review, we concentrate on α-catenin and p120 catenin, which collaborate with β-catenin to coordinate cadherin-mediated AJ dynamics but diverge from their relatives when it comes to the

signaling processes they integrate. The collective view emerging from these various studies is that cadherin-mediated AJs function as molecular sensors to receive extracellular signals and transmit them across the cells of an epithelial sheet, thereby adjusting cellular behavior to fulfill instructive cues from the microenvironment.

α-E-Catenin and Its Roles in Intercellular Junctions and Actin Dynamics

α-E-catenin is the prototypic member of the α-catenin family and was initially characterized as a component of the cadherin-catenin complex. α-catenins bind indirectly to cadherins via interaction with β-catenin. In mammals, there are three α-catenins. α-E-catenin is most prevalent in epithelial tissues; α-N-catenin is restricted to neural tissues; α-T-catenin is expressed primarily in the heart. Additionally, the distant member α-catulin, an α-catenin-like protein, is ubiquitously expressed (Kobielak and Fuchs, 2004). α-catenins share an overall similarity with vinculin, an actin-binding protein, and differ considerably in sequence from the other catenins (β-catenin, p120-catenin, plakoglobin, and plakophilins), which unlike α-catenin belong to the armadillo family of proteins.

Genetic studies in mice have unambiguously shown that α-E-catenin is required to sustain adhesion between cells during mammalian morphogenetic events (Torres et al., 1997; Vasioukhin et al., 2001). In *Drosophila*, cell adhesion is disrupted when the single α-catenin gene harbors a mutation in its encoded binding site for armadillo, the fly homolog of β-catenin (Orsulic and Peifer, 1996).

In vitro, AJ formation and intercellular adhesion can be initiated and monitored by elevating the levels of calcium. During the formation of cadherin-mediated AJs, cells extend filopodial and lamellipodial extensions to promote nascent cadherin contacts, referred to as puncta (Adams et al., 1996; Vasioukhin et al., 2000) (Figure 1). Such dynamic membrane protrusive activity involves the actin cytoskeleton and Rho GTPases (Etienne-Manneville and Hall, 2002).

The ordered structure between E-cadherin and β-catenin is thought to initiate an association with α-catenin through residues within the N-terminal head domain of the armadillo protein. Compounding the complexity is that α-catenin interacts with afadin, an actin-binding protein that associates with another AJ transmembrane protein, Nectin, that localizes earlier at the membrane, thereby promoting the recruitment of cadherin-catenin complexes to these sites (Tachibana et al., 2000). Once recruited to nascent contacts, α-E-catenin plays an integral role in remodeling the actin cytoskeleton into radial actin cables (Adams et al., 1998). Loss-of-function mutations in α-E-catenin generate cells that fail to actively bring themselves together, stabilize cell-cell junctions, and integrate actin networks across an epithelial sheet (Vasioukhin et al., 2000). In addition, drugs that impair actin polymerization weaken cell-cell contacts and reduce adhesion (Vasioukhin et al., 2000).

Exactly how α-catenins coordinate these events remains unclear. In vitro, α-catenin homodimerizes at micromolar concentrations, but in the presence of β-catenin, the homodimer dissociates and a 1:1 heterodimer of α-catenin and β-catenin is observed (Koslov et al., 1997; Pokutta et al., 2002). α-catenin's ability to bind directly to actin is well established (Rimm et al., 1995), but only recently was it discovered that α-catenin binds to F-actin only as a homodimer and that it cannot bind simultaneously to β-catenin and F-actin (Drees et al., 2005; Yamada et al., 2005). At these elevated micromolar concentrations, α-catenin homodimers can also compete with Arp2/3/Wasp to inhibit the formation of branched actin networks and subsequently reduce lamellipodial protrusions (Drees et al., 2005) (Figure 1).

Based upon these findings, it is tempting to speculate that in the early stages of intercellular adhesion, when cells extend filopodial and lamellipodial projections to enhance cellular contact and draw cells together, the local cytoplasmic pool of α-catenin at these sites is largely monomeric. This is in agreement with the fact that α-catenin can exist both as monomers and homodimers in the cytosol (Drees et al., 2005). When nascent contacts begin to form, the regional densities of AJ-associated proteins, including α-catenin rises, which could promote the formation of α-catenin homodimers as well as α-catenin/β-catenin heterodimers. The production of α-catenin homodimers might then serve as a feedback mechanism to dampen lamellipodial movements as cell-cell junction formation progresses (Drees et al., 2005). Although still untested, this model is consistent with the loss-of-function and mutagenesis studies that implicate α-catenins in radial cable formation (Drees et al., 2005; Vasioukhin et al., 2000; Yamada et al., 2005).

These provocative new studies hint at a mechanism of how α-catenin might function independently of cadherin-mediated AJs to govern actin dynamics. However, just as cadherin-mediated AJs are unlikely to function solely as plasma-membrane-associated sinks to prevent β-catenin from transmitting a Wnt signal, they are also unlikely to regulate actin dynamics solely by balancing the pools of α-catenin monomers and homodimers. Indeed, components of AJs bind to many actin-binding proteins, including linear actin-polymerizing factors, and increasing evidence suggests that at least some of these proteins are also involved in integrating the actin-myosin cytoskeleton across an epithelial sheet. In a recent yeast two-hybrid screen, α-catenin was found to bind to formins, which are mediators of linear actin polymerization, and, in vivo, formin-GFP proteins localize to cell-cell borders in wild-type, but not in α-catenin-deficient, keratinocytes (Kobielak et al., 2004). Vasp/Ena proteins are also potential mediators of linear actin cable organization (Bear et al., 2000; Krause et al., 2003), and they too fail to localize to cell-cell junctions in the absence of α-catenin (Vasioukhin et al., 2000). Furthermore, F-actin bundling capabilities might be provided by α-actinin and myosin II as well as by α-catenin homodimers, providing multiple ways in which cadherin-mediated AJs could serve as dynamic instigators of actin remodeling.

Whether α-catenins and/or cadherin-mediated AJs regulate actin dynamics alone in vivo or whether they act in conjunction with Nectins, desmosomes, and/or TJs are all questions for the future. That said, the complexity and possible redundancy make resolving these functions in vivo a difficult problem. Conversely, while in vitro studies can simplify the system, they may do so in ways that are not necessarily physiologically relevant. While further work is needed, these intriguing results suggest that α-catenin may contribute to the

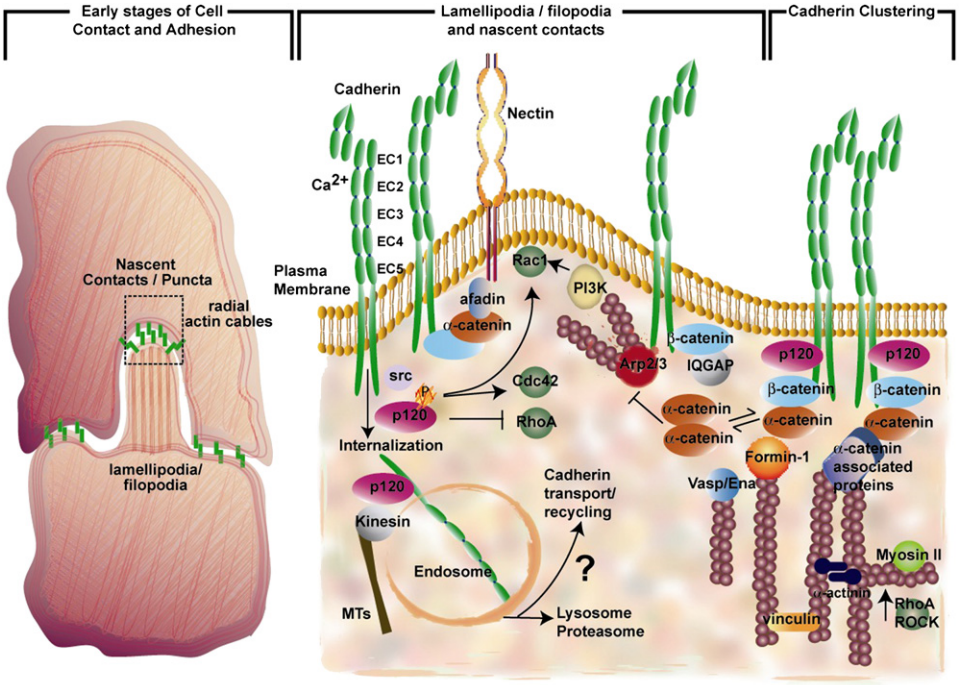

Figure 1. Stages of Cadherin-Mediated Adhesion in Epithelial Cells

During the initial stages of intercellular adhesion, cells extend filopodial/lamellipodial extensions that enhance cell-cell contacts. Such dynamic membrane protrusive activity involves the actin cytoskeleton and Rho GTPases. Cadherin-catenin complexes are recruited to these nascent contacts, referred to as puncta, in a way dependent on Nectin/Afadin-based cell adhesions. *cis*-dimers of cadherin-catenin complexes engage in highly dynamic productive homophilic contacts, together with rearrangements of the actin cytoskeleton. These events are orchestrated by both α-catenin and p120-catenin. When more nascent contacts begin to form, the densities of AJ-associated proteins, including α-catenin, rise and promote the formation of α-catenin homodimers that may then serve as a feedback mechanism to dampen lamellipodial movements and promote the formation of radial actin cables as cell-cell junction formation progresses. At intermediate stages of intercellular adhesion, the lateral clustering of cadherins promotes the association of actin-binding and actin-polymerizing proteins. Under these conditions, membrane sealing is enhanced, and eventually radial actin cables also rearrange and get stabilized and bundled by myosin II, α-actinin, and possibly α-catenin homodimers. Establishment of mature cell contacts reorganizes the actin cytoskeleton to this more static state.

dynamic cytoskeletal and junctional remodeling that is fundamental during embryonic development, tissue remodeling, and wound repair within a tissue.

The formation of cadherin-mediated contacts and the dynamic organization of the actin cytoskeleton are also regulated by the subfamily of Rho GTPases, including Rac1, Cdc42, and RhoA. Upon formation of nascent contacts, Rac1 becomes activated and recruited to these sites in a fashion dependent upon phosphoinositide 3-kinase (PI3K) (Ehrlich et al., 2002; Kovacs et al., 2002; Noren et al., 2001). This leads to the recruitment and activation of Arp2/3 at cadherin-mediated contacts, promoting the formation of actin branched networks (Kovacs et al., 2002). This overall process is suggested to be inhibited by α-E-catenin (Drees et al., 2005) (Figure 1). On the other hand, Rac1 may contribute to the stable formation of nascent contacts through its effector IQGAP. By inhibiting IQGAP, Rac1 facilitates the interaction of α-catenin with β-catenin (Kuroda et al., 1998). In *Xenopus*, IQGAP localizes at AJs in regions undergoing active morphogenetic movements (Yamashiro et al., 2003). Thus, Rac1 may regulate the balance between a dynamic to a more static state.

In addition, Cdc42 has also been show to regulate IQGAP (Kuroda et al., 1998); and in a similar way to Rac1, it gets activated during the early steps of cadherin contacts (Noren et al., 2001). Cdc42 promotes the formation of filopodial protrusions that also facilitate the interactions between neighboring cells. In both *Drosophila* and in the nematode *C. elegans*, these protrusions are required to seal and fuse epithelial cells during tissue morphogenesis (Bloor and Kiehart, 2002; Raich et al., 1999). In primary keratinocytes, filopodial protrusions physically embed into the neighboring cells, drawing cell surfaces together (Vasioukhin et al., 2000). At these sites vinculin, zyxin, VASP, and Mena are all recruited in an α-catenin-dependent manner (Vasioukhin et al., 2000). In the absence of α-catenin or when VASP/Mena function is prevented, keratinocytes still send out filopodia, but they fail to reorganize the actin cytoskeleton at AJs and do not seal cell borders (Vasioukhin et al., 2000).

Later stages of AJ formation include the maturation/expansion of nascent contacts through clustering of cadherins (Adams et al., 1998; Vasioukhin et al., 2000; Yonemura et al., 1995). This is accompanied by the remodeling of the actin-myosin II cytoskeleton by RhoA and the Rho-activated kinase, ROCK. Radial actin cables at junctions appear to function with myosin and generate tension across a growing epithelial sheet (Shewan et al., 2005; Vaezi et al., 2002) (Figure 1). However, their involvement seems to be dependent upon cell context (Noren et al., 2001; Sahai and Marshall, 2002; Vaezi et al., 2002). In keratinocytes Rho/ROCK-dependent

radial actin cables associate with cadherin-mediated AJs in the apical plane of the monolayer in a process dependent on α-catenin (Vaezi et al., 2002). This mechanism promotes the formation of polarized actin-myosin networks and the proper organization of cell monolayers that might be important during wound healing and epidermal stratification. This pathway appears to be conserved in eukaryotes, since in *Drosophila*, Rho1 activity is required for the proper distribution of DE-cadherin at AJs and has a major impact in morphogenetic processes (Bloor and Kiehart, 2002). In addition, both α-catenin and p120-catenin bind to Rho GTPase (Magie et al., 2002). The role of Rho GTPases in coordinating cell adhesion and actin dynamics is also a process that involves p120-catenin, as will be discussed below.

An additional α-catenin-interacting protein that is likely to be involved in the maturation/expansion of cadherin-mediated contacts is vezatin, a myosin-VIIA-interacting protein. This protein might connect cadherin-mediated AJs indirectly to myosin VIIA and to the actin cytoskeleton, thereby strengthening cell-cell adhesion (Kussel-Andermann et al., 2000). In addition to coordinating actin-myosin dynamics, α-catenin also binds to the cortical protein spectrin, which might stabilize intercellular adhesion by integrating the complexes into this macromolecular membrane structure (Pradhan et al., 2001).

α-catenin may also regulate the establishment of other junctional complexes, since it functionally links developing AJs to TJs, in part through its association with ZO-1 (Rajasekaran et al., 1996). In this way, α-catenin's functions may lead to the proper establishment of intercellular contacts contributing to the maintenance of tissue architecture and homeostasis.

p120-Catenin and Its Roles in Adherens Junction Stabilization and Actin Dynamics

p120-catenin is the prototypic member of the subfamily of p120 armadillo-related proteins, which includes the closely related proteins δ-catenin/NPRAP, p0071, and ARVCF (*a*rmadillo-*r*elated gene deleted in *v*elo-*c*ardio-*f*acial syndrome) and the most distantly related proteins plakophilins 1–3 (Hatzfeld, 2005). p120-catenin and its closely related members associate with cadherin-mediated AJs and stabilize them at the membrane (Davis et al., 2003; Ireton et al., 2002; Xiao et al., 2003). The desmosomal plakophilins do play a role in stabilizing desmosomal proteins at the plasma membrane, but whether they do so in a similar way to p120-catenin is not yet clear (Hatzfeld, 2006). Several p120-catenin isoforms can be generated by alternative usage of translation initiation codons and by differential splicing events, offering additional possibilities for further diversification in expression and functions in mammalian cells (Keirsebilck et al., 1998).

p120-catenin functions in different ways to regulate cell adhesion. These include (1) the dynamic regulation of the actin cytoskeleton (Anastasiadis and Reynolds, 2001), (2) transport of cadherins to the membrane, and (3) stability of cadherins at the membrane (Reynolds and Carnahan, 2004). Reminiscent of the newfound cytosolic functions postulated for α-catenin in the regulation of actin dynamics (Drees et al., 2005; Yamada et al., 2005), it is cytosolic p120-catenin that appears to be the modulator of this process, but in this case, through p120-catenin's ability to regulate Rho GTPases (Akhtar and Hotchin, 2001; Anastasiadis and Reynolds, 2001; Apodaca, 2001) (Figure 1).

The precise mechanisms by which p120-catenin modulates the activity of the subfamily of Rho GTPases are still not well understood, but it has been proposed that it acts as a guanine nucleotide dissociation inhibitor (GDI) by binding to and preventing RhoA activity (Anastasiadis and Reynolds, 2000; Magie et al., 2002). Conversely, p120-catenin activates both Rac1 and Cdc42, probably through its interaction with VAV2, a guanine nucleotide exchange factor (GEF) (Anastasiadis et al., 2000; Grosheva et al., 2001; Noren et al., 2000). Interestingly, the association of p120-catenin with cadherins and Rho GTPase regulation seems to be a mutually exclusive event (Anastasiadis et al., 2000).

In this regard, when AJs are abundant (e.g., when cell density within a tissue is high), p120-catenin would be expected to be largely associated with cadherin-mediated AJs. In situations where cell density is reduced (e.g., in a wound-condition), p120-catenin would likely be largely cytoplasmic, RhoA would be suppressed, Rac1/Cdc42 would be activated, and migratory behavior would be stimulated (Grosheva et al., 2001; Noren et al., 2001) (Figure 1). Indeed in epidermal cultures, during the early steps of cell adhesion, cells respond by extending lamellipodia and filopodia, reflective of elevated Rac1/Cdc42 activity (Ehrlich et al., 2002; Vasioukhin et al., 2000) and other signal transducers such as phosphatidylinositol 3-kinase (PI3K) and growth factor ligands for transmembrane receptor tyrosine kinases (Mege et al., 2006; Noren et al., 2001; Yap and Kovacs, 2003). Both p120-catenin and α-catenin are recruited to the contact sites, along with the membrane association of Rac1 (Gavard et al., 2004), which collectively contribute to the extension of the contact surface and maturation of cadherin-mediated AJs (Yap et al., 1998).

p120-catenin also regulates cell adhesion by promoting the transport and stability of cadherins at the membrane. A number of recent advances have shown that the rate of cadherin internalization and degradation is enhanced when p120-catenin expression is either reduced by siRNA (Davis et al., 2003), sequestered by ectopic expression of cadherin molecules that lack the extracellular domain, or sequestered by expression of inappropriate cadherins (Maeda et al., 2006; Xiao et al., 2005). But how are these events related to the regulation of cadherins by p120-catenin under physiological conditions? It is known that cadherin-mediated adhesion can be regulated by several signals emerging from the microenvironment, such activation of receptor tyrosine kinases and phosphatases (Gumbiner, 2000). Indeed, p120-catenin was originally described as a Src substrate (Reynolds et al., 1989) and is phosphorylated by tyrosine and serine kinases (Daniel and Reynolds, 1997; Reynolds and Roczniak-Ferguson, 2004). These events correlate with the spatio-temporal dissociation of p120-catenin from cadherin-catenin complexes that may lead to the recycling or degradation of cadherins required during epithelial remodeling, and when uncontrolled may promote tissue degeneration and cancer (Reynolds and Roczniak-Ferguson, 2004). It has been proposed that exposure of cadherin's JMD could result in a direct interaction with Hakai, an E3-ubiquitin kinase

that binds to tyrosine-phosphorylated E-cadherin (Fujita et al., 2002) and/or the protease presenilin I/γ-secretase (Baki et al., 2001; Marambaud et al., 2002). However upon p120 depletion, neither tyrosine kinase or presenilin inhibitors are able to rescue cadherin levels at the membrane, and instead its degradation is promoted by a mechanism that seems to involve its internalization and targeting to proteasomal or lysosomal compartments (Bryant et al., 2005; Davis et al., 2003).

By regulating the levels of cadherins residing at the membrane, p120-catenin may be able to control the dynamic rearrangement of adhesive complexes during developmental processes and epithelial remodeling within a tissue. How the process is coordinated is still unclear. A priori, it could be that p120 regulates cadherin levels at the membrane by controlling its endocytosis and targeting to degradative compartments. Alternatively, it may do so by recycling cadherins to the membrane. Several studies indicate that cadherins are selectively internalized in epithelial monolayers that are undergoing dynamic remodeling, and this is accompanied by the accumulation of clathrin-coated vesicles at AJs (Le et al., 1999; Palacios et al., 2001; Palacios et al., 2002). However, clathrin-independent pathways have also been described (D'Souza-Schorey, 2005). In endothelial cells, p120-catenin modulates the internalization of VE-cadherin through a clathrin-mediated pathway (Xiao et al., 2005). Endosomes apparently can associate with both actin- and microtubule-based motor proteins. Although p120-catenin does not localize to vesicular pools, it is possible that the underlying mechanism acts through p120-catenin's ability to modulate actin dynamics by regulating Rho GTPases (Apodaca, 2001). Rho GTPases are also known to act in specific cell compartments. Whether p120-catenin's effects on Rho GTPases are compartmentalized, and if so how, awaits further explorations. Finally, it has been described that p120-catenin interacts with microtubules (Franz and Ridley, 2004), and time-lapse imaging of neurons has suggested that delivery of N-cadherin to the growth cone is accelerated by p120-catenin's interactions with kinesin motor proteins (Chen et al., 2003). In these ways, p120-catenin may promote recycling of cadherins that might otherwise be routed to degradation (Figure 1).

α-Catenin: Beyond the Mechanics of Coordinating AJ Formation and Associated Actin Dynamics

In 1997, genetic data unveiled a central role for α-E-catenin in cell adhesion in early mouse embryogenesis. In that study, zygotic mutants for α-E-catenin failed to hold their interactions in the trophoblast epithelium, and the development of the early embryos was blocked at blastocyst stage (Larue et al., 1994; Torres et al., 1997). This phenotype resembled the defects observed in E-cadherin mutant embryos (Larue et al., 1994; Torres et al., 1997), reflective of their shared function in AJ formation. Although *α-catenin* null mutants in *Drosophila* are still not available, mutations in the α-catenin-binding site of the fly β-catenin disrupt adhesion, suggesting that α-catenin's interactions with core AJ components are essential in holding cells together (Orsulic et al., 1999). While these lessons underscore the importance of α-catenin in sustaining cell adhesion, conditional loss-of-function studies with α-catenin have uncovered unexpected cell-autonomous behaviors that could not be readily explained by defects in cell-cell adhesion alone.

Among the early studies leading to this view was the conditional targeting of the *α-catenin* gene in the skin epidermis of E14.5 mouse embryos (Vasioukhin et al., 2001). Several days later, α-catenin was efficiently lost throughout the embryonic skin, but in vivo, E-cadherin/β-catenin complexes still localized to cell-cell borders, and ultrastructurally, cell-cell borders seemed largely intact. Remarkably, however, the epithelium internalized to generate masses of hyperproliferative cells that resemble squamous cell carcinoma (SQCC) in situ (Vasioukhin et al., 2001). Upon grafting, the *α-catenin* null epidermis systematically forms first papilloma-like undulations, followed by breakdown of the underlying basement membrane and finally epithelial-mesenchymal transitions resembling invasive SQCC (Kobielak and Fuchs, 2006) (Figure 2A). In addition, hair follicle morphogenesis was impaired.

Loss-of-function mutations in *α-catenin* have been found in cancer cells from lung, ovary, and prostate. In a recent study, 33 of 40 human SQCCs of the skin exhibited a reduction or loss of α-catenin antibody staining (Kobielak and Fuchs, 2006). By contrast, only two of these tumors displayed obvious signs of nuclear β-catenin, which is a hallmark of familial colon cancers harboring mutations in the APC protein necessary for β-catenin degradation and turnover. Moreover, in both mouse and human skin, stabilizing mutations in β-catenin cause pilomatricomas, a form of hair tumor (Chan et al., 1999; Gat et al., 1998; Lo Celso et al., 2004; Van Mater et al., 2003). Taken together, these findings suggest that the effects of loss-of-function mutations in α-catenin and stabilization mutations in β-catenin can be distinct, even though there are some situations where perturbations in α-catenin can impact on both nuclear accumulation of β-catenin and Wnt signaling (Gottardi and Gumbiner, 2004; Sehgal et al., 1997).

Upon culturing, *α-catenin* null epidermal cells show enhanced migratory behavior, increased sensitivity to insulin growth factor stimulation, and elevated Ras and MAPK activity (Vasioukhin et al., 2001). In addition, both in vivo and in culture, *α-catenin* null keratinocytes display enhanced activation of NFκB and immune infiltration, which are also features of human SQCC (Kobielak and Fuchs, 2006).

In the central nervous system, mutations in *α-N-catenin* result in mice displaying alterations in the lamination and organization of cerebellum, marked by hypoplasia and abnormal lobulation (Park et al., 2002; Takeichi and Abe, 2005). Conversely, when *α-E-catenin* is conditionally ablated in neural progenitors, mice display a loss of intercellular adhesion but brain hyperplasia (Lien et al., 2006a, 2006b) (Figure 2B). In contrast to the hyperplasia in α-E-catenin-deficient skin epithelium, that seen in the *α-E-catenin* null neural progenitor population has been traced to a concomitant superactivation of the sonic hedgehog (Shh) pathway. Shh is a potent stimulator of proliferation and cell survival in the neural progenitor pool, as well as in a number of other cell types. In skin, Shh is normally expressed in hair follicles, whose development is suppressed in the *α-E-catenin* null state. For the neural progenitor study, Vasioukhin and colleagues used a novel pharmacological strategy that

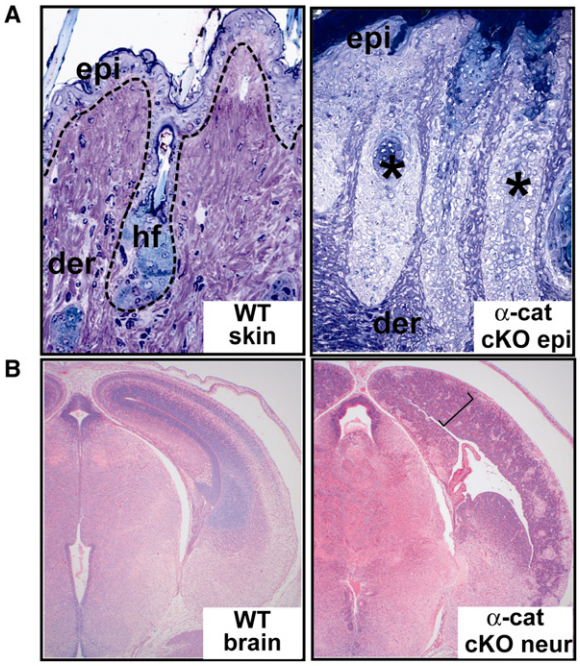

Figure 2. Conditional Ablation of α-E-Catenin Results in a Hyperproliferative State Resembling Cancer Both in Skin Epidermis and in Neuronal Progenitors in the Brain

(A) Skin. Embryonic day 18.5 skins from wild-type (WT) and K14-Cre-mediated, α-E-catenin conditionally targeted (cKO) mice were grafted onto the backs of athymic (*Nude)* mice, defective also in hair formation. The absence of α-E-catenin promotes epidermal hyperproliferation and the recruitment of proinflammatory infiltrates of eosinophils, macrophages, and neutrophils. By 60 days post engraftment (shown), undulating epidermal masses of α-E-catenin null cells exist, with no signs of hair follicle formation (asterisk). By 70 days, the underlying basement membrane has been invaded in discrete areas, and features of epithelial-to-mesenchymal transitions typical of squamous cell carcinoma arise (pictures kindly provided by H. Amalia Pasolli; Kobielak and Fuchs, 2006).

(B) Coronal sections of developing cerebral cortex from E15.5 WT and α-E-catenin conditional mutant mice. The specific deletion of α-E-catenin in neural progenitors causes cortical hyperplasia and dysplasia when compared to controls. Note the abnormal size of the α-catenin conditional null brain, which correlates with a shortening of the cell cycle of neural progenitors, decreased apoptosis, and loss of differentiation (pictures kindly provided by V. Vasioukhin; Lien et al., 2006a).

uncoupled the Shh/proliferative effects from defects in neuroepithelial polarization (Lien et al., 2006a).

The importance of α-catenin has also been underscored in studies centering on spindle orientation in mitotic basal epidermal cells. During embryonic development, epidermal cells change their spindle orientations from being parallel to largely perpendicular to the underlying basement membrane that separates the epidermis from dermis. This change occurs concomitant with stratification and involves a set of proteins, including Par3, aPKC, LGN, and mInsc, that are required for the asymmetric divisions that lead to differentially fated daughter cells in *Drosophila* and *C. elegans* (Lechler and Fuchs, 2005; Morrison and Kimble, 2006). In the fly neuroblast, DE-cadherin has been implicated (Le Borgne et al., 2002; Yamashita et al., 2003), and in the mouse, the absence of α-E-catenin results in randomized spindle orientations, and the proteins associated with these asymmetric divisions lose their apical orientation (Lechler and Fuchs, 2005). Although additional studies will be needed to sort out the underlying mechanisms involved, they seem likely to be rooted in roles for AJ proteins that include properly orienting the Par3/aPKC proteins as well as in organizing not only F-actin but also microtubules in cells (Etienne-Manneville and Hall, 2002).

p120-Catenin: Beyond the Mechanics of Coordinating AJ Formation and Associated Actin Dynamics

In lower eukaryotes, the effects of *p120-catenin* null mutations are relatively modest. p120-catenin may promote cell adhesion and contribute slightly to morphogenesis, but it is dispensable for viability in *Drosophila* and in the nematode *C. elegans* (Fox et al., 2005; Myster et al., 2003; Pettitt et al., 2003).

In flies, *p120-catenin* mutants reveal no overt changes in junction structure or function (Fox et al., 2005; Myster et al., 2003). However, its loss enhances the phenotype of DE-cadherin mutants (Myster et al., 2003), and its absence slows but does not disrupt dorsal closure (Fox et al., 2005; Myster et al., 2003). Similarly, the JMD domain of DE-cadherin is not required for *Drosophila* development in vivo (Pacquelet et al., 2003). Although Rho1 regulates DE-cadherin distribution, it is not clear whether Rho1 does so through its interactions with p120-catenin (Magie et al., 2002; Fox et al., 2005). The ability of Rho GTPases to act in specific cell compartments makes the resolution to such issues difficult.

It has been suggested that p120-catenin participates during developmental processes in sensing signals that inform cells about the position and identity of their neighbors. In a recent study, a broad targeted reduction of the Src kinase inhibitor Csk during fly eye development caused enhanced Src activity accompanied by enlarged organ size due to an increase in proliferation concomitantly with decreases in apoptosis and zonula adherens junctions (functionally equivalent to mammalian AJs) (Vidal et al., 2006). In searching for a link between dCsk and dE-cadherin, Cagan and colleagues (Vidal et al., 2006) became intrigued by p120-catenin, since it was originally identified as a Src substrate (Reynolds et al., 1989). Upon testing, however, reductions in the levels of p120-catenin did not rescue the overall alterations observed in the eye epithelia.

By contrast, loss of dCsk in discrete areas within the *Drosophila* eye caused the removal of *dCsk* null cells surrounded by normal epithelia by a mechanism that involves migration and apoptotic cell death. Remarkably, when mated on a *p120-catenin* null background, the migratory and apoptotic phenotypes of these *dCsk* mutant cells were suppressed. Intriguingly, the mechanism that promotes this behavior involves Rho1 activity, revealing a role for p120-catenin/Rho1 in protecting epithelial tissue integrity, possibly by removing abnormal cells from healthy tissues (Vidal et al., 2006). These data are consistent with those obtained in mammalian cells, where Src activity regulates p120-catenin functions, including its localization to the cytoskeleton (Anastasiadis and Reynolds, 2000). In addition, considerable evidence supports the view that cytoplasmic p120-catenin modulates Rho activities, indicating that this circuitry has ancient origins and providing a possible explanation for

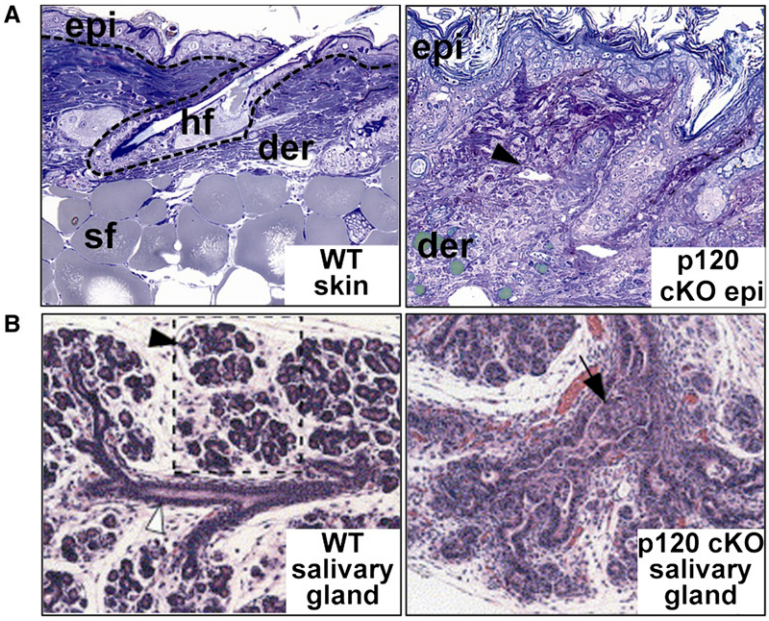

Figure 3. Consequences of p120-Catenin Ablation in Skin and in the Submandibular Salivary Gland

(A) Skin sections from WT and K14-Cre mediated p120-catenin conditional mutant mice (P60). Loss of p120-catenin results in hair loss and epidermal hyperproliferation as a consequence of a chronic inflammatory skin disease. Note that the absence of p120-catenin results in the degeneration of hair follicles, enlarged blood vessels (arrow), and the recruitment of inflammatory infiltrates in the underlying dermis. Epi. epidermis; der, dermis; sf, subcutaneous fat (pictures kindly provided by H. Amalia Pasolli; Perez-Moreno et al., 2006).

(B) Sections of submandibular salivary glands from P1 WT and MMTV-Cre-mediated p120-catenin conditional mutant mice. In the absence of p120-catenin, the acinar compartments in the salivary glands degenerate, and the normal ducts (white arrow) that drain into the mouth are occluded by masses of hyperproliferative cells that display features of high-grade intraepithelial neoplasia (black arrow) (pictures kindly provided by Al Reynolds; Davis and Reynolds, 2006).

why cells at tumor boundaries are more susceptible to acquiring metastatic behavior.

Studies on *Xenopus laevis* embryos reveal that p120-catenin and its close relative ARVCF are essential for gastrulation and axial elongation. The underlying mechanism involves not only Rac/Rho GTPases but, in addition, the transcriptional repressor Kaiso (Fang et al., 2004; Kim et al., 2002, 2004). p120-catenin acts by binding to Kaiso, compromising its association with DNA and resulting in derepression of Kaiso target genes (Daniel and Reynolds, 1999; Prokhortchouk et al., 2001; Rodova et al., 2004). Thus, reminiscent of its close cousin β-catenin, p120-catenin can directly influence not only AJ stability but also gene expression.

Some studies have suggested that Kaiso impacts on noncanonical *Wnt11* gene expression. In an interesting twist, however, depletion of Kaiso in *Xenopus* embryos results in the direct activation of certain canonical Wnt genes such as Siamois (Park et al., 2005). That said, loss-of-function mutations in Kaiso do not alone promote the development of the embryonic axis, even though its expression can inhibit axis duplication promoted by β-catenin. Thus, p120/Kaiso activities may participate by modulating Wnt signaling during *Xenopus* morphogenetic events. However, it is still not clear when and how this balance may be affected by other regulatory factors that control both p120 distribution and its interaction with Kaiso. Interestingly, in this issue of *Developmental Cell*, Park et al. (2006) now show that p120-catenin's stability is altered by Wnt signaling. This involves the interaction of p120-catenin with Frodo, a functional regulator of Dishevelled, enabling p120-catenin to relieve Kaiso-mediated repression. Thus, it thus appears that both Wnt/β-catenin and p120-catenin/Kaiso pathways converge upon Wnt signaling in *Xenopus*.

Given the tantalizing results from *Xenopus*, it came as a surprise that mice lacking Kaiso show no obvious defects. This said, when *Kaiso* null animals are also missing a copy of *APC*, they exhibit resistance to developing polyps and intestinal tumorigenesis (Prokhortchouk et al., 2006). In this regard, it is notable that elevated levels of Kaiso are frequently seen in human cancers (Soubry et al., 2005; van Roy and McCrea, 2005). The simplest explanation, as yet untested, is that functional redundancy in mice, but not frogs, accounts for the strikingly different outcomes observed in these Kaiso depletion experiments. The apparent lack of a Kaiso homolog in lower eukaryotes is likely to impede the rate at which the many remaining questions about Kaiso can be easily addressed.

Irrespective of Kaiso's possible involvement, p120-catenin's ability to regulate the activity of Rho GTPases has a major impact on vertebrate development. In *Xenopus*, morpholino-mediated depletion of p120-catenin in the neuroectodermal tissues of the future head region enhances the activity of Rho GTPases and impairs the migration of cranial neural crest cells from the neural tube into the branchial arches, resulting in defective eye formation and malformation in the craniofacial cartilage structures derivatives of the cranial neural crest (Ciesiolka et al., 2004). A similar role for p120-catenin has been uncovered in mammals, where hippocampal neurons lacking p120-catenin display an increase in RhoA and a decrease in Rac1 activities, resulting in fewer filopodial-like projections (dendritic spines) that are necessary to stabilize synaptic contacts (Elia et al., 2006). In addition, the loss of p120-catenin causes reductions in other synaptic components, e.g., N-cadherin, which leads to further defects in the maturation of synaptic contacts (Elia et al., 2006).

p120-catenin is also required for mammalian epithelial tissue morphogenesis and homeostasis. When p120-catenin is ablated in the salivary gland, intercellular adhesion is severely impaired, acinar differentiation is blocked and hyperproliferation arises (Davis and Reynolds, 2006), consistent with a possible direct link between p120-catenin and neoplasias (Reynolds and Roczniak-Ferguson, 2004) (Figure 3B). Conditional

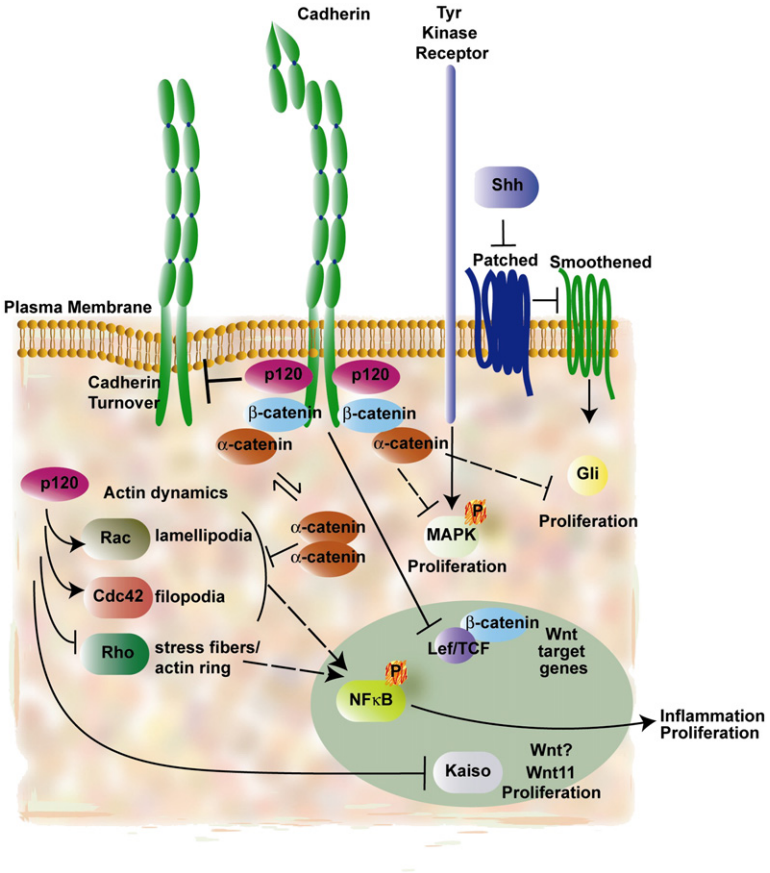

Figure 4. Role of Catenins in Mediating Signaling and Transcriptional Changes

Catenins regulate downstream signals that impact on several aspects of cell behavior. β-catenin has a well-established role in the Wnt signaling pathway, where it associates with members of the Lef/Tcf family of DNA-binding proteins to alter transcription. α-catenin orchestrates the appropriate balance between cell proliferation and differentiation by regulating a diverse number of signaling pathways including: Sonic hedgehog (Shh) and its downstream transcriptional mediator Gli; tyr kinase growth factor receptors and their downstream proliferation effectors Ras/MAPK; and NFκB, which when phosphorylated can enter the nucleus and regulate the expression of genes involved in proinflammatory responses. Loss-of-function mutations in α-catenin are associated with tissue degeneration, cancer, and marked inflammation. Loss-of-function mutations in p120-catenin have minor roles in lower eukaryotes such as *Drosophila* and *C. elegans*. However, in higher eukaryotes, alterations in p120-catenin promote the degradation of cadherins and deregulation of Kaiso. Additionally, cytosolic p120-catenin regulates the activities of Rho GTPases, inhibiting RhoA and activating Rac1 and Cdc42, thereby regulating actin cytoskeleton dynamics and cell migration. In addition, consistent with the broad roles for Rho GTPases in cell behavior, p120-catenin may also regulate several regulatory events, such as the RhoA-GTPase-mediated activation of IKK, the kinase that phosphorylates and activates NFκB. Genetic studies in mice have unambiguously demonstrated that the absence of p120-catenin is deleterious in skin, salivary gland, and brain tissues by modulating signals that promote tissue proliferation, migration, and inflammation, which may predispose the tissue to cancer.

loss-of-function studies in skin epidermis cast yet another interesting role for p120-catenin, this time in activating the nuclear factor NFκB, which in part is mediated by the associated activation of RhoA (Perez-Moreno et al., 2006). The activation of RhoA and NFκB are cell-autonomous and independent of p120's role in cell-cell junction formation, as they occur in cultured *p120-catenin* null keratinocytes and under conditions in which junctions do not form. In vivo, NFκB activation in the *p120-catenin* null epidermis results in the production and release of cytokines and chemokines, which in turn triggers a robust immune response and chronic inflammation (Figure 3A).

The *p120-catenin* null epidermis differs from the *α-catenin* null state in that the epidermis is only mildly hyperproliferative, and this appears to be an indirect consequence of the infiltration of immune cells. In addition, although a quantitative reduction in AJ components is seen, membranes remain sealed, as opposed to the observed effects on the salivary gland. In skin, overall adhesion is maintained, and the epidermis retains its impermeable barrier detected by inside-out and outside-in dye penetration assays. This might be attributable in part to a compensatory action provided by ARVCF. However, the presence of ARVCF did not completely rescue the cadherin and catenin organization at cell-cell junctions.

Whether the loss of p120-catenin and destabilization of AJs affect the ability of epidermal cells to actively repair wounds and/or undergo seemingly normal tissue homeostasis over the animal's lifetime has not yet been addressed in vivo. However, in vitro, where the stress level is high and there is a greater need for dynamic remodeling of cell-cell junctions, primary *p120-catenin* null keratinocytes do exhibit a marked delay in epithelial sheet formation (Perez-Moreno et al., 2006). Taken together, the phenotypes and consequences of null mutations in *p120-catenin* can be explained by a combination of both conventional and unconventional functions for this cadherin-mediated AJ protein.

Concluding Remarks

Recent studies have shaken the conventional perception of cadherin-catenin complexes as static cell-cell junction proteins that anchor AJs to the cortical actin cytoskeleton. In recent years, the functions of catenins have now been extended to establishment, stabilization, and maintenance of tissue architecture. Through direct and indirect mechanisms, catenins bind to F-actin and a myriad of actin-binding and actin-regulatory proteins

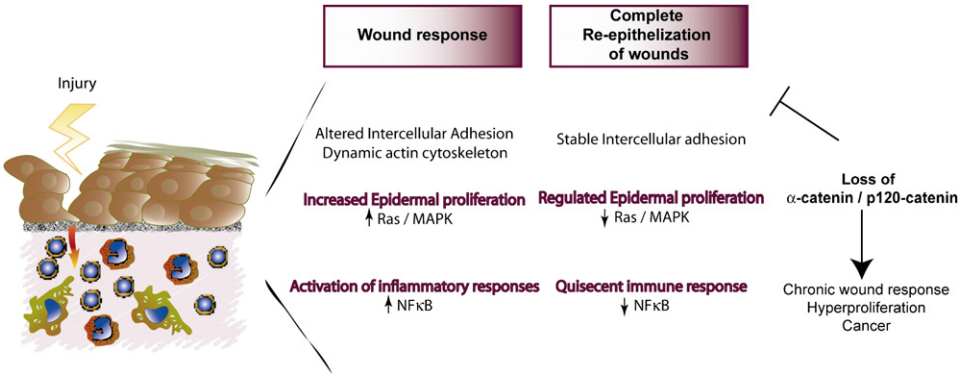

Figure 5. Proposed roles of α-Catenin and p120-Catenin during Wound Healing and Cancer

Overall, the effects of α-catenin and p120-catenin are to dampen Ras/MAPK-mediated proliferation and NFκB -mediated proinflammatory responses. The links between cell-cell adhesion, proliferation, and inflammation may be key during a normal wound response. When cell-cell contacts are severed, proliferation must be triggered to repair the wound, and the immune system needs to be recruited to fight infection. As the wound is sealed and cell-cell junctions are repaired, proliferation and immune infiltration must be dampened again. In cases where α-catenin and/or p120-catenin are genetically defective, however, the cycle continues unchecked, resulting in chronic inflammation, uncontrolled proliferation, and cancer.

and, by doing so, function intimately in organizing and regulating actin dynamics across epithelial sheets. However, catenins can no longer be viewed as simple AJ proteins. The advances over the past several years suggest strongly that catenins do not always function strictly at AJs, and even when they do, their functions can often extend outside of the realm of intercellular adhesion and actin organization. Compounding the underlying complexities are the tissue-specific and species-specific differences that have thus far been uncovered through the course of studying catenin functions. Given that, to date, the roles of catenins have only been studied in a handful of species and tissues, such differences are extraordinary.

For a number of years, it has been well accepted that β-catenin rests at the heart of canonical Wnt signaling. Through its association with Kaiso and Frodo, p120-catenin now appears to participate in this pathway as well. Through its ability to regulate Rho GTPases and actin dynamics, p120-catenin regulates cell migration, and by controlling Rho GTPase and Kaiso activities, it coordinates noncanonical Wnt pathway events including morphogenetic movements during development. And through its potential roles in regulating non-AJ-associated actin dynamics, epithelial polarity, asymmetric divisions, tyrosine kinase receptors, and Shh-mediated proliferative responses, α-catenin has now surfaced as a molecular switch for balancing growth, differentiation, and cell migration in tissues. With the link between p120-catenin, α-catenin, and NFκB activity, the catenins now act as connections between epithelial tissues and the immune system (Figure 4).

It is only through the magnitude and diversity of cellular processes that are perturbed or interrupted by alterations in catenins that researchers have begun to reconsider the prevailing dogma and put into place new models that might account for the bag of molecular tricks endowed to these seemingly jack-of-all-trade proteins. Based upon the evidence at hand, we envision a model whereby cadherins-catenins and their associated proteins integrate a dynamic state of intercellular adhesion, which requires the remodeling of the actin cytoskeleton and microtubule networks to achieve a more static state toward the maintenance of tissue architecture. During a wound response, the density of healthy cells is locally reduced and cellular junctions are severed at the site of injury. Through catenin signaling, this triggers a transient increase in proliferation and migration, as cells move in and repair the injury. In addition, the immune system is transiently recruited to fight against potential infection. As cell density increases and junctions are reassembled, AJs sequester excess catenins and dampen the response. When catenins are defective, the proliferative and/or inflammatory response proceeds unchecked, increasing the likelihood of chronic inflammation and/or cancer (Figure 5). The model is consistent with the data at hand, but given the rapid pace of the field, no doubt the model will necessitate some dynamic remodeling over time as additional pathways and molecular crossroads emerge.

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