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Bench to Bedside and Back Again: Molecular Mechanisms of α -Catenin Function and Roles in Tumorigenesis

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Abstract

The cadherin/catenin complex, comprised of E-cadherin, β -catenin and α -catenin, is essential for initiating cell-cell adhesion, establishing cellular polarity and maintaining tissue organization. Disruption or loss of the cadherin/catenin complex is common in cancer. As the primary cell-cell adhesion protein in epithelial cells, E-cadherin has long been studied in cancer progression. Similarly, additional roles for β -catenin in the Wnt signaling pathway has led to many studies of the role of β -catenin in cancer. Alpha-catenin, in contrast, has received less attention. However, recent data demonstrate novel functions for α -catenin in regulating the actin cytoskeleton and cell-cell adhesion, which when perturbed could contribute to cancer progression. In this review, we use cancer data to evaluate molecular models of α -catenin function, from the canonical role of α -catenin in cell-cell adhesion to non-canonical roles identified following conditional α -catenin deletion. This analysis identifies α -catenin as a prognostic factor in cancer progression.

Keywords

α -catenin; cancer; E-cadherin; cytoskeleton; adhesion

1. Introduction: organization and functions of the cadherin/catenin complex

Tissue integrity in multicellular organisms is dependent upon proper adhesion between adjacent cells. In mammalian epithelial cells, cell-cell adhesion is mediated by protein complexes organized into distinct functional structures termed tight junction, adherens junction and desmosome. The tight junction forms a diffusion barrier between cells and the extracellular environment [1] and desmosomes resist mechanical stress across the epithelium and maintain tissue integrity [2]. While both of these structures are essential for cell-cell adhesion, the adherens junction assembles at initial sites of cell-cell contact and precedes formation of the other junctional complexes [3].

Formation of the adherens junction is essential for compaction and subsequent organization of epithelia in early stages of embryo development [4–6]. Temporal regulation of adherens junction structure is also important for dynamic cell reorganizations that occur during

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embryogenesis, tissue homeostasis and wound healing. This occurs through disassembly of adherens junctions, leading to loss of cell-cell adhesion, loss of apical/basal polarity, cytoskeletal remodeling and increased migration in a process related to epithelial to mesenchymal transition (EMT) [7,8]. Although EMT is essential for proper development, its aberrant regulation is a common occurrence in cancer progression (see section 2) [7,8].

Adherens junctions are comprised of classical cadherins, catenins and associated proteins (Figure 1). E-cadherin, the primary cadherin of epithelial cells, is a trans-membrane glycoprotein that forms Ca^{++} -dependent homophilic and perhaps heterophilic contacts with cadherin molecules on adjacent cells through their extracellular (EC) domains [9]. Individual E-cadherin interactions are weak [10], but local clustering of cadherins may cooperatively increase the strength and stability of adhesion. The highly conserved C-terminal ~150 amino acid cytoplasmic domain of cadherin binds directly and indirectly to several cytoplasmic proteins, including β -catenin, α -catenin and p120, that also play roles in regulating cell-cell adhesion.

The distal C-terminal domain of E-cadherin binds to the 12 armadillo repeats of β -catenin and may be required for proper targeting of the complex to the basal-lateral membrane [11]. This interaction occurs in the endoplasmic reticulum soon after synthesis of E-cadherin [12], stabilizing the unstructured cytoplasmic domain of cadherin and preventing cadherin degradation [13]. At the membrane, E-cadherin and β -catenin form a complex of 1:1:1 stoichiometry with α -catenin, which binds to an N-terminal domain of β -catenin [14]. Alpha-catenin also binds directly to actin filaments [15], and it was assumed that α -catenin could bind actin and β -catenin simultaneously. Hence, adherens junctions were thought to be important in regulating actin reorganization and binding at sites of cell-cell contact, although recent studies have shown these interactions are more dynamic than previously thought (see section 4).

While E-cadherin, β -catenin, and α -catenin are key players in regulating cell-cell adhesion, other associated proteins are also essential in regulating the dynamics of adherens junction organization. p120-catenin, which binds to the juxtamembrane domain of E-cadherin, is important in cadherin stabilization since decreased p120 level causes E-cadherin internalization and loss of cell-cell adhesion [16]. Kinases and phosphatases that bind to cadherin, β -catenin or p120 positively and negatively affect the stabilization of the cadherin/catenin complex [17,18]. In particular, phosphorylation of β -catenin on Y142 by Fer or Fyn disrupts its binding to α -catenin, although mutations of this residue have not been tested for their physiological effects *in vivo* [19]. Taken together, assembly and disassembly of the cadherin/catenin complex is highly regulated and essential for proper cell-cell adhesion and development.

2. The cadherin/catenin complex in cancer

As would be expected for proteins essential in establishing and maintaining tissue integrity, loss of the cadherin/catenin complex plays a prominent role in cancer. Since defects in cadherin expression were first associated with cancer a few years after its discovery, the role and regulation of E-cadherin in many human cancers has been widely studied. The basis for changes in cadherin expression in cancer may be due to somatic or germline mutations, epigenetic modifications, transcriptional repression, or post-transcriptional regulation [20,21]. The majority of cancers of epithelial origin, termed carcinomas, lose E-cadherin mediated cell-cell adhesion [22] and undergo EMT [21].

EMT is thought to be an early and important step in cancer metastasis, a multistep process that leads to the establishment of the tumor in distant secondary tissues. In order to metastasize, cancer cells must lose contact with the primary tumor, invade the lymph or blood circulatory

systems (intravasate), leave the circulatory system for surrounding tissue (extravasate), and eventually maintain growth in their new environment [23]. It is metastasis, and not the primary tumor itself, which is the leading cause of death for the 500,000 people that die annually from cancer. For example, the current 5-year survival for localized breast cancer is 98%, but the rate decreases to 83% if the cancer has spread regionally and 26% for women with distant metastases [24].

Identifying patients that are likely to develop metastatic lesions is essential in determining optimal cancer treatments. For the majority of cancers, physicians commonly use clinical and pathological methods to stage cancers from benign to untreatable. These methods include macroscopic observations to assess cancer stage, including tumor size, lymph node involvement and distant metastasis [24,25], in addition to microscopic observations to assess cancer grade, including invasion into surrounding tissues and cellular dedifferentiation [26]. However, cancer staging/grading is limited by the random sampling of lymph nodes and possible errors in pathological screening. Therefore molecular markers that can be used as prognostic factors for metastasis and patient survival are critical to supplement current methods of cancer staging.

The prognostic value of the cadherin/catenin complex in defining tumor stage, histological grade, invasion, metastasis, cellular differentiation and patient survival has been reported for many human tumors (Table 1). Nevertheless, use of different tissue treatment methods and antibodies has led to variable results between studies, even when analyzing the same tumor type. While determining precisely which adhesion proteins serve as the best prognostic factors has yet to be resolved, it is clear that each component of the adherens junction plays an important role in cancer.

Previous cancer reviews have primarily focused on E-cadherin, p120 [27], and β -catenin [20]. Beta-catenin has been widely studied in cancer due to its dual role in the cadherin/catenin complex and as a critical component of the Wnt signaling pathway; in the presence of Wnt, stabilized β -catenin is translocated to the nucleus where it binds TCF/LEF transcription factors to induce target gene expression [28], including cancer related genes such as MYC, cyclin D1 and matrix metalloproteinase 7 [20]. Both loss of expression and gain-of-function mutations of β -catenin are common in human cancers resulting in loss of cell-cell adhesion and increased gene transcription [20]. In this review, however, our emphasis is on the molecular roles of α -catenin in cancer development and progression, and as a prognostic indicator of disease.

3. Molecular and functional characterization of α -catenin in normal and cancer states

Alpha-catenin was discovered in 1984 by Vestweber and Kemler as a 102 kD protein associated with the adhesion molecule E-cadherin (originally termed uvomorulin) [29,30]. Even before the identification of its amino acid sequence, the function of α -catenin as a linker between E-cadherin and the actin cytoskeleton had been proposed [31]; E-cadherin co-localized with actin bundles, was present in a Triton-X insoluble fraction and became soluble upon deletion of the catenin binding domain [31]. Formal evidence for a role of α -catenin as a cytoskeletal linker was provided by data that α -catenin bound and bundled actin filaments *in vitro* [15] (Figure 1), although simultaneous binding of α -catenin to E-cadherin, β -catenin, and actin was not reported.

The involvement of α -catenin in cancer was first studied in cell lines derived from human cancers; for example the lung cancer cell line PC-9 was found to have a homozygous deletion of part of the α -catenin gene [32]. In addition, loss of α -catenin occurs in cell lines derived from myeloid leukemia, leukocyte, colon, prostate [33–36] and other cancers, as well as

primary human cancers (Table 1). Although many cancer cell lines have mutations in α -catenin, similar mutations have not been identified in primary human cancers. Instead, it is thought that α -catenin expression is down-regulated in human cancer through epigenetic inactivation, such as DNA promoter methylation and histone modification [37], and possibly post-translational modifications [38]. Due to the belief that α -catenin functioned as a linker between E-cadherin and the actin cytoskeleton, loss of α -catenin in cancer progression was assumed to be a loss of cell-cell adhesion, similar to that caused by decreased E-cadherin expression. In support of this idea, some poorly differentiated human cancer cell lines were found to have normal E-cadherin expression but were deficient in α -catenin [39].

However, a more detailed evaluation of cancer data raises inconsistencies in the model that α -catenin serves simply as a link between the cadherin/catenin complex and the actin cytoskeleton. For example, there are cases where loss of both α -catenin and E-cadherin correlates with a worse prognosis than loss of either E-cadherin or α -catenin alone [40–44]. Such a synergistic effect would not be expected since loss of E-cadherin alone should also disrupt α -catenin binding to the actin cytoskeleton. In addition, there are examples in several types of cancers where, in comparison to loss of E-cadherin, loss of α -catenin is a stronger prognostic factor for invasion [43,45,46], survival [42,44,47–50], growth [51], dedifferentiation [45], and metastasis [43,45,46,49,52] (Table 1).

The most striking evidence for differences in the roles of α -catenin and E-cadherin was found when cancers were separated based upon the expression levels of these proteins [42,43,45, 46]. Since loss of E-cadherin and α -catenin are often correlated in cancer, dividing tumors into E-cadherin^(+ or -)/ α -catenin^(+ or -) expression groups can shed light on the differential effects of these proteins on cancer progression and survival. For example, Setoyama *et al.* found that the 5-year survival rate for patients with esophageal squamous cell tumors that were E-cadherin⁽⁺⁾ versus E-cadherin⁽⁻⁾ was 75.5% and 37.1%, respectively [42]. Similarly, the 5-year survival rate for α -catenin⁽⁺⁾ and α -catenin⁽⁻⁾ tumors was 88.6% and 26.3%, respectively. However, when the tumors were divided into E-cadherin⁽⁺⁾/ α -catenin⁽⁺⁾, E-cadherin⁽⁻⁾/ α -catenin⁽⁺⁾, E-cadherin⁽⁺⁾/ α -catenin⁽⁻⁾ and E-cadherin⁽⁻⁾/ α -catenin⁽⁻⁾ expression groups, the 5-year survival rate was 89.5%, 84.8%, 36.9% and 23.4%, respectively. Thus, when analyzed separately loss of either E-cadherin or α -catenin had similar effects on cancer survival, but when expression of E-cadherin and α -catenin were examined together loss of α -catenin resulted in a drastic decrease in 5-year survival compared to patients with tumors in which E-cadherin was also lost [42].

4. A new model of α -catenin as a local regulator of the actin cytoskeleton and membrane dynamics

Although data from human cancers indicate that α -catenin may have functions distinct from those directly associated with E-cadherin, cancer researchers could not explain these data based upon the well-accepted model of α -catenin as a direct link between the cadherin/catenin complex to the actin cytoskeleton. However, the first clues that α -catenin has additional molecular functions came from the conditional deletion of α -catenin in surface and oral epithelia in mouse embryos [53]. Consistent with a role in cell-cell adhesion, loss of α -catenin resulted in defective keratinocytes, including borders with missing epidermal segments and visibly peeling epidermis, although E-cadherin and β -catenin remained localized to cell borders. Unexpectedly, however, cells were also hyperproliferative, multinucleated and exhibited increased migration [53].

Definitive evidence of new roles for α -catenin in cell-cell adhesion and regulation of actin dynamics came from direct studies of protein-protein interactions [54,55]. In contrast to the old model in which E-cadherin, β -catenin, α -catenin and actin were thought to bind

simultaneously in a quaternary complex (Figure 1, left), α -catenin binding to β -catenin and actin was found to be mutually exclusive. This is due to an allosteric switch in the conformation of α -catenin in which α -catenin monomer preferentially binds the E-cadherin/ β -catenin complex while α -catenin homodimer binds and bundles actin filaments [54]. Alpha-catenin homodimers form at a concentration $\sim 10\times$ that of the concentration of α -catenin monomers in the cytoplasm of normal epithelial cells, indicating that α -catenin has to be concentrated in order to undergo dimerization, perhaps through clustering of the cadherin/catenin complex during cell-cell adhesion [54]. Although the binding domains of α -catenin to β -catenin and actin do not overlap, the α -catenin homodimerization and β -catenin binding do [56], thus establishing the mutually exclusive binding that was observed. Interestingly, α -catenin homodimers can functionally inhibit the Arp2/3 complex [54], a multimeric protein complex that nucleates branched actin filaments at the leading edge of cells [57]. These data have led to a re-evaluation of the textbook model of adherens junctions (Figure 1, center and right). The new model posits that in the absence of cell-cell contact, when the concentration of the cadherin/catenin complex at the membrane is low, active Arp2/3-mediated actin polymerization drives lamellipodial protrusion (Figure 1, center). As cell-cell contacts are initiated and mature, the local concentration of the cadherin/catenin complex increases above the critical concentration for α -catenin homodimerization. Since the β -catenin/ α -catenin binding affinity is relatively weak at $\sim 1\ \mu\text{M}$ [54], α -catenin disassociates from the complex, dimerizes, binds and bundles actin filaments and locally inhibits the Arp2/3 complex (Figure 1, right). This reorganization of actin dynamics at sites of cell-cell contact functions to decrease membrane activity, stabilize cadherin-mediated cell-cell adhesion, and possibly decrease cell migration [58].

The new model, in addition to other molecular data, suggests both canonical and non-canonical roles for α -catenin may be involved in cancer progression. For the remainder of the review we will re-consider, in the light of these new data and model of α -catenin functions, molecular roles of α -catenin and how perturbing those functions may lead to cancer.

5. A new interpretation of the consequence of α -catenin mislocalization in human cancers

5.1. Cytoplasmic accumulation of α -catenin

Although loss of α -catenin mRNA and protein in cancer cells can be attributed to epigenetic mechanisms of gene silencing, there are instances where loss of plasma membrane staining and subsequent cytoplasmic accumulation of α -catenin are associated with increased metastasis [59,60] and decreased patient survival [47,61,62]. The new model of α -catenin function posits that α -catenin conformation in the cytoplasmic pool is key to α -catenin function, rather than the membrane associated pool *per se*, since cytoplasmically localized α -catenin homodimers regulate actin and membrane dynamics (Figure 1, right). However, without membrane recruitment of α -catenin, the cytoplasmic concentration of α -catenin is too low for dimerization (Figure 1, center). Therefore, it is a *local* juxta-membrane cytoplasmic pool of α -catenin that exerts its function on the actin cytoskeleton and not the diffuse cytoplasmic pool observed in cancer cells. Loss of α -catenin from the cadherin/catenin complex could occur through two different mechanisms: a decrease in binding affinity to β -catenin and/or direct competition from another protein for binding to β -catenin.

Decreased binding between α -catenin and β -catenin likely occurs through changes in protein phosphorylation. Increased expression, or activation of the protein tyrosine kinases Src, Fer, EGFR or cMet are common in cancer and are associated with aberrant growth, EMT, cell scattering, and metastasis [7,17]. Phosphorylation on Y489 or Y654 in β -catenin decreases its affinity for E-cadherin [17], while phosphorylation of Y142 in β -catenin results in decreased

binding to α -catenin [19]. This latter site can be phosphorylated by Fer, Fyn or cMet and is conserved in all β -catenin homologues that function in cell-cell adhesion [17]. In addition to phosphorylation of β -catenin, a novel phosphorylation site Y148 on α -catenin has been identified that promotes β -catenin binding [63], but the kinase involved has not been determined. Significantly, over-expression of the protein tyrosine phosphatase SHP2, a known oncogene that is mutated and abnormally regulated in several cancers [64], results in decreased binding between α -catenin and β -catenin, perhaps through de-phosphorylation of Y148 [63]. Additional α -catenin phosphorylation sites S641 [65] and S652/655 [66] have been identified by large scale mass spectrometry studies but their biological significance has not yet been tested. Although more studies are required to determine the exact role of α -catenin and β -catenin phosphorylation in cancer, the existing data highlight the potential roles of kinases and phosphatases in disrupting α -catenin/ β -catenin binding from sites of cell-cell contact, thereby promoting tumorigenesis.

A second mechanism for disruption of α -catenin binding to β -catenin may be through competitive binding of a second protein. One candidate is IQGAP, a scaffolding protein whose known binding partners include F-actin, β -catenin, E-cadherin and the Rho GTPases Cdc42 and Rac1 [67]. Significantly, over-expression of IQGAP results in persistent localization of IQGAP to cell-cell contacts, decreased cellular adhesion, and increased cell migration and invasion [68,69]. Over-expression of IQGAP does not affect overall levels of α -catenin but reduces α -catenin binding to the cadherin/catenin complex [68]. Thus, induced dissociation of α -catenin from β -catenin upon IQGAP binding might decrease membrane localization and increase cytoplasmic accumulation of α -catenin, inducing multiple cancer phenotypes observed when IQGAP is over-expressed.

Changes in IQGAP expression and localization are found in human cancer. Over-expression and membrane localization of IQGAP, which is often found at the invasive front of tumors, is associated with poorly differentiated cancer cells and decreased survival in ovarian, lung, colon, endometrial, gastric, and glioma cancers [70–75]. In addition, a 15q26 amplification in gastric cancer cell lines was shown to result in increased IQGAP level [76]. Although increased level of IQGAP may have downstream effects on other cellular processes, its direct effect on α -catenin was shown in a human colon cancer cell line that migrates as a cell sheet when stimulated with HGF/SF [77]. Addition of HGF, which did not increase overall levels of IQGAP, increased localization of IQGAP to the membrane while simultaneously decreasing the amount of membrane-associated α -catenin. Upon addition of HGF, partial disruption of cell-cell adhesion resulted in a group of cells extending leading lamellipodia [77], likely due to the ability of IQGAP to stimulate Arp2/3-mediated actin polymerization [78]. Interestingly, this increase of membrane-associated IQGAP was enhanced if the cells were plated on fibronectin, suggesting extra-cellular environments likely play additional roles in the regulation of IQGAP and α -catenin in cancer [77].

In light of the new model of α -catenin function (Figure 1, right), what might the consequences of loss of membrane-associated α -catenin and increased diffuse cytoplasmic α -catenin be on cell behavior? One outcome may be a loss of inhibition of Arp2/3-mediated actin assembly due to low amounts of α -catenin dimer. Although this has not yet been tested, changes in Arp2/3 activity have been shown to affect cellular dynamics. For example, inhibition of the Arp2/3 complex by RNAi of one of its protein components led to less than 5% of cells with active lamellipodia [79], which demonstrates the importance of Arp2/3 in membrane activity. On the other hand, increased expression of Arp2/3 and its activator WASP in invasive breast cancer is prognostic for decreased survival and cancer recurrence [80]. Therefore, loss of α -catenin from the membrane of cancer cells could lead to increased Arp2/3 activity, membrane activity and cell migration.

5.2. Alpha-catenin in formation of gap junctions and desmosomes

The cadherin/catenin complex is important in initiating cell-cell adhesion but also in formation of other intercellular junctions, such as gap junction and desmosomes. Gap junctions, which allow intercellular communication between adjacent cells, are comprised of oligomeric connexins [81]. Down-regulation or impaired trafficking of connexins is common in human cancers [82]. Connexin expression is important in the control of tumorigenesis since re-expression of connexins in a connexin-deficient prostate cancer cell line was found to promote functional gap junction formation, inhibit growth and tumorigenicity, and induce normal cellular differentiation [83]. Significantly, over-expression of connexins in a PC-3 prostate cancer cell line lacking α -catenin did not result in targeting of connexins to the membrane or formation of functional gap junctions. However, transient expression of α -catenin in those cells resulted in proper trafficking of connexins from intercellular stores to the membrane [84]. Similar results were obtained in an α -catenin null colon cancer cell line unable to traffic desmosomal proteins; exogenous expression of α -catenin resulted in restoration of disorganized desmosomal proteins [85]. Thus, α -catenin regulates assembly of gap junctions and desmosomes in addition to regulating actin reorganization and membrane dynamics, further contributing to reasons why the loss of α -catenin has such deleterious effects in cancer.

5.2. Alpha-catenin expression in cancer metastasis

EMT is a common occurrence in cancer metastasis due to cells gaining an invasive and migratory phenotype, allowing them to detach from the primary tumor and intravasate into blood or lymphatic systems. Not surprisingly, metastatic cancers are often found to have down-regulated levels of α -catenin (Table 1). However, there are instances in which the secondary metastatic tumor site has normal or over-expressed levels of α -catenin compared to the primary tumor (Table 1), and the expression of α -catenin correlates with worse patient survival [86, 87]. This re-expression of α -catenin may be a late step in cancer progression and is likely involved in allowing cancer cells at the secondary site to adhere to surrounding normal cells [88].

6. Roles for α -catenin in cell proliferation, apoptosis and growth factor signaling pathways

6.1. Alpha-catenin in cell proliferation

Loss of α -catenin expression often leads to increased cell proliferation. This has been observed in cancer cell lines [89] and after α -catenin deletion in mouse epidermis and central nervous system [53,90]. As uncontrolled growth is a hallmark of human cancers, understanding the inhibitory effects of α -catenin on proliferation is critical. Although the mechanisms underlying this regulation are not understood, α -catenin is involved in multiple signaling pathways that regulate cell proliferation, including Ras/MAPK, NF κ B, Hedgehog (Hh) and Wnt, in addition to affecting the rate of apoptosis.

Since deletion of α -catenin leads to death at very early stages of mouse development [6], conditional α -catenin deletions have been used to determine roles for α -catenin in tissue maintenance and cancer. Conditional deletion of α -catenin in the skin during late embryonic development resulted in not only adhesion and migration defects, but also hyperproliferation with increased mitoses, due to sustained MAPK activation, that resembled pre-cancerous lesions [53]. MAPK, a kinase that can translocate to the nucleus to activate transcription factors, is downstream of the signal transduction protein Ras, a G protein that regulates cell proliferation, differentiation and morphology [91]. Activating mutations of Ras are common in cancer [92] and have been shown to induce loss of E-cadherin [93] and promote EMT [21], possibly through increasing expression of SLUG, a transcriptional E-cadherin repressor

[94]. In addition, inhibition of oncogenic Ras [95] or MAPK [93] in human cancer cell lines reverted the cancer phenotype by promoting cellular aggregation *in vitro* and decreasing tumor growth and metastasis when transplanted into mice [95]. Previous studies have demonstrated a direct effect of activated Ras on the cadherin/catenin complex, however the results from these α -catenin deletion experiments were the first to show that loss of α -catenin could directly affect Ras signaling, although the mechanism remains unclear.

To further study a link between loss of α -catenin and epidermal hyperplasia that resembled pre-cancerous tissue, skin from α -catenin knockout mice was grafted onto nude mice [96]. After 4–6 weeks the transplanted skin had tumor-like nodules resembling well differentiated grade I human squamous cell carcinoma. After 10 weeks the transplanted tissue resembled poorly differentiated grade III carcinoma. Microarray profiling determined that there was not only an up-regulation of Ras and MAPK, but also NF κ B target genes [96]. NF κ B, an antiapoptotic and proinflammatory gene involved in EMT and cancer progression [21,97], was also required for the maintenance of the transplanted tissue, likely through its ability to inhibit apoptosis [96]. How loss of α -catenin leads to increased activation of NF κ B has not yet been determined.

Conditional deletion of α -catenin in the mouse central nervous system (CNS) stem and neural progenitor cells at embryonic day 10.5 resulted in massive proliferation due to a shorter cell cycle and 50% decrease in apoptosis [90]. Microarray analysis and quantitative PCR showed up-regulation of the Hh target genes *Fgf15* and *Gli1*, in addition to *smoothened* (*Smo*) which participates in Hh signaling [90]. The Hh pathway is involved in stem cell maintenance and pattern formation, and is often mutated in basal cell carcinomas and other cancers [98]. Similar to inhibition of NF κ B in α -catenin deleted epidermis, inhibition of *Smo* resulted in a rescue of cell cycle length and apoptosis and decrease in the Hh target genes *Gli1* and *Fgf15* [90].

Together, these deletion studies highlight the cross-talk between the catenin/complex and proliferative signaling pathways such as Ras, NF κ B and Hh. Although the molecular mechanisms underlying the link between α -catenin and proliferation have not yet been determined, these results indicate that α -catenin functions not only as a cell-cell adhesion molecule, but also as a cell density sensor, thereby linking cell-cell adhesion with cellular proliferation [99].

6.2. Alpha-catenin in apoptosis

A decrease in apoptosis was observed following α -catenin deletion in the CNS [90], presumably due to up-regulated NF κ B similar to that following α -catenin deletion in the epidermis [96]. A link between α -catenin and apoptosis is supported by cancer data in which α -catenin was reintroduced into a myeloid leukemia cell line lacking α -catenin. Transfected cells failed to propagate in culture due to both a decrease in proliferation and increase in apoptosis. Although the mechanisms involving α -catenin in inducing apoptosis are unknown, data from human cancers indicate that p53 may play a role. p53, a transcription factor that induces cell death upon DNA damage and cellular stress, is mutated in half of human cancers [100]. In both lung and gastric cancer, a decrease in α -catenin expression was associated with increased expression of p53, likely a mutant form of p53 [52,101]. In addition, decreased α -catenin expression coupled with increased p53 is an independent prognostic factor for lymph node metastasis from gastric cancer [52]. Clearly further studies of the link between p53 and α -catenin expression are needed, as they may uncover novel roles for α -catenin not identified through classic adhesion studies. It should be noted, however, that deletion of α -catenin in the mouse mammary gland led to an increase in apoptosis with no hyperproliferation of tissue [102]. Thus, α -catenin is involved in apoptosis, but whether loss of α -catenin decreases or increases apoptosis appears to be dependent on the cellular context.

6.3. Alpha-catenin in growth factor signaling

Another pathway in which α -catenin may affect proliferation is through Wnt. While β -catenin is a direct target of the Wnt pathway, the intrinsic binding of α -catenin to β -catenin, which normally occurs at the plasma membrane, could also regulate β -catenin transcriptional activity in the nucleus. Over-expression of α -catenin in cancer cell lines and non-cancerous cartilage precursor cells (chondrocytes) led to decreased β -catenin transcriptional activity [103–105] and reduced interaction of β -catenin/TCF complex with a DNA probe *in vitro* [103]. Although it is not known if α -catenin directly competes binding of β -catenin/TCF to DNA *in vivo*, loss of α -catenin in cancer could lead to up-regulation of β -catenin target genes involved in proliferation and cancer. In support of this, partial depletion of α -catenin by siRNA in chondrocytes led to an increase in the basal level of β -catenin transcriptional activity [105]. Unexpectedly, α -catenin has also been observed in the nucleus of colon cancer cell lines [103,106], although this localization was observed only in dispersed, non-contacting cells in one cell line [106]. The observed nuclear localization of α -catenin in cancer cells may be due to a direct loss of α -catenin from the membrane, but whether this nuclear pool of α -catenin functionally inhibits β -catenin mediated transcription is unknown. A role for α -catenin in inhibiting β -catenin transcriptional activity is another promising area of study that might lead to new insights into how loss of α -catenin might contribute to the induction of tumorigenesis.

7. Concluding remarks

Previously, α -catenin was considered to be a simple structural linker between the cadherin/catenin complex and the actin cytoskeleton. Recent studies, and a re-evaluation of cancer data in light of new models of α -catenin function, indicate that α -catenin is at the nexus of multiple pathways controlling actin and membrane dynamics, proliferation and apoptosis, and growth factor signaling.

In general, disruption of the cadherin/catenin complex is a prognostic factor for cancer progression, but in some instances loss or mis-localization of α -catenin results in a more severe prognosis than loss of E-cadherin. These cancer studies highlight the importance of α -catenin in cancer induction, progression and survival, and indicate that α -catenin has more roles than previously assumed.

A new model of α -catenin function posits that dissociation of α -catenin from the cadherin/catenin complex leads to actin bundling and suppression of Arp2/3-mediated actin assembly; under normal conditions this might lead to decreased cell migration and stabilization of cell-cell adhesion. By analogy, therefore, loss of α -catenin in human cancers could result in rampant Arp2/3-mediated actin polymerization and increased lamellipodial membrane activity, thereby decreasing cell-cell adhesion and increasing cell migration and invasion of tumor cells. In addition to structural effects on the actin cytoskeleton, analysis of cancer data indicates that α -catenin plays roles in regulating cell proliferation. Loss of α -catenin in cancer cell lines and deletion of α -catenin in mouse models are associated with increased proliferation, decreased apoptosis and increased growth factor signaling, all of which are hallmarks of cancer.

Future experiments testing α -catenin roles in these pathways may yield new insights into molecular mechanisms of α -catenin functions in normal tissues, and the role of α -catenin in human cancer and its usefulness as a diagnostic and prognostic marker.

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Figure 1. Schematic representations of protein-protein interactions at sites of cadherin-mediated cell-cell adhesion

Left: the textbook model assumes a quaternary complex of cadherin/ β -catenin/ α -catenin/actin that is involved in cadherin clustering and stabilization of cell-cell adhesion. *Center/Right:* the new model of how the cadherin/catenin complex and actin organization are regulated based on data [54,55]. In the absence of cell-cell adhesion (*center*), a ternary complex of cadherin/ β -catenin/ α -catenin is formed, but the local concentration of α -catenin that may dissociate from the complex is too low to affect actin assembly (by the Arp2/3 complex); under these conditions, cell-cell adhesion is low and cell migration/membrane dynamics are high. *Right:* Upon cell-cell interactions through cadherin extracellular domains, ternary complexes of cadherin/ β -catenin/ α -catenin cluster. Dissociation of α -catenin from the cadherin/catenin complex leads to an increase in the local cytoplasmic concentration of α -catenin above the critical concentration for dimerization. These resulting juxta-membrane α -catenin dimers bundle actin filaments and suppress actin assembly by inhibiting the Arp2/3 complex; under these conditions, cell-cell adhesion is high and cell migration/membrane dynamics are low.

Table 1
Alpha-catenin as a prognostic marker in human cancers

Cancer type	Loss of α -catenin is a statistically significant prognostic factor for the following cancer phenotypes	Loss of α -catenin is more prognostic than loss of E-cadherin for the following cancer phenotypes	Expression of α -catenin in cancer metastasis compared to primary tumor
Breast [47,51,86,107–119]	Histological type and growth [51], grade [47,112,117], stage [47], metastasis [47], survival [47,111]	Survival [47], reduced more frequently in diffuse tumors [51]	Decreased protein levels [109,116,119], normal/increased protein levels [86,114]
Gynecological, [40,41, 120–128]	Grade [41,120], survival [120]	d.n.a.	Decreased mRNA levels [124–126], decreased protein levels [120], increased protein levels [122]
Esophageal/laryngeal [42, 45,48,59,129–131]	Differentiation [45,59], grade [129], stage [42,59, 129], infiltrative growth [45], metastasis [42,45,59], survival [48], [42]	Survival [42,48], metastasis and tumor differentiation [45]	Decreased protein levels [42,45,59]
Colorectal [46,61,87,132–139]	Differentiation [46,132,135, 137], invasion [46,135], metastasis [46,135,137], survival [137], [61]	Invasion and metastasis to lymph/ liver [46]	Decreased expression [46,135,137], increased expression [87],
Prostate [62,140–146], [147]	DNA aneuploidy [62,143], differentiation [144], grade [62,140,142,143,145], metastasis [62,140], survival [140], [147], [145], [62]	d.n.a.	d.n.a.
Thyroid [60,148–150]	Stage, tumor recurrence metastasis [148]	d.n.a.	d.n.a.
Oral [151–153]	d.n.a.	d.n.a.	Decreased expression [151,153]
Lung [49,101,154–157]	Differentiation [156] metastasis, survival [49]	Metastasis to lymph and survival [49]	d.n.a.
Liver [158–162]	Survival [159]	d.n.a.	d.n.a.
Pancreatic [163–168]	Grade [164,166], stage [165], metastasis [165,166], survival [165]	d.n.a.	Normal/increased expression [163]
Gastric [43,52,169–173]	Differentiation [43], depth invasion [43,173], metastasis [52,173]	Metastasis to lymph [43,52], and tumor invasion [43]	Decreased expression [43,52], mixed expression [169]
Skin [174–176]	d.n.a.	Significantly reduced α -catenin levels but not E-cadherin [174]	Decreased expression [176]
Bladder [44,177–180]	Grade [44,180], stage [178, 180], cancer progression [179], invasion, survival [44]	Survival [44]	d.n.a.
Other [50,181–203] [204]	Tumor growth [181], size [183], grade [182], invasion [183,200], survival [50,181]	Survival [50]	d.n.a.

Table 1. denotes α -catenin was an individual prognostic factor in univariate, but not multivariate, analysis. denotes α -catenin was an individual prognostic factor in univariate and multivariate analysis. d.n.a. denotes data not available. Cancers in Table 1 were separated based upon location of primary tumor, not cancer cell type. The table is a thorough report on the expression of α -catenin in cancers published in the past 20 years. However, the authors apologize in advance for any publications that may have been accidentally overlooked.