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A central role for cadherin signaling in cancer

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Abstract

Cadherins are homophilic adhesion molecules with important functions in cell-cell adhesion, tissue morphogenesis, and cancer. In epithelial cells, E-cadherin accumulates at areas of cell-cell contact, coalesces into macromolecular complexes to form the adherens junctions (AJs), and associates via accessory partners with a subcortical ring of actin to form the apical zonula adherens (ZA). As a master regulator of the epithelial phenotype, E-cadherin is essential for the overall maintenance and homeostasis of polarized epithelial monolayers. Its expression is regulated by a host of genetic and epigenetic mechanisms related to cancer, and its function is modulated by mechanical forces at the junctions, by direct binding and phosphorylation of accessory proteins collectively termed catenins, by endocytosis, recycling and degradation, as well as, by multiple signaling pathways and developmental processes, like the epithelial to mesenchymal transition (EMT). Nuclear signaling mediated by the cadherin associated proteins β -catenin and p120 promotes growth, migration and pluripotency. Receptor tyrosine kinase, PI3K/AKT, Rho GTPase, and HIPPO signaling, are all regulated by E-cadherin mediated cell-cell adhesion. Finally, the recruitment of the microprocessor complex to the ZA by PLEKHA7, and the subsequent regulation of a small subset of miRNAs provide an additional mechanism by which the state of epithelial cell-cell adhesion affects translation of target genes to maintain the homeostasis of polarized epithelial monolayers. Collectively, the data indicate that loss of E-cadherin function, especially at the ZA, is a common and crucial step in cancer progression.

Keywords

Cell-cell adhesion; E-cadherin; β -catenin; p120 catenin; Kaiso; Rho GTPases; EMT; Cancer progression; miRNA; PLEKHA7

Introduction

It is increasingly clear that traditional signaling pathways and mechanical forces converge at the cell-cell junctions to regulate the behavior of epithelial monolayers. The fact that the

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majority of human solid tumors are epithelial in origin has focused attention to the adhesion molecules at the junctions of epithelial cells and the signaling pathways involved in the maintenance of the epithelial phenotype. Cadherins, and their associated proteins, have emerged as key players in epithelial homeostasis and cancer.

The cadherin-catenin complex

Cadherins are cell surface glycoproteins with important functions in cell-cell adhesion, tissue patterning and cancer (for review, see¹⁻³). Classical cadherins, one of the five classes of proteins containing cadherin repeats⁴, are a prominent class of adhesion molecules. Through their extracellular domains, they interact with cadherins on adjacent cells in a Ca^{++} dependent, homophilic manner, to form cell-cell adhesions called adherens junctions (AJs)⁵. Mature AJs form at apical regions of polarized epithelia, at the zonula adherens (ZA)⁶ (Figure 1). E-cadherin is a key component of the apical ZA in epithelial monolayers, and is considered a master regulator of the epithelial phenotype, due in part to the association of the ZA with a sub-membrane acto-myosin circumferential ring, which stabilizes the epithelial architecture⁷.

Classical cadherins contain a highly conserved cytoplasmic domain, which interacts with proteins that are collectively termed catenins. The related armadillo repeat proteins β -catenin (CTNNB1; mammalian homologue of *Drosophila* “armadillo”), or γ -catenin (also known as plakoglobin; JUP) bind to the cadherin carboxy terminal catenin-binding domain (CBD). Similarly, the membrane proximal cadherin juxtamembrane domain (JMD) interacts with members of the p120 catenin family of armadillo proteins, including p120 catenin (CTNND1; herein p120), NPRAP/ δ -catenin (CTNND2), ARVCF, and p0071 (also known as plakophilin 4; PKP4)(for review see⁴). Through these interactions catenins regulate AJ function and stability. For example, β -catenin links cadherins to α -catenin, to promote the re-organization of the actin cytoskeleton⁸⁻¹². Whether this reorganization is due to direct binding of actin filaments via α -catenin, via the regulation of monomeric versus dimeric α -catenin pools, tension-induced activation of α -catenin and vinculin, and/or via other actin binding β -catenin partners, like EPLIN, or ZO1, is still a matter of active investigation. Binding of β -catenin to the CBD is essential for cadherin function and for the maturation of AJs at areas of cell-cell contact. Consistent with the significance of the CBD in cadherin function, phosphorylation of either E-cadherin or β -catenin regulates β -catenin binding to the CBD, while phosphorylation of β -catenin regulates binding of α -catenin to the cadherin- β -catenin complex. Additionally, the CBD is thought to overlap, at least in part, with E-cadherin binding sites for the type I γ PI phosphate kinase (PIPKI γ), and of the phosphatase PTPm (for review see⁴). Binding to the lipid kinase PIPKI γ promoted intracellular E-cadherin trafficking by engaging clathrin adaptor proteins¹³, while association with PTPm stabilized cadherin complexes on the cell membrane¹⁴.

p120 catenin (p120) interacts with and stabilizes cadherins at areas of cell-cell contact¹⁵⁻²⁰. Binding of the JMD to the E3 ligase Hakai²¹ and subsequent ubiquitination, prevents further p120 association and induces E-cadherin endocytosis and degradation²¹⁻²³. Alternatively, binding of presenilin to the JMD instead of p120, promotes cleavage of the cadherin cytoplasmic domain²⁴. Therefore, the JMD plays a crucial role in cadherin function by

regulating cadherin stability through its association with p120 family proteins or by promoting cadherin degradation and/or cleavage via its association with alternative binding partners. Additionally, p120 binds to microtubules and kinesins, regulating cadherin and p120 localization^{25,26}, and also associates with PLEKHA7 at the apical ZA, which mediates interaction of the cadherin complex with non-centrosomal microtubules through the PLEKHA7 interacting protein Nezha²⁷. Interestingly, p120 family members are expressed in several isoforms and are subject to heavy phosphorylation in both tyrosine and serine/threonine residues. P120 phosphorylation is now linked to inside-out cadherin signaling, where adhesive function of the cadherin complex is affected by p120 phosphorylation events²⁸.

Another important aspect of p120 function is its ability to regulate the cytoskeleton via RhoGTPases²⁹. P120 can bind directly to RhoA and suppress its activation in the cytoplasm or at the cleavage furrow during cytokinesis^{30,31}, or it can recruit p190RhoGAP to cadherin complexes and suppress RhoA following Rac1 activation³². Binding of cytoplasmic p120 to MPRIP inhibits MPRIP-mediated suppression of Rho/ROCK function, leading to increased ROCK signaling³³, while binding of p120 to ROCK1 recruits ROCK1 and junctional actin to newly formed AJs³⁴. Finally, association of p120 to the RhoGEF Vav2 induces the activation of Rac1 and Cdc42³⁵, which may account for the essential role of the JMD in Rac1 activation following the ligation of E-cadherin extracellular domains at early stages of cell-cell contact³⁶. Importantly, through their association/dissociation with the cadherin cytoplasmic domain, β -catenin and p120 mediate a variety of signaling events that functionally link the cadherin-catenin complex to the cytoskeleton and ultimately regulate the balance between cell-cell adhesion and cell differentiation on the one hand, and cell growth and motility on the other.

Beta-catenin signaling in pluripotency and cancer

Armadillo, the *Drosophila* homologue of vertebrate β -catenin, was originally characterized by its role in the Wingless signaling pathway, which controls changes in gene expression that specify segment polarity and cell fate during *Drosophila* development (reviewed in³⁷). In contrast, β -catenin in vertebrates was initially identified as a binding partner to E-cadherin at the AJs. It is now clear that Armadillo/ β -catenin proteins play dual roles in regulating cell-cell adhesion and gene expression.

β -catenin consists of multiple armadillo repeats at its central region and a transcriptional activator domain at the C-terminal. The central region serves as a platform for binding to E-cadherin and other partners. In epithelial cells, the majority of β -catenin associates closely with cadherin complexes at the AJs. Phosphorylation regulates this association, releasing β -catenin into the cytoplasm where it interacts with a protein complex consisting of Axin, adenomatous polyposis coli (APC), and the Ser/Thr kinase glycogen synthase 3 β (GSK-3 β) (reviewed in³⁸). In this “so-called” degradation pathway, GSK-3 β (as well as casein kinases I and II) phosphorylates β -catenin, thereby inducing its ubiquitination and degradation in the 26S proteasome. The degradation pathway functions to keep cytoplasmic (and hence nuclear) levels of β -catenin low in the absence of Wnt signaling. Wnt (the vertebrate homolog of Wingless) binds its receptor Frizzled and activates Dishevelled (Dsh), which

inhibits the Axin/APC/GSK-3 β complex, thus preventing degradation of β -catenin. Intact cytoplasmic β -catenin can then translocate to the nucleus, where it binds to and activates transcription factors of the T cell factor/lymphoid enhancer factor (Tcf/Lef) family, thereby increasing transcription of target genes^{39–41} (see figure 1).

Numerous studies indicate that nuclear β -catenin signaling is a major contributor to human cancer (reviewed in⁴²). Initially, mutations in the APC gene were recognized as the predominant cause of hereditary colon cancer, by activating nuclear β -catenin signaling via the disruption of the β -catenin degradation pathway^{43–45}. Deregulation of Wnt/ β -catenin signaling by genetic alterations of APC, β -catenin or Axin was shown to lead to colorectal cancer^{46–49}. Wnt/ β -catenin signaling is also implicated in other cancers, such as leukemia, melanoma, hepatocellular, medulloblastoma, lymphoma, pancreas, and breast cancer (reviewed in^{42,50}). Finally, elevated expression of Wnt proteins, or decreased expression of sFRP1 or DKK1, soluble proteins that inhibit Wnt function, is common in many human cancers, indicating that activation of Wnt/ β -catenin signaling is a major pro-tumorigenic pathway in human disease⁴².

In addition to playing key roles in cancer progression, the β -catenin nuclear signaling pathway is crucial for the pluripotent phenotype and self-renewal of both normal and cancer stem cells^{51,52}. Cancer stem cells are resistant to classic chemotherapy and radiotherapy, and as such, they are thought to contribute to the reappearance of cancer following treatment. While the mechanism of action is still unclear, nuclear β -catenin binds to the Telomerase reverse transcriptase (TERT) promoter and enhances TERT expression^{53,54}. TERT maintains long telomeres and its up-regulation is a hallmark of stemness.

p120 nuclear signaling

Similar to β -catenin, p120 can also localize to the nucleus⁵⁵ and effect changes in nuclear signaling (for review see⁵⁶). Daniel and Reynolds originally reported the association of p120 with the transcription factor Kaiso⁵⁷. More recently, additional interactions of p120 with the transcription factor Glis2, and the REST/CoREST complex have also been reported^{58,59}.

Kaiso (ZBTB33) is a member of the BTB/POZ family of zinc finger transcription factors. p120 binds to a C-terminal region of Kaiso that overlaps the zinc finger domains, preventing association of Kaiso to DNA⁶⁰. It is generally thought that Kaiso binds promoter regions via two different mechanisms: a specific DNA consensus sequence⁶¹, or through binding to methylated CpG dinucleotides⁶². Consistent with reported roles of the BTB/POZ family of transcription factors in repressing transcription, Kaiso represses transcription of Siamois, Matrilysin, Wnt11, through the recruitment of transcriptional co-repressors, like N-CoR^{56,60}. While massively understudied compared to nuclear β -catenin signaling, available data suggest that Kaiso acts primarily as a transcriptional repressor and that p120 binding activates transcription of Kaiso targets via de-repression. In agreement, p120 overexpression reversed Kaiso-mediated reduction in Siamois reporter activity in *Xenopus*, while p120 depletion had the opposite effect⁶³.

Increasing data support an overlap between the nuclear signaling roles of p120 and β -catenin⁵⁶. Through binding to Kaiso, p120 is able to regulate gene targets, such as Siamois, CCND1, and MMP7, which are also regulated by β -catenin signaling. In this model, the nuclear translocation and transcriptional activation function of β -catenin is not sufficient to induce expression of its target genes, due to the repressive function of nearby Kaiso binding sites. Therefore, binding of p120 to Kaiso and subsequent de-repression of target genes may be essential for the expression of at least some nuclear β -catenin targets. Interestingly, while p120 is not rapidly degraded when uncoupled from E-cadherin, Wnt signaling promotes p120 stability, via inhibition of GSK3 β -induced phosphorylation and degradation of p120 isoform 1⁶⁴, or via direct association of p120 with Frodo, a downstream target of Dsh⁶⁵. Indeed, the increased binding of p120 to Kaiso may also lead to de-repression of the Kaiso target Wnt11, and promote further signaling through the non-canonical Wnt signaling pathway⁶⁶.

In addition to Kaiso, p120 was shown to interact with Gli-similar 2 (Glis2), a Kruppel-like protein known to repress transcription⁶⁷. p120 binding induced cleavage of Glis2, an effect that was enhanced by co-expression of p120 with the tyrosine kinase SRC and abrogated by co-expression of p120 with E-cadherin⁵⁸. This suggests that p120 is able to bind and promote cleavage of Glis2 when it is not bound to E-cadherin. However, unlike the p120-Kaiso interaction, binding of p120 to Glis2 did not alter its ability to bind DNA⁵⁸. At present, the functional significance of p120 binding to Glis2 is largely unknown, although this binding promotes nuclear translocation of p120⁵⁸. Finally, p120 also associates with REST and CoREST, a complex involved in transcriptional repression of target genes and embryonic stem cell differentiation⁵⁹. As with Kaiso, p120 binds to the DNA binding zinc finger region of REST and displaces the REST-CoREST complex from its gene targets. The interaction of p120 with REST is mediated by p120's central Arm repeat region, and is exclusive of its association with E-cadherin. Additionally, p120 depletion resulted in increased expression of the pluripotency factors Nanog, Oct4 and Sox2, and a reduction of neuronal differentiation markers⁵⁹, possibly through the REST-CoREST complex⁵⁹.

While the mechanistic details are still under investigation, the data argue that E-cadherin binding to p120 prevents p120 from binding to Kaiso, Glis2, or to the REST-CoREST complex, and therefore blocks nuclear p120 functions^{58,59} (see figure 1). In addition to Wnt signals, it is likely that other mechanisms also regulate nuclear p120 signaling. The increased phosphorylation, cytoplasmic mislocalization, loss, or nuclear translocation of p120 in cancer, may therefore affect nuclear signaling, and play crucial roles in cancer progression.

Cadherin dysfunction in cancer

Normal cells inhibit their growth and migration when they adhere to each other. These properties are progressively lost in tumor cells, contributing to increased rates of cell proliferation and migration. The processes imply that adhesion-triggered signaling events regulate both cell growth and motility. Not surprisingly, E-cadherin loss is relatively common in cancers of epithelial origin.

Studies in a variety of cancers have documented E-cadherin's role as a tumor suppressor⁶⁸. Cancer-associated germline mutations in the E-cadherin gene have been reported in patients with hereditary diffuse gastric cancer⁶⁹. Some of these mutations reportedly affect the adhesive state of the cadherin by interfering with inside-out cadherin signaling, a mechanism whereby binding of intracellular catenins and their phosphorylation status²⁸ affects the overall conformation of the cadherin complex to induce strong adhesion⁷⁰. Additionally, loss of heterozygosity in 16q22.1, the chromosomal region encoding E-cadherin (*CDH1*), is frequent in lobular carcinoma of the breast, a subtype characterized by single cell invasion⁷¹. A tumor suppressor role for E-cadherin has been established in many other epithelial malignancies, including hepatocellular carcinoma, squamous cell carcinomas of the skin, head and neck, esophagus, and melanoma (for review see^{4,68,72}). In most of these cases, E-cadherin expression is downregulated by promoter hypermethylation⁷³, while in others (i.e. lung cancer) E-cadherin is degraded as a result of the frequent loss of p120 expression^{74,75}.

In experimental models, E-cadherin depletion leads to mesenchymal morphology and increased cell migration and invasion^{76,77}. Conversely, ectopic expression of E-cadherin in cell lines lacking endogenous expression leads to reversal of undifferentiated, highly invasive carcinoma phenotypes^{78–80}. These effects may be mediated by many distinct functions of the E-cadherin complex, including the organization of epithelial cell architecture and polarity, and the regulation of signaling events driven by changes in the state of cell-cell adhesion.

As mentioned earlier, a major pathway related to tumor progression and pluripotency is the nuclear β -catenin/TCF signaling pathway. However, the relationship of E-cadherin mediated cell-cell adhesion and β -catenin signaling appears to be complex. E-cadherin loss by itself is insufficient to promote β -catenin nuclear signaling in the presence of an intact β -catenin degradation pathway. In contrast, when the degradation pathway is disrupted, increased expression of E-cadherin can provide a “sink” that affects nuclear β -catenin levels and counteracts β -catenin signaling (for review see⁷²). This model is consistent with the early loss of APC function in colon cancer associated with increased β -catenin nuclear signaling and the formation of colon adenomas, followed by the later loss of E-cadherin, which is associated with carcinoma transition and metastatic spread. In pancreatic cancer, depletion of E-cadherin using the Rip-Tag system was associated with the transition from an adenoma to a carcinoma without involvement of β -catenin nuclear signaling⁷⁷. It is likely that the role of E-cadherin in maintaining the proper structure and polarity of epithelial monolayers contributes to this transition, in addition to any effects on intracellular signaling.

In addition to β -catenin nuclear signaling, a number of oncogenic signaling pathways are known to be regulated by E-cadherin mediated cell-cell adhesion. These include, regulation of the overall levels of the cyclin kinase inhibitor p27^{81,82}, activation of mitogen activated kinase (MAPK), rat sarcoma viral oncogene (Ras) and ras-related C3 botulinum toxin substrate (Rac1) signaling^{83,84}, phosphatidylinositol-3-kinase (PI3K)/AKT signaling^{85–87}, as well as regulation of Hippo signaling⁸⁸. While several potential mechanisms may underlie these effects, one likely explanation is that E-cadherin engagement during cell-cell adhesion suppresses signaling from a variety of receptor tyrosine kinases (RTKs), including EGF receptor (EGFR) and c-Met⁸⁹, resulting in decreased rates of cell growth. This inhibition is

thought to be mediated by direct binding of the E-cadherin extracellular domain to RTKs and the subsequent segregation of RTKs away from their ligands. Binding of cadherin complexes to phosphatases, i.e. PTPm, PTPj (otherwise known as density-enhanced phosphatase1), or PTPN14 is also thought to contribute to these events, by stabilizing cadherin complexes¹⁴, dephosphorylating catenins^{90,91}, or by affecting YAP1 localization⁹² during cell adhesion. In the case of PI3K, direct recruitment of the p85 subunit to the cadherin complexes was demonstrated following phosphorylation by Src^{85,86}, leading to AKT activation and adhesion-mediated cell survival⁸⁵. Under normal conditions, cadherin-mediated PI3K signaling was required for calcium-induced phospholipase-C- γ 1 activation and epidermal keratinocyte differentiation⁹³. In ovarian cancer, the increased levels of E-cadherin expression directly contributed to the increased PI3K/AKT signaling of ovarian carcinoma cells⁸⁷.

An important aspect of cadherin-mediated cell-cell adhesion is the regulation of Rho family GTPases⁹⁴. p120 and the p120-binding JMD domain of E-cadherin are thought to mediate these effects^{29,94}. Rho GTPases, including RhoA, Rac1 and Cdc42, act to reorganize the actin cytoskeleton and play crucial roles in cell-cell adhesion and cell migration⁹⁵. Consistent with this, p120 was essential for the increased migration of cancer cells lacking E-cadherin expression and expressing mesenchymal cadherins, by regulating the activity of Rho family GTPases^{79,96–98}. Combined, the data argue that E-cadherin mediated AJs are hubs of intracellular signaling that regulate growth and migration of epithelial cells and are commonly deregulated in cancer.

Cadherins and EMT

Loss of E-cadherin expression during cancer progression is often the result of a phenomenon known as the epithelial-to-mesenchymal transition (EMT). EMT normally occurs during embryogenesis and development, enabling processes such as gastrulation, neural crest development, placenta formation and others. A key event during EMT is the loss of strong cell-cell adhesion due to suppression of E-cadherin expression and the subsequent transformation of epithelial cells into a more migratory and mesenchymal phenotype characterized by loose cell-cell contacts and by the expression of other types of cadherins, such as N-cadherin, R-cadherin, P-cadherin, or Cadherin-11⁹⁹. This event is widely known as “cadherin switch” and is primarily the result of transcriptional regulation of cadherin expression through a number of factors, such as SNAI1, SLUG, TWIST, ZEB1, ZEB2^{99,100}. The main signaling cascades leading to transcriptional activation of EMT are the Wnt/ β -catenin, TGF- β , and Hedgehog signaling pathways, which can act in response to a series of endocrine or paracrine cues^{99–102}. A number of post-transcriptional mechanisms are also involved in the induction of EMT, such as the proteasomal regulation of factors like SNAI1, or miRNA-mediated regulation^{103–105}. For example, the miR-200 and miR-205 miRNAs are key suppressors of ZEB1 and ZEB2 expression and thus negative regulators of EMT, whereas their downregulation is observed in tumors that have undergone EMT^{106,107}. Several environmental factors can also induce EMT, such as increased hypoxia and subsequent activation of HIF-1 α , which can upregulate TWIST and ZEB1^{108,109}. Furthermore, the role of the extracellular matrix in the activation of EMT has been well-

documented, mainly involving integrin signaling upstream or downstream of TGF- β and through signaling molecules such as ILK, FAK and SRC¹¹⁰.

Although an essential process during development or wound healing, the occurrence of EMT in mature epithelial tissues has been considered for a long time as a strong driver of tumor progression and metastasis. Indeed, downregulation of E-cadherin and upregulation of mesenchymal cadherins is frequent in tumors of epithelial origin and promotes cell migration and tumor invasiveness^{2,84,111–113}. Loss of E-cadherin can alleviate suppression of ligand-dependent RTK signaling^{89,114} and results in upregulation of the JUN oncogene via a so far undocumented post-transcriptional mechanism¹¹⁵. It also results in p120-mediated induction of Rac1 and cellular transformation⁸³. Overall, p120 catenin has been recognized as an important rheostat in the regulation of downstream signaling and cell behavior upon a cadherin switch. Indeed, although p120 binding to E-cadherin is essential for maintenance of the epithelial phenotype and its tumor-suppressing functions^{18,116,117}, its association with mesenchymal cadherins promotes p120's Rac1-activating functions and subsequent induction of cell invasiveness¹¹⁸. In agreement, P-cadherin overexpression in pancreatic cancer cells induces p120-dependent activation of Rac1 and Cdc42¹¹⁹. Interestingly, p120 seems to be preferentially sequestered to ectopically overexpressed N-cadherin or R-cadherin, which results in subsequent endocytosis and degradation of endogenous E-cadherin and increased cell migration^{120–122}. E-cadherin and N-cadherin also associate with different p120 isoforms with critical functional consequences: N-cadherin associates with the long phosphorylated p120 isoform 1 that can promote invasiveness, whereas E-cadherin binds predominantly to the small non-phosphorylated p120 isoform 3 that lacks this function^{123,124}.

Beyond the important role of p120 in mediating cadherin signaling, several other mechanisms of action have been reported downstream of mesenchymal cadherins during EMT that promote cellular transformation and pro-tumorigenic phenotypes. Cadherin-11 promotes lamellipodia and filopodia formation and cell migration via activation of the Trio GEF¹²⁵. N-cadherin promotes anchorage-independent growth via loss of contact inhibition¹²⁶ and protects from bile acid-induced apoptosis in hepatocellular carcinomas¹²⁷. N-cadherin also facilitates FGF receptor and PDGF receptor activities, thus promoting cell motility and metastatic behavior^{128,129}. Interestingly, N-cadherin enables stronger epithelial-endothelial cell interactions, which suggests for a role in promoting invasion and metastasis via the vasculature¹³⁰. Similarly, an E-cadherin to N-cadherin switch in melanocytes results in reduced contacts between melanocytes and keratinocytes and increased melanocyte-fibroblast interactions that enable increased melanocytic growth and migration and decreased apoptosis via AKT activation¹³¹. P-cadherin overexpression leads to induction of MMP activity, which in turn results in P-cadherin cleavage and ectodomain fragments that promote cell invasion¹³². R-cadherin promotes cell motility via Rho GTPase activity¹³³. Notably, the expression of mesenchymal cadherins is often sufficient for the induction of pro-tumorigenic cell behavior, even in the presence of E-cadherin^{122,132,134}. Cumulatively, the role of cadherins is central during EMT and significantly determines intracellular and intercellular signaling, overall cell behavior, and tumor progression (see Figure 2).

Beyond EMT: cadherin complexes and the RNAi machinery

The loss of E-cadherin during EMT is generally considered a major driver of cancer progression and metastasis. However, recent studies argue that EMT is actually not required for tumorigenic transformation or metastasis^{135,136}. In addition, E-cadherin expression is robust in many cancer types, even at metastatic sites^{137–142}. Strikingly, the presence of an E-cadherin-based junctional complex is essential in these cancer types for: a) the transmission of pro-tumorigenic signals stemming from oncogenes such as SRC, Rac1, EGFR, ERBB2^{143–146}, b) collective cell migration^{147,148}, c) cell proliferation under conditions of high confluence¹⁴⁶, and d) increased anchorage-independent growth and chemoresistance in Ewing sarcomas¹⁴⁹. Paradoxically, E-cadherin is essential for the progression of some very aggressive tumors, such as inflammatory breast cancer and a subtype of glioblastoma^{139,150}. These results indicated that in addition to its well-established tumor suppressive functions, E-cadherin can also promote tumor progression in many cases¹⁴⁰.

To resolve this conundrum, a recent study tested the hypothesis that the presence or absence of accessory junctional components eventually determines E-cadherin function. Indeed, it appears that E-cadherin forms two distinct complexes at the junctions of non-transformed polarized epithelial cells: one restricted to the apical junctions at the ZA, and another along the basolateral membrane in these cells^{151,152}. The apical complex is characterized by the presence of the p120-binding partner PLEKHA7, as well as by non-phosphorylated p120 and SRC, and activated RhoA, whereas the basolateral lacks PLEKHA7 and contains phosphorylated p120, activated Rac1 and SRC, p190RhoGAP and p130CAS¹⁵². The presence of PLEKHA7 at the apical cadherin complex confers the anti-tumorigenic properties of E-cadherin¹⁵². More specifically, loss of PLEKHA7 promoted anchorage-independent growth, induced activation of SRC and phosphorylation of p120, and increased the expression of a series of pro-tumorigenic markers, such as SNAIL1, Cadherin-11, MYC and CCND1¹⁵². Notably, these events were not followed by an EMT, since E-cadherin levels remained unaltered. Furthermore, the presence of the basolateral E-cadherin complex was required for the induction of these pro-tumorigenic signals, via SRC activation and p120 phosphorylation¹⁵². Consistent with these results, this and other studies have shown extensive and early loss of PLEKHA7 in breast and kidney tumors, whereas E-cadherin was still expressed to a large extent and p120 phosphorylation was also increased in tumors^{152–154}. Collectively, these findings provided an explanation for the conflicting reports regarding the role of E-cadherin in anti- vs. pro-tumorigenic signaling.

Unexpectedly, mechanistic studies revealed that the apical E-cadherin complex suppresses pro-tumorigenic signals by recruiting the microprocessor complex, one of the main components of the RNA interference (RNAi) machinery^{152,155}. In particular, PLEKHA7 mediates the association of non-nuclear fractions of the core members of the microprocessor DROSHA and DGCR8, as well as of a set of primary miRNAs (pri-miRNAs), which are the substrates of the complex, at the apical ZA¹⁵² (Figure 2). As a result, the apical cadherin complex possesses miRNA processing activity and regulates the levels of a set of miRNAs with tumor suppressing function, such as miR-30b, which eventually mediates the PLEKHA7-driven suppression of SNAIL1¹⁵². This was the first demonstration of any interaction of junctional complexes with the RNAi machinery and particularly with the

microprocessor complex. Previously thought to reside solely in the nucleus^{156,157}, these findings revealed a non-nuclear microprocessor at the junctions of polarized epithelial cells¹⁵⁵, as part of the E-cadherin complex. A possible reason that the junctional presence of the microprocessor wasn't previously noticed is that all microprocessor-related studies were performed in cells that have undergone some degree of tumorigenic transformation and therefore lack mature AJs. PLEKHA7 is required for the recruitment of DROSHA and DGCR8 to the junctions and SRC activity negatively affects localization of PLEKHA7, DROSHA and DGCR8 to the ZA¹⁵², which is consistent with the well-established function of SRC in perturbing strong adhesion and mature junction formation^{158,159}. Therefore, the above suggest that the microprocessor may be junctional only in non-transformed epithelial cells that normally localize PLEKHA7 at the ZA and form mature AJs (Figure 2). Further investigation of the localization patterns of DROSHA and DGCR8 in a broad range of cells and tissues would be important to confirm this notion and further investigate this new role of AJs in tumor progression.

Apart from the association with the microprocessor complex, proteomics analysis revealed a preferential enrichment of the apical cadherin complex with several additional RNA-binding proteins¹⁵². The data implied that the functional crosstalk of the apical cadherin complex with mechanisms involved in RNA-processing and expression may be extensive and going beyond the relationship with the microprocessor. This new direction of investigation could define the functional relevance of RNA regulation at the junctions, shed more light on the complicated roles of cadherin complexes in cancer, and potentially provide new targets for therapeutic intervention¹⁵⁵.

Summary

Combined, existing data indicate that the E-cadherin/catenin complex is essential for the homeostasis and maintenance of epithelial monolayers. As most solid tumors are epithelial in origin, deregulation of E-cadherin complexes has long been thought to play important roles in cancer progression. E-cadherin loss, mutation, or destabilization through loss of p120 binding, all contribute to cancer progression. Similarly, nuclear β -catenin and p120 signaling promote cell growth, migration and pluripotency. EMT provides one mechanism of overcoming the tumor-suppressing function of E-cadherin complexes. Another mechanism is the disruption of the crosstalk between mature AJs and the RNAi machinery. Indeed, loss of mature AJs at the apical ZA, through disruption of PLEKHA7 binding to cadherin complexes, uncovers a tumor promoting function of E-cadherin. Therefore, it is not simply the presence but also the association of E-cadherin with key accessory proteins and the formation of mature junctions that underlie its ability to act as a tumor suppressor. Collectively, it is clear that loss or disruption of mature AJs at the apical ZA occurs by a multitude of mechanisms, and the resulting loss of anti-tumorigenic E-cadherin signaling combined with the gain of nuclear catenin signaling and the activation of various additional pathways (RTK, Rho GTPases, PI3K, Hippo), are central events in tumor progression and metastasis.

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Highlights

- General review of the cadherin-catenin complex
- Nuclear signaling events regulated by β -catenin, p120, and E-cadherin
- Cadherin dysfunction in cancer
- Crosstalk between cadherin complexes and the RNAi machinery

Figure 1.

Schematic diagram illustrating the main components of the cadherin-catenin complex at mature adherens junctions, and catenin-mediated signaling events to the nucleus. Under conditions of strong cell-cell adhesion, nuclear signaling by catenins (either β -catenin or p120) is suppressed. Upon activation of Wnt signaling, or under conditions that deregulate E-cadherin mediated adhesion (i.e. phosphorylation, endocytosis, loss of E-cadherin expression, etc.), β -catenin and p120 are free to bind their nuclear effectors. With the exception of Glis2, binding of p120 to Kaiso or REST/COREST prevents DNA binding and allows activation of target genes. Binding of β -catenin to Tcf/LEF alone, or combined with loss of Kaiso repressive activity, promotes the expression of Wnt target genes.

Figure 2.

Schematic summarizing the role of cadherin complexes during pro-tumorigenic transformation. Normal epithelial cells primarily express E-cadherin, which is essential for mature monolayer formation. A number of cues can trigger EMT, which results in downregulation of E-cadherin, loss of the epithelial phenotype and upregulation of mesenchymal cadherins that promote migratory and invasive cell behavior. Alternatively, E-cadherin expression is maintained in many tumors and is required for their progression. This is due to the deregulation of the fine balance between an apical E-cadherin complex at the zonula adherens (ZA) that suppresses pro-tumorigenic signaling via miRNA processing, and a basolateral complex that promotes this signaling. Disruption of the ZA-specific complex in cancer results in miRNA deregulation and increased anchorage-independent growth, which depends on the presence and activity of the basolateral E-cadherin complex.