

The Physiological Roles of Cadherin Mediated Cell Adhesion

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Abstract

Cadherins are a family of cell adhesion molecules (CAMs) that mediate calcium dependent cell-cell interactions. These cellular interactions promote the formation of intercellular junctions, the establishment of cell polarity, and cell sorting during development, ultimately affecting the formation of tissues and the maintenance of tissue architecture. Additionally, cadherin mediated adhesion is involved in the regulation of cellular growth and differentiation, as well as apoptosis. However, the aberrant expression of cadherins may contribute to tumour progression. Thus, the precise regulation of cadherin expression is needed to ensure their proper functions. This paper reviews the structure and regulation of cadherins, as well as the physiological roles served by cadherin mediated adhesion.

Introduction

Cadherins encompass a family of structurally related cell adhesion molecules (CAMs) that mediate calcium dependent cell-cell homotypic adhesion in vertebrates and invertebrates (reviewed in 1-7). The cadherin superfamily is divided into several families according to the number of extracellular (EC) domains tandemly repeated in the extracellular segments of cadherins.⁵ The type I (also referred to as classical) cadherins are the most extensively studied and comprise E-cadherin, N-cadherin, and P-cadherin. E-cadherin is expressed mainly in epithelial tissues, while N-cadherin and P-cadherin are expressed mainly in neural and placental tissues, respectively.

Other members of the cadherin superfamily include the type II classic cadherins, desmosomal cadherins, protocadherins, and other more distantly related cadherins.¹ This paper will focus on the structure and regulation of the classical cadherins, as well as the signalling pathways implicated in cadherin mediated adhesion. The function of cadherins will be reviewed in the context of tumour progression, cell survival, and immune regulation.

Structure of the Classical Cadherins and the Cadherin-Catenin Complex

The classical cadherins are synthesized as precursor molecules with an approximate molecular weight of 135 kDa. Following glycosylation, phosphorylation, and proteolytic cleavage, a mature cadherin protein with a molecular weight of 120 kDa is produced.⁸⁻¹¹ Each member contains five EC domains (each containing approximately 110 amino acids), a single transmembrane domain, and two cytoplasmic domains (as shown in Figure 1).¹²⁻²⁴

The tripeptide histidine-alanine-valine (HAV), found in the first EC domain,¹⁵ is the cell adhesion recognition (CAR) sequence of cadherins responsible for homotypic binding. It is now known that histidine and valine form the adhesive interface and alanine is recessed in the hydrophobic core fragment of the CAR sequence.¹⁶ Antibodies and synthetic peptides directed against the CAR sequence block cadherin mediated adhesion and function. Residues flanking the HAV sequence are believed to play a role in binding specificity. The binding specificities of P- and E-cadherins are interchanged in recombinant chimeric proteins generated by switching their amino-terminal EC domains.¹⁷ The roles of the four other EC repeats have yet to be elucidated but it is believed that they may simply act as

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spacers in order to project the receptor to a necessary distance from the cell membrane.¹⁸ The five EC repeats form four calcium binding pockets, each between two successive repeats.¹⁹⁻²⁰ The acidic amino acid motifs DXNDN and DXD are conserved motifs capable of binding calcium.²¹ The binding of calcium is necessary for cadherin function and confers protection from proteases.²² The role of calcium is likely to form and maintain the active conformation of the classical cadherins.²³

The cytoplasmic domain (CD) is highly conserved and interacts with several proteins collectively known as the catenins, which link cadherins to the cytoskeleton (Figure 1).²⁴⁻²⁶ The formation of the cadherin-catenin complex is required for stable cell adhesion.²⁴⁻²⁶ Studies employing deletion mutagenesis of the cytoplasmic domain of E-cadherin have localized the catenin binding domain to a 30 amino acid region containing a series of phosphorylated serine residues.¹⁴ Deletion of the cytoplasmic tail or of the catenin binding site abrogates cadherin mediated aggregation of cultured cells.^{14,25,27}

The catenin family is comprised of several members, including α -catenin, β -catenin, γ -catenin, and p120^{ctn} (reviewed in 28, 29). β -catenin and γ -catenin (plakoglobin) bind in a mutually exclusive manner to the conserved catenin-binding domain (Figure 1). α -catenin then links either the β - or γ -catenin-cadherin com-

plex to actin, either directly, or indirectly via α -actinin.³⁰ Protein tyrosine phosphatases interact directly with the cytoplasmic region of N-cadherin, regulating tyrosine phosphorylation events of β -catenin, and in turn, modulating cadherin function.^{31,32} Agents which inhibit the activity of the phosphatase lead to an accumulation of tyrosine phosphate on β -catenin, which will therefore uncouple N-cadherin from the cytoskeleton, subsequently leading to a loss of cadherin function. Recently, it has been shown that the non-receptor protein tyrosine phosphatase PTP1B is a candidate N-cadherin associated phosphatase.³²

Despite the high degree of homology between γ -catenin and β -catenin, the physiological role of γ -catenin is unclear. γ -catenin is a major component of desmosomes and is capable of interacting with desmosomal cadherins.³³ β -catenin knock out mice show a deficiency in adhesion indicating that γ -catenin cannot substitute for β -catenin.³⁴

p120^{ctn} was initially defined as a substrate for the oncogenic tyrosine kinase *src* and growth factor receptor tyrosine kinases.³⁵ However, p120^{ctn} lacks structural motifs such as the SH2 and SH3 domains normally found in tyrosine kinase receptors. p120^{ctn} associates with the carboxyl terminal tail of cadherins in the juxtamembrane region close to the β/γ -catenin binding

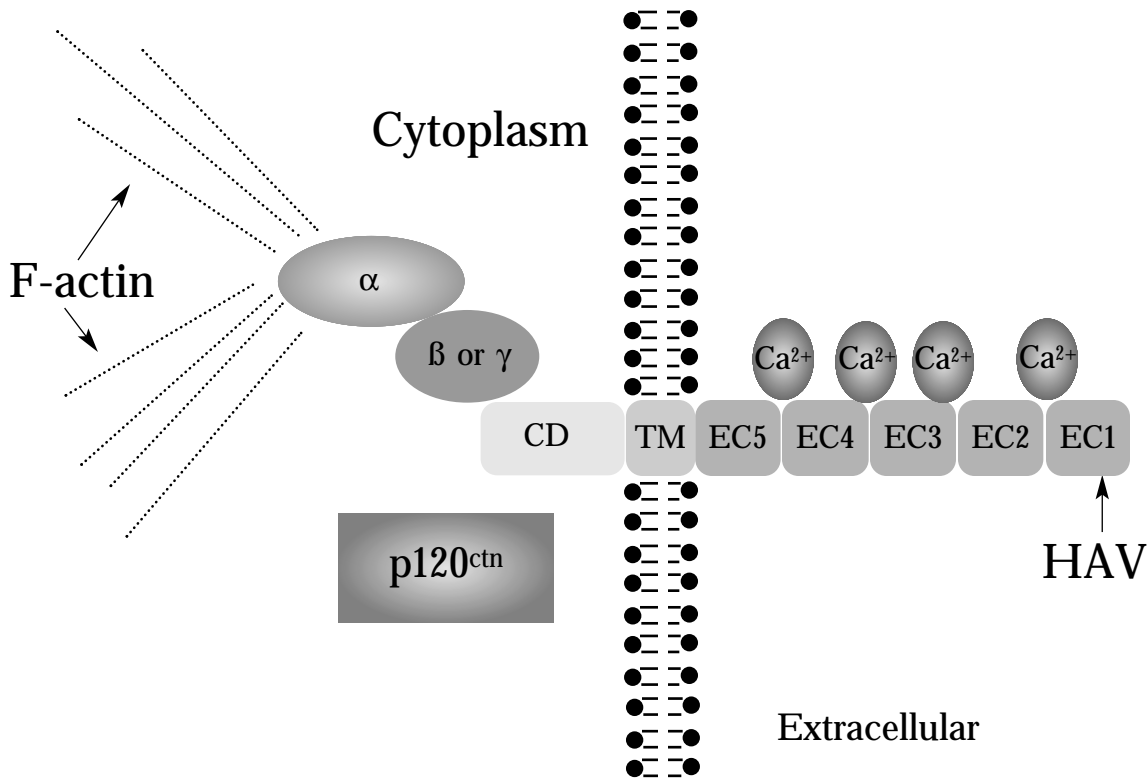


Figure 1. Structure of the cadherin-catenin complex.

domain.^{36,37} The role of p120^{ctn} is not exactly known, although authors have speculated a role in cadherin dimerization,³⁸ and others have suggested that tyrosine phosphorylation of p120^{ctn} induces its dissociation from cadherin-catenin complexes, allowing it to interact with other effector molecules.³⁹

The Role of Cadherin Clustering in Cell-Cell Adhesion

Recent observations support cadherin dimerization or clustering, as a means of enhancing cell adhesion.^{26,38,40} It was initially shown by Briehner *et al.* that a C-cadherin ectodomain existed as a stable dimer, and that the dimeric forms were necessary to induce the aggregation of substrates coated with C-cadherin.²⁶ Yap *et al.* constructed a chimeric protein in which the cytoplasmic tail of C-cadherin was replaced by three tandem repeats of FKBP modules. The addition of FK-1012, which concurrently binds to FKBP domains on separate cadherin molecules, induced dimerization, leading to a substantial increase in adhesion.⁴¹ E-cadherin homophilic adhesion requires the formation of parallel *cis* dimers (on the same surface) for the formation of antiparallel *trans* dimers (cell to cell).⁴¹ It is postulated that *cis* interaction may initiate a change in conformation and allow effective adhesion to occur.⁴¹ The two subunits of the lateral dimers of E-cadherin are joined at the calcium binding site between EC1 and EC2.¹⁹ Calcium mediates this interaction indirectly. Analysis of the crystal structure of the EC1 domain of N-cadherin also indicates that a stable, parallel, lateral dimer is a prerequisite for homophilic binding activity.¹⁶ However, in this model, lateral dimers are formed via a hydrophobic interaction, in which a tryptophan of one subunit of the lateral dimer integrates into the hydrophobic pocket of the other subunit.¹⁶ While it is clear that lateral dimerization plays a significant role in cadherin mediated homophilic adhesion, the exact mechanism by which this occurs is unknown. The strengthening of the adhesion could be mediated simply by the increased avidity of the dimeric form or, alternatively, *cis* dimerization may be a key regulatory step to the production of an active conformation. Finally, Shapiro *et al.* have suggested that lateral cadherin dimers projecting from the two cell surfaces could interdigitate to form a continuous linear supramolecular zipper.¹⁸

p120^{ctn} has been implicated in cadherin clustering. Cells expressing cadherins lacking the putative p120^{ctn} binding site were not able to dimerize.³⁸ It is speculated that a homodimer cadherin p120^{ctn} complex may be necessary to increase the rates of initial homotypic recognition and subsequent binding between cadherin molecules on two adhering cells. Subsequently, α -catenin, β -catenin and the actin skeleton may stabilize the complex and allow for a strengthening of cell-cell adhesion.

Cadherin-Catenin Signal Transduction

The role of cadherins has traditionally been associated with cell-cell adhesion and the maintenance of tissue architecture. There is emerging evidence that cadherins may mediate signalling events that influence gene transcription and ultimately

affect cell growth and differentiation. In a recent study, homophilic cell-cell adhesion was mimicked by the use of Madin-Darby canine kidney (MDCK) cells and human breast MCF10A cells incubated with immobilized E-cadherin antibodies. This led to an increase of tyrosine phosphorylated proteins with molecular weights of 120, 130, and 180 kDa, one of which was identified as a ras-GTPase activating protein (GAP).⁴² Since actin recruitment to cadherin-based junctions requires Rac and Rho activity, it is possible that cadherin signalling may activate ras-GAP, which may in turn activate Rac and Rho, leading to the formation of stable adherens junctions.^{29,43} In addition, N-cadherin-mediated binding results in increased cadherin and β -catenin levels in adherens junctions, as well as an increased level of tyrosine phosphorylated proteins in cell-cell junctions.⁴⁴

Cytoplasmic β -catenin interacts with other proteins and is an integral part of the Wnt signalling pathway in vertebrates (reviewed in 45, 46). Wnt proteins are secreted glycoproteins implicated in the regulation of cell fate decisions during vertebrate formation. Wnt proteins interact with transmembrane receptors of the Frizzled (Fz) family, activating Dishevelled (Dsh) proteins, which in turn, inhibit glycogen synthase kinase 3 β (GSK3 β). The inhibition of GSK3 β leads to the activation of β -catenin, allowing for its accumulation^{39,47} and association with transcription factors of the T cell factor (TCF) / lymphocyte enhancing factor (LEF-1) family.^{48,49} This complex translocates to the nucleus and influences gene transcription. In the absence of a Wnt-1 ligand, β -catenin complexes with the tumour suppressor adenomatous polyposis coli (APC) and is then degraded via ubiquitination and proteasome mediated proteolysis.⁵⁰ It has been shown that β -catenin levels were enhanced in colon cancers^{51,52} and melanomas⁵³ where mutations in APC existed. It has been suggested that the accumulation of β -catenin results in the continuous activation of the Wnt signal transduction cascade, activating the transcription of genes associated with cell survival and proliferation.⁵⁴ Connexins,⁵⁵ homeobox genes,⁵⁶ and *c-myc*⁵⁷ are among the genes targeted by the Wnt pathway. There is also evidence of cross-talk between integrin-mediated and Wnt-mediated signalling pathways.⁵⁸ Integrin-linked kinase (ILK) is a serine/threonine kinase whose overexpression causes loss of cell-cell adhesion, translocation of β -catenin and the activation of β -catenin/LEF-1 dependent transcription.⁵⁸

Classical Cadherin Expression and Its Implication in Tumour Invasiveness

The first cadherins identified by cDNA cloning were E-cadherin, N-cadherin, and P-cadherin (reviewed in 4, 6, 29). E-cadherin is expressed mainly in epithelial tissues, N-cadherin in neural tissues and striated muscle, and P-cadherin is limited to skin, placenta, and prostate. Table 1 summarizes the main characteristics of classical cadherins.

Cadherins are found mainly in adherens junctions, such as zonula adherens junctions, synaptic junctions, autotypic junc-

Table 1
Human classical cadherins. Modified from Potter *et al.*²⁹

Name	Symbol	Locus	Main Expression	Molecular Weight
E-cadherin	CDH1	16q22.1	Epithelia	124kDa
N-cadherin	CDH2	18q11.2	Neuronal cells, skeletal muscle, and cardiac muscle	130 kDa
P-cadherin	CDH3	16q22.1	Skin, prostate, and placenta	118 kDa

tions in the myelin sheath, and the intercalated disks of cardiac myocytes (reviewed in 2, 4, 6). These junctions, in association with the actin skeleton, serve to bring about morphological transitions that underlie tissue formation and maintain tissue architecture in the adult organism. The distribution of cadherins during embryogenesis is tightly regulated, as the loss of cadherin expression or its ectopic expression can alter the phenotype of a cell, and disrupt cell differentiation. For example, cultured epiblast cells from primitive streak stage embryos exhibit a loss of E-cadherin concurrent with a gain in N-cadherin expression.⁵⁹ N-cadherin positive cells, in turn, continue to differentiate into skeletal and cardiac muscle. Antibodies blocking N-cadherin result in the arrest of muscle differentiation.⁶⁰ In a second example, melanocyte development from migrating neural crest cells requires the detachment of neural crest cells from the neural tube, which occurs only upon the downregulation of N-cadherin and the upregulation of cadherin-7 on neural crest cells.⁶¹

It has been shown that in some cases, cultured cells derived from oral squamous cell carcinomas expressing N-cadherin display an increase in cell motility and invasion, as compared to cultured cells derived from E-cadherin positive carcinomas.⁶² It was suggested that E-cadherin mediates signal transduction events that would maintain an epithelial phenotype, while N-cadherin signalling instructs the cell to adopt a motile, fibroblastic-like phenotype. A number of studies have associated a reduced expression of E-cadherin with a wide range of carcinomas, including breast,⁶³⁻⁶⁵ head and neck,^{66,67} gastrointestinal,⁶⁸ thyroid,^{69,70} and prostate.⁷¹ In general, many of these studies have correlated the loss of E-cadherin-mediated adhesion with dedifferentiated tumours, increased tumour invasiveness, and poor clinical prognosis. Recently, germline mutations of the E-cadherin gene were shown to induce a familial form of gastric cancer.⁷² However, E-cadherin expression has not been seen to be uniformly successful in reversing the invasiveness and malignancy of tumour cells,⁷³ suggesting that while the loss of E-cadherin may contribute to the invasive and metastatic potential of a malignancy, it is unlikely to be the sole determinant. In summary, cadherin expression must be tightly regulated during morphogenesis, as well as for the maintenance of tis-

sue organization. Disturbances in this regulation may lead to tumour progression.

Cadherins and Apoptosis

The formation of E-cadherin mediated multicellular aggregates has been shown to provide resistance to apoptosis.⁷⁴⁻⁷⁶ These studies showed that E-cadherin mediated protection from apoptosis was paralleled by an upregulation of the Bcl-2 oncogene,⁷⁴ activation of the tumour suppressor Retinoblastoma (Rb),⁷⁵ as well as the phosphatidylinositol (PI) 3-Kinase dependent activation of Akt.⁷⁶ The PI 3-kinase/Akt cascade is a signalling cascade that is critical for promoting cell survival in response to stress or growth factor deprivation. Similarly, investigators have demonstrated that N-cadherin mediated adhesion inhibits apoptosis.⁷⁷⁻⁸⁰ Rat granulosa cells that express N-cadherin exhibit an increased rate of apoptosis when cultured in the presence of N-cadherin disrupting antibodies or the synthetic blocking peptide N-Ac-CHAVC-NH₂.⁷⁷ It is postulated that N-cadherin expression by these cells mediates homophilic-homotypic adhesion promoting cell aggregation, and thereby promoting cell survival.⁷⁷ Peluso *et al.* have shown that N-cadherin interacts with the fibroblast growth factor (FGF) receptor, promoting signal transduction events through the FGF receptor.⁸⁰ It is hypothesized that such signal transduction pathways prevent apoptosis via protein kinase C (PKC) dependent mechanisms and the maintenance of calcium homeostasis.⁸⁰ The initiation of apoptosis requires the activity of a number of proteases and endonucleases that are calcium dependent.⁸⁰ It is likely that the survival pathway initiated by N-cadherin facilitates the uptake of calcium into intracellular stores, thereby sequestering the calcium from proteolytic enzymes and endonucleases.⁸⁰

The Role of Cadherins in the Immune System

Recent publications have addressed the possibility that cadherins may play a role in the immune system. E-cadherin is expressed by both thymocytes and stromal cells in the murine thymus.^{81,82} The inhibition of homotypic E-cadherin interaction in the thymus inhibit epithelial organization and thymocyte development.⁸² Murine epidermal $\gamma\delta$ T-cells and T-cell lymphoma lines derived from patients with cutaneous T-cell lym-

phoma express E-cadherin and can interact directly with keratinocytes *in vitro*.^{83,84} E-cadherin can mediate heterophilic cell-cell adhesion with the integrin, $\alpha_E\beta_7$.⁸⁵⁻⁸⁷ This heterotypic interaction has been demonstrated between T lymphocytes and epithelial cells,^{85,86} and there is evidence that the $\alpha_E\beta_7$ -E-cadherin interaction is important in the pathology of rheumatoid arthritis.⁸⁸ Finally, pro-inflammatory cytokines interleukin 1 (IL-1) and tumour necrosis factor alpha (TNF- α), as well as lipopolysaccharide (LPS), induced a decrease in E-cadherin mRNA, paralleled by diminished homotypic cell-cell adhesion in fetal-skin derived dendritic cells.⁸⁹ Langerhans cells are a type of dendritic cell that reside in the stratified squamous epithelia and are responsible for antigen trapping. Upon antigen exposure, a subset of Langerhans cells will display an activated phenotype, including an enhanced antigen presenting capacity, and will subsequently migrate to the T-cell regions of the regional lymph nodes.⁹⁰ It is hypothesized that a down-regulation of E-cadherin may be the initial step in Langerhans cell mobilization from the epidermis to lymphoid tissue.⁹¹ Collectively, these studies suggest that E-cadherin may play an important role in the localization of Langerhans cells and dendritic epidermal T-cells to the epidermis, of immature thymocytes to the epithelial thymic rudiment, and of malignant T-cells to the skin of patients with cutaneous T-cell lymphoma. Finally, E-cadherin is also expressed in the bone marrow and mediates cell-cell interaction between the bone marrow stromal cells and hematopoietic cells during differentiation.⁹²

N-cadherin is another potentially important cell adhesion molecule in the regulation of the immune system. N-cadherin is expressed by the leukemic T-cell line Jurkat^{93,94} and it has been suggested that its expression may provide lymphoma T-cells with the ability to invade and metastasize into the mesenchymal tissue in the central nervous system,⁹⁵ a property that has long been noted in lymphoma cells. Furthermore, N-cadherin expression is regulated by β_1 and β_3 integrins,⁹⁶ cell adhesion molecules that are expressed by lymphocytes. It is possible that N-cadherin plays a role during lymphocyte recirculation and immune surveillance, or during lymphocyte development.

Summary

In recent years, we have come to realize that the role of cadherins in cell-cell adhesion is more complex than previously believed. Cadherin mediated adhesion is not only critical to the preservation of tissue integrity but may initiate signal transduction cascades that regulate the growth and differentiation of cells. This may occur directly, or via the Wnt pathway, mediated by β -catenin. In addition, cadherins may facilitate close cell-cell contact thereby allowing other potential receptors and ligands to interact and generate signals that modulate cell growth and survival. Regardless of the precise mechanism, it is implicit that tight regulation of cadherin expression is needed, as a loss or gain of cadherin expression may alter the cellular phenotype, and adversely modulate embryogenesis and cell differentiation. Inappropriate expression of cadherin molecules has been proposed to be involved in various pathological

mechanisms, from the protection of cell death and the dissemination of malignancy, to immune mediated disease processes. Identification of the specific molecular pathways triggered by cadherin mediated adhesion would allow us to better understand the physiological role of cadherins, as well as the potential pathophysiological consequences of cadherin dysregulation.

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