J Gastroenterol 2004; 39:413–421
DOI 10.1007/s00535-004-1335-8

Journal of Gastroenterology

Review

Cadherins: an integral role in inflammatory bowel disease and mucosal restitution

Andrew P. Zbar[1], Constantinos Simopoulos[2], and Anastasios J. Karayiannakis[2]

[1] Department of Surgery, University of the West Indies, School of Clinical Medicine and Research, Bridgetown, Barbados
[2] Second Department of Surgery, Democritus University of Thrace, Medical School, 6 I. Kaviri Street, 68 100 Alexandroupolis, Greece

The intestinal epithelium is characterized by rapid cellular turnover with continuous proliferation of multipotential stem cells within Lieberkuhn's crypts, cellular migration along the crypt–villus axis, cellular differentiation, polarization, apical apoptosis, and luminal shedding. These processes are critical for the development and maintenance of normal intestinal epithelial architecture and function and involve complex cell–cell and cell-substratum interactions, which are mediated by epithelial (E)-cadherin and the integrins, respectively. This review outlines the role of E-cadherin and its cytoplasmic binding proteins, the catenins, as well as the interplay with other mucosal adhesion and restitution molecules during physiological processes in the intestinal epithelium mediating embryogenesis, cellular differentiation, cellular migration, and mucosal repair, as well as what is known about the dysregulation of assembly of the E-cadherin–catenin adhesion complex in inflammatory bowel disease.

Key words: E-cadherin, catenins, cell adhesion, inflammatory bowel disease, mucosal restitution, trefoil peptides

Introduction

The regulated formation of cell–cell and cell–matrix junctions plays a crucial role in normal embryogenesis and in the induction and physiological maintenance of cellular architecture and integrity in adult tissues.[1–3] Over the past decade, several related families of cellular adhesion molecules involved in these processes have been identified, including the cadherins (which control cell–cell interactions), the integrins (which mediate cell–stromal cross talk), the selectins (which are coexpressed on leukocytes and endothelial cells), and members of the immunoglobulin and proteoglycan superfamilies.[4]

Specialized intestinal epithelium undergoes rapid cellular turnover with controlled proliferation of multipotential stem cells within the crypts of Leiberkuhn, ordered cellular migration along the crypt–villus axis, cellular differentiation, polarization, apical apoptosis, and luminal shedding. This coordinated process is central for the development, morphogenesis, and maintenance of normal intestinal epithelial architecture, providing a specific interaction between molecules responsible for cellular integrity and mucosal repair. Inflammatory bowel disease and its in vitro wounded colonic epithelial monolayer models have shown altered cadherin expression[5,6] as well as alterations in the constitutively expressed trefoil peptides, which have been implicated in normal gastrointestinal epithelial restitution.[7–9]

This review outlines the role of epithelial (E)-cadherin and its cytoplasmic binding proteins, the catenins, and the interplay with other mucosal adhesion and restitution molecules during physiological processes in the intestinal epithelium mediating embryogenesis, normal mucosal differentiation, cellular migration, and mucosal repair, as well as what is known about the dysregulation of assembly of the E-cadherin–catenin adhesion complex in inflammatory bowel disease.

The E-cadherin–catenin complex and integrins in normal intestinal mucosa: evidence for receptor cross talk

E-cadherin (also known as L-CAM, uvomorulin, ARC-1, or cell-CAM 120/80), is the principal mediator of cell–

Received: August 25, 2003 / Accepted: February 20, 2004
Reprint requests to: A. J. Karayiannakis

cell adhesion between epithelial cells.[1] It is a 120-kDa transmembrane glycoprotein that is localized mainly to the zonula adherens junction, signaling extracellular domain cell–cell adhesion through calcium-dependent homotypic interactions. Its carboxy-cytoplasmic domain is associated with a group of undercoat cytoplasmic proteins, the α-, β-, and γ-catenins, which share common structural and functional features and which are necessary for direct and indirect E-cadherin binding.[10] Each catenin contains the Arm domain (a 42-amino-acid motif originally described for the *Drosophila* segment polarity gene product armadillo),[11] with both β- and γ-catenins binding directly to E-cadherin and α-catenin linking bound β- and γ-catenin to the actin microfilament network of the cellular cytoskeleton.[12,13] Binding is essential for the establishment of stable cell–cell adhesion, and survival studies have shown that structural and functional integrity of the components of the complex is necessary for the basic adhesive function of E-cadherin.[14–20] Recently, a novel member of the catenin family, the p120 protein, has been described.[21] This molecule has been identified as a common substrate for several receptor tyrosine kinases, sharing some homology with both β- and γ-catenin and binding directly with the cytoplasmic domain of E-cadherin[22,23] (Fig. 1).

The integrins are transmembrane glycoproteins with overlapping receptor specificity expressed along the

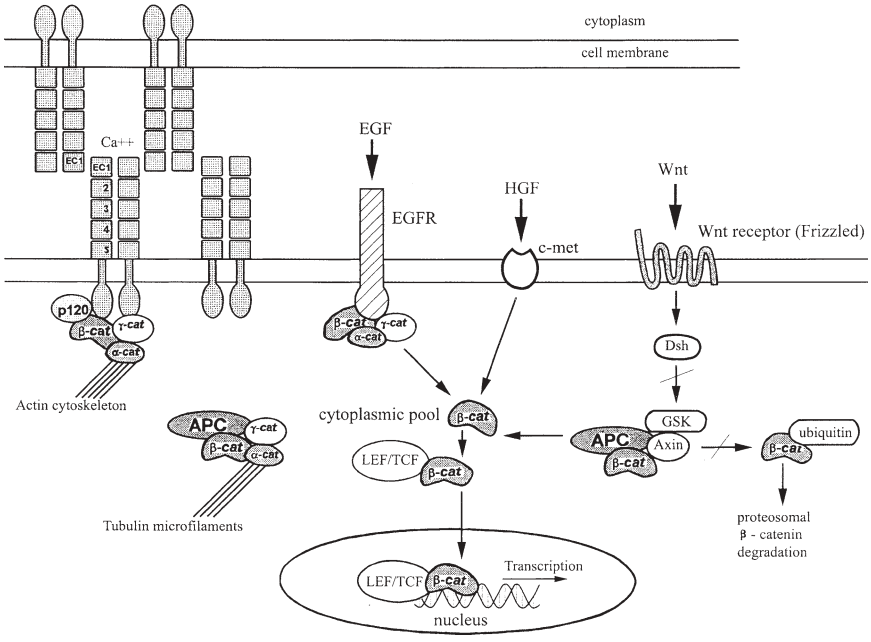

Fig. 1. Schematic presentation of E-cadherin and the catenins and their cellular interactions with each other and with other proteins. The extracellular domains of the E-cadherin homodimers bind in the presence of calcium ions in a "zipper" fashion to establish tight physical cell–cell adhesion. Their cytoplasmic domains bind to β- or γ-catenin in a mutually exclusive pattern whereas α-catenin links bound β- or γ-catenin to the actin cytoskeleton. p120 also binds to the cytoplasmic domain of E-cadherin in a distinct and separate site to that of other catenins. Catenins also form E-cadherin-independent complexes with other growth regulatory and signaling proteins such as the epidermal growth factor receptor (*EGFR*) and the adenomatous polyposis coli (*APC*) gene product and through this gene product to the tubulin microfilament network, the Wnt-signaling pathway, T-cell factor 4 (*TCF*), and lymphoid enhancer factor 1 (*LEF*) transcription factors (see text). The presence of a free cytoplasmic β-catenin pool is postulated to play an important role in controling the stoichiometry of cadherin–catenin interactions and to influence the titration of catenins between cadherin and APC complexes. In the absence of Wnt ligand–receptor interaction, glycogen synthetase kinase 3-β (*GSK*) is activated and, with wild-type APC and axin, binds to free cytoplasmic β-catenin, resulting in its degradation through an ubiquitination and proteosome pathway. In the presence of a Wnt signal, GSK activity is inhibited in response to activation of the phosphorprotein dishevelled (*Dsh*), resulting in decreased degradation of β-catenin and elevated cytoplasmic levels of β-catenin, permitting interaction with transcription factors (TCF/LEF). This complex translocates to the nucleus and modulates the transcription of target genes including negative regulation of E-cadherin gene expression itself. Other abnormalities in the Wnt signaling pathway, such as mutated APC gene product, mutated β-catenin, or tyrosine phosphorylation of β-catenin on epidermal growth factor receptor (*EGFR*) and hepatocyte growth factor receptor (c-*met*) activation, can also result in an increased cytoplasmic pool of β-catenin, with modulation of the stoichiometry of cadherin–catenin interactions and subsequent perturbation of E-cadherin-mediated cell adhesion resulting in enhanced cell motility and cell migration. α-*cat*, α-catenin; β-*cat*, β-catenin; γ-*cat*, γ-catenin; *APC*, adenomatous polyposis coli; *c-met*, hepatocyte growth factor receptor; *Dsh*, dishevelled; *ECl*, extracellular domain; *EGF*, epidermal growth factor; *EGFR*, epidermal growth factor receptor; *GSK*, glycogen synthetase kinase 3-β; *HGF*, hepatocyte growth factor; *LEF*, lymphoid enhancer factor 1; *TCF*, T-cell factor 4

basolateral surface of enterocytes and on the cell surface of all cells derived from the three primary germ cell layers, being composed of α- and β-chains associating noncovalently as heterodimers. Their extracellular domains contain ligand-binding regions whereas the cytoplasmic domains comprise regions capable of binding to particular cytoskeletal elements including talin, vinculin, and α-actinin.[2] These molecules modulate cellular interactions with components of the extracellular matrix including collagen, laminin, and fibronectin as well as with other integral cell-surface plasmalemmal proteins, with at least 15 different α- and 8 different β-chains for combination as more than 20 heterodimeric combinations.[2] They represent a vital heterophilic interaction between integrins and cadherins because specialized intraepithelial lymphocytes with the cytotoxic (CD8+) surface receptor phenotype expressing the αEβ7 (CD 103) integrin also lie along the basolateral region of enterocytes, where they are believed to regulate tissue-specific lymphocyte tracking and adherence during lymphocyte movement from the circulation to gastrointestinal-associated lymphatic tissue of the Peyer's patches.[24,25] Here, the inhibition of cadherin-mediated cellular adhesion has been shown to downregulate constitutive integrin expression in differentiating cells.[26,27] Further evidence of cadherin–integrin cross talk in intestinal epithelium is provided by studies showing that the c-*erbB*-2 oncogene coinhibits E-cadherin and $\alpha_2\beta_1$ integrin (an integrin acting as a principal collagen receptor in epithelial cells) gene transcription in human mammary epithelial cell culture.[28]

Although integrins were originally identified as mediators of cell–matrix adhesion, they have recently been shown to participate in the intrinsic organization of the actin cellular cytoskeleton and in bidirectional transmembrane signal transduction through tyrosine phosphorylation of focal adhesion kinases, increases in intracellular calcium levels, inositol lipid and cyclin synthesis, activation of mitogen-stimulated kinases, and changes in crucial cellular growth genes.[3,29] Catenins, apart from linking E-cadherin to the actin cytoskeleton, also link the cell membrane to downstream intracellular signaling pathways, providing a further interaction between integrins and cadherins as well as contributing to E-cadherin-independent binding to growth regulatory and signaling proteins such as epidermal growth factor (EGF),[30] the c-*erbB*-2 oncogene product,[31,32] and the adenomatous polyposis coli (APC) gene product.[33,34] Here, the APC gene product, which is an integral mutated protein in the colorectal adenoma–carcinoma sequence as well as in colitis-associated carcinoma,[35] has been shown to control intracellular β-catenin levels and APC–catenin and E-cadherin–catenin complex assembly[36,37] by competing directly with E-cadherin for β-catenin binding and forming separable α-, β-, and γ-catenin complexes that are independent of cadherin.[37–39] In this respect, it has recently been shown that APC mutations (similar to β-catenin mutations) appear to enhance the association of β-catenin with transcription factors such as T-cell factor 4 and lymphoid enhancer factor 1, both of which have been implicated in the transcriptional regulation of E-cadherin[40–42] (see Fig. 1).

In effect, integrins, catenins, and cadherins play complex integrative roles in signaling for the cellular motility and migration, proliferation, differentiation, and apoptosis, with stimulatory and inhibitory interactions that are affected by constitutive mutations and mutations in central genes like the APC gene. This complicated association in normal intestinal homeostasis and its interaction with growth factors, cytokines, and hormone-induced signaling in health and colitic disease remain to be defined.[3,43]

The E-cadherin–catenin complex in embryogenesis, morphogenesis, and differentiation

The expression of cadherins is regulated during development. In embryogenesis, a complex variety of morphological events denote cellular aggregation and epithelial/mesenchymal transition, partly as a result of differential expression and spatiotemporal changes in the surface cellular expression of the different cadherins.[44] Experimental evidence in developmental models has shown a crucial role for E-cadherin in early morphogenesis where expression of a dominant negative cadherin mutant in *Xenopus laevis* embryos results in perturbation of normal cell adhesion and normal tissue polarity.[45,46] Similarly, mutations of the β-catenin homologue in *Drosophila* (armadillo) create defective segment polarity[47] whereas ectopic overexpression of either β- or γ-catenin induces body axis duplication in the *Xenopus* embryo.[48,49] Here, the timed administration of antisense β-catenin oligonucleotides or β-catenin-specific monoclonal antibodies leads to defective dorsal development.[50,51]

The role of the cadherins and catenins in embryonic development and morphogenesis of the intestinal epithelium has been evaluated in vivo by gene targeting experiments in mouse embryonic stem cells and by generating transgenic and chimeric animals. Studies on E-cadherin gene knockout mice have revealed that E-cadherin-mediated cell adhesion is essential for the compaction of mesenchymal cells and their transition into a polarized epithelium. Homologous deletion of E-cadherin is also associated with lack of trophoectodermal epithelium or blastocyst cavity formation, resulting in early embryonic lethality.[52,53] Similarly, β-catenin deletion results in failed mesoderm formation with a disturbed ectoderm development and early

death.[54] Further evidence for the crucial role of cadherin-mediated cell adhesion within the intestinal epithelium comes from studies using chimeric-transgenic mice in which islets of enterocytes transfected with truncated N-cadherin lacking the extracellular domain were introduced into C57 BL/6 mouse blastocysts, where isolated expression of this construct in the villus enterocytes results in disruption of normal cell–cell and cell–matrix adhesion.[55] Perturbation in cell–cell adhesion in this model was associated with increased cell migration along the crypt–villus axis, loss of cellular differentiation and polarization, and increased apoptosis.[56] When the dominant negative N-cadherin mutant was expressed along the entire crypt–villus axis, disrupted cell–cell adhesion resulted in increased cell proliferation and apoptosis in the crypts and increased cell migration in the villi. Alterations of the cell cycle in the crypts caused adenoma formation, impairing mucosal barrier function and inducing a progressive transmural inflammation resembling Crohn's disease. In this model, histopathological changes observed in the adult chimeric mice included lymphoid aggregates, cryptitis, and crypt abscesses with goblet cell depletion, Paneth cell hyperplasia, and aphthoid or linear mucosal ulcers.[55] In contrast, forced expression of E-cadherin in the same model resulted in decreased cell proliferation and migration with increased apoptosis of cells in the upper part of the intestinal crypt.[57]

Cell adhesion and epithelial cell migration

Disturbance or modulation of cadherin–catenin and APC–catenin cell–matrix adhesion and phenotypic expression may have an important place in the cellular migration process, which is believed to be necessary for the initial stages of tumor metastasis. Cellular migration is a fundamental process involved in many physiological and pathological processes. It is now apparent that cell motility requires dynamic and coordinated interactions between cells, their extracellular substratum, and the cytoskeletal network.[58] The transition from a stationary to a motile cellular phenotype is associated with spatial and temporal changes in cell–cell and cell–matrix interactions, which involve perturbation of E-cadherin-mediated cell adhesion and the coordinated modulation of the expression and function of integrins.[59,60]

The extending lamellipodia at the leading edge of the migrating cell bind to the substratum through integrin receptors to establish stable cell–substratum adhesion and to generate adequate traction force for forward movement, followed by release of adhesion contacts at the rear of the cell.[59] Both β- and α-catenin have been shown to bind to the actin bundling proteins fascin and α-actinin, respectively,[61,62] with these proteins being crucial for the dynamic assembly and organization of actin bundles and networks during the extension of the cellular lamellipodia. The interaction between catenins and proteins involved in cell motility requires an organized regulation of E-cadherin/catenin-mediated cell–cell adhesion and cell migration where disruption of E-cadherin-mediated intercellular adhesion can occur through downregulation of E-cadherin expression and/or function, altered E-cadherin binding to β-catenin through tyrosine phosphorylation of β-catenin by type I tyrosine kinase growth factor receptors (such as the EGF receptor), or stoichiometric changes in the cytoplasmic pool of catenins and their complexes (see Fig. 1). This latter mechanism influences the titration of catenins between E-cadherin and other protein complexes impairing the adhesive function of E-cadherin. Here, the interactions between β-catenin and APC gene products appear to play a central role in cell migration, with APC localizing to the tip of the microtubule bundles[63] as well as to the end of cell processes.[64] In this respect, wild-type APC has been shown to induce disordered cell migration in the intestinal epithelium[65] and to downregulate the cytoplasmic levels of β-catenin,[37] where it is possible that a shift toward the "motility complexes" of β-catenin–APC or β-catenin–fascin could result in decreased β-catenin binding to E-cadherin, loss of E-cadherin-mediated intercellular adhesion, increased cell motility, and an induction of cell migration. An improved understanding of these interactions may provide future avenues for potential gene therapies in disordered cell migration associated with micrometastatic disease.[36,66]

Cellular adhesion and inflammatory bowel disease

Ulcerative colitis and Crohn's disease represent gastrointestinal diseases which, although clinicopathologically distinct, share common characteristic features of chronic inflammation, epithelial damage, mucosal ulceration, and epithelial restitution. It is now apparent that the reparative mechanism of epithelial restitution is induced immediately after superficial ulceration of the gastrointestinal mucosa[67] consisting of a rapid response mechanism of migrating surviving epithelial cells from the ulcer margins over the denuded area to cover the defect with reestablishment of epithelial continuity to restore mucosal barrier function.[68–70] During this phase, there is no cell proliferation as such with cell migration acting as the main factor contributing to mucosal repair. Later, both cell proliferation and differentiation occur to establish normal villus architecture and absorptive/secretory function.

There is considerable evidence that cell migration occurring during epithelial restitution is associated with

alterations in E-cadherin and catenin expression and E-cadherin-mediated cell adhesion. This change has been noted in in vitro wounded monolayer models using colorectal cancer cells[6] where there is reduced membranous expression and a cytoplasmic localization of E-cadherin, α-catenin, and p120, an effect that has also been demonstrated in vivo in peptic ulcer disease, Crohn's disease, and ulcerative colitis tissue.[5,6,71] The changes observed in these in vivo models occur in the regenerating and migrating epithelium adjacent to ulcers and appear to correlate directly with disease activity. Differential changes in the expression of the E-cadherin–catenin complex in inflammatory bowel disease result in focal upregulation of these adhesion molecules in areas of active inflammation with downregulation in the reparative epithelium of healing ulcers, absent expression of the E-cadherin–catenin complex in the ulcer-associated cell lineage, and dysregulation of epithelial desmoid and tight junction molecules and mRNA expression.[72,73] All these changes correlate with the recognizable severity of intestinal inflammation.

Decreased E-cadherin and catenin expression and subsequent disruption of E-cadherin-mediated cell adhesion (probably in response to the stimulatory effect of various motogenic factors) will enhance cell motility and promote cell migration in the regenerating mucosa. Importantly, a decrease in αEβ7-integrin-positive intestinal intraepithelial lymphocytes has also been demonstrated in the intestinal mucosa from patients with Crohn's disease[74] along with a focal upregulation of the E-cadherin–catenin complex in the subclinically inflamed bowel mucosa derived from spondyloarthropathy patients,[75] indicating an inverse relationship between αEβ7-integrin-positive lymphocyte infiltration and E-cadherin expression. This associated downregulation of epithelial tight junction molecules with cellular permeability and lymphocyte transmigration occurs in accordance with colitis activity and the activity of extracolonic disease.[76] Further evidence suggests that there is a differential expression of both E- and P-cadherins in inflammatory bowel disease, where left-sided ulcerative colitis results in either the downregulation of E-cadherin or specific single-base-pair mutations resulting in upregulation of P-cadherin specifically in dysplastic ulcerative colitis tissue.[66,71]

Many recent studies have shown that aberrant 5′-CpG DNA methylation plays a vital role in the inactivation of tumor suppressor and DNA repair genes or as an early de novo phenomenon in colorectal carcinogenesis.[77] This finding has been shown with gene methylation-specific polymerase chain reaction techniques[78] in aberrant crypt foci,[79] adenomas,[80] and in dysplasia-associated ulcerative colitis.[81] These CpG islands are short stretches of CpG-rich regions frequently associated with the promoter regions of specific genes that may undergo age-related methylation (so-called type A methylation), affecting the growth and differentiation of cells and cancer-specific methylation (so-called type C methylation), which produce a tumor-specific CpG island methylator phenotype.[82,83] The manner in which these changes in DNA methylation of critically important cell regulators such as E-cadherin cooperate in aberrant mucosal healing and dysplasia is at present relatively poorly understood, although as a feature of dysplastic samples in ulcerative colitis mucosa, it suggests that it is subject to epigenetic regulation during colonic ulceration and may be potentially useful as a marker in those patients with long-standing colitis at risk for malignant degeneration.[84] An improved understanding concerning the small subsets of colorectal cells that express such mutant cadherins associated with areas of active ulceration and epithelial resistance to mucosal damage and denudation, or which are more likely to display an inherently dysplastic phenotype, will assist in the development of new therapies and in defining those patients at risk for the colitis–carcinoma sequence.

The trefoil peptide family of molecules represent a group of highly protease-resistant peptides actively secreted onto the intestinal mucosal surface that promote mucosal repair through epithelial restitution following injurious insult. These factors are allied to a number of agents such as EGF, the transforming growth factors alpha (TGF-α) and beta (TGF-β), and the hepatocyte growth factor/scatter factor (HGF/SF), which with the trefoil peptides has a specific motogenic effect promoting cell migration during epithelial restitution and mucosal repair through modulation of cell–cell and cell–matrix adhesion. Both EGF and TGF-α have been shown to promote cell migration of colonic epithelial cells in vitro and to upregulate the functional activity of $\alpha_2\beta_1$ and $\alpha_3\beta_1$ integrin receptors for laminin and collagen.[85,86] Conversely, blocking of α_2 and β_1 integrin chains by specific monoclonal antibodies inhibits cell migration, whereas TGF-α stimulation results in an increased binding of $\alpha_2\beta_1$ integrin to the E-cadherin–catenin complex through β-catenin,[87] suggesting that the interactions between integrins and E-cadherin affect the stability of cell–matrix binding that is normally necessary during cell migration.

The trefoil peptides are a highly conserved family of small, secretory-stable molecules bearing one or more trefoil structural motifs of three interchain loops secured by disulfide bonds.[7] To date, three trefoil peptides have been identified in humans; namely, pS2 (trefoil factor 1, TFF1), human spasmolytic polypeptide (trefoil factor 2, TFF2), and intestinal trefoil factor (trefoil factor 3, TFF3). These peptides are constitutively expressed in the gastrointestinal tract in a region-

ally specific pattern, particularly in association with mucins, implying a role in maintaining the mucosal barrier. They are also ectopically overexpressed within gastrointestinal mucosa affected by chronically ulcerating and inflammatory lesions such as peptic ulceration, Crohn's disease, and ulcerative colitis.[8,88–90] In vitro studies using wounded monolayers as a model of mucosal injury have shown that at least two of these peptides (TFF1 and TFF2) stimulate cell migration and promote wound healing,[91,92] whereas in vivo both TFF2 and TFF3 appear to provide sufficient mucosal protection to reduce the extent and severity of ethanol- and indomethacin-induced acute gastric injury in the rat.[91,93,94] Following experimentally induced mucosal ulceration, there is an immediate increase in TFF2 expression in the ulcerated area, followed by an ectopic expression of TFF3.[95]

Targeted deletion of the gene encoding TFF3 in particular produces a high sensitivity to colonic injury, in which activation of these pathways redistributes E-cadherin from the cell surface to an intracellular locale resulting in catenin complexing, kinase activation, and apoptosis. In this regard, the trefoil peptides appear to block p53-dependent and p53-independent apoptosis enabling cellular migration with or without the programmed cell death normally associated with cellular detachment. Other trefoil peptides, most notably TFF3, require disturbance of calcium-dependent E-cadherin function where they have been shown to stimulate the migration of HT29 colorectal cancer cells by phosphorylation of β-catenin and reduced E-cadherin expression.[96] Moreover, knockout TFF3 mice tend to show an expanded intestinal proliferative epithelial phenotype with impaired mucosal healing,[97] whereas transgenic mice overexpressing TFF1 have an enhanced resistance to mucosal intestinal injury.[98] In this way, local trefoil peptides modulate E-cadherin-mediated cellular adhesion and cadherin–catenin complex formation by their interaction with key growth factor receptors.

The evidence that the stimulatory effect of various growth and trefoil factors has on cell migration and epithelial restitution acts through direct modulation of the E-cadherin adhesion system comes mostly from in vitro work with tumor cell lines where frameshift delections in E-cadherin gene repeat regions result in replication error-positive cell lines with altered cellular adhesion, differentiation, proliferation, and tumorigenicity as well as an altered sensitivity to motogenic trefoil factors; all these effects are restored to the cell lines by full-length E-cadherin cDNA transfection.[99]

Because tyrosine phosphorylation of β-catenin appears to be a common mechanism by which the motogenic factors express their effects in migrating cells, it is conceivable that β-catenin phosphorylation results in dissociation of the E-cadherin–catenin complex from the actin cytoskeleton with accumulation of β-catenin in the cytoplasmic pool. This effect may contribute to disassembly of adherens junctions, diminished cell–cell adhesion, and increased cell motility. The cytoplasmic accumulation of β-catenin may involve additional interactions with other proteins, most notably the APC protein as a central regulator of directed cell migration.[36] The synergistic effect of TFF3 and EGF on cell migration suggests a functional or physical interaction between these peptides and the relevant receptors, possibly through β-catenin.[94,96]

In conclusion, the efficient and coordinated repair of the gastrointestinal mucosa safely prevents the entry of pathogens and antigens across the intestinal lumen. There is now considerable evidence from wounded monolayer and primary cell culture models showing that epithelial cell migration is vital in this epithelial restitution with a complex interplay between and tight spatiotemporal control of soluble extracellular molecules (growth factors, trefoil peitides, and cytokines), matrix components (collagen, laminin, and fibronectin), signaling surface receptor-specific kinases and principal regulators of cell–cell (cadherin) and cell–matrix (integrins, hyaluronate receptors) adhesion. The E-cadherin–catenin complex appears to function as a master molecule in the regulation of cell adhesion, polarity, differentiation, migration, proliferation, and survival of gastrointestinal epithelial cells. Its fundamental role in embryogenesis has been clearly defined by the lethality seen in E-cadherin–catenin knockout mice, and loss of E-cadherin–catenin function is an important step in the development of both inflammatory and neoplastic lesions of the gastrointestinal tract. Much needs to be elucidated in human colitis and colitis models to provide potential therapies that can primarily influence epithelial restitution through deliberate E-caderin and catenin modulation.

References

1. Takeichi M. Cadherin cell adhesion receptors as a morphogenetic regulator. Science 1991;251:1451–5.
2. Hynes RO. Integrins: versatility, modulation and signaling in cell adhesion. Cell 1992;69:11–25.
3. Yamada K, Miyamoto S. Integrin transmembrane signaling and cytoskeletal control. Curr Opin Cell Biol 1995;7:681–9.
4. Pignatelli M, Vessey CJ. Adhesion molecules: novel molcular tools in tumor pathology. Hum Pathol 1994;25:849–56.
5. Karayiannakis AJ, Syrigos KN, Efstathiou J, Valizadeh A, Noda M, Playford RJ, et al. Expression of catenins and E-cadherin during epithelial restitution in inflammatory bowel disease. J Pathol 1998;185:413–8.
6. Hanby AM, Chinery R, Poulsom R, Playford RJ, Pignatelli M. Downregulation of E-cadherin in the reparative epithelium of the human gastrointestinal tract. Am J Pathol 1996;148:723–9.
7. Poulsom R, Wright NA. Trefoil peptides: a newly recognized family of epithelial mucin-associated molecules. Am J Physiol 1993;265:G205–13.

8. Wright NA, Pulsom R, Stamp G, Van Noorden S, Sarraf C, Elia G, et al. Trefoil peptide gene expression in gastrointestinal epithelial cells in inflammatory bowel disease. Gastroenterology 1993; 104:12–20.
9. Podolsky DK. Mechanisms of regulatory peptide action in the gastrointestinal tract: trefoil peptides. J Gastroenterol 2000; 35(suppl 12):69–74.
10. Gumbiner BM, McCrea PD. Catenins as mediators of the cytoplasmic functions of cadherins. J Cell Sci 1993;17(suppl):155–8.
11. Peifer M, Berg S, Reynolds AB. A repeating amino acid motif shared by proteins with diverse cellular roles. Cell 1994;76:789–91.
12. Nathke IS, Hinck L, Swedlow JR, Papkoff J, Nelson WJ. Defining interactions and distributions of cadherin and catenin complexes in polarized epithelial cells. J Cell Biol 1994;125:1341–52.
13. Hinck L, Nathke IS, Papkoff J, Nelson WJ. Dynamics of cadherin/catenin complex formation: novel protein interactions and pathways of complex assembly. J Cell Biol 1994;125:1327–40.
14. Nagafuchi A, Shirayoshi Y, Okazaki K, Yasuda K, Takeichi M. Transformation of cell adhesion properties by exogenously introduced E-cadherin cDNA. Nature (Lond) 1987;329:341–3.
15. Ozawa M, Engel J, Kemler R. Single amino acid substitutions in one Ca^{2+} binding site of uvomorulin abolish the adhesive function. Cell 1990;63:1033–8.
16. Hirano S, Kimoto N, Shimoyama Y, Hirohasi S, Takeichi M. Identification of a neural α-catenin as a key regulator of cadherin function and multicellular organization. Cell 1992;70:293–301.
17. Fujimori T, Takeichi M. Disruption of epithelial cell-cell adhesion by exogenous expression of a mutated nonfunctional N-cadherin. Mol Biol Cell 1993;4:37–47.
18. Shimoyama Y, Nagafuchi A, Fujita S, Gotoh M, Takeichi M, Tsukita S, et al. Cadherin dysfunction in a human cancer cell line: possible involvement of loss of α-catenin expression in reduced cell-cell adhesiveness. Cancer Res 1992;52:5770–4.
19. Kawanishi J, Kato J, Sasaki K, Fujii S, Watanabe N, Niitsu Y. Loss of E-cadherin-dependent cell-cell adhesion due to mutation of the β-catenin gene in a human cancer cell line, HSC-39. Mol Cell Biol 1995;15:1175–81.
20. Liu D, Nigam AK, Lalani EN, Stamp GWH, Pignatelli M. Transfection of E-cadherin into a human colon carcinoma cell line induces differentiation and inhibits growth in vitro. Gut 1993; 34(suppl 4):S27.
21. Reynolds AB, Herbert L, Cleveland JL, Berg ST, Gaut JR. p120, a novel substrate of protein tyrosine kinase receptors and of p60v-src, is related to cadherin-binding factors β-catenin, plakoglobin and armadillo. Oncogene 1992;7:2439–45.
22. Daniel JM, Reynolds AB. The tyrosine kinase substrate p120cas binds directly to E-cadherin but not to the adenomatous polyposis coli protein or α-catenin. Mol Cell Biol 1995;15:4819–24.
23. Shibamoto S, Hayakawa M, Takeuchi K, Hori T, Miyazawa K, Kitamura N, et al. Association of p120, a tyrosine kinase substrate, with E-cadherin/catenin complexes. J Cell Biol 1995;128: 949–57.
24. Pignatelli M, Liu D, Nasim MM, Stamp GWH, Hirano S, Takeichi M. Morphoregulatory activities of E-cadherin and β-1 integrins in colorectal tumour cells. Br J Cancer 1992;66:629–34.
25. Hodivala KJ, Watt FM. Evidence that cadherins play a role in the downregulation of integrin expression that occurs during keratinocyte terminal differentiation. J Cell Biol 1994;124:589–600.
26. Cepek KL, Shaw SK, Parker CM, Russell GJ, Morrow JS, Rimm DL, et al. Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and αEβ7 integrin. Nature (Lond) 1994; 372:190–3.
27. Zbar AP, Karayiannakis AJ. The gastrointestinal immune system—an overview. In: Zbar AP, Guillou PJ, Bland KI, Syrigos KN, editors. Immunology for surgeons. Berlin: Springer; 2002. p. 398–405.
28. D'Souza B, Taylor-Papadimitriou J. Overexpression of ERBB2 in human mammary epithelial cells signals inhibition of transcription of the E-cadherin gene. Proc Natl Acad Sci U S A 1994;81: 7202–6.
29. Dedhar S, Hannigan GE. Integrin cytoplasmic interactions and bidirectional transmembrane signalling. Curr Opin Cell Biol 1996;8:657–69.
30. Hoschuetzky H, Aberle H, Kemler R. β-Catenin mediates the interaction of the cadherin-catenin complex with epidermal growth factor receptor. J Cell Biol 1994;127:1375–80.
31. Ochiai A, Akimoto S, Kanai Y, Shibata T, Oyama T, Hirohasi S. c-erbB-2 gene product associates with catenins in human cancer cells. Biochem Biophys Res Commun 1994;205:73–8.
32. Kanai Y, Ochiai A, Shibata T, Oyama T, Ushijima S, Akimoto S, et al. c-erbB-2 gene product directly associates with β-catenin and plakoglobin. Biochem Biophys Res Commun 1995;208:1067–72.
33. Rubinfeld B, Souza B, Albert I, Muller O, Chamberlain SH, Masiarz FR, et al. Association of the APC gene product with β-catenin. Science 1993;262:1731–4.
34. Su L-K, Vogelstein B, Kinzler KW. Association of the APC tumor suppressor protein with catenins. Science 1993;262:1734–7.
35. Aust DE, Terdiman JP, Willenbucher RF, Chew K, Ferrell L, Florendo C, et al. Altered distribution of β-catenin, and its binding proteins E-cadherin and APC, in ulcerative colitis-related colorectal cancers. Mod Pathol 2001;14:29–39.
36. Efstathiou JA, Noda M, Rowan A, Dixon C, Chinery R, Jawhari A, et al. Intestinal trefoil factor controls the expression of the adenomatous polyposis coli-catenin and the E-cadherin-catenin complexes in human colon carcinoma cells. Proc Natl Acad Sci U S A 1998;95:3122–7.
37. Munemitsu S, Albert I, Souza B, Rubinfeld B, Polakis P. Regulation of intracellular β-catenin levels by the adenomatous polyposis coli (APC) tumor-suppressor protein. Proc Natl Acad Sci U S A 1995;92:3046–50.
38. Hulsken J, Birchmeier W, Behrens J. E-cadherin and APC compete for the interaction with β-catenin and the cytoskeleton. J Cell Biol 1994;127:2061–9.
39. Rubinfeld B, Souza B, Albert I, Munemitsu S, Polakis P. The APC protein and E-cadherin form similar but independent complexes with α-catenin, β-catenin, and plakoglobin. J Biol Chem 1995;270:5549–55.
40. Morin PJ, Sparks AB, Korinek V, Barker N, Clevers H, Vogelstein B, et al. Activation of β-catenin-Tcf signaling in colon cancer by mutations in β-catenin or APC. Science 1997;275:1787–90.
41. Rubinfeld B, Robbins P, El-Gamil M, Albert I, Porfiri E, Polakis P. Stabilization of β-catenin by genetic defects in melanoma cell lines. Science 1997;275:1790–2.
42. Behrens J, von Kries JP, Kuhl M, Bruhn L, Wedlich D, Grosschedl R, et al. Functional interaction of β-catenin with the transcription factor LEF-1. Nature (Lond) 1996:382:638–42.
43. Wilson AJ, Gibson PR. Epithelial migration in the colon: filling in the gaps. Clin Sci (Lond) 1997;93:97–108.
44. Takeichi M. The cadherins: cell-cell adhesion molecules controlling animal morphogenesis. Development (Camb) 1988;102:639–55.
45. Levine E, Lee CH, Kintner C, Gumbiner BM. Selective disruption of E-cadherin function in early *Xenopus* embryos by a dominant negative mutant. Development (Camb) 1994;120:901–9.
46. Dufour S, Saint-Jeannet JP, Broders F, Wedlich D, Thiery JP. Differential perturbations in the morphogenesis of anterior structures induced by overexpression of truncated XB- and N-cadherins in *Xenopus* embryos. J Cell Biol 1994;127:521–35.
47. Peifer M, Orsulic S, Sweeton D, Wieschaus E. A role for the *Drosophila* segment polarity gene armadillo in cell adhesion and cytoskeletal integrity during oogenesis. Development (Camb) 1993;118:1191–207.
48. Funayama N, Fagotto F, McCrea P, Gumbiner BM. Embryonic axis induction by the armadillo repeat domain of beta-catenin: evidence for intracellular signaling. J Cell Biol 1995;128:959–68.

49. Karnovsky A, Klymkowsky MW. Anterior axis duplication in *Xenopus* induced by the over-expression of the cadherin-binding protein plakoglobin. Proc Natl Acad Sci U S A 1995;92:4522–6.
50. Heasman J, Crawford A, Goldstone K, Garner-Hamrick P, Gumbiner B, McCrea P, et al. Overexpression of cadherins and underexpression of β-catenin inhibit dorsal mesoderm induction in early *Xenopus* embryos. Cell 1994;79:791–803.
51. McCrea PD, Brieher WM, Gumbiner BM. Induction of a secondary body axis in *Xenopus* by antibodies to beta-catenin. J Cell Biol 1993;123:477–84.
52. Larue L, Ohsugi M, Hirchenhain J, Kemler R. E-cadherin null mutant embryos fail to form a trophectoderm epithelium. Proc Natl Acad Sci U S A 1994;91:8263–7.
53. Riethmacher D, Brinkmann V, Birchmeier C. A targeted mutation in the mouse E-cadherin gene results in defective preimplantation development. Proc Natl Acad Sci U S A 1995;92:855–9.
54. Haegel H, Larue L, Ohsugi M, Fedorov L, Herrenknecht K, Kemler R. Lack of beta-catenin affects mouse development at gastrulation. Development (Camb) 1995;121:3529–37.
55. Hermiston ML, Gordon JI. Inflammatory bowel disease and adenomas in mice expressing a dominant negative N-cadherin. Science 1995;270:1203–7.
56. Hermiston ML, Gordon JI. In vivo analysis of cadherin function in the mouse intestinal epithelium: essential roles in adhesion, maintenance of differentiation, and regulation of programmed cell death. J Cell Biol 1995;129:489–506.
57. Hermiston ML, Wong MH, Gordon JI. Forced expression of E-cadherin in the mouse intestinal epithelium slows cell migration and provides evidence for nonautonomous regulation of cell fate in a self-renewing system. Genes Dev 1996;10:985–96.
58. Lauffenburger DA, Horwitz AF. Cell migration: a physically integrated molecular process. Cell 1996;84:359–69.
59. Huttenlocher A, Sandborg RR, Horwitz AF. Adhesion in cell migration. Curr Opin Cell Biol 1995;7:697–706.
60. Hynes RO, Lander AD. Contact and adhesive specificities in the associations, migrations and targeting of cells and axons. Cell 1992;68:303–22.
61. Tao YS, Edwards RA, Tubb B, Wang S, Bryan J, McCrea PD. β-Catenin associates with the actin-bundling protein fascin in a noncadherin complex. J Cell Biol 1996;134:1271–81.
62. Knudsen KA, Loler AP, Johnson KR, Wheelock MJ. Interaction of α-actinin with the cadherin-catenin cell-cell adhesion complex via α-catenin. J Cell Biol 1995;130:67–77.
63. Pollack AL, Barth AIM, Altschuler Y, Nelson WJ, Mostov KE. Dynamics of β-catenin interactions with APC protein regulate epithelial tubulogenesis. J Cell Biol 1997;137:1651–62.
64. Nathke IS, Adams CL, Polakis P, Sellin JH, Nelson WJ. The adenomatous polyposis coli tumor suppressor protein localizes to plasma membrane sites involved in active cell migration. J Cell Biol 1996;134:165–79.
65. Wong MH, Hermiston ML, Synder AJ, Gordon JI. Forced expression of the tumor suppressor adenomatous polyposis coli protein induces disordered cell migration in the intestinal epithelium. Proc Natl Acad Sci U S A 1996;93:9588–93.
66. Sanders DS, Perry I, Hardy R, Jankowski J. Aberrant P-cadherin expression is a feature of clonal expansion in the gastrointestinal tract associated with repair and neoplasia. J Pathol 2000;190:526–30.
67. Itoh S, Lacy ER, Rutten MJ, Critchlow J, Silen W. Rapid repair of injured gastric mucosa. Scand J Gastroenterol 1984;19(suppl 101):87–95.
68. Buck RC. Ultrastructural features of rectal epithelium of the mouse during the early phases of migration to repair a defect. Virchows Arch [B] 1986;51:331–40.
69. Waller DA, Thomas NW, Self TJ. Epithelial restitution in the large intestine of the rat following insult with bile salts. Virchows Arch [A] Pathol Anat 1988;414:77–81.
70. Feil W, Lacy ER, Wong Y-MM, Burger D, Wenzl E, Starlinger M, et al. Rapid epithelial restitution of human and rabbit colonic mucosa. Gastroenterology 1989;97:685–701.
71. Jankowski JA, Bedford FK, Boulton RA, Cruickshank N, Hall C, Elder J, et al. Alterations in classical cadherins associated with progression in ulcerative and Crohn's colitis. Lab Invest 1998;78:1155–67.
72. Gassler N, Schnolzer M, Rohr C, Helmke B, Kartenbeck J, Grunewald S, et al. Inflammatory bowel disease is associated with changes of enterocytic junctions. Am J Physiol Gastrointest Liver Physiol 2001;281:G216–28.
73. Demetter P, De Vos M, Van Damme N, Baeten D, Elewaut D, Vermeulen S, et al. Focal up-regulation of E-cadherin-catenin complex in inflamed bowel mucosa but reduced expression in ulcer-associated cell lineage. Am J Clin Pathol 2000;114:364–70.
74. Elewaut D, Van Damme N, De Keyser F, Baeten D, De Paepe P, Van Vlierberghe H, et al. Altered expression of αEβ7-integrin on intra-epithelial and lamina propria lymphocytes in patients with Crohn's disease. Acta Gastroenterol Belg 1998;61:288–94.
75. Demetter P, Baeten D, De Keyser F, De Vos M, Van Damme N, Verbruggen G, et al. Subclinical gut inflammation in spondyloarthropathy patients is associated with upregulation of the E-cadherin/catenin complex. Ann Rheum Dis 2000;59:211–6.
76. Kucharzik T, Walsh SV, Chen J, Parkos CA, Nusrat A. Neutrophil transmigration in inflammatory bowel disease is associated with differential expression of epithelial intercellular junction proteins. Am J Pathol 2001;159:2001–9.
77. Jubb AM, Bell SM, Quirke P. Methylation and colorectal cancer. J Pathol 2001;195:111–34.
78. Herman JG, Graff JR, Myohanen S, Nelkin BD, Baylin SB. Methylation-specific PCR: a novel PCR assay for methylation status of CpG islands. Proc Natl Acad Sci USA 1996;93:9821–6.
79. Chan AO, Broaddus RR, Houlihan PS, Issa JP, Hamilton SR, Rashid A. CpG island methylation in aberrant crypt foci of the colorectum. Am J Pathol 2002;160:1823–30.
80. Rashid A, Shen L, Morris JS, Issa JP, Hamilton SR. CpG island methylation in colorectal adenomas. Am J Pathol 2001;159:1129–35.
81. Azarschab P, Porschen R, Gregor M, Blin N, Holzmann K. Epigenetic control of the E-cadherin gene (CDH1) by CpG methylation in colectomy samples of patients with ulcerative colitis. Genes Chromosomes Cancer 2002;35:121–6.
82. Toyota M, Issa JP. CpG island methylator phenotypes in aging and cancer. Semin Cancer Biol 1999;9:349–57.
83. Toyota M, Itoh F, Kikuchi T, Satoh A, Obata T, Suzuki H, et al. DNA methylation changes in gastrointestinal disease. J Gastroenterol 2002;37(suppl 14):97–101.
84. Wheeler JM, Kim HC, Efstathiou JA, Ilyas M, Mortensen NJ, Bodmer WF. Hypermethylation of the promoter region of the E-cadherin gene (CDH1) in sporadic and ulcerative colitis associated colorectal cancer. Gut 2001;48:367–71.
85. Basson MD, Modlin IM, Madri JA. Human enterocytes (Caco-2) migration is modulated in vitro by extracellular matrix composition and epidermal growth factor. J Clin Invest 1992;90:15–23.
86. Liu D, Gagliardi G, Nasim MM, Alison MR, Oates T, Lalani EN, et al. TGF-α can act as morphogen and/or mitogen in a colorectal carcinoma cell line. Int J Cancer 1994;56:603–8.
87. Jawhari A, Noda M, Farthing M, Pignatelli M. New evidence of cross talk between the E-cadherin-catenin complex and α2 integrin: an interaction influenced by transforming growth factor-α and the trefoil peptide hSP. Gut 1997;41(suppl 3):A27.
88. Khulusi S, Hanby AM, Marrero JM, Patel P, Mendall MA, Badve S, et al. Expression of trefoil peptides pS2 and human spasmolytic polypeptide in gastric metaplasia at the margin of duodenal ulcers. Gut 1995;37:205–9.
89. Rio MC, Chenard MP, Wolf C, Marcellin L, Tomasetto C, Lathe R, et al. Induction of pS2 and hSP genes as markers of mucosal ulceration of the digestive tract. Gastroenterology 1991;100:375–9.

90. Wright NA, Poulsom R, Stamp GWH, Hall PA, Jeffery RE, Longcroft JM, et al. Epidermal growth factor (EGF/URO) induces expression of regulatory peptides in damaged human gastrointestinal tissues. J Pathol 1990;162:279–84.
91. Playford RJ, Marchbank T, Chinery R, Evison R, Pignatelli M, Boulton RA, et al. Human spasmolytic polypeptide is a cytoprotective agent that stimulates cell migration. Gastroenterology 1995;108:108–16.
92. Dignass A, Lynch-Devaney K, Kindon H, Thim L, Podolsky DK. Trefoil peptides promote epithelial migration through a transforming growth factor β-independent pathway. J Clin Invest 1994;94:376–83.
93. Babyatsky MW, deBeaumont M, Thim L, Podolsky DK. Oral trefoil peptides protect against ethanol- and indomethacin-induced gastric injury in rats. Gastroenterology 1996;110:489–97.
94. Chinery R, Playford RJ. Combined intestinal trefoil factor and epidermal growth factor is prophylactic against indomethacin-induced gastric damage in the rat. Clin Sci 1995;88:401–3.
95. Alison MR, Chinery R, Poulsom R, Ashwood P, Longcroft JM, Wright NA. Experimental ulceration leads to sequential expression of spasmolytic polypeptide, intestinal trefoil factor, epidermal growth factor and transforming growth factor alpha mRNAs in rat stomach. J Pathol 1995;175;405–14.
96. Liu D, El-Hariry I, Karayiannakis AJ, Wilding J, Chinery R, Kmiot W, et al. Phosphorylation of β-catenin and epidermal growth factor receptor by intestinal trefoil factor. Lab Invest 1997;77:557–63.
97. Mashimo H, Wu DC, Podolsky DK, Fishman MC. Impaired defense of intestinal mucosa in mice lacking intestinal trefoil factor Science 1996;274:262–5.
98. Playford RJ, Marchbank T, Goodlad RA, Chinery RA, Poulsom R, Hanby AM. Transgenic mice that overexpress the human trefoil factor peptide pS2 have an increased resistance to intestinal damage. Proc Natl Acad Sci U S A 1996;93:2137–42.
99. Efstathiou JA, Liu D, Wheeler JM, Kim HC, Beck NE, Ilyas M, et al. Mutated epithelial cadherin is associated with increased tumorigenicity and loss of adhesion and of responsiveness to the motogenic trefoil factor 2 in colon carcinoma cells. Proc Natl Acad Sci U S A 1999;96:2316–21.