

Review

The E-Cadherin Adhesion Molecule and Colorectal Cancer. A Global Literature Approach

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Abstract. *The E-cadherin–catenin complex plays a crucial role in epithelial cell cell adhesion and in the maintenance of tissue architecture. Down-regulation of E-cadherin expression correlates with a strong invasive potential, resulting in poor prognosis in human carcinomas. Progress has been made in understanding the interaction between the different components of this protein complex and how this cell-cell adhesion complex is modulated in cancer cells. The present study is an update of the role of E-cadherin in human colorectal cancer. It emphasizes new features and the possible role of the complex in clinical practice, discussed in the light of references obtained from the Medline database from 1987 to 2007. In colorectal carcinomas, changes in E-cadherin expression have been correlated with tumour size, histopathology and differentiation, but results are still inconsistent. Further studies may yield greater insight into the early molecular interactions critical to the interaction between adhesion molecules and tumour initiation and progression. This should aid the development of novel strategies for both prevention and treatment of cancer.*

Cell-cell adhesion is considered to play a fundamental role in the development and maintenance of epithelial structures integrity (1). During the multi-step process of carcinogenesis (2, 4), cancer cells acquire the capacity to invade adjacent structures, such as blood or lymph vessels and therefore metastasize. This ability of cancerous cells is strongly associated with loss of cell-cell adhesiveness, which is the major phenomenon accounting for the invasive properties of a tumour.

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In recent years, there has been increasing interest in a large family of transmembrane glucoproteins, termed cadherins (5, 6), which are the main mediators of calcium-dependent cell-cell adhesion, as they facilitate the assembly of specialized intercellular junctions necessary for the linkage of epithelial cells. These molecules have been implicated in the progress of tumour invasion. There is evidence that defects in the function of these proteins are crucial for the initiation and progression of human cancer, including colorectal cancer.

Colorectal Carcinogenesis

Colon cancer has become a model for studying multistage carcinogenesis (Figure 1). Four distinct sequential mutations have been described in the development of colon cancer (7). These mutations result in the overexpression of oncogenes and the deletion of anti-oncogenes, the combination of which results in cancer. With each mutation, progressive changes are seen in the colonic epithelium. For the initiation of colon cancer, mutations of the *APC* (adenomatous polyposis coli) gene is required (8, 10), as it is detected in 75% of sporadic carcinomas (11), while germline mutations in this gene cause familial adenomatous polyposis coli (FAP). Mutations in *APC* lead to dysplasia (abnormalities in adult cells) or polyp formation (usually benign growths on the surface of mucous membranes). *APC* gene mutations alter cell adhesion by affecting the binding of β -catenin (12, 17). When one cell in such a polyp develops a second mutation, in the *K-ras* gene, it grows at a faster rate, resulting in a larger tumour or intermediate adenoma (18). *K-ras* gene mutations induce proliferation *via* the EGFR-RAS-RAF-ERK-JUN/FOS pathway and inhibit apoptosis by phosphorylating procaspase, providing a growth advantage in these cells.

In this model, mutation at the deleted in colon cancer (DCC) locus represents the third step in the genetic pathway. DCC is a neural cell adhesion molecule homologue and may play a role in tumour progression, invasion and metastasis.

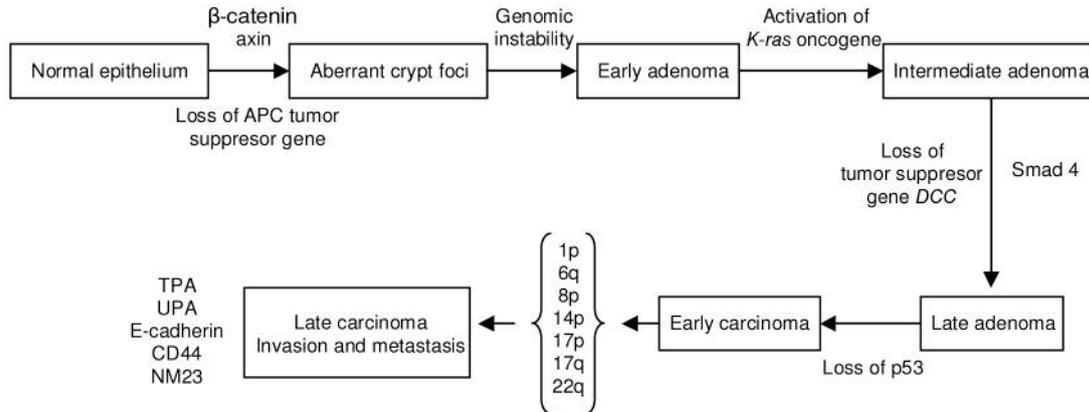


Figure 1. Genetic model of colorectal carcinogenesis. Mutations of APC and β -catenin or axin genes are required for tumor initiation. Subsequent progression is accompanied by genomic instability and sequential mutations in *K-ras*, *Smad4* and *p53* genes.

There is evidence that other targets of allele loss in chromosome 18q are SMAD4 and SMAD2, which in turn may interfere with transforming growth factor- β signaling (19). Mutations of *p53* are described in 75% of colorectal carcinomas and there is no doubt about its role in tumor progression, as these mutations tend to occur at the late adenoma stage (20, 22). Locations of other tumor suppressor loci that might be involved include chromosomes 1p, 6q, 8p, 14q, 22q (23, 29).

Cell adhesion molecules are involved in the process of invasion and metastasis of colorectal cancer. Mutations at their loci may have effects on growth, in addition to those on adhesion. Loss of E-cadherin protein is associated with the development of invasive properties (30, 32).

Other proteins that may be associated with invasion of colorectal cancer include those involved in tissue degradation, such as urokinase plasminogen activators (33). Variation at several gene loci may alter the behaviour pattern of the mature colorectal cancer. These include the *nm23* gene, which has a possible role in the metastasis of several types of cancer, and *CD44* (34, 35).

E-Cadherin–Catenin Adhesion Complex

E-Cadherin and the cadherin family. Cadherins, transmembrane glucoproteins, are the major mediators of cell-cell adhesion (36), which in turn is accomplished through homotypic reactions (an E-cadherin molecule on one cell binds to an E-cadherin on another) totally dependent on the presence of calcium ions (37). The subfamily of classical cadherins (38) consists of more than 16 molecules which, although encoded by different genes, make up a distinct group of phylogenetically and structurally related molecules, with molecular weights of approximately 120 kDa. Depending on their tissue distribution, several subclasses of cadherins exist,

including epithelial E-cadherin (also named L-CAM, uvomorulin, Arc-1, and cell-CAM 120/80), neural N-cadherin, placental P-cadherin and VE-cadherin (vascular endothelial cadherin).

E-Cadherin, encoded by the *CDH1* gene (39) which is located on chromosome 16q22, is a transmembrane protein confined to epithelial cells and is mainly responsible for adherence junctions between them. E-cadherin has an extracellular domain consisting of five cadherin-type repeats (40) that interact in a calcium-dependent fashion with cadherin molecules on neighbouring cells, essentially forming a “molecular zipper”. A prerequisite for intercellular adhesion is the cytoplasmic linkage of E-cadherin to either β -catenin or γ -catenin and the subsequent α -catenin mediated linkage of this complex to the microfilament network of the cellular cytoskeleton. β -Catenin also binds to the cytoplasmic domain of the epidermal growth factor (EGF) receptor (41).

E-cadherin is not distributed randomly over the surface of the cell but, rather, tends to localize to specialized junctions of the zonula adherens-type, playing a crucial role in the development of multi molecular structures with a “zipper” conformation.

The critical importance of E-cadherin to normal development and tissue function is demonstrated (42) by the lethality of *E-cadherin* gene knockouts in mice at a very early stage in embryogenesis. Loss of E-cadherin-mediated adhesion thus appears to be of fundamental importance in the neoplastic process, allowing cells to escape normal growth control signals, resulting in loss of differentiation and increased cell proliferation associated with invasive behaviour (43).

Catenins. The functions of E-cadherin are mediated through its cytoplasmic linkage to the actin cytoskeleton via certain cytoplasmic plaque proteins known as the catenins (44, 45).

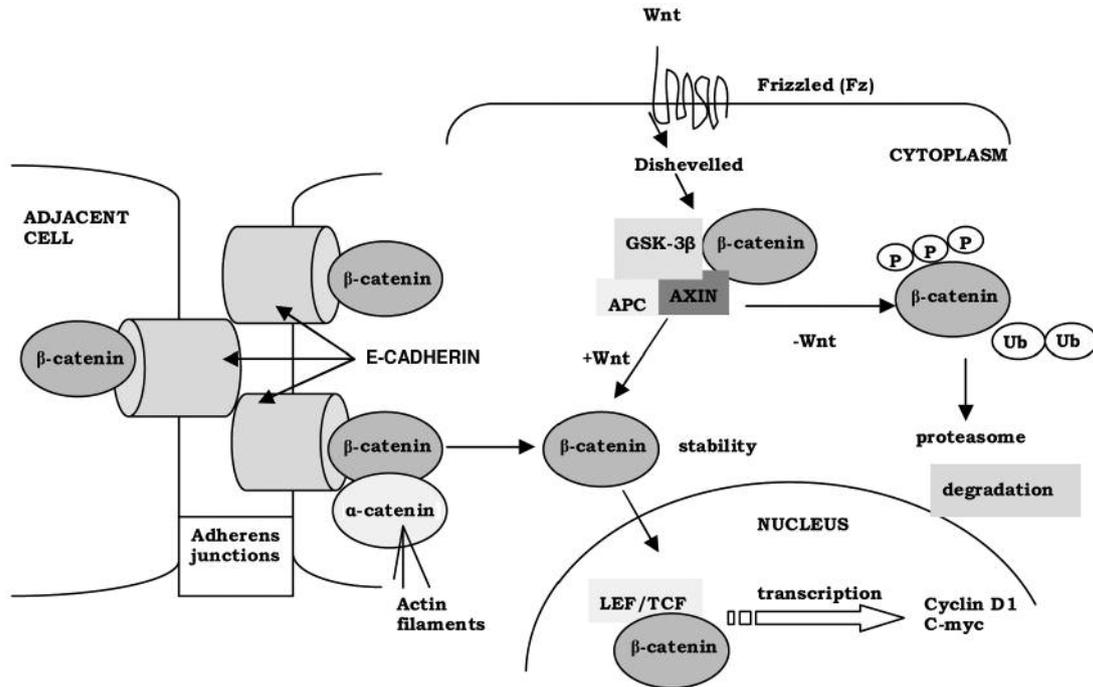


Figure 2. Cadherin extracellular domains mediate homophilic cell-cell adhesion, while their intracellular domains associate with catenins, which mediate linkage to the actin cytoskeleton and adhesion-induced signaling. β -Catenin binds directly to the C-terminal "catenin-binding domain" of the cadherin cytoplasmic tail. β -Catenin interacts further with α -catenin, which increases cell adhesion. The Wnt pathway encodes for a large family of proteins that act as extracellular signalling factors. The Frizzled (Frz) transmembrane receptor family initiates the Wnt cascade. Activation of Dishevelled (*dsh*) by hyperphosphorylation prevents β -catenin degradation, by complex with APC/axin/GSK-3 β . Upon stabilization of cytoplasmic β -catenin by Wnt signaling or oncogenic activation, β -catenin translocates to the nucleus, where it induces transcriptional events via its association with TCF/LEF transcription factors.

The catenin complex consists of α -catenin (102 kDa, chromosome 5q), β -catenin (92 kDa, chromosome 3p) and γ -catenin (83 kDa, chromosome 17q). The E-cadherin-catenin complex is found at sites of cell-cell contact known as the adherens junction or zonula adherens, and their formation is a prerequisite for normal functioning of E-cadherin because a dysfunctional catenin complex leads to defective E-cadherin activity: reversible down-regulation of E-cadherin function through phosphorylation of catenins has been shown to cause adherens junction destabilization (46). α -catenin plays an important role in linking the E-cadherin-catenin complex to the actin cytoskeleton. Nevertheless, α -catenin does not bind directly to E-cadherin, but interacts with it *via* β - and γ -catenins (47). β -Catenin is involved in organogenesis and tissue morphogenesis, playing an important role in normal development and tissue function (48). It also plays a critical role in regulation of cadherin-mediated cell recognition and adhesion). Tyrosine phosphorylation of β -catenin in response to growth factor stimulation induces disassembly of the E-cadherin-catenin complex, disrupting normal cell adhesion processes (46). The precise cellular role of γ -catenin, which shares very high sequence homology with β -catenin, has not been clearly

defined. It is present in the zonula adherens junction and may function within the desmosomal plaque (49).

The p120 protein is another catenin-like molecule, which like its structural homologues β - and γ -catenin, binds directly to the cytoplasmic domain of E-cadherin (50). Recent data suggest that p120 may participate in the modulation of E-cadherin-mediated cell adhesion, perhaps independently from the catenins (51, 42).

The critical value of intact E-cadherin-catenin complex expression. One of the major roles of this complex in tumour development is associated with its function as an invasion suppressor molecule, through interrupted cellular adhesion and perturbation of cytoskeletal organization (Figure 2). Specifically, loss of cadherin-mediated adhesion may act as a promoter of tumour cell detachment from the primary site, concurrent invasion of adjacent normal tissue and dissemination to distant places. Many immunohistochemical studies (3, 52-55) have clearly shown that a variety of human cancer demonstrates aberrant expression levels of E-cadherin and/or catenin complexes compared to their normal counterparts. In particular, well-differentiated tumours exhibit a strong staining pattern of E-cadherin/catenin

compared to poorly differentiated ones and this epithelioid morphology is more frequently associated with the presence of functional E-cadherin, when compared with sarcomatous tumour cell morphology (7). We can postulate that loss of expression of these molecules is associated with an aggressive tumour phenotype (16, 56), and in turn, with highly invasive neoplasms. It should be noted that abnormal expression of E-cadherin has been detected in precancerous lesions, such as Barrett's oesophagus (57), chronic active B-type gastritis (58) and cervical intraepithelial neoplasia (59). A study conducted by Hermiston *et al.* (60) demonstrated that loss of functional E-cadherin in intestinal crypt cells, may lead to the formation of adenomas, lesions that can progress into cancer.

The second main function of this complex in carcinogenesis is that of proliferation suppression. This is accomplished *via* up-regulation of a well-known cell cycle inhibitor, p27, by E-cadherin (2).

The E-cadherin-catenin adhesion complex and cancer.

Reports have emphasized the critical role of *E-cadherin* gene mutation as the major mechanism responsible for its inactivation in cancer cells (61). This aberration has been strongly associated with specific carcinomas, such as lobular breast carcinoma (62), diffuse-type gastric cancer (63), hepatocellular carcinoma (64), but is a rare event in oesophageal (65), thyroid (66) and colorectal cancer (67). Its inactivation through mutation is proposed to be an early event in tumorigenesis, as it has been observed that even *in situ* gastric (68) and lobular breast carcinomas (69) carry this aberration. Another route resulting in inactivation of *E-cadherin* is attributed to dysfunctional promoter activity, due to chromatin rearrangement in the regulatory domain (60) or DNA methylation at the promoter region (70). Using immunohistochemical techniques, the staining pattern of E-cadherin is not always indicative of the functional condition of the protein in many cancer cell types. The altered expression may be attributed not only to partial or total protein loss, but also to redistribution from a peripheral membranous to a cytoplasmic position, resulting in failure of the protein to act as an intercellular bond (71-76). This redistribution may be associated with hypophosphorylation of E-cadherin and/or catenin molecules (73). Conversely, increased expression of E-cadherin and/or catenin in cancer cells is not indicative of the functional integrity of the complex (72-77), as dysfunctional binding to the cytoskeleton proteins may occur. As a result of disrupted E-cadherin/ β -catenin complex, β -catenin is released from the membranous pool, then non-degraded molecules translocate into the nucleus inducing the transcription of genes involved in tumor progression. (78)

Concerning catenins (α -, β -, γ -), only gene mutations in cancer cell lines have been described, while there is no report of occurrence in tumours *in vivo* (79, 80, 34).

We have already mentioned that highly aggressive neoplasms presenting with a single cell pattern, such as lobular and signet ring carcinoma, usually present with loss of E-cadherin expression. In these instances, abnormal expression of E-cadherin-catenin complex is correlated with differentiation, invasive capacity and vascular penetration, lymph node involvement, presence of distal metastasis and stage (81-88). In many cancer cell types abnormal expression of E-cadherin and α -, β - and γ -catenins are correlated with clinical variables, such as disease-free and overall survival, and can significantly predict relapse rate (89-94). On the other hand, some studies (95, 96) have failed to establish a prognostic value for E-cadherin.

It is critical to mention that every component of the complex should be investigated in order to evaluate its prognostic impact in cancer patients. Indeed, it has been reported that the combination of E-cadherin and one of the catenins provides a better prognostic value than the evaluation of individual components (97).

Expression of E-cadherin in colon cancer.

Colorectal carcinogenesis is a multistep process where normal epithelial cells progress through a series of premalignant lesions to invasive and metastatic cancer (98). Throughout the normal and inflamed colon, E-cadherin is expressed on the basolateral aspects of the cell membrane, in all crypt and surface enterocytes, establishing in this way mucosal integrity (85). This reflects the normal localization of an intercellular adhesion molecule to permit homotypic adhesion since cytoplasmic E-cadherin is by definition non-functional. E-cadherin reduction, as will be presented in this review, is obvious in all premalignant dysplastic lesions and appears to be associated with dedifferentiation, invasion, metastasis and poor prognosis. It should be stressed that the application of different methodologies, such as mRNA analysis, Western blot and immunohistochemical studies, often are combined and the use of different antibodies directed against either the extracellular or intracellular domains of E-cadherins is the reason for the observed discrepancies.

Many studies have described abnormal expression of E-cadherin in the majority of colon cancer cases (4, 36, 99). Most studies show an overall decrease in the expression of E-cadherin compared to adjacent normal mucosa (67, 100). Abnormal staining reaction was defined as reduced immunoreactivity compared to case-matched non-tumorous mucosa and/or cytoplasmic reaction instead of membranous. Cytoplasmic staining seems to be a reflection of defective transition, failure to translocate or anchor, or integration of E-cadherin to the cell membrane, or a result of abnormal association with cytoplasmic proteins. It is highly likely that that most of the cytoplasmic E-cadherin is functional in cell-cell adhesion, as it is not located at the adherens junction.

Despite this, at least one study failed to demonstrate loss of E-cadherin, probably because the model used concerned early-stage carcinogenesis, as the majority examined were adenomas (101). Another study also revealed E-cadherin overexpression in 80% of the cases, but this was associated with cytoplasmic accumulation (102). The same was observed in metastatic lymph nodes from the respective cases. The same authors revealed in a recent study that this overexpression was also observed in colorectal carcinoma cell lines, emphasizing that the cellular localisation of E-cadherin is influenced by physical contact between cells, which results in the acquisition of membranous position (103).

We therefore conclude that E-cadherin expression is diminished in invasive colorectal cancer (72-104, 105-106). Indeed this reduced membranous expression has been used in differentiating invasive foci from misplaced epithelium in the stalk of colonic adenomas (107).

It is known that germline mutations in the *APC* gene result in the autosomal dominantly inherited disease FAP, characterized by the development of multiple colorectal adenomatous polyps with invariable progression to carcinoma (7). In one study, it was demonstrated that 80% of adenomas overexpressed E-cadherin and, in contrast to data concerning sporadic cancer, high levels of E-cadherin, both cytoplasmic and membranous were found, even in poorly differentiated carcinomas (103). Recently, an important study found highly significant differences between FAP and non-FAP adenomas, especially with respect to the expression of E-cadherin (108). While the considerable heterogeneity with respect to E-cadherin expression in sporadic adenomas was compatible with previous findings, the uniform reduction of E-cadherin expression in FAP-associated adenoma was unexpected (3, 99). The mechanism of this difference remains to be elucidated.

Transfection of *E-cadherin* cDNA into poorly differentiated human colon carcinoma cell lines increases cell polarity and intercellular cohesion and inhibits invasion *in vitro*. Furthermore, low E-cadherin expression was strongly related to a high migratory activity of colon carcinoma cell lines, a phenomenon that was independent of the differentiation grade (10). All these data show that perturbation of E-cadherin in colorectal cancer is a functional perturbation rather than a simple decrease or failure of expression.

Mechanisms of E-cadherin deregulation in colon cancer. Recent findings indicate that down-regulation of E-cadherin facilitates tumour cell invasion (109). In colorectal as well in oesophageal cancer, this down-regulation is rarely attributed to *E-cadherin* gene mutation (67, 104, 110), a phenomenon commonly observed in diffuse-type gastric and lobular breast carcinomas (61). Efstathiou *et al.* (111) detected E-cadherin inactivating mutations in only 7% (3/43) of colorectal carcinoma cell lines, and in two of them in only one allele.

Since structural mutations or loss of heterozygosity do not play a crucial role for E-cadherin inactivation in colon cancer, other epigenetic events (110, 112) such as promoter methylation resulting in transcriptional silencing have to be considered. Specifically, this hypermethylation was most commonly observed in ulcerative colitis associated colorectal cancer compared to sporadic colorectal cancer, but no statistically significant association was present (110). In experiments on human colon cancer cell lines, it was observed that anoxia and subsequent reoxygenation can induce reduction of E-cadherin, measured by immunofluorescent staining and enzyme-linked immunosorbent assays, resulting in almost total disappearance of the molecule from the cell membrane (113). However using Western blotting, no reduction of the amount of total E-cadherin was found, which is indicative of the fact that there is no true reduction, but in fact a redistribution, mainly internalization, of surface E-cadherin and the subsequent failure to bind the cytoskeleton. We can postulate that in these colon cancer cell lines, down-regulation of E-cadherin is the result of post-translational modifications. This is further supported by previous studies, also conducted in colonic cancer cell lines, that revealed no differences between *E-cadherin* mRNA between highly and weakly metastatic cell lines (114).

Possible molecules implicated in the transcriptional down-regulation of E-cadherin are those associated with activation of nuclear factor κ B (NF- κ B). This was proven by the observation that inhibition of agents that interfere with activation of NF- κ B significantly attenuated anoxia-induced down-regulation of E-cadherin.

In addition, the possible correlation between abnormal E-cadherin expression and up-regulation of transcriptional suppressors that directly inhibit mRNA has been studied. Specifically, one transcription factor, *SNAIL*, located on 20q13.1 locus, is often amplified in colon cancer (115, 116). However, in two independent studies (100, 117), this amplification was not correlated with concurrent *SNAIL* mRNA up-regulation and therefore that this repressor at least does not play a crucial role in colon carcinogenesis. However, other transcriptional repressors, such as SIP1 and SLUG, have been implicated in transcriptional repression of E-cadherin by binding to critical E-box elements in the *E-cadherin* promoter (21, 118). The roles of SNAIL and LUG in colorectal carcinogenesis remain to be established.

Loss of expression of tumour suppressor genes predominantly involved in gastrointestinal carcinogenesis (119), such as *SMAD4*, has been implicated in the regulation of E-cadherin in primary human carcinomas and carcinoma cell lines, and was shown to function as a positive regulator of cadherins (120, 121). In this last study, co-segregation of E-cadherin and Smad4 were statistically significant association in 51 human late-stage colorectal carcinomas (121).

Inappropriate expression of mesenchymal N-cadherin was detected in 44% of a series of colon cancer (100). One

interesting finding was that N-cadherin was almost exclusively expressed in cases with normal E-cadherin expression, showing that E-cadherin reduction is mutually exclusive of N-cadherin up-regulation. This raises the possibility that such N-cadherin expression leads to tumour promotion *via* interactions of tumour cells with stromal components (122).

Src kinase activity has been implicated (123) in the development and progression of human colon cancer, as nearly all colorectal carcinomas display increased activity of this kinase. Activated Src expression may be a critical factor in the release of viable cells from the primary tumour. It has been hypothesised (124) that this process is linked to the disruption of the cadherin-catenin complex as a result of cadherin phosphorylation, mediated through Ras and FAK pathways.

Role of β -catenin in colorectal carcinogenesis. β -catenin plays a key role in colorectal carcinogenesis (Figure 2). In normal colonic mucosa, β -catenin is mainly membranous, while in adenomas and carcinomas it appears with both cytoplasmic and nuclear localization. Nuclear β -catenin increases from early adenoma to adenocarcinoma (125) and higher levels of nuclear expression have been detected in the invasive front of carcinomas. Mutations of the *APC* gene or the *catenin* gene (126-128) result in nuclear accumulation of β -catenin and subsequent activation of Tcf-Lef-dependent transcription and up-regulation of target genes important in carcinogenesis (*c-myc*, *cyclin D1*) (129). Mutations in the regulatory region of β -catenin have been identified in approximately 50% of colon cancer expressing wild-type APC (130), while several changes have been described outside this region (96). The most common mutation in the β -catenin encoding gene affects the serine and threonine residues of the protein that are targeted by GSK-3 β , a serine threonine kinase that negatively regulates β -catenin (38). This mutation allows β -catenin to escape proteosomal degradation, cytoplasmic accumulation and subsequent nuclear translocation. As a result, increased nuclear expression of β -catenin in both familial and sporadic colorectal cancer has been described (60, 103, 131, 132).

Association with differentiation and metastasis. Based on the hypothesis that selective adhesion molecule interactions can be involved in metastasis formation, studies carried out on human cancers showed the existence of a negative correlation between invasive capacity and cadherin expression (133, 134). However, as far as colon cancer is concerned, data for this association are much less conclusive. Loss of expression of E-cadherin and catenins is found to be associated with dedifferentiation, invasion and metastasis, and is therefore suggested (97, 135) as a potential prognostic factor in colorectal cancer.

When E-cadherin is down-regulated, epithelial cells acquire a fibroblastic phenotype accompanied by invasion and migratory properties (136). The process that achieves this morphogenetic transformation is known as the epithelial-mesenchymal transition (EMT) (137). Not surprisingly, loss of E-cadherin expression, the switch from E- to N-cadherin, and N-cadherin neoexpression is a defining characteristic of EMT in colorectal cancer (100, 138, 139). N-Cadherin interacts with stromal fibroblasts, endothelial and neuronal cells, and thus facilitates invasion and metastasis. Transcriptional repressors of E-cadherin and other epithelial markers, such as Snail, Sip1, Slug and Twist may be implicated in EMT (140). However, induction of Snail and Sip1 were not the underlying mechanisms of E- to N-cadherin transition in colon cancer (100). The role of other transcription factors remains to be elucidated.

Some studies failed to demonstrate any correlation between reduced and/or cytoplasmic expression of E-cadherin with conventional staging, tumour differentiation, invasive metastatic potential or prognosis (132, 141-143). Furthermore, tumours with a hypermethylated promoter region did not exhibit adverse clinicopathological parameters, such as advanced stage or poor differentiation (110). On the other hand, several studies have demonstrated that loss of E-cadherin expression is associated with tumour size, histopathology, growth patterns and extent of dysplasia (4, 36, 99). Indeed, a negative correlation was found between the degree of membranous expression of E-cadherin and progressively higher degree of dysplasia in colonic adenomas and carcinomas (125). This has been observed in colorectal cancer, where E-cadherin measured by flow cytometry in isolated tumour cells was absent in relapsing patients but present in non-relapsing ones (144). In contrast, others have failed to observe a relation between loss of E-cadherin expression and higher recurrence risk (145).

Some studies have focused on the role of E-cadherin in the metastatic process including adhesion and proliferation. This is essential as the role of this molecule in metastasis is still controversial. In colorectal cancer, a reduced E-cadherin expression in the primary site is directly proportional to the frequency of lymph node and liver metastasis (72, 142). One study divided carcinomas into three groups, taking into account the combined aberrant expression of E-cadherin, α -catenin and β -catenin (131). They found that the incidence of lymph node metastasis increased according to the degree that adhesion molecule expression was reduced. Furthermore, the presence of concurrent aberrations of the three molecules was correlated with short survival. An interesting finding was that when comparing the adhesion molecule levels of primary tumours with those of metastatic tumours, increased expression was found in 43% of metastatic lymph nodes and in 46% of metastatic liver tumours. This result suggests that increased expression of adhesion molecules in tumour metastatic cells is important and perhaps necessary for their

anchorage at distant sites. However, the clinical importance of this induction of adhesion molecule expression is not yet clear, though in this study, patients in whom adhesion molecules were overexpressed in metastases compared to the primary site had a more unfavourable prognosis, but no statistically significant difference was observed. Takayama *et al.* (136), reported that colorectal carcinoma with reduced expression in E-cadherin, β -catenin, or α -catenin frequently showed lymph node metastasis. It has been reported that E-cadherin expression score in the tumour centre was statistically significant greater than that at the tumour margin, in primary tumours as well as in metastatic liver sites. Furthermore, *E-cadherin* mRNA expression was greater in adjacent normal hepatocytes of tumour metastasis, next greater in the primary tumour and least in the metastatic liver tumour cell. *E-cadherin* mRNA expression in the primary tumour also showed an inverse correlation with the number of metastatic lymph nodes (142). In experimental models, E-cadherin function was preserved when the metastatic foci were small (less than 2 or 3 mm), while it was reduced in large metastatic tumours (more than 2.3 mm) with induced neovascularization, suggesting an inverse correlation of E-cadherin with tumor size (22). In one study, a bizarre association of reduced or absent immunoreactivity for E-cadherin with better survival was demonstrated (41).

Although E-cadherin acts as an invasion-suppressor gene, the lack of correlation with standard prognostic factors may be evidence that interaction between E-cadherin and colorectal tumour behaviour is complicated (146). Other cell adhesion molecules such as DCC, CD44, nm23 and catenins, could outweigh the potential beneficial effect of normal E-cadherin expression.

The E-cadherin–catenin complex: A possible target for anticancer therapy? Treatment of colorectal cancer generally comprises a combination of the three classic strategies of oncology: surgery accompanied by radio- and chemotherapy. Advanced colorectal disease is routinely treated with adjuvant therapy such as 5-fluorouracil (5-FU) combined with leucovorin or levamisole.

We suggest that restoration of normal levels of functional E-cadherin may be a promising strategy in the context of anticancer treatment in colorectal cancer. The expression and function of E-cadherin may be regulated at the genetic, transcriptional, and protein level; in colon cancer it is still unclear which is the dominant regulatory level. Several agents such as insulin-like growth factor I (IGF-I), tamoxifen, paclitaxel, retinoic acid and progestogens have been reported to up-regulate the function of the E-cadherin–catenin complex via up-regulation of *E-cadherin*, α -catenin, and β -catenin mRNA expression, dephosphorylation of β -catenin, increased stability of β -catenin protein, and localization of β -catenin at cell–cell junctions. Furthermore, induction of E-cadherin may

represent a common theme in the mechanisms through which a variety of structurally unrelated agents (ursodeoxycholic acid and vitamin D analogues) may protect against colon carcinogenesis

Conclusion

An intact E-cadherin–catenin complex is required for normal intercellular connection. In most cases of human gastrointestinal cancer, the E-cadherin–catenin or related complexes are disturbed and this underscores their pivotal role in the progression of these tumours. In colorectal cancer, loss of E-cadherin function permits or accelerates invasion and is thus associated with a more malignant phenotype and poor differentiation. Conflicting opinions do, however, exist on the prognostic value of such immunohistochemical aberrations. The major benefit from an understanding of the E-cadherin–catenin-mediated pathways of invasion will be the development of new anti-invasive treatment strategies.

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