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Cadherin/Catenin Complex: A Target for Antiinvasive Therapy?

Marc Mareel, Geert Berx, Frans Van Roy, and Marc Bracke

Laboratory of Experimental Cancerology (M.M., M.B.), Department of Radiotherapy and Nuclear Medicine, University Hospital, B-9000 Gent, and Laboratory of Molecular Cell Biology (G.B., F.V.R.), Department of Molecular Genetics, University of Gent, B-9000 Gent, Belgium

Abstract Invasion is a major challenge for cancer therapy. Invasion or noninvasion results from the cross talk between cancer cells and host cells, building molecular invasion-promoter and invasion-suppressor complexes. The E-cadherin/catenin invasion-suppressor complex is attractive as a target for a putative antiinvasive therapy because of its multifactorial regulation at multiple levels and sometimes in a reversible way. Mutations in the E-cadherin gene combined with loss of the wild type allele causes irreversible downregulation in some human cancers. Posttranslational and reversible downregulation may occur by tyrosine phosphorylation of β-catenin. Phosphorylation is implicated also in transmembrane receptor signal transduction through the E-cadherin/catenin complex. Homophilic interaction with E-cadherin on another cell through a dimeric adhesion zipper, involving the HAV sequence of the first extracellular domains, is the major extracellular link of the E-cadherin/catenin complex. Intracellularly, the list of proteins that bind to or signal through the complex or one or more of its elements is growing. In vitro, insulin-like growth factor-I, and tamoxifen may upregulate the functions of the E-cadherin/catenin complex and inhibit invasion, demonstrating that this complex may serve as a target for antiinvasive therapy.

Key words: invasion, cadherin, catenins, IGF-I, tamoxifen

Invasion causes therapy failure in cancer. Half of all cancer deaths is due to local invasion with or without involvement of regional lymph nodes; the other half is due to metastases in distant organs. Invasion is, therefore, a major challenge for therapy. Alternatively, transition from the noninvasive towards the invasive state of tumor development is an attractive target for secondary cancer prevention. New concepts of cancer invasion have opened possibilities for strategies of anti-invasion treatment. Invasion occurs within the frame of a micro-ecosystem in which there is a continuous cross talk between the cancer cells and the host cells that together are forming the tumor. This implicates that host cells constitute targets for therapy that are as interesting as the proper cancer cells. Invasion or noninvasion results from the balance of activation or inactivation of invasion-suppressor and invasion-promoter molecular complexes, which are sensitive to up- and downregulation at multiple levels. Agents that shift this balance towards invasion-suppression may have therapeutic value. The epithelial cell adhesion molecule E-cadherin, when linked to its associated catenins, has been recognized as a powerful invasion-suppressor and this has been documented extensively in experimental as well as in human cancer [Vleminckx et al., 1991; Mareel et al., 1994; Takeichi, 1993; Birchmeier and Behrens, 1994].

With regard to the E-cadherin/catenin complex as a putative target for anti-invasive therapy, we discuss here the levels of regulation of the complex that have an effect on its invasion-suppressor function and the elements involved in this regulation. Based on these findings we shall speculate on novel treatment strategies.

UP- AND DOWNREGULATION OF THE E-CADHERIN/CATENIN COMPLEX

E-cadherin is a member of a large superfamily of calcium-dependent cell-cell adhesion molecules and forms a molecular complex with cytoplasmic proteins: β- or γ-catenin, belonging to the *armadillo* family and possibly playing a pivotal role in signal transduction; and α-catenin, belonging to the vinculin family and linking the

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Address reprint requests to Prof. Dr. M. Mareel, Department of Radiotherapy and Nuclear Medicine, University Hospital, De Pintelaan, 185, B-9000 Gent, Belgium.

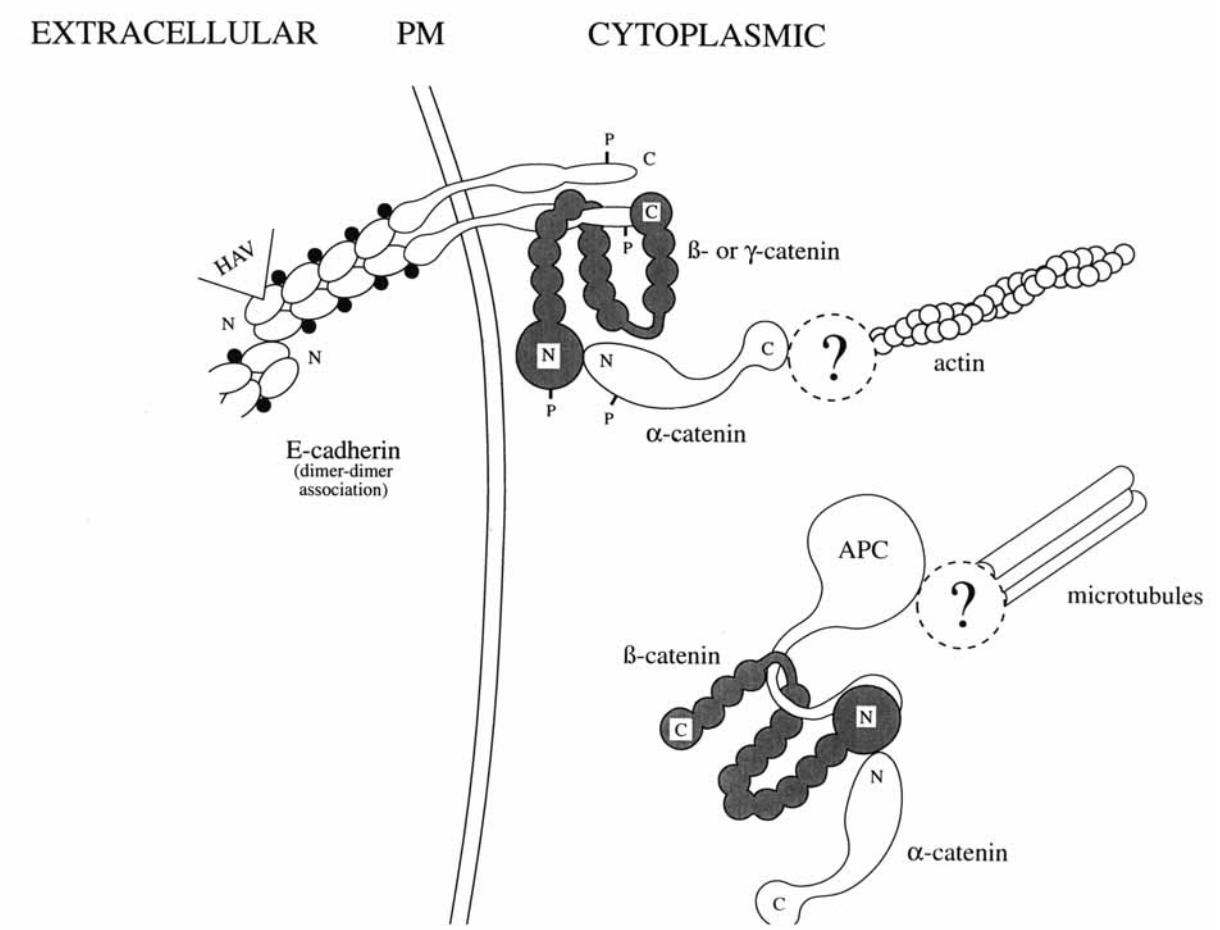

Fig. 1. Schematic representation of the E-cadherin/catenin and catenin/APC complexes. PM, plasmamembrane; APC, adenomatous polyposis coli protein; N and C, respectively amino- and carboxyl-terminal residues; HAV, histidine-alanine-valine sequence, characteristic for the first extracellular domain of type 1 cadherins; P, phosphorylation site; ?, unidentified protein(s). Filled circles indicate the position of Ca^{2+} ions at the cell surface proximal end of cadherin protomers. The schema was drawn in accordance with data from Aberle et al., 1994; Hülsken et al., 1994; Näthke et al., 1994; Rubinfeld et al., 1995; and Shapiro et al., 1995.

transmembrane adhesion molecules to the actin cytoskeleton (Fig. 1).

Normal and abnormal regulation of the E-cadherin/catenin complex offers two features that are interesting for designing therapeutic approaches. First, it occurs via different elements of the complex and for each of the elements more than one level of regulation has been found. Second, downregulation, causing invasion of cancer cells may be transient, hence sensitive to reversion. The latter has been demonstrated by in vitro/in vivo/ex vivo manipulations [Mareel et al., 1991]. MDCK dog kidney cells that homogeneously expressed E-cadherin and were noninvasive in vitro did produce E-cadherin-lacking invasive carcinomas in nude mice. When tumor cells were recultured in vitro, E-cadherin was reexpressed and the cells lost their invasive capability. These observations suggest that elements in the host may be responsible for the invasive behavior of the cancer cells.

REGULATION AT THE GENOMIC LEVEL

Human E-cadherin maps to chromosome 16q22.1 and loss of heterozygosity (LOH) for 16q22.1 has been demonstrated in several human cancers. When combined with mutations in the remaining allele, this may result in E-cadherin-negative cell populations.

Nevertheless, mutations and deletions in genes encoding the elements of the cadherin/catenin complex, seem to be the exception rather than the rule in cancer cells. Mutations in the E-cadherin gene with or without retention of the wild type allele have been found in human can-

cers [Becker et al., 1994]. At least in the gastric cancers, mutations cause skipping of exons encoding domains that are crucial for proper function. One may, therefore, presume that the mutations caused loss of function and may have served the transition towards the invasive state. Similarly, invasion-related mutations and deletions occur in genes encoding α-catenin [Morton et al., 1993] or β-catenin [Oyama et al., 1994].

With regard to transcriptional regulation, we note that the E-cadherin gene promoter contains tissue-specific responsive sequences [Behrens et al., 1991; Bussemakers et al., 1994] and that intron 1 holds a methylation-sensitive 5′ CpG-island [Berx et al., 1995]. Decrease in detectable quantities of E-cadherin-specific mRNA may be due also to decreased stability of the mRNA [Birchmeier and Behrens, 1994]. The 3′ untranslated region of the human E-cadherin mRNA is particularly long and contains AU-rich sequences, which is suggestive for degradation-inducing signals.

POSTTRANSLATIONAL REGULATION

Phosphorylation is the best documented way of posttranslational regulation of the E-cadherin/catenin complex [Stappert and Kemler, 1994]. It is the opinion of Takeichi [1993] that tyrosine phosphorylation hinders E-cadherin-dependent functions because it interferes with lateral coaggregation of the molecule within the plane of the plasma membrane. Experimental data support the idea that tyrosine phosphorylation of β-catenin downregulates the function of the complex and induces invasion. Such phosphorylation may occur through activation of the Src oncoprotein $p60^{src}$, or by triggering receptors for scatter factor/hepatocyte growth factor (SF/HGF) or epidermal growth factor (EGF) (Fig. 2). Experiments with recombinant proteins demonstrated that EGF-receptor interacts with the core region of β-catenin [Hoschuetzky et al., 1994]. Overexpression of exogenous *erb*-B2 resulted in decreased levels of E-cadherin protein, presumably through transcriptional downregulation, and in loss of E-cadherin-dependent cell compaction in collagen [D'Souza and Taylor-Papadimitriou, 1994]. These disturbances were restored by treatment with an antibody that blocked phosphorylation of the Erb-B2 receptor. Reynolds et al. [1994] have suggested a crucial role for the tyrosine kinase substrate $p120^{CAS}$ (cadherin-associated src substrate) in signal transduction from EGF-, PDGF- (platelet-derived growth factor), and CSF (colony-stimulating factor)-receptors. Interestingly, $p120^{CAS}$ coimmunoprecipitates with E-cadherin and the catenins. In src-transformed cells $p120^{CAS}$ was heavily phosphorylated, together with plakoglobin and β-catenin but not E-cadherin or α-catenin.

Taken together, transmembrane receptors seem to signal through the E-cadherin/catenin complex (Fig. 2). Since many of these molecules belong to the family of tyrosine kinase receptors, it is not surprising that they cause changes in phosporylation of the complex and impair its function. The insulin-like growth factor-I (IGF-I) receptor stands as an exception, since IGF-I restored the antiinvasive function of the E-cadherin complex [Bracke et al., 1993]. IGF-I caused rapid tyrosine phosphorylation of the IGF-I receptor but changes in phosphorylation of the E-cadherin/catenin complex could not be demonstrated [S. Vermeulen, personal communication]. Phosphorylation of serine and threonine by protein kinase C (PKC) served as a signal in E-cadherin-mediated organisation of junctional complexes in cultured keratinocytes [Lewis et al., 1994]. PKC has also been implicated in signalling through the M3 muscarinic acetylcholine receptor, which is linked to pertussis toxin-insensitive G-proteins. Activation of the receptor with carbachol rapidly induced E-cadherin-specific adhesion in a small cell lung cancer cell line [Williams et al., 1993]. Conversely, activation of the type I TGF-β (transforming growth factor-β) serine kinase receptor, caused downregulation of E-cadherin, invasion, and epithelial mesenchymal transdifferentiation [Van Roy et al., 1992; Miettinen et al., 1994].

EXTRACELLULAR ASSOCIATIONS

Linkage to other proteins, both extracellular and intracellular, is crucial for the function of E-cadherin. Cadherins are characterised by a sequence motif which is tandemly repeated in their extracellular segments. Nevertheless, cadherin subtypes have unique binding specificities. Homophilic interaction with another E-cadherin molecule on a neighbouring homotypic (of the same type) cell is the major extracellular association. Recently, we have started to understand the mechanism of this homophilic interaction due to the crystallographic study of the first extracellular cadherin repeat [Shapiro et al., 1995]. The structure of this protomer revealed a

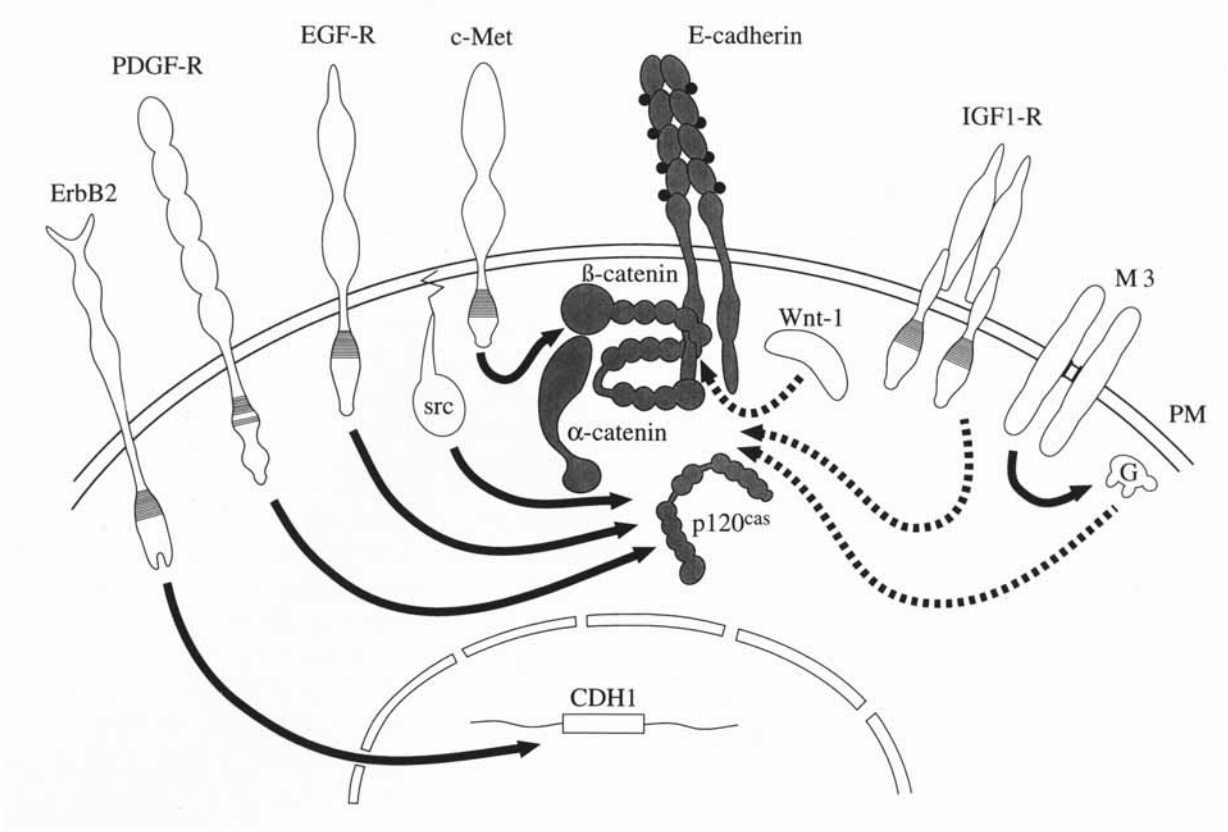

Fig. 2. Schematic representation of signalling through the E-cadherin/catenin complex. **Full arrows** mark documented pathways; **broken arrows** mark unknown pathways. ErbB2, p185 transmembrane receptor also called Neu/HER-2; PDGF-R, platelet-derived growth factor receptor; EGF-R, epidermal growth factor receptor; c-MET, hepatocyte growth factor/scatter factor (HGF/SF) receptor; IGF1-R, insulin-like growth factor-1 receptor; M3, muscarinic acetylcholine receptor; G, GTP-binding GTPase; SRC, phosphoprotein encoded by the *src* (proto)oncogene; Wnt-1, protooncogene-encoded protein homologous to the product of the *Drosophila* segment polarity gene *wingless;* $p120^{CAS}$, cadherin-associated SRC substrate; CDH1, human E-caherin gene; PM, plasma membrane. The schema was drawn after data from Bracke et al., 1993; Behrens et al., 1993; Williams et al., 1993; D'Souza and Taylor-Papadimitriou, 1994; Hinck et al., 1994; Hoschuetzky et al., 1994; Reynolds et al., 1994; Shibamoto et al., 1994; and Shiozaki et al., 1995.

strand-dimer interface, linking two neighbouring cadherins, besides an adhesion dimer interface, linking dimers of neighbouring cells. The latter engages the HAV (histidine-alanine-valine) sequence (see Fig. 1). The combination of these interfaces results in an adhesion zipper that fits most of the previous molecular and ultrastructural observations. In this model, the Ca^{2+}-binding site at the cell-surface proximal part of each repeat is compatible with its known role in stabilisation of E-cadherin. The specificity of homophilic cadherin interactions, however, remains to be explained in detail.

Moreover, recent data necessitated reconsideration of our views on extracellular E-cadherin interactions. Besides homophilic homotypic interactions, homophilic heterotypic [Tang et al., 1993] and heterophilic heterotypic [Cepek et al., 1994] interactions have been demonstrated. These new data are particularly important for our understanding of regulation through soluble factors that may bind to the extracellular domain of E-cadherin. Blaschuk et al. [1990] were the first to show that synthetic decapeptides, containing the HAV sequence, may inhibit E-cadherin-mediated activities such as compaction of 8-cell-stage mouse embryos and neurite outgrowth on astrocytes. Their interpretation was that the tripeptide HAV is a component of a cadherin cell adhesion recognition sequence and this is confirmed by the recent crystallographic data. The demonstration that decapeptides, identical or similar to the one in the extracellular domains of E-cadherin, may influence E-cadherin functions raises the question whether fragments released from this molecule have similar effects. That such fragments may survive in the extracellular milieu was shown by Katayama et

al. [1994], who found 80-kDa E-cadherin fragments in the circulation of cancer patients. This observation may reflect enhanced breakdown of E-cadherin. If such fragments acted like the decapeptides, one might imagine a cascade of locally enhanced breakdown followed by local functional inhibition.

An HAV sequence was also found in the CAM-homology domain of FGF-receptors [Mason, 1994]. Antibodies to FGFR partially inhibited neurite outgrowth on N-cadherin-expressing substrate [Williams et al., 1994]. The interaction between the FGFR and cadherin might occur in the plane of the same cell membrane or between molecules on the surface of opposing cells. Interactions between E-cadherin and other molecules on the plasma membrane of the same cells have been described [Vleminckx et al., 1994]. In two types of cells that fully expressed E-cadherin without displaying its functions, plasma membrane-associated proteoglycans were found to be enlarged. The functions of E-cadherin were restored by treatment with 4-methylumbelliferyl β-D-xyloside, a xyloside analogue that inhibits the anchorage of glycosaminoglycan chains to the proteoglycan core protein. The authors explained their observations through shielding of homophilic E-cadherin interactions by the large proteoglycans.

THE E-CADHERIN/CATENIN COMPLEX: A TARGET FOR ANTIINVASIVE THERAPY?

The multifactorial regulation of a molecular complex with a strong influence on invasion makes this complex an attractive target for antiinvasive treatment. Since such a treatment has not yet been established, the following considerations are admittedly speculative. In general, the invasion-promoter/-suppressor balance concept and the possibility of metastases formation by temporary expression of invasion necessitates a chronic, hence nontoxic treatment. Furthermore, host cells influencing invasion could be considered as targets too. The feasibility of a chronic nontoxic treatment with host cells as a target has been demonstrated by bisphosphonate treatment of bone metastases, widely used in the clinic. Can e.g., tumor-associated myofibroblasts serve as targets for treatment of primary invasion in the way osteoclasts do for the treatment of metastatic bone destruction? Some of our speculations are based on new insights into the molecular pathways of the regulation of the E-cadherin/catenin complex; others are related to the serependitous finding of antiinvasive agents. In experimental systems in vitro, introduction of genes, encoding E-cadherin [Vleminckx et al., 1991], or α-catenin [Breen et al., 1993] into cells deficient for the respective gene products, resulted in the conversion from the invasive to the noninvasive phenotype. Considering gene therapy in vivo, we have to solve not only the problems of specific cell and gene targeting but also those of downregulation of transfected genes by in vivo host factors. Although the relevance for silencing E-cadherin transcription by methylation still has to be proved, the presence of the 5′ CpG-island suggests possible therapy with DNA methyltransferase inhibitors. The recent data about the role of phosphorylation in the regulation of the E-cadherin/catenin complex pleads for testing of tyrosine kinase inhibitors and PKC stimulators, although specificity might be a major obstacle. It is fortunate that today major efforts are paid to design large series of such drugs in view of the treatment of cancer and other diseases [Levitzki and Gazit, 1995]. IGF-I, acting on E-cadherin via an unknown pathway, inhibited the invasion of human MCF-7/6 breast cancer cells [Bracke et al., 1993]. However, at antiinvasive concentrations, IGF-I stimulated growth of the cancer cells, confirming its role as a growth factor. Despite documented independence between growth and invasion, it is difficult to advocate a growth factor as an anticancer drug. Differential effects on growth and invasion may be mediated through the E-cadherin/catenin complex [Hinck et al., 1994]. The oncoprotein Src stimulated growth and decreased cell-cell adhesion, whereas Wnt-1 stimulated growth but stabilized cell-cell adhesion. Tamoxifen is more attractive than IGF-I because it inhibits growth and is already used in the clinic on a very large scale. Like IGF-I, but through a different mechanism of action, tamoxifen also inhibited invasion of MCF-7/6 cells in an E-cadherin-dependent way [Bracke et al., 1994]. Similar effects were also found with all-*trans* retinoic acid and with the citrus flavonoid tangeretin. This opens perspectives for combinatorial treatments following both antiinvasive and preventive strategies.

Taken together, these findings clearly demonstrate that the E-cadherin/catenin complex may serve as a target for antiinvasive treatment. In vivo experiments are now warranted. If invasive cancer is a disease of epithelial polarity, then

epithelial reorganisation and maintenance of epithelial organisation is a major therapeutic goal.

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REFERENCES

Aberle H, Butz S, Stappert J, Weissig H, Kemler R, Hoschuetzky H (1994): Assembly of the cadherin-catenin complex in vitro with recombinant proteins. J Cell Sci 107: 3655–3663.

Becker K-F, Atkinson MJ, Reich U, Becker I, Nekarda H, Siewert JR, Höfler H (1994): E-cadherin gene mutations provide clues to diffuse type gastric carcinomas. Cancer Res 54:3845–3852.

Behrens J, Löwrick O, Klein-Hitpass L, Birchmeier W (1991): The E-cadherin promoter: functional analysis of a GC-rich region and an epithelial cell-specific palindromic regulatory element. Proc Natl Acad Sci USA 88:11495–11499.

Behrens J, Vakaet L, Friis R, Winterhager E, Van Roy F, Mareel MM, Birchmeier W (1993): Loss of epithelial morphotype and gain of invasiveness correlates with tyrosine phosphorylation of the E-cadherin/β-catenin complex in cells transformed with a temperature-sensitive v-*src* gene. J Cell Biol 120:757–766.

Berx G, Staes K, van Hengel J, Molemans F, Bussemakers MJG, van Bokhoven A, Van Roy F (1995): Cloning and characterization of the human invasion suppressor gene E-cadherin (CDH1). Genomics 26:281–289.

Birchmeier W, Behrens J (1994): Cadherin expression in carcinomas: role in the formation of cell junctions and the prevention of invasiveness. Biochim Biophys Acta 1198: 11–26.

Blaschuk OW, Sullivan R, David S, Pouliot Y (1990): Identification of a cadherin cell adhesion recognition sequence. Dev Biol 139:227–229.

Bracke ME, Vyncke BM, Bruyneel EA, Vermeulen SJ, De Bruyne GK, Van Larebeke NA, Vleminckx K, Van Roy FM, Mareel MM (1993): Insulin-like growth factor I activates the invasion suppressor function of E-cadherin in MCF-7 human mammary carcinoma cells in vitro. Br J Cancer 68:282–289.

Bracke ME, Charlier C, Bruyneel EA, Labit C, Mareel MM, Castronovo V (1994): Tamoxifen restores the E-cadherin function in human breast cancer MCF-7/6 cells and suppresses their invasive phenotype. Cancer Res 54:4607–4609.

Breen E, Clarke A, Steele G Jr, Mercurio AM (1993): Poorly differentiated colon carcinoma cell lines deficient in α-catenin expression express high levels of surface E-cadherin but lack Ca^{2+}-dependent cell-cell adhesion. Cell Adhesion and Communication 1:239–250.

Bussemakers MJ, Giroldi LA, van Bokhoven A, Schalken JA (1994): Transcriptional regulation of the human E-cadherin gene in human prostate cancer cell lines: characterization of the human E-cadherin gene promoter. Biochem Biophys Res Commun 203:1284–1290.

Cepek KL, Shaw SK, Parker CM, Russell GJ, Morrow JS, Rimm DL, Brenner MB (1994): Adhesion between epithelial cells and T lymphocytes mediated by E-cadherin and the $\alpha^E\beta_7$ integrin. Nature 372:190–193.

D'Souza B, Taylor-Papadimitriou J (1994): Overexpression of ERBB2 in human mammary epithelial cells signals inhibition of transcription of the E-cadherin gene. Proc Natl Acad Sci USA 91:7202–7206.

Hinck L, Näthke IS, Papkoff J, Nelson WJ (1994): β-catenin: a common target for the regulation of cell adhesion by Wnt-1 and Src signaling pathways. Trends Biochem Sci 19:538–542.

Hoschuetzky H, Aberle H, Kemler R (1994): β-catenin mediates the interaction of the cadherin-catenin complex with epidermal growth factor receptor. J Cell Biol 127:1375–1380.

Hülsken J, Birchmeier W, Behrens J (1994): E-cadherin and APC compete for the interaction with β-catenin and the cytoskeleton. J Cell Biol 127:2061–2069.

Katayama M, Hirai S, Kamihagi K, Nakagawa K, Yasumoto M, Kato I (1994): Soluble E-cadherin fragments increased in circulation of cancer patients. Br J Cancer 69:580–585.

Levitzki A, Gazit A (1995): Tyrosine kinase inhibition: an approach to drug development. Science 267:1782–1788.

Lewis JE, Jensen PJ, Wheelock MJ (1994): Cadherin function is required for human keratinocytes to assemble desmosomes and stratify in response to calcium. J Invest Dermatol 102:870–877.

Mareel MM, Behrens J, Birchmeier W, De Bruyne GK, Vleminckx K, Hoogewijs A, Fiers WC, Van Roy FM (1991): Downregulation of E-cadherin expression in Madin Darby canine kidney (MDCK) cells inside nude mice tumors. Int J Cancer 47:922–928.

Mareel M, Vleminckx K, Vermeulen S, Yan G, Bracke M, Van Roy F (1994): Downregulation in vivo of the invasion-suppressor molecule E-cadherin in experimental and clinical cancer. In Hirohashi S, Moses HL, Ruoslahti E, Sugimura T, Takeichi M, Terada M (eds): "Molecular and Cellular Basis for Cell to Cell Interaction: Its Significance in Cancer." Proceedings of the 24th International Symposium of the Princess Takamatsu Cancer Research Fund. The Princeton Scientific Publishing Co, Inc, Princeton, New Jersey, USA, pp 63–80.

Mason I (1994): Do adhesion molecules signal via FGF receptors? Current Biology 4:1158–1161.

Miettinen PJ, Ebner R, Lopez AR, Derynck R (1994): TGF-β induced transdifferentiation of mammary epithelial cells to mesenchymal cells: involvement of type I receptors. J Cell Biol 127:2021–2036.

Morton RA, Ewing CM, Nagafuchi A, Tsukita S, Isaacs WB (1993): Reduction of E-cadherin levels and deletion of the α-catenin gene in human prostate cancer cells. Cancer Res 53:3585–3590.

Näthke IS, Hinck L, Swedlow JR, Papkoff J, Nelson WJ (1994): Defining interactions and distributions of cadherin and catenin complexes in polarized epithelial cells. J Cell Biol 125:1341–1352.

Oyama T, Kanai Y, Ochiai A, Akimoto S, Oda T, Yanagihara K, Nagafuchi A, Tsukita S, Shibamoto S, Ito F, Takeichi M, Matsuda H, Hirohashi S (1994): A truncated β-catenin disrupts the interaction between E-cadherin and α-catenin: a cause of loss of intercellular adhesiveness in human cancer cell lines. Cancer Res 54:6282–6287.

Reynolds AB, Daniel J, McCrea PD, Wheelock MJ, Wu J, Zhang Z (1994): Identification of a new catenin: the tyrosine kinase substrate p120^{cas} associates with E-cadherin complexes. Mol Cell Biol 14:8333–8342.

Rubinfeld B, Souza B, Albert I, Munemitsu S, Polakis P (1995): The APC protein and E-cadherin form similar but independent complexes with α-catenin, β-catenin, and plakoglobin. J Biol Chem 270:5549–5555.

Shapiro L, Fannon AM, Kwong PD, Thompson A, Lehmann MS, Grübel G, Legrand JF, Als-Nielsen J, Colman DR, Hendrickson WA (1995): Structural basis of cell-cell adhesion by cadherins. Nature 374:327–337.

Shibamoto S, Hayakawa M, Takeuchi K, Hori T, Oku N, Miyazawa K, Kitamura N, Takeichi M, Ito F (1994): Tyrosine phosphorylation of β-catenin and plakoglobin enhanced by hepatocyte growth factor and epidermal growth factor in human carcinoma cells. Cell Adhesion and Communication 1:295–305.

Shiozaki H, Kadowaki T, Doki Y, Inoue M, Tamura S, Oka H, Iwazawa T, Matsui S, Shimaya K, Takeichi M, Mori T (1995): Effect of epidermal growth factor on cadherin-mediated adhesion in a human oesophageal cancer cell line. Br J Cancer 71:250–258.

Stappert J, Kemler R (1994): A short core region of E-cadherin is essential for catenin binding and is highly phosphorylated. Cell Adhesion and Communication 2:319–327.

Takeichi M (1993): Cadherins in cancer: implications for invasion and metastasis. Current Opin Cell Biol 5:806–811.

Tang A, Amagai M, Granger LG, Stanley JR, Udey MC (1993): Adhesion of epidermal Langerhans cells to keratinocytes mediated by E-cadherin. Nature 361:82–85.

Van Roy F, Vleminckx K, Vakaet L Jr, Berx G, Fiers W, Mareel M (1992): The invasion suppressor role of E-cadherin. In: Rabes H, Peters PE, Munk K (eds): "Metastasis: Basic Research and its Clinical Applications." Contrib Oncol Basel, Karger, pp 108–126.

Vleminckx K, Vakaet L Jr, Mareel M, Fiers W, Van Roy F (1991): Genetic manipulation of E-cadherin expression by epithelial tumor cells reveals an invasion suppressor role. Cell 66:107–119.

Vleminckx KL, Deman JJ, Bruyneel EA, Vandenbossche GMR, Keirsebilck AA, Mareel MM, Van Roy FM (1994): Enlarged cell-associated proteoglycans abolish E-cadherin functionality in invasive tumor cells. Cancer Res 54:873–877.

Williams E, Furness J, Walsh FS, Doherty P (1994): Activation of the FGF receptor underlies neurite outgrowth stimulated by L1, NCAM and N-cadherin. Neuron 13:583–594.

Williams CL, Hayes VY, Hummel AM, Tarara JE, Halsey TJ (1993): Regulation of E-cadherin-mediated adhesion by muscarinic acetylcholine receptors in small cell lung carcinoma. J Cell Biol 121:643–654.