Beta-catenin expression pattern in small cell lung cancer: correlation with clinical and evolutive features

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Summary. ß-catenin expression in small cell lung carcinomas (SCLC) was investigated by immunohisto-chemical method using antibodies against ß-catenin. 50 pre-treatment biopsies were examined and the relationship between ß-catenin expression and the patients' relevant clinical characteristics, response to chemotherapy, time to relapse or progression, and overall survival, were analyzed. ß-catenin expression exhibited different intensity within each sample, predominantly localized in the cytoplasm, and no sample showed nuclear expression. There was cytoplasmic hyperexpression in 14 cases, hypoexpression in 15 cases, and normal expression in 21 cases. We did not find any association between ß-catenin expression and clinical data. Our results show, however, correlation between ß-catenin cytoplasmic hyperexpression with a shorter time to progression (p=0.0437) as well as with a shorter overall survival (p=0.0253). ß-catenin hyperexpression could have prognostic significance in SCLC.

Key words: ß-catenin, Small cell lung cancer, Time to progression, Overall survival, Immunohistochemistry

Introduction

ß-catenin is a multifunctional protein encoded in chromosome 3p21 (Nollet et al., 1996). One of the most important functions of this protein is cell-cell adhesion. ß-catenin binds the intracytoplasmic domain of E-cadherin, the major adhesion molecule in epithelial tissues, and interacts with α-catenin, which binds the actin cytoskeleton (Shiozaki et al., 1996). This adhesion complex is essential in very many processes such as morphogenesis, control of cell motility during embryogenesis, maintenance of tissue integrity and control of contact-inhibition proliferation as well as being involved in the control of programmed cell-death (apoptosis) (Bullions and Levine, 1998).

ß-catenin is also able to bind cytoskeleton, independently of the cadherin system, in two ways: ß-catenin can bind actin filaments that link a protein called fascin, thereby helping to control cell motility (Tao et al., 1996); and it can also interact with microtubules when they form a complex with α-catenin and the product of the adenomatous polyposis coli gene (APC) (Barth et al., 1997).

In addition, ß-catenin is involved in signal transduction by the Wnt/Wingless growth factor; it activates gene transcription when it forms a complex with the DNA-binding proteins of the T-cell factor/Lymphoid enhanced factor family (Tcf/Lef). The presence of a Wnt signal in normal cells stabilizes ß-catenin, which accumulates in the cytoplasm, where it binds to Tcf/Lef factors, forming a complex that is translocated to the nucleus to trigger gene expression (Nakamura, 1997; Willert and Nusse, 1998; Bullions and Levine, 1998).

The cytoplasmic level of free ß-catenin is low in normal cells because the protein is targeted for destruction by APC protein, which is essential for the clearance of unneccesary ß-catenin from the cytoplasm (Ilyas and Tomlinson, 1997). This homeostatic process may be altered by different mutations in APC (Korinek et al., 1997; Morin et al., 1997; Rubinfeld et al., 1997) or ß-catenin (Ilyas et al., 1997; Fukuchi et al., 1998; Iwao et al., 1998; Palacios and Gamallo, 1998; Voeller et al., 1998), that increase free ß-catenin levels. Binding transcriptional factors, ß-catenin increases the transcription of target genes that may increase cell proliferation or inhibit apoptosis. In this sense ß-catenin can act as an oncoprotein (Peifer, 1997; Hirohashi; 1998).

In summary, in normal cells ß-catenin is located in three cell compartments: the cell membrane where it acts in the cell-cell adhesion complex; in the cytoplasm where it acts in a free manner, and in the cell nuclei where it forms a complex with transcriptional factors (Stewart and Nelson, 1997; Papkoff, 1997). In the cytoplasm ß-catenin may form a complex with the product of the polyposis coli gene (APC) that induces ß-catenin protein degradation. Other cytoplasmic proteins, such as axin or conductin, form different complexes with ß-catenin and APC (Behrens et al., 1998). The glucogen-

synthetase kinase 3ß (GSK-3ß) binds these three types of complexes, induces the phosphorylation in serine-threonin residues of APC and ß-catenin and then leads the degradation of the protein by the ubiquitization process in the proteosomes (Aberle et al., 1997; Orford et al., 1997; Solomon et al., 1997).

Since it was known ß-catenin could act as an oncogen and could have an important role in the pathogenesis of some tumours, some studies were performed in several neoplasms, but we did not find any studies of ß-catenin expression in small cell lung carcinomas (SCLC), the most aggressive type of lung cancer. In the present study, we examined ß-catenin expression in 50 small cell lung carcinomas, and also assessed the association between this expression and clinical characteristics, response to treatment and survival.

Materials and methods

Patients

We revised all patients with small cell lung carcinoma between 1990 and 1995 (a total of 163 patients), and selected a total of 50 patients with histologically proven small cell lung carcinoma with biopsy tissue optimal to perform immunohistochemistry studies. Only those patients that underwent chemo-therapy treatment and with available evolutive data were selected. Patients were enrolled between January of 1990 and December of 1995. The last follow-up was in December 1997 and all cases had a minimal follow-up of two years. All received alternating chemotherapy with Cyclophosphamide, Doxorubicin and Vincristin, alternating with Cisplatin and Etoposide (CAV/PE schedule). No patient was lost to follow-up and no patient was alive after December 1997.

Patients were considered to have limited disease if computed tomography (CT) scan of the chest and CT scan or ultrasound examination of the abdomen indicated that the tumour was confined to one hemithorax, to the mediastinal and supraclavicular lymph nodes, or there was an ipsilateral pleural effusion. Otherwise, patients were considered to have extensive disease. The limited status of these patients' disease was also supported by the absence of metastases on a bone scan, a CT scan of the head, and a bone marrow biopsy.

Response to treatment was considered to be complete if all disease found at the initial staging was absent as judged by imaging repeated at the completion of all treatments. A partial response was considered if imaging demonstrated at least 50% reduction in measurable tumor mass. Survival was calculated from the date of diagnosis to the date of death.

Histological classification

Specimens taken by bronchoscopy were routinely processed, fixed in 10% buffered formalin, embedded in parafin wax, sectioned at 4 μm, and stained with haematoxylin and eosin. All specimens were type I SCLC in the IASLC (International Association for the Study of Lung Cancer) classification (Hirsh et al., 1988). All samples were diagnosed and classified independently by two pathologists.

Immunohistochemistry

Immunostaining was performed using the avidin-biotin-phosphatase-alkalin method. Briefly de-paraffinized, rehydrated sections were boiled in 10 mM citrate buffer (pH 6) for 3 min in a pressure cooker to retrieve antigens. Excess citrate buffer was drained off, and sections were incubated at room temperature for 1 hour with the anti-ß-catenin mouse antibody (C19220, IgG 1 class, at 1:500 dilution, Transduction, United Kingdom). After being washed with Tris buffer, the secondary biotinylated antibody was added for 30 minutes. Following the avidin-biotin complex (Vectastain ABC kit, Vector), slides were washed with Tris-buffer, and the Fast Red ITR chromogen procedure was performed. Finally, slides were counterstained with haematoxylin. The primary antibody was omitted or replaced by an irrelevant antibody in negative controls.

Staining evaluation

The CAS 200 Analyzer (Cell Analysis System, Lombard, IL) was used to quantitate ß-catenin expression in tumour tissue and in adjacent normal respiratory epithelium. We created an index with these quantitative data: expression in tumour compared with expression in normal adjacent bronchial tissue in order to analyze the results. This index indicates how the expression in the tumour is deviated from that in normal tissue (Fig. 2). We considered ß-catenin to be hypo-expressed if this index was lower than 1 (<0.70), when it was near 1 (0.70-1.30) we considered ß-catenin to be normal or similar to the normal epithelium, and when it was much higher than 1 (>1.30) we considered ß-catenin to be hyperexpressed. Two groups were created for the statistical analysis: one with ß-catenin hyperexpressed and the other without hyperexpresion of ß-catenin.

Statistical methods

The association between ß-catenin expression and biological or pathological variables (age, sex, performance status, weigh loss, stage, number of metastasis, response to treatment, time to progression and overall survival) was assessed using the chi-squared test with the Yates correction. The Fisher test was used to compare categorical data. Non-parametric Kruskall-Wallis one way analysis of variance was used to evaluate numerical data. The joint effect of each presumedly prognostic variable was evaluated by multivariate analysis using a linear and a logistic-regression model. Significant was set at $p<0.05$.

All analyses were conducted with the statistical packages Epi-Info 6.04a (Center for Disease Control and Prevention, USA) and SPSS 7.5 (Statistical Product and Service Solutions, Chicago, IL) for PC computers.

Results

Immunohistochemistry showed that all 50 SCLC examined had ß-catenin expression. This expression was heterogeneous and located in the cytoplasm with different intensity. We did not find nuclear expression in any sample.

We found that 21 cases had a global reduction of ß-catenin expression (Fig. 1a), 15 cases had normal expression (compared with the protein expression in normal adjacent bronchial epithelium) (Fig. 1b), and 14 cases had a cytoplasmic hyper-expression of the protein (Fig. 1c) (index ≥ 1.3). We grouped the 14 cases with ß-catenin hyperexpression, and compared them to a group formed of patients with reduced expression and patients with conserved expression. We related these two groups with their clinical data and outcome. The results are shown in Table 1.

Patient age, sex, performance status or weight loss were unrelated to ß catenin expression. There was a tendency toward association between stage, number of metastatic locations and type of chemotherapy response and ß-catenin expression, but it was not satistically significant. Patients with increased ß-catenin accumulation had a tendency towards having extensive disease, more metastatic locations and fewer complete responses to treatment.

The univariate analysis showed a statistical association between ß-catenin expression, time to progression and overall survival. These were shorter if ß-catenin was hyperexpressed than if it was not, ranging 154.55±252.32 vs 210.87±209.16 (p= 0.0437), and 298.14+222.41 vs 417.16± 225.72 (p=0.0253), respectively (Figs. 2, 3).

Multivariant analysis was performed to analyze response to chemotherapy (logistic regression), overall survival (linear regression), and time to relapse (linear regression). ß-catenin was not selected as an independent predictive factor of the dependent variable. The variables selected as predictive factors were stage and number of metastatic locations in the analysis of
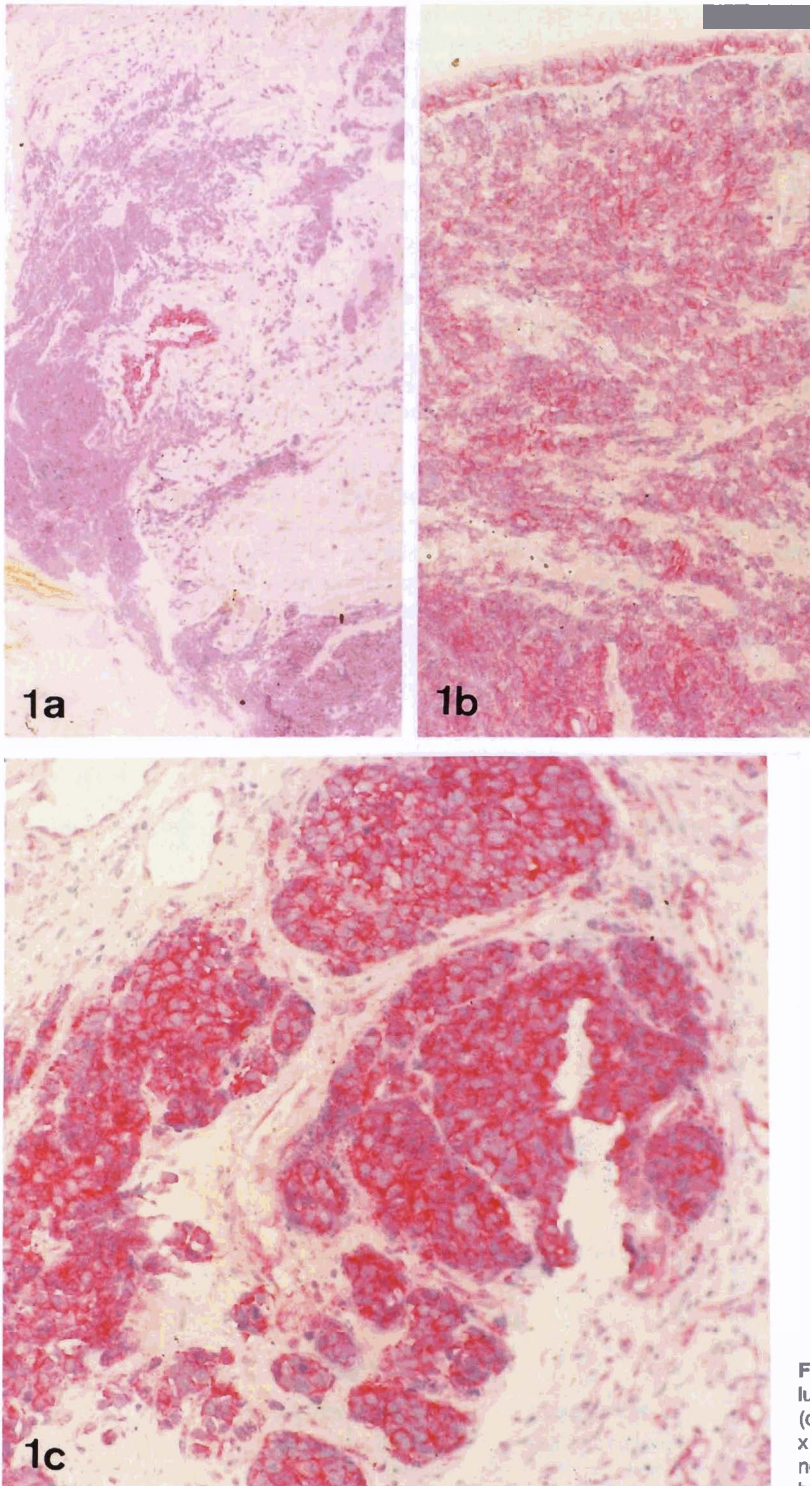

Fig. 1. Different beta-catenin expression patern in small cell lung carcinoma. **a.** Reduced/absent beta-catenin expression (compare with normal epithelium at the center of the field). x 2.5. **b.** Preserved beta-catenin expression (compare with normal epithelium at the top of the field). x 5. **c.** Beta-catenin hyperexpression. x 12.5

response to treatment; stage and type of chemotherapy response in the overall survival analysis; and finally, in the multivariate analysis of time to relapse or progression, the most important predictive factor was stage (data not shown).

Discussion

This study demonstrates the presence of ß-catenin expression in all the small cell lung carcinoma cases, independently of the intensity of the expression. This finding has an interesting potential for the differential diagnosis with the lymphoproliferative disorders in the lung, that do not express ß-catenin, as was demonstrated by Takayama (Takayama et al., 1996, 1998).

The most interesting finding was the abnormal cytoplasmic hyperexpression of ß-catenin in fourteen cases without nuclear expression. The only study on this tumor type that reports similar findings, is Nawrocki's recent report (Nawrocki et al., 1998). They studied ß-catenin and E-cadherin expression in bronchopulmonary carcinomas, analyzing 44 samples resected from lung tumors, 4 of them being neuroendocrin tumors. These four samples showed cytoplasmic expression of ß-catenin, one with faint intensity, one with moderate intensity, and two with strong intensity. The authors did not report any association with clinical data.

Alteration of the ß-catenin degradation system can promote an abnormal increase in the ß-catenin cytoplasmic and nuclear pools. This fact has been demonstrated in vitro and in different neoplasms, such as ovarian (Palacios and Gamallo, 1998), endometrium (Fukuchi et al., 1998), prostate (Voeller et al., 1998) and colon carcinomas (Iwao et al., 1998). The alteration could be caused by different mechanisms: gene mutations (generally in exon 3 which alters the target of the GSK-3ß phosphorylation sites) (Fukuchi et al., 1998; Iwao et al., 1998; Palacios and Gamallo, 1998; Voeller et al., 1998) and mutations or inactivation of the APC function (Korinek et al., 1997; Morin et al., 1997; Peifer, 1997; Rubinfeld et al., 1997), probably by the abnormal activation of Wnt signalling. It has been recently defined how the oncogenic activation of H-Ras oncogene can promote cytoplasmic and nuclear accumulation of ß-catenin (Espada et al., 1999). The final result is a lower level of ß-catenin degradation that could bind the Tcf/Lef transcriptional factors, thereby forming a complex that is translocated to the nucleus and activates gene transcription. The results we observed in SCLC could not be explained by this process, as no sample had nuclear ß-catenin.

When ß-catenin is located in the cell membrane, forming adhesion complexes with cadherins, it can be phosphorylated into tyrosin residues by different tyrosin-kinases such as membrane receptors (epidermal growth factor receptor, hepatocyte growth factor receptor) or the product of different oncogenes (c-erbB2, c-met, c-src, c-kit) (Daniel and Reynolds, 1997). This process

Table 1. Clinical characteristics and ß-catenin expression.

CHARACTERISTIC	No. OF PATIENTS (%)	ß-CATENIN EXPRESSION		P VALUE
		Normal	Increased	
Sex				
Male	48 (96%)	34	14	0.51*
Female	2 (4%)	2	0	
Mean age ± SD	61±8	61.25±9.9	61.28±8.1	0.98**
ECOG				
0-2	47	34	13	0.70*
3-4	3	2	1	
Weigh loss,%				
<5	25	20	5	0.46***
≥5	25	16	9	
Disease stage				
Limited	21 (42%)	18	3	0.12***
Extensive	29 (58%)	18	11	
Number of metastasis	0:21			
	1:14			
	2:10	Mean:0.97+1.2	Mean:1.14+0.8	0.63**
	3:4			
	4:2			
Response				
Complete	20 (40%)	16	4	0.12***
Other	30 (60%)	20	10	
Mean time to progression ±SD	162±210	210.87±209.1	154.55±252.32	0.043**
Mean overall survival ±SD	383±228	417.16±225.72	298.14±222.41	0.025**

SD: Standard Deviation; *: Fisher´s exact test; **: Kruskall-Wallis non parametric test; ***: Chi square and Yates correction.

disassembles the cell-cell adhesion complex and tyrosin-phosphorylated ß-catenin remains in the cytoplasm. In normal tissues this process is reversible by the action of membrane tyrosin-phosphatases (Hirohashi, 1998). The dynamic regulation of cell adhesion allows the repair of tissues, as demonstrated in ulceration areas in gastric mucosa (Takeichi, 1993; Smith and Pignatelli, 1997; Muller et al., 1999).

The alteration of the ß-catenin homeostatic mechanism could explain our results. The exclusive cytoplasmic accumulation of ß-catenin could perhaps be the consequence of an abnomal tyrosin phosphorylation of the protein. Tyrosin phosphorylation would be caused either by an abnormal activation of membrane receptors with tirosin-kinase activity, by hypofunction of the regulatory tyrosin-phosphatases, or by some regulatory mechanims, as yet unknown. Supporting this hypothesis, it has been demonstrated that different oncogenes with tyrosin-kinase activity, such as c-kit and c-src, are frequently altered in SCLC (Kiefer et al., 1987; Hibi et al., 1991; Mellstrom et al., 1987; Sekido et al., 1991; Takeda et al., 1995; Krystal et al., 1996).

Our results suggest that ß-catenin could play an important role in the pathogenesis of SCLC related to a loss of cadherin-catenin cell adhesion function. This loss is perhaps caused by an abnormal tyrosin-phosphorylation that disassembles the complex, giving the cell a more invasive and disseminative quality because of an increase in cell motility and loss of contact-inhibition growth. Further studies, which should be completed with an analysis of the phosphorylation status of the protein and of alteration in the c-kit and c-src genes may corroborate our hipothesis.

These biological facts may help to explain the patients' clinical data and outcome. We found a tendency or marginal correlation between stage and the number of metastatic locations, they were larger in cases with hyperexpressed ß-catenin. If further studies corroborate our hypothesis, ß-catenin may possibly be a prognostic marker of tumoral dissemination.

The finding of a correlation between time to relapse or progression after treatment and overall survival, which were shorter when there was ß-catenin hyperexpression, is important. Few studies relate ß-catenin expression to patient outcome; only two of them, gastric (Jawhari et al., 1997) and oesophageal (Krishnadath et al., 1997) carcinomas, demonstrated that membrane hypoexpression of the protein was an independent prognostic factor for survival. More extensive studies must be done to corroborate our findings.

The multivariate analysis did not select ß-catenin as an independent predictive factor for response, time to relapse or progression, or of overall survival. Our study could not perform a strong analysis of prognostic factors as the number of patients enrolled was reduced. Additionally, the value of ß-catenin cannot substitute the value of stage as predictive factor for patient outcome in SCLC (Garrido et al., 1994; Ihde et al., 1997).

References

Aberle H., Bauer A., Stappert J., Kispert A. and Kemler R. (1997). ß-catenin is a target for the ubiquitin-proteasome pathway. EMBO J. 16, 3797-3804.

Barth A., Näthke I. and Nelson W.J. (1997). Cadherins, catenins and APC protein: interplay between cytoskeletal complexes and signaling pathways. Curr. Opin. Cell Biol. 9, 683-690.

Behrens J., Jerchow B.A., Würtele M., Grimm J., Asbrand C., Wirtz R., Kühl M., Wedlich D and Birchmeier W. (1998). Functional interaction of an axin homolog, conductin, with ß-catenin, APC, and GSK3ß. Science 280, 596-599.

Bullions L.C. and Levine A.J. (1998). The role of ß-catenin in cell adhesion, signal transduction and cancer. Curr. Opin. Oncol. 10, 81-87.

Daniel J.M. and Reynolds A.B. (1997). Tyrosine phosphorylation and cadherin-catenin function. BioEssays 19, 883-891.

Espada J., Pérez-Moreno M., Braga V., Rodríguez-Viciana P. and Cano A. (1999). H-Ras activation promotes cytoplasmic accumulation and phosphoinositide 3-OH Kinase association of ß-catenin in epidermal keratinocites. J. Cell Biol. 146, 967-980.

Fukuchi T., Sakamoto M., Tsuda H., Maruyama K., Nozawa S. and Hirohashi S. (1998). ß-catenin mutation in carcinoma of the uterine endometrium. Cancer Res. 58, 3526-3528.

Garrido P., González Barón M. and Ordóñez A. (1994). Factores pronósticos en el carcinoma broncopulmonar de células pequeñas. In: Factores pronósticos en oncología. González Barón M (ed). Interamericana Mc Graw-Hill. Madrid. pp 83-93.

Hibi K., Takahashi T. and Sekido Y. (1991). Coexpression of the stem cell factor and c-kit genes in small cell lung cancer. Oncogene 6, 2291-2296.

Hirohashi S. (1998). Inactivation of the E-cadherin-mediated cell adhesion system in human cancers. Am. J. Pathol. 153, 333-339.

Hirsch F., Mathews M. and Aisner S. (1988). Histopathologic classification of small cell lung cancer. Cancer 62, 973-977.

Ihde D.C., Pass H.I. and Glatstein E. (1997). Small cell lung cancer. In: Principles and practice of oncology. De Vita V.T. (ed). JB Lippincott Co. Philadelphia, PA. pp 911-949.

Ilyas M. and Tomlinson I.P.M. (1997). The interactions of APC, E-cadherin and ß-catenin in tumour development and progression. J. Pathol. 182, 128-137.

Iwao K., Nakamori S., Kameyama M., Imaoka S., Kinoshita M., Fukui T., Ishiguru S., Nakamura Y. and Miyoshi Y. (1998). Activation of the ß-catenin gene by interstitial deletions involving exon 3 in primary colorectal carcinomas without adenomatous polyposis coli mutations. Cancer Res. 58, 1021-1026.

Jawhari A., Jordan S., Poole S., Browne P., Pignatelli M. and Farthing M. (1997). Abnormal immunoreactivity of the E-cadherin-catenin

complex in gastric carcinoma: relationship with patient survival. Gastroenterology 112, 46-54.

Kiefer P., Bepler G. and Kubassch M. (1987). Amplification and expression of protooncogenes in human small cell lung cancer cell lines. Cancer Res. 47, 6236-6242.

Korinek V., Barker N., Morin P.J., Van Winchen D., Weger R., Kinzler K., Vogelstein B. and Clevers H. (1997). Constitutive transcriptional activation by a ß-catenin-Tcf complex in APC-/- colon carcinoma. Science 275, 1784-1787.

Krishnadath K., Tilanus H.W., Van Blankenstein M., Hop W.C.J., Kremers E.D., Dinjens W.N.D. and Bosman F.T. (1997). Reduced expression of the cadherin-catenin complex in oesophageal adenocarcinoma correlates with poor prognosis. J. Pathol. 182, 331-338.

Krystal G., Hines S.J. and Organ C.P. (1996). Autocrine growth of small cell lung cancer mediated by coexpression of c-kit and stem cell factor. Cancer Res. 56, 370-376.

Mellstrom K., Bjelfman C. and Hammerling V. (1987). Expression of c-src in cultures of human neuroblastoma and small cell lung carcinoma cell lines correlates with neuroendocrine differentiation. Mol. Cell Biol. 7, 4178-4184.

Morin P.J., Sparks A.B., Korinek V., Barker N., Clevers H., Vogelstein B. and Kinzler K. (1997). Activation of ß-catenin-Tcf signaling in colon cancer by mutations in ß-catenin or APC. Science 275, 1787-1790.

Muller T., Choidas A., Reichmann E. and Ulrich A. (1999). Phosphorylation and free pool of beta-catenin are regulated by tyrosin kinases and tirosin phosphatases during epithelial cell migration. J. Biol. Chem. 274, 10173-10183.

Nakamura Y. (1997). Cleaning up on ß-catenin. Nat. Med. 3, 499-500.

Nawrocki B., Polette M., Van Hengel J., Tournier J.M., Van Roy F. and Birembaut P. (1998). Cytoplasmic redistribution of E-cadherin-catenin adhesion complex is associated with down-regulated tyrosin phosphorylation of E-cadherin in human bronchopulmonary carcinomas. Am. J. Pathol. 153, 1521-1530.

Nollet F., Berx G., Molemeans F. and Van Roy F. (1996). Genomic organization of the human ß-catenin gen (CTNNB1). Genomics 32, 413-424.

Orford K., Crockett C., Jensen J.P., Weissman A.M. and Byers S.W. (1997). Serine phosphorylation regulated ubiquitination and degradation of ß-catenin. J. Biol. Chem. 272, 24735-24738 .

Palacios J. and Gamallo C. (1998). Mutations in ß-catenin gene (CTNNB1) in endometrioid ovarian carcinomas. Cancer Res. 58, 1344-1347.

Papkoff J. (1997). Regulation of complexed and free catenin pools by distinct mechanims. J. Biol. Chem. 272, 4536-4543.

Pelfer M. (1997). ß-catenin as oncogene: the smoking gun. Science 275, 1752-1753.

Rubinfeld B., Robbins P., El-Gamil M., Alberts I., Porfiri E. and Polakis P. (1997) Stabilization of ß-catenin by genetic defects in melanoma cell lines. Science 275, 1790-1792.

Sekido Y., Obata Y. and Ueda R. (1991). Preferential expression of c-kit protooncogene transcripts in small cell lung cancer. Cancer Res. 51, 2416-2419.

Shiozaki H., Oka H., Inoue M., Tamura S. and Monden M. (1996). E-cadherin mediated adhesion system in cancer cells. Cancer 77, 1605-1613.

Smith M.E.F. and Pignatelli M. (1997). The molecular histology of neoplasia: the role of the cadherin/catenin complex. Histopathology 31, 107-111.

Solomon D., Sacco P.A., Roy S.G., Simcha I., Johnson K.R., Wheelock M.J. and Ben-Ze'Ev A. (1997). Regulation of ß-catenin levels and localization by overexpression of plakoglobin and inhibition of the ubiquitin-proteasome system. J. Cell Biol. 139, 1325-1335.

Stewart D.B. and Nelson W.J. (1997). Identification of four distinct pools of catenins in mammalian cells and transformation-dependent changes in catenin distributions among these pools. J. Biol. Chem. 272, 29652-29662.

Takayama T., Shiozaki H., Doki Y., Oka H., Inoue M., Yamamoto M., Tamura S., Shibamoto S., Ito F. and Monden M. (1998). Aberrant expression and phosphorylation of ß-catenin in human colorectal cancer. Br. J. Cancer 77, 605-613.

Takayama T., Shiozaki H., Shibamoto S., Oka H., Kimura Y., Tamura S., Inoue M., Monden T., Ito F. and Monden M. (1996). ß-catenin expression in human cancers. Am. J. Pathol. 148, 39-46.

Takeda H., Nagafuchi A., Yonemura S., Tsukita S.A., Behrens J., Birchmeier W. and Tsukita S.H. (1995). V-src kinase shifts the cadherin-based cell adhesion from the strong to the weak state and ß-catenin is not required for the shift. J. Cell Biol. 131, 1839-1847.

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

Tao Y.S., Edwards R.A., Tubb B., Wang S., Bryan J. and Mccrea P.D. (1996). ß-catenin associates with the actin-bundling protein fascin in a noncadherin complex. J. Cell Biol. 134, 1271-1281.

Voeller H.J., Truica C.I. and Gelmann E.P. (1998). ß-catenin mutations in human prostate cancer. Cancer Res. 58, 2520-2523.

Willert K. and Nusse R. (1998). ß-catenin: a key mediator of Wnt signaling. Curr. Opin. Genet. Dev. 8, 95-102.