Virchows Arch (2001) 438:464–469
DOI 10.1007/s004280000371

ORIGINAL ARTICLE

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β- And γ-catenin expression in endometrial carcinoma. Relationship with clinicopathological features and microsatellite instability

Received: 22 August 2000 / Accepted: 20 November 2000 / Published online: 20 February 2001

Abstract The activation of the adenomatous polyposis coli (APC)/β-catenin/T-cell factor (Tcf) pathway due to β-catenin gene mutation has been recently implicated in the development of some endometrial carcinomas. β- And γ-catenin are structurally and functionally related molecules that participate in cell adhesion and signal transduction. Nuclear accumulation of β- and γ-catenin have been related to the activation of the APC/β-catenin/Tcf pathway. In this study, we investigate the immunohistochemical expression pattern (nuclear vs membranous) of β- and γ-catenin in 40 endometrial carcinomas and their correlation with clinicopathological features and microsatellite instability (MI) status. MI was detected at three or more loci in 12 tumors: 11 were endometrioid and one was non-endometrioid. Nuclear catenin expression was found in 13 carcinomas: ten carcinomas had nuclear β-catenin expression and three carcinomas had nuclear γ-catenin expression. The nuclear catenin expression pattern significantly correlated with the histological type, International Federation of Gynecology and Obstetrics (FIGO) grade, and the presence of a second neoplasm. Nuclear catenin expression was always observed in low-grade endometrioid carcinomas; it was also more frequently associated with a second carcinoma. No correlation was observed between the catenin expression pattern and the level of myometrial infiltration, stage, associated endometrial hyperplasia, the existence of a source of estrogenic stimulation, and MI. However, four of 13 endometrioid carcinomas in this series had both catenin nuclear expression and MI. These data suggest that at least two different neoplastic pathways can lead to endometrial carcinomas with an endometrioid phenotype. In one, MI would be a key event, while in the other, the APC/β-catenin/Tcf signaling pathways could be activated. Probably, in some cases, both pathways could simultaneously occur.

Keywords β-Catenin · γ-Catenin · Endometrial carcinoma · Microsatellite instability

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Introduction

The molecular basis of endometrial cancer is largely unknown, and different studies have proposed different molecular pathways to explain the genesis of endometrioid and non-endometrioid tumors [36]. This latter type of tumor, prototypically represented by serous carcinomas, seems to have a more homogeneous pattern of molecular alterations. Some reports have found that p53 mutations occur in 90% of the cases and suggested that this mutation would be an early molecular event that participates in tumor initiation [35, 40]. In contrast, endometrioid tumors seem to be a more heterogeneous group of neoplasias in which no molecular alteration is consistent enough to explain the majority of the cases. Nevertheless, some genetic defects have been described with relative frequency in association with endometrioid tumors, such as microsatellite instability (MI) [8, 9, 10, 21, 29] and PTEN/MMAC 1 (phosphatase and tensin homologue deleted on chromosome ten/mutated in multiple advanced cancer) mutations [21, 22, 39].

Recently, β-catenin mutations have been reported in about 15% of endometrioid carcinomas [12, 19]. β-Catenin was first described as a component of the cadherin/catenin complexes mediating calcium-dependent intercellular adhesion [44]. Subsequent studies demonstrated that β-catenin can be localized not only in the cell

membrane but also in the cytoplasm and nuclei participating in signal transduction and transcriptional activation through the formation of complexes with the DNA-binding proteins that are members of the T-cell factor–lymphoid enhancer factor (TcF-Lef) family [20]. The free (cytoplasmic) β-catenin level is low in normal cells since the protein is targeted for destruction in the ubiquitin–proteasome system [1] by adenomatous polyposis coli (APC) protein together with glycogen synthetase kinase-3β (GSK-3β) [32] and other molecules, such as axin or conductin [5]. Mutations that inactivate APC or affect the GSK-3β-phosphorylation sequence in the β-catenin gene itself increase cytoplasmic levels of free β-catenin [20, 25], which translocates into the cell nucleus and then acts as an oncoprotein through constitutive β-catenin-Tcf-regulated transcription [25, 33]. Thus β-catenin is now considered as an oncogene that participates in the development of different human neoplasias, such as colon [13, 15, 18, 25, 37], ovary [26], endometrium [12, 19], prostate [42], and hepatocellular carcinomas [24], and medulloblastomas [45].

γ-Catenin or plakoglobin is structurally related to β-catenin and is thought to play a role similar to that of β-catenin in regulating cadherin adhesive activity in adherens junctions and modulating the activity of desmosomal cadherins [43]. In addition, it is one of the molecules that binds to APC, and it has also been linked to the APC/β-catenin/Tcf pathway through biochemical and genetic studies in diverse organisms [30, 31]. γ-Catenin and β-catenin bind in a mutually exclusive manner to cadherins, APC, and transcription factors [28]. Overexpression of γ-catenin leads to a decrease in β-catenin level by degradation of β-catenin. Exogenous γ-catenin competes with β-catenin for cadherin binding, directing the displaced β-catenin to the ubiquitin–proteasome system. Excess cytoplasmic γ-catenin can also translocate into the cell nucleus [34].

This study analyzes β- and γ-catenin expression in a group of endometrial carcinomas. The expression pattern (nuclear vs membranous) was correlated with clinicopathological features. One of our specific objectives was to explore the possible association between catenin expression pattern and MI, since this genetic alteration is common in endometrial carcinomas, and β-catenin gene mutations have been reported in MI-positive colon carcinomas [18].

Materials and methods

Patients

This study comprised 40 endometrial carcinomas in a group of 42 tumors, whose clinicopathological features and MI status have been previously reported [9]. Briefly, the series consisted of 31 endometrioid and nine non-endometrioid carcinomas (seven serous and two clear cells carcinomas). Tumors were graded according to International Federation of Gynecology and Obstetrics (FIGO) guidelines: ten tumors were grade I, 11 were grade II, and 19 were grade III, and 27 carcinomas were stage I, nine were stage II, and four were stage III. Of 18 patients who had a source of estrogenic stimulation, 13 patients were obese, 3 had hormonal therapy, and 2 had either stromal hypertecosis or stromal hyperplasia of the ovary. Of 11 patients who had a history of a second carcinoma, eight women had beast cancer, one of which was associated with colon carcinoma, one had bladder carcinoma, one had gastric carcinoma, and one had ovary carcinoma. For MI analysis, somatic microsatellite alterations at five different (CA)n repeats (Research Genetics, Inc. Huntsville, Ala.) were analyzed using the polymerase chain reaction (PCR), as reported previously [9]. Tumors were defined as MI-positive if at least three markers showed an altered sized band. Reconfirmation of MI was performed using primer sets *BAT*-26 and *BAT*-25 by means of single strand conformational polymorphism (SSCP). By following these criteria, MI was detected in 12 tumors: 11 were endometrioid and one was non-endometrioid.

Immunohistochemistry

Immunohistochemistry for β- and γ-catenin was performed using the avidin–biotin alkaline phosphatase method, as previously reported [26]. A heat-induced antigen retrieval step (deparaffinized sections were immersed in 0.01 M sodium citrate buffer, pH 6.0, and incubated in a pressure cooker for 3 min) was performed. The mouse anti-human β- and γ-catenin monoclonal antibodies (Transduction Laboratories, Lexington, Ky.) were applied overnight at a dilution of 1:400 and 1:200, respectively.

In negative controls, the primary antibodies were omitted or replaced with an irrelevant antibody. Immunohistochemistry was performed on tumor tissue sections, and no areas of normal or hyperplastic endometrium were analyzed. Two patterns of catenin expression were considered: membranous, when catenins were localized in the cell membrane only, and nuclear, when expression was observed in the nuclei, regardless of the amount of nuclei stained or the simultaneous expression of catenins in membrane and cytoplasm.

Results

Catenin expression pattern and correlation with clinicopathological and molecular features

Nuclear catenin expression was observed in 13 tumors (nuclear pattern) and was always associated with some degree of membrane expression (Fig. 1A, B, and D). The remaining endometrial carcinomas only showed membrane catenin expression of variable extension and intensity (membranous pattern; Fig. 1C). Of these 13 carcinomas with nuclear catenin expression, ten had nuclear β-catenin expression in areas of glandular and squamous differentiation (Fig. 1A, B), and three had nuclear γ-catenin expression (Fig. 1D). No tumors showed nuclear co-expression of β- and γ-catenin. The catenin expression pattern (nuclear vs membranous) correlated significantly with the histological type, FIGO grade, and the presence of a second neoplasm (Table 1). Thus, nuclear catenin expression was always observed in endometrioid carcinomas and was more frequently found in tumors of patients with a second carcinoma. With respect to FIGO grade, nuclear catenin expression was more frequently associated with grade 1 and 2 tumors, but this association lost statistical significance when non-endometrioid tumors were excluded from the analysis (data not shown). No correlation was observed between the catenin expression pattern and the level of

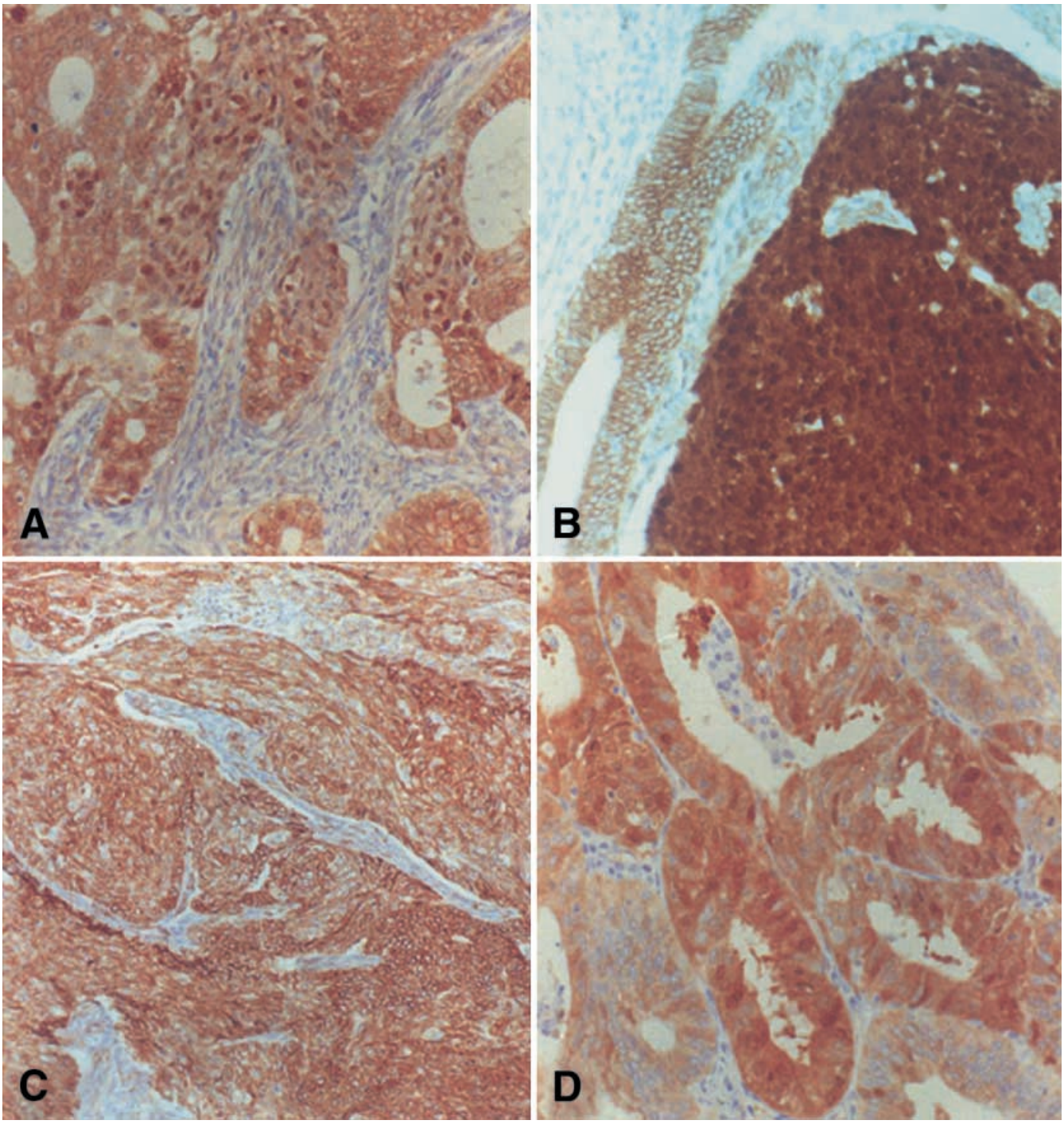

Fig. 1 **A**, **B** β-Catenin nuclear expression pattern in areas of squamous differentiation in two endometrioid carcinomas. Note membranous expression pattern in adjacent areas (**B**). **C** β-Catenin membranous expression pattern in areas of squamous differentiation of an endometrioid carcinoma. **D** γ-Catenin nuclear expression pattern in an endometrioid carcinoma

myometrial infiltration, stage, associated endometrial hyperplasia, the existence of a source of estrogenic stimulation, and MI (Table 1). The same relationships were observed when only the β-catenin expression pattern was evaluated (data not shown).

Discussion

On a molecular basis, non-endometrioid endometrial carcinomas are related to p53 mutations [35, 40], and endometrioid carcinomas could be divided into two groups: MI-positive and MI-negative. However, no clear clinicopathological differences exist between these two groups of endometrioid tumors. In this series, no differences were found with respect to age, stage, evidence of estrogenic stimulation, mucinous differentiation, and estrogen receptor, c-erbB2, and p53 immunostaining [9]. These results are, in general, in accordance with previous series

Table 1 Relationships between the catenin expression pattern and clinicopathological features and microsatellite instability (MI) in endometrial carcinomas (χ^2 test)

	Membranous catenin expression pattern[a]	Nuclear catenin expression pattern[b]	*P* value
Histological type			
Endometrioid	(*n*=31)	18 (58%)	13 (42%)
Non-endometrioid (*n*=9)	9 (100%)	0	0.017
Grade			
I (*n*=10)	6 (60%)	4 (40%)	
II (*n*=11)	4 (36%)	7 (64%)	
III (*n*=19)	17 (89%)	2 (11%)	0.007
Myometrial infiltration			
Absent (*n*=5)	4 (80%)	1 (20%)	
<50% (*n*=15)	9 (60%)	6 (40%)	
>50% (*n*=20)	14 (70%)	6 (30%)	0.671
Stage			
I (*n*=27)	19 (21.7%)	8 (78.3%)	
II (*n*=9)	5 (21.7%)	4 (78.3%)	
III (*n*=4)	3 (15.2%)	1 (84.8%)	0.681
Associated hyperplasia			
Yes (*n*=4)	1 (25%)	3 (75%)	
No (*n*=36)	26 (72%)	10 (28%)	0.092
Estrogen source			
Yes (*n*=18)	11 (61%)	7 (39%)	
No (*n*=22)	16 (73%)	6 (27%)	0.328
Second neoplasia			
Yes (*n*=12)	5 (41%)	7 (59%)	
No (*n*=28)	22 (79%)	6 (21%)	0.029
MI			
Yes (*n*=12)	8 (67%)	4 (33%)	
No (*n*=28)	19 (68%)	9 (32%)	0.675

[a] Membranous catenin expression pattern: if catenins were localized in the cell membrane only

[b] Nuclear catenin expression pattern: when the protein was expressed in the nucleus, irrespective of the percentage of stained nuclei or simultaneous expression of catenin in membrane and cytoplasm

[7, 10, 29]. The only molecular alterations so far described as being frequently associated with MI are PTEN/MMAC mutations. PTEN/MMAC mutations occur in approximately 40% of endometrioid carcinomas [21, 22, 39]. However, the mutational spectrum of PTEN/MMAC does not appear to differ between MI-positive and MI-negative endometrioid carcinomas [39].

Activation of the APC/β-catenin/Tcf pathway has been implicated in several human neoplasias, including endometrial carcinomas [12, 19] and ovarian carcinomas with an endometrioid phenotype [26]. In vitro and in vivo studies have demonstrated that activation of this neoplastic pathway is usually associated with nuclear β-catenin accumulation and, in some cases, probably also with nuclear γ-catenin accumulation. In this series, we observed catenin nuclear accumulation in 32% of the endometrial carcinomas analyzed (β-catenin in 25% and γ-catenin was in 7%). Fukuchi et al. previously reported β-catenin nuclear accumulation in 29 of 76 (38%) endometrial carcinomas [12]. In both studies, the presence of nuclear catenin immunoexpression was associated with an endometrioid phenotype. These findings might further support the model that considers distinctive pathways in the development of endometrioid and non-endometrioid endometrial carcinomas.

An association between the APC/β-catenin/Tcf pathway and MI in colon carcinomas has been suggested [18, 23]. Since MI is common in endometrioid carcinomas, we have analyzed whether or not MI is associated with nuclear catenin expression. Although we could not find a statistical correlation between both alterations, four of 13 endometrioid carcinomas in this series had both catenin nuclear expression and MI. In contrast, Kobayasi et al. [19] studied a series of 35 endometrial carcinomas and did not find any tumor with both MI and β-catenin nuclear expression. Mirabelli-Primdahl et al. [23] observed that β-catenin mutations occur in endometrial carcinomas irrespective of the mutator pathway. Another difference between colon and endometrioid carcinomas is that *TCF*-4 is frequently mutated in an (A)9 coding repeat in MI-positive colon cancer, whereas this mutation is very infrequent in MI-positive endometrial carcinomas [11]. The data in present and previous studies suggest that at least two different neoplastic pathways can lead to endometrioid carcinomas. In one of them, MI would be a key event. In the other, the APC/β-catenin/Tcf signaling pathways could be activated. However, in some cases both pathways could occur simultaneously.

The nucleo-cytoplasmic pattern of β-catenin immunoexpression observed in this and previous reports could be hypothetically due to an alteration in any molecule that participates in the β-catenin/Tcf signaling pathway. At present, it seems that the intracellular pool of β-catenin is regulated by an active GSK-3β, which recognizes an APC/β-catenin complex [5]. It has been suggested that APC may be involved in directing β-catenin to proteasomes [1]. In addition, the cytoplasmic β-catenin pool would increase in response to extracellular wingless (Wg)/Wnt signaling [27], which inactivates GSK-3β by acting on the appropriate receptors. To date, the only molecular alterations described in this pathway in human endometrial carcinomas are muta-

tions in the β-catenin gene itself. Thus Fukuchi et al. [12] and Kobayasi et al. [19] reported that ten (13%) and five (14%) endometrial carcinomas of their series had single-base missense mutations, affecting serine–threonine residues on the GSK-3β consensus motif in exon 3 of the β-catenin gene. These mutations render a fraction of free β-catenin, which is insensitive to GSK-3β phosphorylation, so that it accumulates in the cytoplasm and translocates into the nucleus. However, the percentage of mutations so far described does not explain all cases with nuclear β-catenin accumulation, suggesting that probably other molecules in the β-catenin route could be affected.

Expression of different Wnt factors has been described in human endometrial carcinomas [6] but, to date, their effect in β-catenin levels have not been reported. The human frizzled family (Fz) of transmembrane proteins have been shown to act as receptors for Wnt proteins. It has been suggested that different Fz proteins may be uniquely expressed in different tumor cell types. For example, Tanaka et al. [27] observed that a novel member of this family, FzE3, is specifically expressed in squamous cell esophageal carcinomas compared with uninvolved adjacent normal mucosa. In addition, transfected FzE3 in an esophageal carcinoma cell line induces cytoplasmic and nuclear β-catenin localization in contrast to mock-transfected cells that had β-catenin located at the cell membrane. The authors suggested that Fz gene expression enhances β-catenin mediated signals. Recently, Abu-Jawdeh et al. [2] cloned a novel human stromal protein of the secreted frizzled gene family. The protein is up-regulated in endometrial hyperplasia and carcinomas and seems to regulate the Wnt pathway.

The role of GSK-3β in human oncogenesis is not well known. In a recent study, Zurawel et al. [28] did not find any alteration of GSK-3β in a series of 67 medulloblastomas, some of them having mutations of the β-catenin gene. Spark et al. [37] studied three colon carcinoma cell lines and did not find any mutation in the entire coding region of GSK-3β and its homologue GSK-3α. Increased β-catenin cytoplasmic and nuclear levels can also be observed in cases of APC inactivation: mutations of APC in colorectal polyps and carcinoma [14] and other conditions as sporadic aggressive fibromatosis [3]. However, in sporadic endometrial carcinomas, loss of heterozygosity at the APC locus is infrequent [16].

We observed that three endometrioid carcinomas had a nuclear pattern of γ-catenin expression. γ-Catenin is a protein of the Armadillo family, closely related to β-catenin, and has signaling activity similar to β-catenin in *Xenopus* [17]. In addition, γ-catenin also bind to APC, α-catenin, and E-cadherin and shares strong amino acid similarities with β-catenin in its amino terminus (NH_2) regulatory motif. Thus, the phosphorylation sequence for GSK-3β is highly homologous in the β-and γ-catenin genes [34]. In vitro studies demonstrated that excess γ-catenin translocates into the nucleus. In cell lines, when the ubiquitin–proteasome proteolytic pathway was inhibited, plakoglobin was not organized in cell–cell junctions but was diffusely distributed in the cytoplasm with a significant accumulation in the cell nuclei [34]. Nuclear γ-catenin has also been observed in vivo in two of 20 adenomatous polyps of the colon [41], two cases of Barret's esophagus with dysplasia, and two esophageal adenocarcinomas [4]. At present, the mechanisms implicated in nuclear γ-catenin translocation in endometrial and digestive tumors are unknown. It has been suggested that the activating mutation in the phosphorylation sequence for GSK-3β in the γ-catenin gene could reasonably be expected to substitute for loss of APC or β-catenin mutations in the activation of the APC/β-catenin signaling pathway [37]. In the only series that has explored this hypothesis, no mutations in the γ-catenin NH_2-regulatory region were detected in 33 colorectal tumors, including 13 cases without APC or β-catenin gene mutations. However, these tumors were not studied using immunohistochemistry, and the location of γ-catenin expression was unknown [37]. Recently, Caca et al. [7] described a mutation in S28 of γ-catenin in a gastric cancer cell line with constitutive Tcf transcriptional activity. Further studies in endometrial or digestive neoplasias with nuclear γ-catenin expression must be performed in order to elucidate whether or not the γ-catenin gene is a target for oncogenic mutations similar to those observed in the β-catenin gene.

In summary, the pattern of catenin expression differs between histological types of endometrial carcinomas. Nuclear accumulation of β- and γ-catenin occurs only in endometrioid carcinomas, supporting the dualistic model of endometrial cancer development. Nuclear catenin expression is frequently independent of MI. These findings suggest at least two different molecular pathways leading to an endometrioid phenotype in endometrial cancer: the APC/β-catenin/Tcf signaling pathway activation and MI. In some cases, both pathways can simultaneously occur.

Acknowledgements The authors thank Vicente Sánchez, Petra Rubio, and Inmaculada Briones for technical assistance with the immunohistochemical study and Pilar Machín for obtaining clinicopathological data. This work was supported by research grants 98/0151 from the Fondo de Investigaciones Sanitarias de la Seguridad Social, CAM 08.1/0020/1997 from the Comunidad Autónoma de Madrid, and SAF 98-0085-C03-03 from the Ministerio de Educación y Cultura, Spain.

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