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Immunohistochemical Expression of E-cadherin and β-catenin in the Normal and Malignant Human Endometrium: An Inverse Correlation Between E-cadherin and Nuclear β-catenin Expression

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Abstract. *Background: The E-cadherin/β-catenin complex plays a crucial role in epithelial cell-cell adhesion and in the maintenance of tissue architecture. We previously reported aberrant expression of β-catenin in endometrial carcinomas. However, the expression and correlation of E-cadherin and β-catenin in normal and malignant endometrial tissues are not fully understood. Materials and Methods: Immunohistochemical expression of E-cadherin and β-catenin was detected in 30 cases of normal endometrium and 73 cases of endometrial carcinoma. Results: In the normal endometrium, the expression of E-cadherin and cytoplasmic β-catenin in glandular cells was predominantly observed in the proliferative phase, and decreased in the secretory phase. In endometrial carcinomas, the expression of E-cadherin and cytoplasmic β-catenin decreased compared to that in the normal proliferative endometrial glands. The expression of E-cadherin and cytoplasmic β-catenin tended to be reduced in histologically high-grade tumors compared to low-grade tumors. Nuclear expression of β-catenin was observed in the glandular cells in the late proliferative and early secretory phases, as well as in high-grade endometrial carcinomas. Interestingly, nuclear β-catenin expression was associated with the loss of E-cadherin expression in normal and carcinoma cells, indicating an inverse correlation. Conclusion: The cyclic expression of E-cadherin and β-catenin in the normal endometrium suggests that the adhesion complex may act to maintain the endometrial architectures. In addition, nuclear β-catenin expression associated with loss of E-cadherin expression may be involved in the acquisition of aggressive biological behavior, especially in high-grade tumors.*

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Cadherins are a family of cell-cell adhesion molecules essential for tight connections between cells, and are membrane glycoproteins involved in cell-cell adhesion in a homophylic manner (1, 2). Cell adhesion is essential to maintain cell and tissue morphological architecture through cell-cell tight connections and lymphocyte homing to inflammatory sites (3, 4). In cancer cells, cadherins function as suppressors of metastasis, as decreased expression of cadherins at primary sites accelerated the detachment of the cancer cells and subsequent distant metastasis (5,6). β-catenin is a cytoplasmic molecule, that binds to the intracytoplasmic domain of cadherins, and supports the adhesion capability of cadherins (6-8). The expression of β-catenin is induced by stimuli like extracellular Wnt/Wingless signals (9), and is metabolized by GSK3b and APC (10, 11). Mutation in the catenin gene or APC gene thus induces intracellular accumulation of β-catenin (12, 13). The accumulated β-catenin is reported to bind TCL and be translocated to the nucleus (14, 15), and the nuclear β-catenin acts as a transcriptional activator for c-Myc and cyclin D1 for cell growth acceleration (16). In endometrial carcinoma, tumor cells with reduced expression of E-cadherin are reported to be associated with lymph node metastasis and a poor prognosis (17, 18). Nuclear accumulation of β-catenin associated with β-catenin gene mutation is also reported in endometrial carcinomas (19-22). In addition, we previously reported that the immunohistochemical expression of nuclear β-catenin is topologically correlated with the overexpression of cyclin D1 in endometrial carcinoma, suggesting the possible involvement of β-catenin in the acquisition of the abnormal growth potential of this tumor (23). However, although E-cadherin and β-catenin are considered to act as a functional

complex, correlation of the expression of E-cadherin and the nuclear/cytoplasmic expression of β-catenin in endometrial tissues is not yet well documented. In the present study, therefore, we investigated the immunohistochemical expression of E-cadherin in normal and malignant endometrial tissues, and compared this expression with that of β-catenin, to explore the significance of the expression of these two molecules.

Materials and Methods

Histological materials. Thirty normal endometrial tissue specimens were obtained from 30 women, all of whom had regular menstrual cycles and a previous history of pregnancy. The normal tissue was extirpated during a hysterectomy for uterine myoma or cervical carcinoma *in situ*. Seventy-three endometrial carcinoma tissues were obtained from biopsy or hysterectomy. The tissues were used with the approval of the Ethics Committee of Shinshu University, Japan, after obtaining written consent from the patients. Each specimen was immediately fixed in 10% phosphate-buffered formalin for 24 hours and embedded in paraffin. Serial sections 3 μm thick were made for hematoxylin and eosin (H.E.) staining and immunostaining. Histological diagnosis and endometrial dating (24) were performed using H.E.-stained slides. Of the 30 endometrial tissue specimens, 10 were in the proliferative phase and 20 were in the secretory phase. Of the 73 cases of endometrial carcinoma, 45, 9, 15 and 4 were FIGO stage I, II, III and IV, respectively. Histologically, 68 were endometrioid carcinomas, 2 were clear cell carcinomas, 2 were serous papillary carcinomas and one was squamous cell carcinoma. In non-endometrioid subtypes, histological grading was based on the degree of nuclear atypia. Of 73 cases, 35 were grade 1, 23 were grade 2 and 15 were grade 3.

Staining procedures. Indirect immunostaining was performed using specific antibodies against E-cadherin and β-catenin. An antibody for E-cadherin was purchased from NeoMarkers (Fremont, CA, USA). Antibodies for β-catenin were from Transduction laboratories (Lexington, KY, USA). Each immunohistochemical staining was performed using the avidin-biotin-peroxidase complex method with a Histofine SAB-PO detector kit (Nichirei, Tokyo, Japan). Briefly, after routine deparaffinization and rehydration, sections were treated with microwaves in a 0.01 M citrate buffer (pH 6.0) for 15 minutes. After the blocking of endogenous peroxidase activity, the sections were incubated with specific primary antibodies [diluted 1:100 with PBS/bovine serum albumin (BSA)] or control non-immunized mouse serum at 4˚C overnight. After a wash with PBS, biotinylated anti-mouse IgG was applied for 30 minutes at room temperature. For a negative control of the secondary antibody, biotinylated anti-rabbit IgG was applied. After a wash with PBS, a peroxidase-conjugated streptoavidin solution was applied for 30 minutes and visualized with 0.05% 3'-3' diaminobenzidine (DAB). Counterstaining was performed lightly with hematoxylin.

Interpretation of immunohistochemical staining. Specific staining for E-cadherin was identified in the cytoplasm, and that for β-catenin in the nucleus and/or cytoplasm. All the control slides yielded negative staining. The degree of staining was also described using a positivity index (PI), which indicates the percentage of positive cells in 200 cells from 3 high-powered fields in each section. The statistical analysis for the comparison of the PI among menstrual phases, histological grades and clinical stages of endometrial carcinomas was done with the Mann-Whitney *U*-test or Sheffe's test as appropriate. A tied-*p* value of less than 0.05 was considered significant.

Results

The PI of E-cadherin and β-catenin in the glandular cells of the normal endometrium is listed in Table I, and that in endometrial carcinoma in Table II. Representative immunostainings for these molecules are shown in Figures 1 and 2.

Normal endometrium. The expression of E-cadherin in glandular cells was observed mainly in the proliferative phase. The mean PI in the early proliferative phase was 15.2 in functionalis (Figure 1a-c, Figure 3, Table I), and increased in the late proliferative phase (PI: 39.2 in functionalis). The E-cadherin expression decreased significantly in the secretory phases both in the functionalis (PI: 4.1 in the early proliferative phase, 10.1 in the mid-proliferative phase, and 9.0 in the late secretory phase) and in the basalis compared to levels in the proliferative phase (Figure 1d and e). The expression of E-cadherin was observed in both the functionalis and basalis, however, it was more frequently observed in the basalis throughout the menstrual cycle, and with significant differences in the proliferative and early secretory phases (Table I). Stromal cells showed positive staining for E-cadherin in the proliferative and early secretory phases, but the positive staining disappeared in the mid- and late secretory phases. Surface epithelial cells showed positive staining for E-cadherin throughout the menstrual cycle with a slight predominance in the secretory phase.

The expression of β-catenin was observed in the cytoplasm and nucleus of the glandular cells. Cytoplasmic staining of β-catenin was mainly observed from the proliferative to early secretory phase; the mean PI of β-catenin-positive cells in the early proliferative, late proliferative and early secretory phases (functionalis) was 18.5, 73.7, and 31.9, respectively (Figures 1f-i, Figure 3, Table I). The staining markedly decreased in the mid- and late secretory phases; the mean PI (functionalis) was 7.6 and 6.3, respectively (Figure 1j). Cytoplasmic staining for β-catenin was more strongly observed in the basalis than functionalis throughout the menstrual cycle, with a significant difference in the early proliferative and early secretory phases. Nuclear staining for β-catenin was sporadically observed in the late proliferative phase (mean PI: 6.6 in the functionalis, Figure 1h) and increased in the early secretory phase (mean PI: 13.5) (Figure 1i, Figure 3, Table I). However, nuclear staining for β-catenin was not observed in the mid- and late secretory phases. The nuclear β-catenin-positivity in the late proliferative and early secretory phases was associated with cytoplasmic β-catenin staining. In stromal cells, cytoplasmic

Table I. *Result of immunostaining for E-cadherin and β-catenin in normal endometrium.*

	Proliferative phase		Secretory phase		
	early	late	early	mid	late
E-cadherin:					
Glandular cell					
Functionalis (C)	15.2±23.6	39.2±40.4	4.1±1.6*	10.1±4.7*	9.0±5.9*
Basalis (C)	62.8±40.3**	58.7±45.2**	40.4±33.4**	14.1±12.3*	6.0±2.9*
Stromal cell					
Functionalis (C)	14.3±32.3	15.2±28.2	1.0±2.6*	3.9±6.4*	2.5±5.0*
Basalis (C)	6.8±15.8	0	0	0.2 ±0.6	1.0±2.0
Surface epithel (C)	33.5±31.8	63.1±29.4	74.6±26.0	67.9±25.3	83.0±11.2
β-catenin					
Glandular cell					
Functionalis (C)	18.5±24.0	73.7±29.9	31.9±44.0*	7.6±7.3*	6.3±8.1*
(N)	1.0±0.6	6.6±9.2	13.5±9.6	0	0
Basalis (C)	77.5±32.9**	87.4±13.1	76.7±22.0**	17.7±17.8*	6.3±4.6*
(N)	0	2.3±1.5	2.7±2.1**	0	0
Stromal cell					
Functionalis (C)	30.8±42.7	32.2±36.4	1.1±2.0*	0	0
Basalis (C)	13.2±18.0	0.3±0.7	0.1±0.3	0	0
Surface epithel (C)	30.8±30.1	65.2±28.8	76.3±17.6	48.4±25.8	68.0±31.4

Each number indicates mean±standard deviation. Abbreviations: C; cytoplasm, N; nucleus. epithel; epithelium, *: significantly different from that in the late proliferative phase **: significantly different from that in the functionalis.

Table II. *Result of immunostaining for E-cadherin and β-catenin in endometrial carcinoma.*

	Stage		Histological grade			
Factors (sites)	I+II	III+IV	Grade 1	Grade 2	Grade 3	Total (73cases)
E-cadherin (C)	12.2±17.7	10.6±16.8	13.8±18.0	13.0±20.0	6.0±9.6	11.8±17.3
β-catenin (C)	36.7±33.9	41.5±31.4	40.4±34.2	35.2±31.4	36.4±34.6	38.0±33.2
(N)	5.0±4.9	6.0±5.2	5.2±4.6	5.7±5.4	6.4±5.3	5.4±5.1

Abbreviations: C; cytoplasm, N; nucleus

expression of β-catenin was observed in the proliferative phase in both the functionalis and basalis, and decreased in the secretory phase. Surface epithelial cells showed positive staining for cytoplasmic β-catenin throughout the menstrual cycle, with a slight predominance in the secretory phase.

Endometrial carcinoma. Positive staining for E-cadherin was observed in the cell membrane and cytoplasm. The spatial distribution of the E-cadherin-positive sites varied among cases and there was no apparent tendency in the distribution of the positive cells, *i.e.*, some samples predominantly showed tumor cells located at the luminal border of tumors protruding into the uterine cavity, while others showed more basal or invasive sites close to the myometrium. The mean PI of E-cadherin in total was 11.8 (Table II). The PI was slightly higher in stage I+II tumors (PI:12.2) than stage III+IV tumors (PI:10.6), as well as in grade 1 and 2 tumors (PI: 13.8 for grade 1, 13.0 for grade 2) compared to grade 3 tumors (PI: 6.0)(Figures 2a-c, Figure 4). However, these differences were not significant. In each case of clear cell carcinoma and serous papillary carcinoma, the expression of E-cadherin was nearly negative. The mean PI of the cytoplasmic β-catenin staining was 38.0. The PI of cytoplasmic β-catenin tended to be higher in advanced stage tumors (PI of stage I+II: 36.7, stage III+IV: 41.5) and low-grade tumors (PI of grade 1: 40.4, grade 3; 36.4) (Figures 2d-f, Figure 4), however, there was no significant difference among these categories.

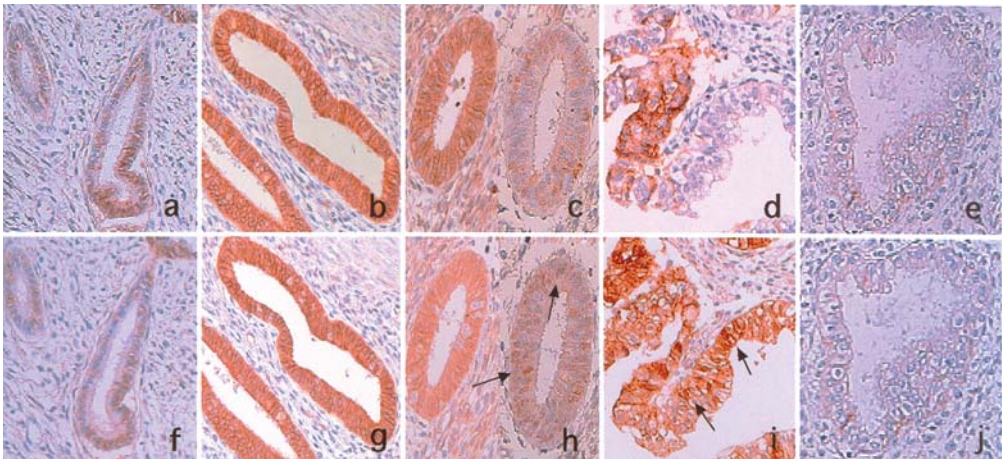

Figure 1. *Result of immunostaining for E-cadherin (a-e) and β-catenin (f-j) in the normal endometrium. (a and f, b and g, c and h, d and i, e and j are serial sections.) a and f: positive staining for E-cadherin is observed in the cytoplasm of glandular cells in the functionalis in the early proliferative phase, and cytoplasmic staining for β-catenin is also noted at similar sites. (x100) b and g: strong staining for E-cadherin and cytoplasmic β-catenin is observed in the basalis in the early proliferative phase. (x100) c and h: E-cadherin-positive staining in the late proliferative phase (c). Positive staining for β-catenin is observed both in the cytoplasm and in the nucleus (arrows in h). Note that the nuclear β-catenin-positive cells are negative for E-cadherin. (x120) d and i: E-cadherin-positive staining is focally observed in the early secretory phase (d). Positive staining for β-catenin is observed both in the cytoplasm and in the nucleus (arrows in i). Note that the nuclear β-catenin-positive cells lack E-cadherin expression. (x120) e and j: The expression of E-cadherin and β-catenin is nearly absent in the late secretory phase. (x100)*

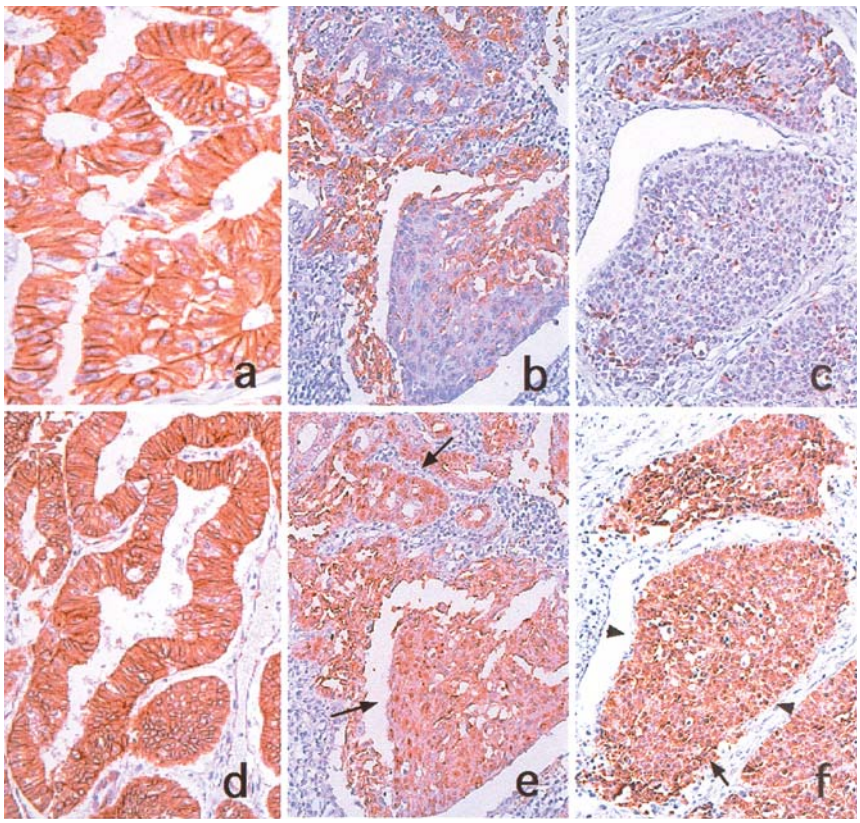

Figure 2. *Result of immunostaining for E-cadherin (a-c) and β-catenin (d-f) in grade 1 (a and d), grade 2 (b and e), and grade 3 (c and f) endometrial carcinomas. (b and e, c and f are serial sections) a: cytoplasmic staining of E-cadherin and β-catenin (d) is observed. (a and d, x150) b and e: the E-cadherin-positive tumor cells are intermingled with negative cells (b). Positive staining for β-catenin is observed in the cytoplasm and in the nucleus (e). Note that the tumor cells with nuclear staining for β-catenin (e, arrows) are negative for E-cadherin. (x100) c and f: The nuclear β-catenin-positive cells (f, arrows) lack the expression of E-cadherin (c) in a grade 3 tumor. (x100)*

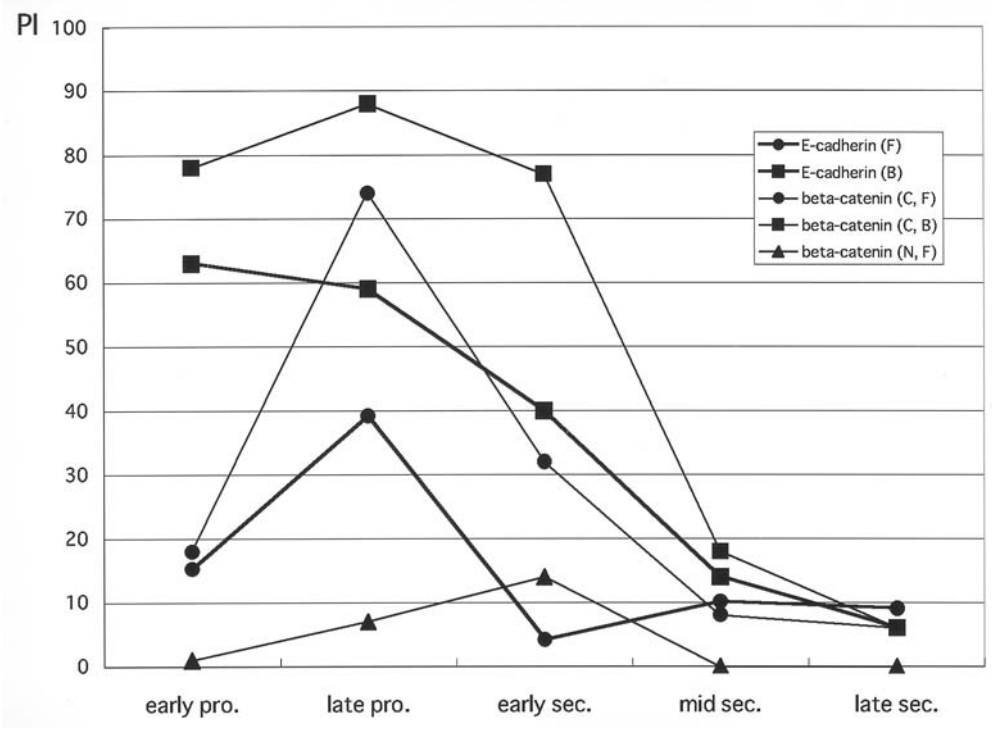

Figure 3. *Graphic demonstration of the positivity index (PI) of E-cadherin and β-catenin in the normal endometrium. Abbreviations: pro.; proliferative phase, sec.; secretory phase. F; functionalis, B; basalis, C; cytoplasm, N; nucleus.*

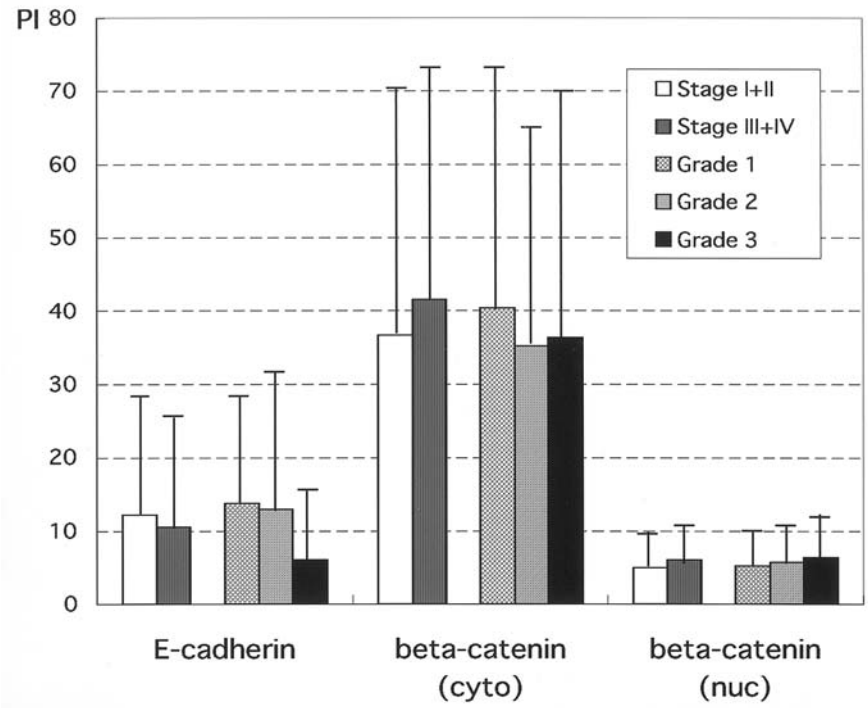

Figure 4. *Positivity index (PI) of each staining. Each number and bar indicates the mean±standard deviation. Abbreviations: cyto; cytoplasm, nuc: nucleus.*

The distribution pattern of cytoplasmic, as well as nuclear, β-catenin-positive cells also differed among cases, being predominant on the luminal, or else on the basal side of the tumors. The nuclear staining of β-catenin was often associated with cytoplasmic β-catenin staining. Tumor cells with squamous differentiation (morules) frequently showed positive staining for β-catenin in the nucleus. The PI of the nuclear β-catenin staining was slightly higher in advanced stage tumors (stage: 5.0, stage III+IV: 6.0), as well as grade 3 tumors (PI: 6.4) than grade 1 (PI: 5.2) or grade 2 (PI: 5.7) tumors, however, the difference among the three histological grades was not significant.

Correlation of the expression between E-cadherin and β-catenin. In normal glandular cells, the E-cadherin-positive cells were frequently associated with cytoplasmic staining for β-catenin, especially in the proliferative phase, including both the functionalis and basalis (Figures 1a and f, b and g, c and h). In the secretory phase, the PI for both stainings was decreased, and a topological dissociation of the stainings was also noted. Nuclear staining for β-catenin was observed in the late proliferative phase and early secretory phase. In glandular cells with positive staining for nuclear β-catenin, the expression of E-cadherin was negative (Figures 1c and h, d and i), showing an inverse correlation between nuclear β-catenin staining and E-cadherin staining.

In endometrial carcinoma, a spatial observation of E-cadherin and nuclear /cytoplasmic catenin using serial sections revealed that the nuclear β-catenin-positive cells were noted in E-cadherin-negative cells (Figures 2b and e, c and f), also indicating an inverse correlation between E-cadherin expression and nuclear β-catenin expression in endometrial carcinoma. The number of cases which showed this inverse correlation was 4 in grade 1 (11%), 3 in grade 2 (13%) and 5 in grade 3 (33%). Such an inverse correlation was focally or regionally observed, and this inverse relationship was often found in cases with relatively elevated PIs for nuclear β-catenin, *i.e.* those with a value of 5 or more. However, in one case of grade 3, the nuclear β-catenin-positive cells were associated with positive E-cadherin staining, showing a positive correlation. In contrast, the topological distribution of cytoplasmic β-catenin in cells which lacked nuclear staining for β-catenin was similar to that of E-cadherin, indicating a positive correlation between E-cadherin and cytoplasmic β-catenin in 12 (34%), 3 (13%) and 2 (23%) cases of grade 1, 2 and 3, respectively.

Discussion

The present study demonstrated that the cytoplasmic expression of E-cadherin in endometrial glandular cells occurred mainly in the proliferative phase, and decreased in the secretory phase. In addition, the expression of E-cadherin was observed both in the functionalis and in the basalis, with a predominance in the basalis. van der Linden *et al.* (25) reported that the expression of E-cadherin in 16 cases of normal endometrium was observed in both the proliferative and secretory phases, however, no detailed information was available as to the topological distribution of this molecule. Tabibzadeh *et al.* (26) reported that immunohistochemical expression of E-cadherin was localized to intercellular borders as well as the luminal and basal regions of the glandular epithelium during the proliferative and secretory phases. However, no quantitative difference of E-cadherin expression between the phases of the menstrual cycle was evident. Therefore, this is the first report to describe the cyclic expression of E-cadherin in normal endometrium.

The expression of cytoplasmic β-catenin in glandular cells was also more clearly observed in the proliferative than secretory phase. This staining pattern was similar to that of E-cadherin, and was consistent with a previous report (27). In addition, the expression of β-catenin was predominantly observed in the basalis rather than the functionalis, also showing a similar expression pattern to that of cytoplasmic E-cadherin. These findings suggest that a considerable number of glandular cells co-express E-cadherin and cytoplasmic β-catenin, and that the co-localization may support the possibility that these molecules form a complex to function as adhesion molecules. Based on these observations, the staining pattern of E-cadherin/cytoplasmic β-catenin was characterized as follows: i) the E-cadherin/cytoplasmic β-catenin-positive cells increased in the proliferative phase, and decreased in the secretory phase of the glandular cells, ii) these positive cells were more frequently observed in the basalis compared to the functionalis of glandular cells throughout the menstrual cycle, and iii) the expression of E-cadherin and cytoplasmic β-catenin in stromal cells was more abundantly observed in the proliferative than secretory phase. This distribution pattern of E-cadherin and β-catenin-positive cells seems to be advantageous in the maintenance of the architecture of the endometrium during the menstrual cycle. In the proliferative phase, the glandular cells must adhere to each other to achieve a stable replication of the glands. On the other hand, decreased expression of both E-cadherin and cytoplasmic β-catenin in the functionalis in the mid- and late secretory phases, suggesting weakened adhesion among glandular cells, was observed. Secretory phase endometria are known to exhibit secretory protrusions that resemble apocrine secretion (28). Thus, the reduced expression of E-cadherin and cytoplasmic β-catenin seems to be reasonable for this type of secretion. This expression pattern of E-cadherin/β-catenin is similar to that of connexins, which are involved

in cell-cell communications (29). The reduced expression of connexins, together with the loosened adhesion caused by reduced E-cadherin/β-catenin, may result in the non-communicating epithelium in the premenstrual phase. In addition, the reduced expression of E-cadherin/β-catenin was also observed in stromal cells. Collectively, these molecular events in the mid-to-late secretory phase may contribute to menstrual breakdown.

The expression of E-cadherin and cytoplasmic β-catenin was also observed in the surface epithelium with augmented expression in the secretory phase. Trophoblastic cells are reported to express E-cadherin, in response to progesterone (30,31). Therefore, elevated expression of E-cadherin/cytoplasmic β-catenin seems to be plausible for the preparation of implantation.

The nuclear expression of β-catenin was noted in the glandular cells of the proliferative and early secretory phase endometria. This result was also consistent with a previous report (27). β-catenin is now known to act as a signal transducer in Wnt/Wingless pathways, and the Wnt/Wingless signal has been reported to induce the cytoplasmic accumulation of β-catenin (9). Wnt family proteins are reportedly present in normal endometrium (32). In addition, a study reported that progestin treatment induced the nuclear translocation of β-catenin in endometrial carcinoma (33). Although the mechanism of the translocation of β-catenin to the nucleus in the normal endometrial cell is unknown, the Wnt/Wingless signal or progestin-related mechanisms might be involved in the change of intracellular distribution of β-catenin. In addition, interestingly, the present study revealed that the nuclear β-catenin-positive cells lacked E-cadherin expression, indicating an inverse correlation between E-cadherin and nuclear β-catenin expression. Although the mechanisms behind the reduced expression of E-cadherin at nuclear β-catenin-positive sites are unknown, we speculate that the translocation of β-catenin to the nucleus results in the loss of a scaffold of E-cadherin on the cell membrane, and subsequently induces the release of E-cadherin from the cell membrane.

The present study showed that the expression of E-cadherin was reduced in endometrial carcinomas compared to the normal proliferative phase endometrial glands. In addition, the PI of E-cadherin tended to be decreased in advanced stage tumors and histologically high-grade tumors. This result was similar to previous reports (18, 34, 35). Holcomb *et al.* (18) reported that E-cadherin-negative tumors were more likely to be poorly-differentiated and have cervical extension, a positive peritoneal cytology and adnexal spread when compared with E-cadherin-positive tumors. Kim *et al.* (17) reported that the aberrant expression of E-cadherin correlated with lymph node metastasis and poor survival. However, we could not detect such correlations with clinicopathological variables in the present study (data not shown). With regard to the non-endometrioid subtypes, the expression of E-cadherin was nearly negative in clear cell carcinomas and serous papillary carcinomas. Although the number of cases examined was limited, this result was in line with a previous report (18). The mechanism of reduced expression of E-cadherin has not been fully elucidated, however, loss of E-cadherin expression is reportedly caused by promoter methylation of the E-cadherin gene (36).

The cytoplasmic expression of β-catenin also tended to be decreased in high-grade tumors, being consistent with a previous report (19). The reduced expression of cytoplasmic β-catenin and E-cadherin in high-grade tumors suggests that the adhesion among tumors cells became less tight in this tumor type, which in general is associated with a poor prognosis. In contrast, the nuclear expression of β-catenin tended to be increased in histologically high-grade tumors. The mechanisms of nuclear accumulation of β-catenin are reported to be responsible for the mutation of β-catenin and related genes. In colorectral cancers, mutation of the adenomatosis polyposis coli (APC) or β-catenin gene results in the stabilization of β-catenin and its significant accumulation in the cell (12). Mutation of the β-catenin gene has also been reported in colon cancer with wild-type APC (13). In endometrial carcinoma, β-catenin mutations have been reported to be present in 13-23% of cases (19-22), but mutation of the APC gene is rare (37). In the present study, interestingly, the nuclear β-catenin-positive carcinoma cells were negative for E-cadherin expression, as observed in the normal endometrial glands. In addition, we previously reported that the nuclear accumulation of β-catenin is often associated with the accumulation of cyclin D1, a potent stimulator of cell cycle progression, that confers active growth potential to the tumor cells (23). Therefore, loss of E-cadherin expression associated with nuclear β-catenin expression, especially in high-grade tumors, may not only provide favorable circumstances for potential metastasis, but also vigorous growth activity, and this molecular pattern may help the tumor cells to gain malignant biological behavior.

In conclusion, the cyclic expression of E-cadherin and β-catenin in the normal endometrium suggests that these two adhesion complexes may act to maintain the architecture as well as to make menstrual breakdown more feasible. In addition, nuclear β-catenin expression associated with loss of E-cadherin expression may be involved in the acquisition of aggressive biological behavior, especially in high-grade endometrial carcinomas.

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