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E-cadherin and CD10 expression in atypical hyperplastic and malignant endometrial lesions

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KEYWORDS

Endometrial carcinoma;
E-cadherin;
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Abstract *Background:* Loss of E-cadherin is a critical step for development and progression of malignant tumors. CD10; a marker of non-neoplastic and neoplastic endometrial stroma, is associated with aggressiveness of many epithelial malignancies.

Aims: To evaluate expression and correlation of E-cadherin and CD10 in endometrial lesions and their possible role in differentiating atypical endometrial hyperplasia from endometrial carcinoma. The association of E-cadherin and CD10 expression with clinico-pathological parameters of endometrial carcinoma was also investigated.

Materials and methods: Fifty four cases including 28 endometrial carcinomas; 19 endometrial hyperplasia and 7 cases of normal endometrial changes were enrolled for this study. The expression of E-cadherin and CD10 was evaluated by immunohistochemistry using the streptavidin–biotin technique.

Results: There was a strong association between malignant change of endometrial glands and membranous-cytoplasmic localization of E-cadherin ($p < 0.001$). Expression of E-cadherin but not CD10 was significantly higher in endometrial carcinomas compared to atypical endometrial hyperplasia ($p < 0.01$). Expression of E-cadherin was not associated with CD10 expression in different endometrial lesions. High grade tumors expressed low levels of both E-cadherin ($p < 0.01$) and CD10 ($p < 0.05$) and serous endometrial carcinoma had low E-cadherin and CD10 expression compared to endometrioid carcinoma ($p < 0.01$ and < 0.05 , respectively). Expression of both molecules showed no association with depth of tumor invasion or FIGO stage. Tumors with lower E-cadherin or CD10 expression had higher rates of vascular tumor emboli ($p < 0.01$ and < 0.07 , respectively). *Conclusions:* Although expression of E-cadherin and CD10 in endometrial lesions was not correlated, reduced expression of both molecules could be critical for progression of endometrial carcinoma.

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Introduction

Endometrial carcinoma is the sixth most common cancer of women worldwide [1]. It is a primary malignant tumor arising in the endometrium and has the potential to invade the

myometrium and to spread to distant sites [2]. The 5-year survival rate is 96% if the cancer is diagnosed at a local stage, but markedly decreases to 17% if diagnosed at an advanced stage [3]. As invasion and metastasis at the time of diagnosis significantly worsen the prognosis, awareness of the biomarkers that may be clinically relevant to malignant change of the endometrium is appreciated.

Cell-cell adhesion is essential to maintain the normal morphological and functional properties of different epithelial, endothelial and neural tissues. E-cadherin is a trans-membrane epithelial cell adhesion protein with a cytoplasmic domain connected to the actin cytoskeleton through α -, β - and γ -catenins. E-cadherin/catenin complexes are important pre-requisites for normal intact epithelial lining [4,5]. Several *in vitro* studies correlated low expression of E cadherin with progression of malignant tumors [6,7] and disturbed expression of E-cadherin and β -catenin had been implicated in the invasive and metastatic potential of different epithelial tumors including breast [8,9], prostatic [10], gastric [11] and thyroid carcinomas [12]. E-cadherin down-regulation and re-localization were documented in oral squamous cell carcinoma and its low expression was correlated with poorly differentiated tumors, aggressive behavior and low survival rate [13]. Additionally; disturbed E-cadherin/catenin adhesion complex had been described in several gynecologic carcinomas, including cervical [14,15], endometrial [16,17] and ovarian carcinomas [18]. In endometrial cancer, the role of E-cadherin molecule has not been fully understood. It has been recently reported that methylation of several gene promoters including *E-cadherin*, *ER α* and *PR* is involved in early progression of endometrial carcinoma. Never the less, the authors indicated a clear tendency of increasing methylation of promoters of these genes from benign to peri-tumoral to malignant endometrial lesions [19].

CD10 is a 94 kDa zinc-dependent cell membrane metalloproteinase; also called the common acute lymphoblastic leukemia antigen. It is involved in several biological activities through regulation of signal transduction of bioactive neuropeptides and vasoactive peptides [20,21]. CD10 is considered as a marker for germinal center cells of the normal lymphoid tissue and their derivative follicular lymphomas [22]. It is widely distributed in the kidney, liver, small intestine, placenta, choroid plexus, brain, gonads, adrenal cortex and leucocytes [23]. It was reported that CD10 expression in cancer stromal cells is associated with neoplastic transformation, tumor progression and biological tumor aggressiveness [24–26]. In gynecologic pathology, CD10 is a sensitive marker to identify normal and neoplastic endometrial stromal cells [27]. It can be used perfectly to differentiate endometrial stromal sarcoma from uterine cellular leiomyoma and leiomyosarcoma [28].

Evaluation of the relationship between stromal expression of CD10 and epithelial expression of E-cadherin in tumor progression is generally deficient and the association between these two molecules in endometrial carcinoma has not been previously clarified. The aims of this study are to evaluate expression of E-cadherin and CD10 in atypical endometrial hyperplasia and endometrial carcinoma by immunohistochemistry and to test the association between expression of each of E-cadherin and CD10 with other clinical and pathological parameters of endometrial carcinoma.

Material and methods

Tissue samples

Formalin-fixed paraffin-embedded endometrial tissue blocks from 54 patients diagnosed within the Pathology Department, Sohag University Hospital from January 2011 to December 2012 were obtained for this study. These included all cases diagnosed as endometrial carcinoma ($n = 28$) or atypical endometrial hyperplasia ($n = 14$). Representative cases of non atypical endometrial hyperplasia ($n = 5$), proliferative endometrium ($n = 4$) and endometrium with secretory changes ($n = 3$) were also included in this study. Approval to perform this work was obtained from the Institutional Research Ethics Committee. The clinical data of the investigated cases were obtained from patients' clinical files.

Immunohistochemistry

The antibodies and chromogen detection system used in this work were purchased from Thermo Scientific. Sections of 4 μ m thick of the selected paraffin blocks were de-paraffinized in xylene for 20 min, rehydrated in graded alcohol and incubated in 0.5% hydrogen peroxide/methanol for 10 min to block endogenous peroxidase activity. The antigens were retrieved by boiling for 10 min in 10 mM citrate buffer, pH 6.0, using a microwave, followed by cooling to room temperature for 20 min. After washing in phosphate buffered saline (PBS), different sections were incubated with ready to use mouse monoclonal anti-E-cadherin (clone MS-1479R7, Thermo Scientific) and mouse monoclonal anti-CD10 (clone 56C6, Thermo scientific) antibodies for overnight at 4 °C. Next day, the sections were washed in PBS before incubation with goat anti-mouse biotinylated secondary antibody for 10 min at room temperature. The sections were then washed in PBS, incubated with streptavidin for 10 min at room temperature, washed and exposed to 3,3'-diaminobenzidine tetrahydrochloride solution (DAB) to yield an insoluble brown deposit. Finally, the sections were counterstained with hematoxylin, washed in running water, dehydrated in graded alcohol and mounted as usual. Sections of skin were used as a positive control for E-cadherin expression and sections of endometrial stromal tumor were used as a positive control for CD10 expression. Replacement of the primary antibodies with PBS worked as negative controls for the immunohistochemistry process.

Scoring of immunoreactions and statistical analyses

The immunohistochemistry results were analyzed independently of the clinico-pathological data. The expression level of E-cadherin and CD10 was measured by the histoscore that combines intensity of the immunoreactions with percentage of positive cells. Cells present in four 400 $\times$ high power fields were counted and scored in each case. The intensities of immunoreactions were stated as negative, weakly positive, moderately positive, or strongly positive. These four categories were weighed as 0, 1, 3, and 10, respectively. The final histoscore was calculated by multiplying the intensity of immunoreaction with percentage of positive cells [29]. Final score ranged

between 0 when all scored cells were negative to 1000 when all scored cells were strongly positive.

The commercially available statistical software (IBM-SPSS version 19.0 for Windows; IBM Inc.) was used for data analysis. The frequency of a categorical observation among atypical endometrial hyperplasia and endometrial carcinoma was compared by Chi-Square Test (χ^2). Mann-Whitney *U* Test and Kruskal-Wallis Test were used to compare the mean rank of E-cadherin and CD10 histoscores among different study groups. Bonferroni adjustment for pairwise analysis was applied when more than two categories were compared. The cut-off for significance of all used statistical analyses was rated as $p < 0.05$.

Results

Patients' clinical and pathological characteristics

This study included 54 patients aged between 19 and 71 years with a mean $\pm$ SD of 52.5 ± 11.2 years. Thirty three (61.1%) of the patients were postmenopausal, while perimenopausal and premenopausal status were recorded in 14 (25.9%) and 7 (13.0%) patients, respectively. All patients were presented with abnormal uterine bleeding and clinical examination revealed a palpable mass at uterine cervix in one patient. The tissue specimens were radical hysterectomy and bilateral salpingo-oophorectomy in 35 cases, dilatation and curettage in 17 cases, vaginal hysterectomy in one case and endometrial polypectomy in one case. Malignant endometrial lesions present in 28 cases while endometrial hyperplastic lesions present in 19 cases; of which 14 cases were atypical and 5 were non-atypical hyperplasia.

Among the 28 cases of endometrial carcinomas, 17 had a localized uterine mass and 11 had a diffusely thickened endometrium and the tumor size ranged between 1 and 6 cm with a mean $\pm$ SD of 2.4 ± 1.4 cm. Histologically, 23 of the malignant lesions were endometrioid adenocarcinomas versus 5 serous endometrial adenocarcinomas. Tumors were graded as I, II and III in 9, 11 and 8 of the cases, respectively. Two tumors were limited to the endometrium (FIGO IA) and the tumor extended to inner half of myometrium (FIGO IB) in 7 cases, to outer half of myometrium (FIGO IC) in 7 cases, to uterine cervix (FIGO IIB) in 3 cases and to serosal covering of the uterus (FIGO IIIA) in 6 cases. Vascular tumor emboli were histologically evident in 10 out of the 25 radically excised malignant endometrial lesions.

Profile of E-cadherin and CD10 expression

Expression of E-cadherin and CD10 was demonstrated in all cases of proliferative, secretory and hyperplastic endometrial changes. Two cases of the 28 investigated endometrial carcinomas were E-cadherin negative and different two cases were CD10-negative. E-cadherin was expressed by endometrial glands while CD10 was expressed by endometrial stroma. The encountered myometrium was always negative for both E-cadherin and CD10 immunostaining. The expression of E-cadherin was predominantly membranous in non neoplastic endometrial tissue (Fig. 1A-C) while neoplastic lesions showed predominantly mixed membranous and cytoplasmic

immunoreactions (Fig. 1D and E). There was a strong association between malignant change of endometrial glands and membrano-cytoplasmic immunoreaction to anti-E-cadherin antibody [χ^2 (1) = 11.5, $p = 0.001$]. Membrano-cytoplasmic immune staining was demonstrated in 20 out of the 26 positive endometrial carcinomas compared to three of the 14 atypical endometrial hyperplasia. On the other hand, CD10 immunoreaction was membranous or membrano-cytoplasmic with no recorded association with a specific pathological endometrial change (Fig. 1F-I). In some occasions, it was difficult to identify whether CD10 immunoreaction was membranous or membrano-cytoplasmic especially in cases with high histoscores. It was noted that CD10 expression made a zone of stromal expression deep into tumors limited to endometrium and to villoglandular endometrioid adenocarcinomas. Additionally, CD10 expression decreased remarkably as the stroma became desmoplastic. The two cases with zero histoscore of CD10 had a predominantly desmoplastic stroma.

Expression of E cadherin and CD10 was detected in all cases of atypical endometrial hyperplasia and expression of both was retained in 92.6% of endometrial adenocarcinoma cases. The histoscore of both E-cadherin and CD10 expression ranged from 0 to 1000 and the median value of E-cadherin histoscore was 378 and that of CD10 histoscore was 750.5. The 1st and 3rd quartiles of E-cadherin histoscore were 172 and 668.8, respectively and those of CD10 histoscore were 468.8 and 921.3, respectively. Statistical analysis showed no association between expression of E-cadherin and CD10 in hyperplastic or neoplastic endometrial lesions.

The expression of E-cadherin was significantly higher in endometrial adenocarcinomas compared to atypical endometrial hyperplasia (Table 1). The mean rank of E-cadherin histoscore in adenocarcinomas was significantly higher than the corresponding mean rank of atypical endometrial hyperplasia (Mann-Whitney *U*, $p = 0.009$). CD10 expression showed no association with either of these two lesions (Mann-Whitney *U*, $p = 0.153$).

The association of E-cadherin and CD10 expression with different pathological parameters of endometrial adenocarcinoma was tested (Table 1). Neither of these two molecules showed significant relationships to tumor gross type or tumor size. The expression of both E-cadherin and CD10 molecules was inversely associated with tumor grade. High grade tumors tended to express significantly low levels of both E-cadherin (Kruskal-Wallis Test, $p = 0.007$) and CD10 (Kruskal-Wallis Test, $p = 0.015$). Using Bonferroni adjustment for pairwise comparisons among different tumor grades, both grade I and grade II tumors showed significant higher expression of E-cadherin when compared to grade III tumors ($p = 0.045$ and $p = 0.005$, respectively) while no significant difference of E-cadherin expression among grade I and grade II tumors was observed. Similarly CD10 histoscores were significantly higher in grade I and grade III endometrial carcinomas compared to grade II lesions ($p = 0.017$ and $p = 0.016$, respectively) and no recorded significant difference of CD10 histoscores between grade I and grade II tumors was observed. Compared to endometrioid adenocarcinoma; serous endometrial adenocarcinoma had significantly low histoscores of E-cadherin (Mann-Whitney *U*, $p = 0.002$) as well as significantly low histoscores of CD10 (Mann-Whitney *U*, $p = 0.048$).

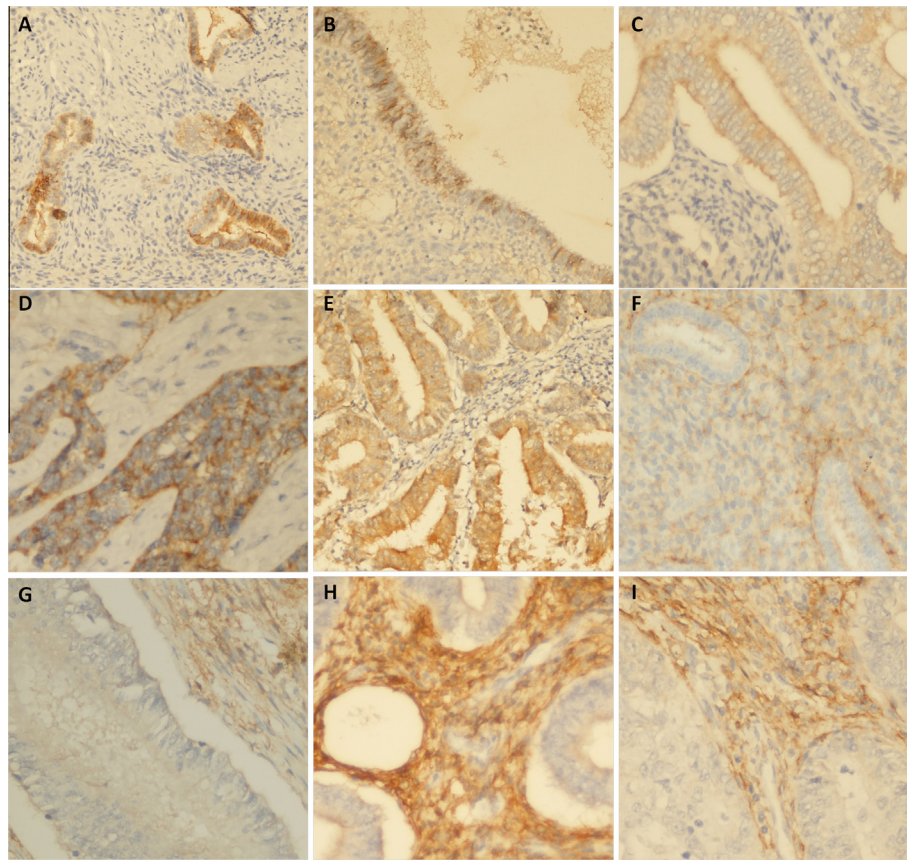


Figure 1 Membranous expression of E cadherin in proliferative (A), non-atypical (B) and atypical (C) endometrial hyperplasia compared to membranous (D) and membrano-cytoplasmic (E) expression in endometrial adenocarcinoma. Stromal expression of CD10 in proliferative (F), non-atypical (G) and atypical (H) endometrial hyperplasia and endometrial carcinoma (I). Original magnifications are 200× in B and 400× in others.

The correlation of E-cadherin and CD10 expression with invasive potential of endometrial adenocarcinoma was studied. Although there was a steady decrease of E-cadherin histoscores as the tumor became more invasive, this relationship was not statistically significant (Kruskal–Wallis Test, $p = 0.673$). Similarly; endometrial carcinomas with higher FIGO stage expressed lower levels of E-cadherin; but the relationship did not reach the significance level (Kruskal–Wallis Test, $p = 0.521$). CD10 expression showed no association with either depth of tumor invasion or FIGO stage of uterine adenocarcinoma. More importantly, statistical analyses showed that tumors with lower histoscores of E-cadherin had a significantly higher potential to access vascular spaces and form tumor emboli. The mean rank of E-cadherin histoscores for tumor with positive vascular emboli was 7.85 compared to 16.43 for tumors in which vascular tumor emboli were undetectable (Mann–Whitney U , $p = 0.004$). For CD10 molecule, decreased expression was also potentially associated with a higher risk for the presence of vascular tumor emboli (Mann–Whitney U , $p = 0.067$).

Discussion

Invasion and metastasis are general hallmarks of tumor progression. Atypical endometrial hyperplasia and endometrial carcinoma limited within the uterus can be cured surgically while invasive tumors extended beyond uterus or accessed vascular

channels are no longer localized diseases and systemic postoperative adjuvant therapy is usually required. The histopathological differentiation between atypical endometrial hyperplasia and well-differentiated endometrioid carcinoma is very tricky particularly in a D&C biopsy [30]; and a differentiating marker is still sought. Reduced cell–cell adhesiveness allows cancer cells to disobey the normal social orders and allows invasive clones of tumor cells to emerge. Additionally, the tumor stromal cells and molecules of extracellular matrix play a vital role in tumor spread [31,32]. In this study; E-cadherin; a well known epithelial adhesion molecule and CD10; an endometrial stromal marker, expression in cases of endometrial hyperplasia and endometrial carcinoma were evaluated by immunohistochemistry.

Glandular expression of E-cadherin was demonstrated in all benign and hyperplastic endometrial tissues and in the vast majority of malignant endometrial lesions. The only two cases with negative E-cadherin expression were serous adenocarcinomas. Previous reports showed a homogenous glandular expression of E-cadherin in the most normal, non-atypical and atypical hyperplastic endometrial tissues and only heterogenous expression in 18 out of 22 investigated endometrial adenocarcinomas [33]. In the series investigated by Shih and his colleagues, both serous and clear cell endometrial adenocarcinomas were E-cadherin negative [17]. These results imply that reduced E-cadherin expression is important for the progression of endometrial carcinoma. Malignant change of endometrial glands was associ-

Table 1 Correlation of E-cadherin and CD10 histoscores with different pathological parameters of endometrial carcinoma measured by Mann–Whitney *U* Test^a or Kruskal–Wallis Test^b. Statistically significant relationships are highlighted.

Feature	Number	E-cadherin histoscore				CD10 histoscore			
		Median	1st quartile	3rd quartile	<i>p</i> Value	Median	1st quartile	3rd quartile	<i>p</i> Value
Pathological lesion									
-Atypical endometrial hyperplasia	14	163.5	62.3	392.0	0.009 ^a	803.5	590.0	921.5	0.153 ^a
-Endometrial carcinoma	28	423.5	229.5	715.5		633.5	388.3	882.3	
Tumor gross pattern									
-Diffuse growth	11	392	215.0	775.0	0.925 ^a	597	426.0	908.3	0.525 ^a
-Localized mass	17	434	242.0	693.0		676	160.0	874.5	
Tumor size									
-≤2 cm	11	434	215.0	775.0	0.778 ^a	543	401.0	908.0	0.981 ^a
->2 cm	17	413	242.0	693.0		705	190.5	874.5	
Tumor grade									
-I	9	631	247.0	823.5		670	504.5	922.5	
-II	11	690	393.0	733.0	0.007 ^b	812	426.0	908.0	0.015 ^b
-III	8	211.5	43.0	360.8		381	3.3	517.5	
Tumor type									
-Endometrioid	23	631	365.0	733.0	0.002 ^a	705	426.0	908.0	0.048 ^a
-Serous	5	73	16.5	211.5		361	6.5	609.5	
Tumor stage									
-Limited to uterine corpus (FIGO I)	16	646.5	371.8	730.3	0.107 ^a	721.5	452.3	922.8	0.113 ^a
-Extends beyond uterine corpus (FIGO II and III)	9	267	124.0	629.5		478	6.5	835.5	
Tumor vascular emboli									
-No	15	689	413.0	818.0	0.004 ^a	812	531.0	923.0	0.067 ^a
-Yes	10	273	169.5	434.8		459.5	9.8	776.0	

^a Mann–Whitney *U* Test.^b Kruskal–Wallis Test, highlights refer to statistically significant relationships.

ated with change of pure membranous expression to membrano-cytoplasmic expression of E-cadherin ($p = 0.001$); a finding that could help in differentiation of atypical endometrial hyperplastic lesions from early carcinomatous change. Such a re-distribution of E-cadherin molecule could be associated with impairment of its intercellular adhesion function. Additionally, reduced expression of this adhesion molecule was statistically associated with a higher tumor grade ($p < 0.01$), with aggressive histological subtype (serous versus endometrioid carcinoma, $p < 0.01$) and with increased possibility or lymphovascular invasion ($p < 0.01$); all of which are indicators of aggressive tumor cell behavior. In the same context, E-cadherin histoscore showed a steady decline as the tumor had a higher FIGO stage (Table 1). This is concordant to previous reports about tumor suppressor effects of E-cadherin in several epithelial tumors [34] including endometrial carcinoma [33,35]. The only finding that could argue against the potential protective effect of E-cadherin against progression of endometrial cancer is its higher expression in endometrial carcinoma compared to atypical endometrial hyperplasia ($p < 0.01$). This could be due to considering both membranous and cytoplasmic immunostaining in the histoscore system. In addition, liberation of E-cadherin molecule from cell membrane to the cytoplasm may be associated with increased number of epitopes detected by the monoclonal antibody; resulting in stronger immunoreaction and hence higher histoscores.

Expression of CD10 protein was detected as a membrano-cytoplasmic molecule in the stromal cells of all non-malignant endometrial tissues and in 26 of the 28 investigated endometrial carcinomas (Fig. 1F–I). The endometrial glands and the myometrium were always CD10-negative. In a study which included several normal and tumorous endometrial and myometrial tissues; CD10 showed moderate to strong diffuse cytoplasmic immunoreaction within endometrial stromal cells with no recorded positivity in endometrial glands, in myometrial tissue or their derivative tumors. The final conclusion was to consider CD10 as a sensitive marker to identify endometrial stromal cells and to differentiate endometrial stromal nodule and low grade endometrial stromal sarcoma from cellular leiomyoma and low grade leiomyosarcoma [27]. There was no significant difference of CD10 expression among atypical hyperplastic and neoplastic endometrial lesions ($p = 0.153$). In superficial endometrial tumors, CD10 tended to be strongly expressed at the base of the tumor forming a zone between tumor tissue and myometrium. CD10 expression decreased significantly in high grade tumors ($p < 0.05$) and low expression of CD10 was associated with tumor invasion to vascular channels ($p = 0.67$). The two cases with negative CD10 expression were high grade endometrioid adenocarcinoma and serous carcinoma; both of which were of FIGO stage IIIA. All these findings imply that CD10 is an endometrial stromal molecule that could reduce progression of glandular endometrial

carcinoma. Suzuki and his colleagues reported a strong stromal expression of CD10 in normal endometrium and such expression was down-regulated after carcinomatous change and markedly reduced in high grade endometrial carcinoma [36]. Additionally, it has been reported that CD10 expression was demonstrated in ovarian surface epithelial tumors and the immunoreaction decreased in advanced histological grades [37]. The exact role of CD10 in cancer progression is a matter of controversy. Although some reports considered CD10 as a tumor suppressor molecule in certain tumors including ovarian carcinoma [37] and renal cell carcinoma [38], CD10 seems to have a tumor progression effect in others including large B cell lymphoma [39] and urothelial and squamous cell carcinoma of the urinary bladder [40,41]. Additionally, the expression of stromal CD10 changed from negative in normal skin to moderate and strong positive in dysplasia and squamous cell carcinoma of the skin; respectively [42]. Stromal CD10 expression was positively correlated with a large tumor size, high tumor grade, presence of lymph node metastasis and low overall survival of invasive duct carcinoma of the breast [43,44].

According to this study, there was no association between expression of E-cadherin and CD10 in endometrial carcinoma tissues. This finding cannot exclude potential augmenting functions between the two molecules to reduce the progression of endometrial carcinoma. Kim et al. demonstrated a significant association between CD10 expression and increased cytoplasmic rather than membranous expression of β -catenin in breast cancer but showed no association between CD10 and E-cadherin expression [44]. It has been documented that CD10 is structurally similar to matrix metalloproteinases and stromelysin [45]. Additionally, CD10 can lead to up-regulation of gene expression of matrix metalloproteinase [46] which has functional interactions between matrix metalloproteinases and the E-cadherin/catenin complex [32]. Further studying the expression and functional relationships between E-cadherin, β -catenin and CD10 molecules in addition to extracellular matrix metalloproteinases in endometrial carcinoma is required to address this potential augmenting effect.

Conflict of interest

None declared.

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