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Original Research

PTEN and CD146 expression in endometrioid adenocarcinoma

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Summary

Objective: Endometrioid adenocarcinoma is the most common pathological type of endometrial carcinoma. This study aimed to examine the expression of PTEN and CD146 in endometrioid adenocarcinoma, and to investigate their relationship with clinical characteristics of endometrioid adenocarcinoma. *Materials and Methods:* The expression of PTEN and CD146 in 126 specimens of endometrioid adenocarcinoma was detected by immunohistochemical technique, and the correlation of their expression with clinical parameters of the patients was analyzed. *Results:* PTEN expression in endometrioid adenocarcinoma group was lower than that in endometrial hyperplasia group and endometrial polyp group, while CD146 expression in endometrioid adenocarcinoma group was higher than that in endometrial hyperplasia group and endometrial polyp group ($p < 0.05$). High expression of CD146 was associated with his tological grade and depth of invasion of endometrioid adenocarcinoma, but there was no correlation between PTEN expression and clinical parameters. *Conclusions:* CD146 and PTEN may be promising biomarkers and targets for the diagnosis and treatment of endometrioid adenocarcinoma.

Key words: Endometrioid adenocarcinoma; PTEN; CD146; Pathology.

Introduction

Endometrioid adenocarcinoma is the most common pathological type of endometrial carcinoma, accounting for more than 80% of various subtypes of endometrial carcinoma [1]. In recent years, the incidence of endometrioid adenocarcinoma has gradually increased and shown a trend of increase in younger women [2]. Currently, the pathogenesis of endometrioid adenocarcinoma remains unclear and controversial [3-5].

Despite the application of hormone therapy, patients with metastatic and recurrent endometrioid carcinoma have worse prognosis, and the side effects of current chemotherapy are the main cause of treatment failure [6]. Therefore, it is important to develop effective diagnostic and prognostic markers of endometrioid adenocarcinoma for early diagnosis and treatment.

CD146, also called MCAM or MUC18, is a cell adhesion molecule and a member of immune superfamily. CD146 plays an important role in the progression, metastasis, and angiogenesis of a variety of malignant tumor tissues [7-10]. PTEN (phosphatase and tensin homolog deleted on chromosome 10) is a well-known tumor suppressor with bispecific phosphatase activity, and the absence of its function is closely related to tumorigenesis of various types of cancers, including endometrial cancer [11]. In this study we aimed to examine the expression of PTEN and CD146 in endometrioid adenocarcinoma and investigate their relationship with clinical characteristics of endometrioid adenocarcinoma.

Materials and Methods

126 specimens of patients with endometrioid adenocarcinoma were collected from the First Affiliated Hospital of Yangtze University from January 2008 to April 2014. The patients received no chemotherapy or radiotherapy before operation. The patients aged 32-63 years, with a mean age of 46.6 ± 7.4 years. Forty-eight atypical endometrial hyperplasia specimens, 40 endometrial polyps, and 30 normal endometrial hyperplasia specimens were collected as control, and the patients in control group had no tumor, acute infection or other diseases. All specimens were examined and diagnosed by experienced pathologists. This study was approved by the ethics committee of Medical School Yangtze University, and all patients provided written informed consent.

Immunohistochemical staining was performed as described previously [12]. Briefly, tissue samples were fixed with 4% paraformaldehyde, paraffin embedded and then continuously sliced in 4 μm sections. The sections were microwaved for antigen repair. Immunohistochemistry S-P kit was used for immunohistochemistry with PTEN monoclonal antibody (working concentration 1 : 10) or CD146 monoclonal antibody (working concentration 1 : 100). After DAB color development, the sections were sealed and observed under optical microscope.

PTEN positive staining presented as brown particles located in the nucleus or cytoplasm. CD146 positive staining presented as brown granules mainly located in tumor cells, stromal vascular endothelial cells, and the membrane and/or cytoplasm of fibrolasts. Five high power fields were randomly selected from each section and staining was scored

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Table 1. — *Immunohistochemical staining of PTEN in endometrial lesions.*

Endometrial lesions	cases	PETN		χ^2	*P*
		Positive, n (%)	Negative, n (%)		
Endometrioid adenocarcinoma	126	36 (28.6)	90 (71.4)		
Endometrial atypical hyperplasia	40	15 (37.5)	25 (62.5)	0.120	0.729
Endometrial polyps	40	36 (90.00)	4 (10.00)	46.650	0.000
Endometrial proliferative changes	30	100 (100.00)	0 (0.00)	118.200	0.000

based on the percentage of positive cells: 0 point if the percentage was 0, 1 point if the percentage was $\leq$ 10%, 2 points for the percentage of 11%-50%, and 3 points for the percentage of 51%-75%. Final staining was judged as negative for score of 0-1 points, and positive for score of 2-3 points.

All data were processed with SPSS 17.0 software, and chisquare test was used for the comparison between groups. The correlation of protein staining and clinicopathological parameters was analyzed by Spearman correlation analysis. $p < 0.05$ indicated that the difference was statistically significant.

Results

Pathologically diagnosed tissue specimens of endometrioid adenocarcinoma, atypical hyperplasia, endometrial polyps, and endometrial hyperplasia were analyzed by immunohistochemical technique, and PTEN staining in each group is shown in Figure 1A. PTEN expression in endometrioid adenocarcinoma group was significantly lower than that in endometrial hyperplasia group and endometrial polyp group ($p < 0.001$), but there was no significant difference in PTEN expression between endometrioid adenocarcinoma group and atypical hyperplasia group ($p > 0.05$, Table 1).

As shown in Table 2, PTEN expression was not associated with histological grade, depth of tumor invasion, age, FIGO Stage, and lymph node metastasis of endometrioid adenocarcinoma ($p > 0.05$).

CD146 staining in tissue specimens of endometrioid adenocarcinoma, atypical hyperplasia, endometrial polyps, and endometrial hyperplasia is shown in Figure 1B. CD146 expression in endometrioid adenocarcinoma group was significantly higher than in endometrial hyperplasia group and endometrial polyp group ($p < 0.05$, but there was no significant difference in CD146 expression between endometrioid adenocarcinoma group and atypical hyperplasia group ($p > 0.05$, Table 3).

As shown in Table 4, CD146 expression was significantly correlated with histological grading, depth of tumor invasion and lymph node metastasis of endometrioid adenocarcinoma ($p < 0.05$), but was not associated with the age of patients and the stage of FIGO ($p > 0.05$).

Table 2. — *Relationship between PTEN and clinicopathological parameters of endometrioid adenocarcinoma.*

variable	cases	PTEN		χ^2	*P*
		Positive, n	Negative, n		
Age (years)				0.029	0.864
≤ 56	72	21	51		
> 56	54	15	39		
Histological grade				5.591	0.052
G1	30	6	24		
G2	42	18	24		
G3	54	12	42		
FIGO staging				0.92	0.338
I	96	30	66		
II-IV	30	6	24		
depth of tumor invasion (cm)				1.401	0.237
≤ 0.5	102	32	70		
> 0.5	24	4	20		
Lymph node metastasis				3.860	0.053
No	102	30	72		
Yes	24	6	18		

Table 3. — *mmunohistochemical staining of CD146 in endometrial lesions.*

Endometrial lesions	cases	CD146		χ^2	*P*
		Positive, n (%)	Negative, n (%)		
Endometrioid adenocarcinoma	126	72 (57.14)	54 (42.86)		
Endometrial atypical hyperplasia	40	24 (60.00)	16 (40.00)	0.020	0.887
Endometrial polyps	40	12 (30.00)	28 (70.00)	8.949	0.003
Endometrial proliferative changes	30	6 (20.00)	24 (80.00)	13.37	0.000

Table 4. — *Relationship between CD146 and clinicopathological parameters of endometrioid adenocarcinoma.*

variable	cases	CD146		χ^2	*P*
		Positive, n	Negative, n		
Age (years)				0.097	0.755
≤ 56	72	42	30		
> 56	54	30	24		
Histological grade				10.688	0.004
G1	30	10	20		
G2	42	24	18		
G3	54	38	16		
FIGO staging				0.131	0.717
I	96	54	42		
II-IV	30	18	12		
depth of tumor invasion (cm)				22.059	0.000
≤ 0.5	102	48	54		
> 0.5	24	24	0		
Lymph node metastasis				3.860	0.049
no	102	54	48		
yes	24	18	6		

Discussion

Endometrioid adenocarcinoma is the most common pathological type of endometrial carcinoma, accounting for more than 80% of various subtypes. Endometrioid adenocarcinoma patients mainly receive surgically-based comprehensive treatments including total hysterectomy and bilateral annex excision. Although these treatments improve patient survival, young patients often lose fertility and ovarian endocrine function, leading to systemic metabolic disorders and related complications, which seriously affect the life quality of patients. Therefore, it is urgent to better understand the pathogenesis of endometrioid adenocarcinoma and identify novel therapeutic targets.

PTEN is a tumor suppressor which inhibits cancer cell growth, proliferation, and invasion, while it promotes cancer cell apoptosis. PTEN loss of function is closely related to the development of tumors. PTEN mutations have been detected in endometrioid adenocarcinoma, as well as endometrial cancer precancerous lesions and the early stage of endometrioid adenocarcinoma, indicating that PTEN plays an important role to prevent the initiation of endometrioid adenocarcinoma [11].

In this study, we found that PTEN expression in endometrioid adenocarcinoma specimens was significantly lower than that in endometrial polyps and hyperplastic endometrial specimens, but was not different from that in atypical hyperplasia specimens. These data support the role of PTEN in the prevention of the initiation of endometrioid adenocarcinoma. Furthermore, we found that PTEN expression was not associated with histological grade, depth of invasion, FIGO Stage, and lymph node metastasis of endometrioid adenocarcinoma. These results suggest that PTEN may play an important role in the early stage of endometrial carcinogenesis and may serve as a potential molecular marker for the carcinogenesis of endometrium. However, PTEN expression is not associated with clinical parameters, and it is not suited to be used as a prognostic marker of endometrioid adenocarcinoma.

CD146 is a cell adhesion molecule mainly expressed on epithelial cell surface. CD146 plays an important role in tumorigenesis and development, and has been recognized as a biomarker of various malignant tumor metastasis [13, 14]. In addition, CD146 antibody could inhibit tumor, indicating that CD146 is a target for cancer therapy [15, 16]. In this study, immunohistochemical staining showed that CD146 expression in endometrioid adenocarcinoma specimens was significantly higher than that in endometrial polyp and hy-

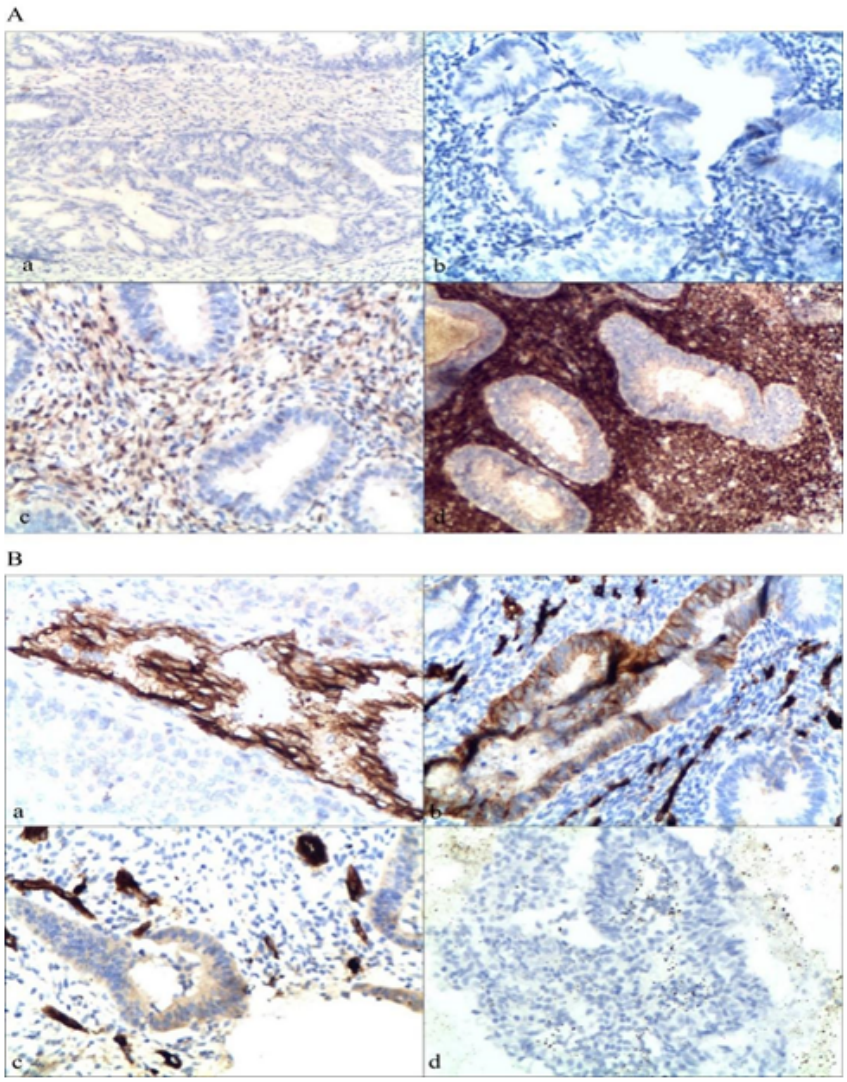

Figure 1. — PTEN and CD146 expression in different pathological types of endometrial tissues. A: Immunohistochemical analysis of PTEN expression in endometrioid adenocarcinoma (a), atypical hyperplasia of endometrium (b), endometrial polyps (c), and endometrial hyperplasia (d). B: Immunohistochemical analysis of CD146 expression in endometrioid adenocarcinoma (a), atypical hyperplasia of endometrium (b), endometrial polyps (c), and endometrial hyperplasia (d). Original magnification $\times 100$.

perplastic endometrium specimens. Notably, CD146 expression in endometrioid adenocarcinoma was associated with histological grade, depth of tumor invasion, lymphnode metastasis, but not associated with the age and FIGO Stage. These data suggest that CD146 is implicated in both the imitation and the development of endometrioid adenocarcinoma. CD146 could be not only a new biomarker but also a prognostic indicator of endometrioid adenocarcinoma.

The present study has several limitations. First, the sample size is not very large. Second, this is a description study and we could not explore the mechanism by which loss of PTEN and CD146 overexpression contribute to endometrioid adenocarcinoma. Third, we did not examine the correlation of aberrant expression of CD146 and PTEN. Whether the loss of PTEN expression causes abnormal high expression of CD146 remains to be investigated.

In summary, in this study we show that low expression of PTEN and high expression of CD146 are crucially implicated in the occurrence and development of endometrioid adenocarcinoma. CD146 and PTEN may be promising biomarkers and targets for the diagnosis and treatment of endometrioid adenocarcinoma.

Author contributions

Q. Huang, Y. He, and X. Cao collected the samples and performed the analysis, C. Yidesigned the study.

Ethics approval and consent to participate

This study was approved by the ethics committee of Medical School Yangtze University, and all patients pro-

vided written informed consent.

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Conflict of interest

All authors declare no conflict of interest.

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