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Original Article

Clinical significance of BCL11A expression in ER-negative and PR-negative endometrial carcinoma

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Abstract: Objective: To study the mechanism and clinical significance of B-cell lymphoma/leukemia 11A (BCL11A) gene in the development of endometrial carcinoma (EC). Methods: 100 EC, 20 normal endometrium and 20 atypical hyperplasia endometrium specimens were collected from West China Second University Hospital from January 2005 to January 2015. The expression of BCL11A was detected by immunohistochemistry and its relationships with clinicopathological features and survival were analyzed. Results: The expression of BCL11A in ER-/PR-EC was higher than that in normal endometrium, atypical hyperplasia endometrium, and ER+/PR+EC ($P < 0.001$). The expression of BCL11A in EC was associated with age, menopause, EC classification, para-aortic lymph node metastasis, tumor differentiation, histological type, ER/PR expression and p53 expression ($P < 0.05$). The expression of BCL11A in the deceased group was significantly higher than that in the survival group ($P = 0.011$). Survival analysis indicated that the high expression of BCL11A was associated with low survival rate ($P < 0.001$). Conclusions: BCL11A may play an important role in the development of ER-/PR-EC. It may serve as a potential target for therapy and a predict factor for prognosis. It can also provide molecular basis for new EC classification.

Keywords: Endometrial carcinoma (EC), BCL11A, estrogen receptor (ER), progesterone receptor (PR), immunohistochemistry (IHC), survival analysis

Introduction

Endometrial carcinoma (EC) is one of three major malignancies in the female reproductive system. It is the most common gynecological cancer in developed countries and developed cities in China [1]. EC is classified into two distinct types, type I and type II [2]. Type I EC is estrogen-dependent, comprising about 80-85% of all ECs. Histologically, it is endometrioid adenocarcinoma. The positive rates of estrogen receptor (ER) and progesterone receptor (PR) are high. The prognosis is normally good. Type II EC is non-estrogen-dependent, with ER/PR mostly negative. Two major histological types are serous adenocarcinoma and clear cell carcinoma. The prognosis of type II EC is often poor. However, the traditional classification developed more than 30 years ago, has been shown to have limitations today. Hormone replacement therapy and the increased overweight and obese population may have altered the characteristics of EC. It has been found clinically that there are overlaps between the two types and heterogeneities within each type.

The BCL gene family plays an important role in anti-apoptosis and cell proliferation. B-cell lymphoma/leukemia 11A (BCL11A) gene is located on human chromosome 2pl6.1, which is about 102 kb in length. It was first found in chronic lymphocytic leukemia and fetal brain tissue with t (2; 14) (p16; q32.3) [3]. BCL11A has now been shown to be associated with many hematologic disorders such as β-thalassemia [4, 5], hematologic malignancies [3, 6-8], etc. In addition, it is also associated with non-hematological disease, like type II diabetes [9], breast cancer [10], ovarian cancer [11], non-small cell lung cancer [12-14], etc.

In 2015, Khaled et al. [10] found that overexpression of BCL11A gene was involved in the formation and development of triple negative

Table 1. BCL11A expression in different endometrial tissues

Group	Case	MD = $\bar{x}$±s	*P*-value
Normal endometrium	20	0.02328±0.02292	< 0.001[a]
Atypical hyperplasia	20	0.04282±0.02385	< 0.001[b]
ER+/PR+EC	40	0.04718±0.02401	< 0.001[c]
ER-/PR-EC	59	0.12080±0.07762	< 0.001[d]

Note: a. Comparison of BCL11A expression in ER-/PR-EC group and normal endometrium group; b. Comparison of BCL11A expression in ER-/PR-EC group and atypical hyperplasia group; c. Comparison of BCL11A expression in ER-/PR-EC group and ER+/PR+EC group; d. Comparison of BCL11A among 3 groups.

breast cancer, including basal-like breast cancer (BLBC). EC is similar to breast cancer. It was found that endometrial serous adenocarcinoma, one of the major pathological types of type II EC, had some similar genetic characteristics as BLBC [15]. There are no reports on the expression of BCL11A in EC currently. In order to explore the clinical significance of BCL11A in the development of EC, we detected the expression of BCL11A in various endometrial tissues, and analyzed its association with pathological features and patient survival time of EC.

Materials and methods

Specimen and clinicopathological information

60 paraffin-embedded ER- and PR-EC (ER-/PR-) specimens and 40 ER+ and PR+EC (ER+/PR+) specimens with complete clinicopathological data were retrieved from the West China Second University Hospital of Sichuan University from January 2005 to January 2015 (except January 2010-January 2012). One ER-/PR- section fell off the slide during the staining process. A total of 59 ER-/PR-EC specimens and 40 ER+/PR+EC specimens were included in the study (**Table 2**). None of the patients received chemotherapy, radiotherapy, hormone therapy or biological treatment before surgery. Pathological diagnoses were made by two pathologists specialized in gynecological oncology. Regular postoperative followed-ups were deployed. Last follow-up was December 30, 2015. We also collected non-neoplastic endometrium specimens from surgically removed uterus because of the benign lesions during the same period, including 20 cases of normal endometrium and 20 cases of atypical hyperplasia endometrium.

Reagents and immunohistochemistry protocol

Reagents: Mouse anti-human BCL11A monoclonal antibody (Abcam, USA); Two-step IHC polymer-based detection kit, DAB substrate kit and pH 9.0 Tris/EDTA buffer (Beijing ZhongShan Golden Bridge Biotechnology Co. Ltd, China).

IHC protocol: Deparaffinization and rehydration → antigen retrieval (pH 9.0 Tris/EDTA buffer) → blocking endogenous peroxidase activity (3% H_2O_2, incubation in the dark at room temperature for 15 minutes) →incubation with BCL11A antibody (1:250) in 37°C water bath for 60 minutes → incubation with enhancer at room temperature for 20 minutes → incubation with polymer HRP-goat anti-mouse/rabbit IgG at room temperature for 20 minutes → color development with DAB → rinse → counterstaining with hematoxylin → dehydration and mounting. BCL11A expressing tonsil tissues were used as positive controls each time; PBS buffer was used as the negative control for primary antibody.

Interpretation of the results semi-quantitatively

After the brightness was adjusted using an Olympus microscope (400 ×), 5 fields of each slice were randomly selected for study. The area of coverslipped slide without tissue was used to set the background gray scale. Image-pro plus 6.0 image software (MEDIA CYBERNETICS) was used to analyze of the integrated optical density (IOD) and area. Mean optical score (MD) = IOD/area. Average MD of 5 fields was taken.

Statistical analysis

SPSS 21.0 was used to analyze the data. T-test was used to compare the mean of the two groups in the measurement data. ANOVA was used to compare the mean of multiple groups. LSD-t test and SNK-q test was used to compare two means among multiple groups. Survival curves were plotted by Kaplan-Meier method, and the differences between survival curves were analyzed by log-rank test. Factors that affect survival were identified by Cox's proportional hazards model. Significance level of the test was 0.05 ($\alpha = 0.05$) and p-value < 0.05 was considered statistically significant.

Table 2. BCL11A expression and clinicopathological characteristics of ER-/PR-EC

Clinicopathological features	Case	BCL11A MD = $\bar{x}$±s	*P*-value
Age			
≤ 50 y	21	0.04849±0.02639	0.002
> 50 y	78	0.10252±0.00755	
Memopausal status			
Postmenopausal	79	0.09819±0.07325	0.027
Premenopausal	20	0.06290±0.05748	
Myometrial invasion			
< 1/2	48	0.08252±0.06733	0.249
≥ 1/2	51	0.09910±0.07501	
Cervical interstitial infiltration			
Negative	81	0.08499±0.06934	0.103
Potive	18	0.11839±0.07674	
FIGO stage			
I and II	74	0.08743±0.06511	0.460
III and IV	25	0.10181±0.08846	
Classification			
I	41	0.06612±0.04685	0.003
II	58	0.10870±0.08055	
Pelvic metastasis			
Positive	19	0.09490±0.07443	0.803
Negative	80	0.09015±0.07125	
Pelvic lymph nodes metastasis			
Positive	16	0.11978±0.09916	0.223
Negative	71	0.08693±0.06659	
Para-aortic lymph node metastasis			
Positive	2	0.22310±0.20614	0.048
Negative	38	0.09704±0.07921	
Differentiation			
G1, G1-2, G2	39	0.06547±0.05839	0.010
G2-3, G3	56	0.10004±0.06655	
Unknown	4	-	
Histological type			0.001
Endometrioid adenocarcinoma	41	0.06647±0.04658	
Serous adenocarcinoma	5	0.18044±0.14408	
Clear cell adenocarcinoma	7	0.11831±0.06138	
Mixed adenocarcinoma*	33	0.08848±0.07074	
Other	13	0.12614±0.07211	
IHC			
ER&PR			
Positive	40	0.04718±0.02401	< 0.001
Negative	59	0.12080±0.07762	
p53			
Positive	54	0.10356±0.07302	0.041
Negative	28	0.06788±0.07331	
Unknown	17	-	
Ki-67			

Results

Expression of BCL11A in different endometrial tissues

Positive BCL11A immunostaining is a brown granular chromogenic deposition, mainly located in the cytoplasm and nucleus in endometrial gland cells and cancer cells. The intensities of the staining may be different among normal endometrium, atypical hyperplasia, and cancer cells. The current study showed that the expression of BCL11A in ER-/PR-EC tissues was significantly higher than that in the other three groups (P < 0.001, **Table 1**; **Figure 1**).

The associations between BCL11A expression and clinicopathological features of EC

The expression of BCL11A in EC was correlated with age (P = 0.002), menopause (P = 0.027), classification (P = 0.003); para-aortic lymph node metastasis (P = 0.048), differentiation (P = 0.010); histological type (P = 0.001) and p53 expression (P = 0.041). However, it had no significant correlation with myometrial invasion, cervical interstitial infiltration, pathological stage, pelvic metastasis, pelvic lymph nodes metastasis, or Ki-67 expression (P > 0.05, **Table 2**).

The association between BCL11A expression and prognosis of EC

99 cases of EC were divided into three groups according to the measured MD value of BCL-11A (0.00780~0.36886): low expression group (MD = 0.00780-0.12815), medium expression group (MD = 0.12816~0.24850) and high expression group (MD value 0.24851~0.36886). De-

≥ 50	37	0.10210±0.07025	0.697
< 50	29	0.09419±0.08936	
Unknown	33	-	

Mixed adenocarcinoma*: A histological type that contains both type I and type II EC [21].

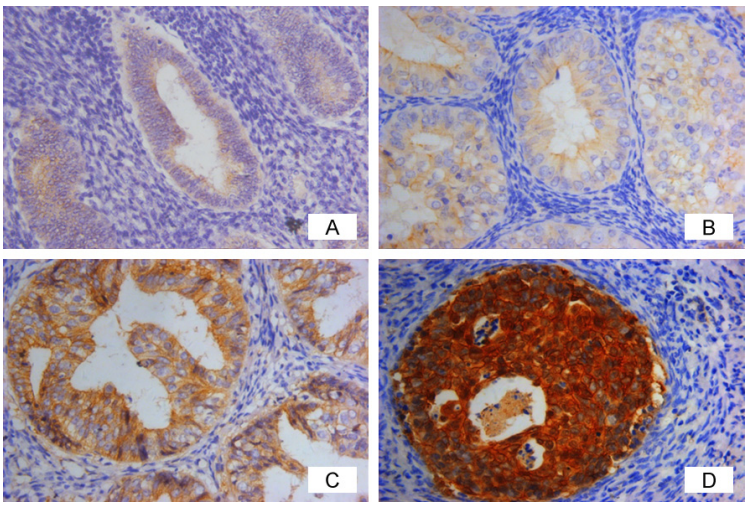

Figure 1. BCL11A expression in normal endometrium (A), atypical hyperplastic endometrium (B), ER/PR+EC (C), ER/PR-EC (D).

tailed follow-up results are listed in **Table 3.** The expression level of BCL11A in the survival group (MD = 0.08138±0.06098) was significantly lower than that in the deceased group (MD = 0.12919±0.09632, P = 0.011).

Kaplan-Meier method was used to plot the survival curves of three groups with different levels of BCL11A expression (**Figure 2**).

Significant difference was observed in survivals among three groups when compared by log-rank test (χ^2 = 19.424, P < 0.001). However, further study using multivariate Cox regression model to analyze the influence of multiple factors on the survival rate showed that there was no significant difference in the survivals of groups of different BCL11A expression levels (P = 0.760).

Discussion

Expression of BCL11A in different endometrial tissues

Khaled et al. [10] studied 368 breast cancer samples by IHC staining and found that the expression of BCL11A in BLBC was significantly stronger than in other types. Among 24 BLBCs, 16 cases had strong expression of BCL11A. In addition, RNA level in BCL11A positive samples was significantly higher than in BCL11A negative samples, further confirming the high expression of BCL11A in BLBCs.

Our study showed that BCL-11A expression was significantly higher in ER-/PR-EC than in other types of endometrial tissues. The result indicated that the expression level of BCL11A might be correlated with the expression of ER and PR, and BCL11A expression is associated with the development of ER-/PR-EC.

Associations between BCL11A expression and clinicopathological features of EC

We studied the relationship between BCL11A expression and the clinicopathological features of EC and found that the expression of BCL11A was associated with 8 features, including age, tumor classification, menopause, para-aortic lymph node metastasis, differentiation, histological type, ER/PR expression, and p53 expression. However, the expression had no significant correlation with myometrial invasion, cervical interstitial infiltration, pathological stage, pelvic metastasis, pelvic lymph node metastasis, or Ki-67 expression (P > 0.05).

Age is considered as an independent predictor and a prognostic factor of EC. According to the Gynecologic Oncology Group (GOG), 5-year survival of EC is 96.3% in patients under 50 years, 87.3% in patients of 51-60 years, 78% in patients of 61-70 years, 70.7% in patients of 71-80 years, and 53.6% in patients over 80 years [16]. In this study, the expression of BCL11A in patients over 50 years was significantly higher than in patients under 50 years (P = 0.002), suggesting that the expression level of BCL11A may also be associated with the occurrence and prognosis of EC.

Although menopause is associated with EC classification and ER/PR expression, it is not an independent prognostic factor of EC. Our

Table 3. Follow-up of EC patients

BCL11A expression	Survival group (%)	Deceased group* (%)	Lost to follow-up (%)	Total	*P*-value
Low	57 (75.0)	10 (13.2)	9 (11.8)	76	-
Medium	12 (63.2)	5 (26.3)	2 (10.5)	19	
High	1 (25.0)	3 (75.0)	0 (0.0)	4	-
Total	70 (70.7)	18 (18.2)	11 (11.1)	99	-
MD	0.08138±0.06098	0.12919±0.09632	-	-	0.011

Death*: All the deaths were due to EC recurrence, metastasis, or complications (complete data).

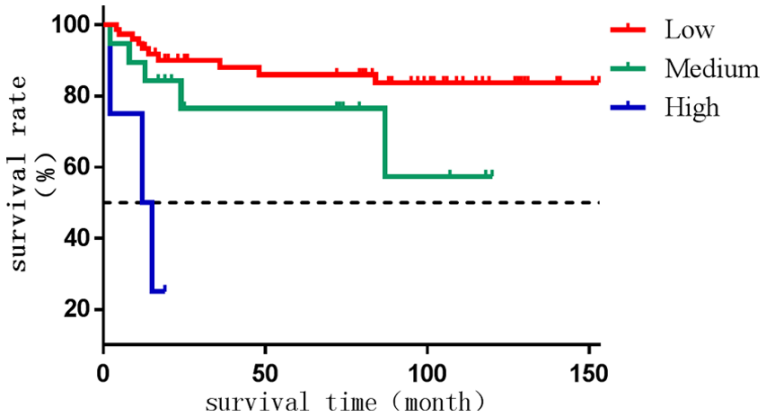

Figure 2. Comparison of survival among three groups of patients.

result showed that BCL11A was significantly higher in the premenopausal group than in the postmenopausal group (P = 0.027), suggesting that BCL11A is highly expressed in postmenopausal women with EC.

The expression of BCL11A in type II EC was significantly higher than in type I group in the current study, suggesting that BCL11A might be a characteristic gene expression in type II EC.

Lymph node is the most common extrauterine metastatic site of EC. Studies have showed that lymph node metastasis is an important prognostic factor of patients with EC. Currently, the mechanism of EC lymph node metastasis is still not clear. Unlike cervical carcinoma, lymph node metastasis of EC is not regular because of the bilateral and bidirectional lymphatic drainage. In this study, the expression of BCL-11A in patients with para-aortic lymph node metastasis was significantly higher than that in patients without lymph node metastasis (P = 0.048). But there was no significant association between BCL11A and pelvic lymph node metastasis (P > 0.05). This is probably because that the sample size was too small, and the analysis method was not precise enough. Therefore, the relation between BCL11A expression and pelvic lymph node metastasis was not revealed, and further study is needed.

Although differentiation of EC is closely associated with myometrial invasion, cervical interstitial infiltration, lymph node metastasis, local and distant recurrence, they are not independent prognostic factors of EC. In this study, the expression of BCL11A in patients with moderate-poor differentiation was significantly higher than that in patients with high-moderate differentiation (P = 0.010), suggesting that BCL11A is highly expressed in poorly differentiated EC, and its expression may be related to the differentiation of EC.

Histological type has long been considered as an important predictor for the biological behavior of EC. Serous adenocarcinoma is an invasive adenocarcinoma, belonging to type II EC. It is highly malignant with poor differentiation, early vascular invasion, deep muscular involvement and pelvic lymph node metastasis. Prognosis is poor. Recurrence and metastasis rate of stage Iserous adenocarcinoma is 31-50%. 5-year survival of disease in early stage is 40%-50%, and less than 15% in late stage [17].

Mixed adenocarcinoma is a mixed type of EC including endometrioid carcinoma (including its various subtypes and mucinous differentiation) from type I EC, and serous adenocarcinoma, clear cell adenocarcinoma and some other special types from type II EC [16]. Generally it is believed that the prognosis of EC would be

poor if the type II component is above 25%, there was a study showing that the prognosis was not good even when the type II component was below 10% [18]. Endometrioid carcinoma and serous adenocarcinoma are different in clinical, pathological, immunohistochemical and molecular characteristics. In our study, the expression of BCL11A in serous adenocarcinoma was significantly higher than in endometrioid adenocarcinoma ($P < 0.001$) and mixed adenocarcinoma ($P = 0.005$), suggesting that the expression level of BCL11A was associated with the proportion of type II components, like serous adenocarcinoma. The greater the proportion of type II components, the higher the expression level of BCL11A.

The expression level of ER and PR is an important marker for tumor differentiation, which is associated with FIGO staging, histological differentiation and survival. The presence of ER indicates that the hormone-regulating function of tumor cells has not been completely lost and tumor can still respond to hormone stimulation, which is an indicator for effective endocrine therapy [16]. In this study, the expression level of BCL11A in the ER-/PR- group was significantly higher than that in ER+/PR+ group ($P < 0.001$). These results provided theoretical support for the development of targeted therapy of BCL11A gene as an individualized treatment for EC patients whose steroid hormone receptor is absent or endocrine therapy has failed.

Tumor suppressor gene p53 is considered a pro-apoptotic gene. It is mainly expressed in EC, but not in normal endometrial tissue, which plays an important role in tumorigenesis, cell proliferation, and malignant transformation [16]. In this study, the expression of BCL11A in the p53-positive group was significantly higher than that in the negative group ($P = 0.041$), suggesting that BCL11A may work together with the mutant p53 gene to promote cell proliferation and tumor transformation, and to increase carcinogenic potential of the cells. However, other studies have suggested that BCL11A inhibits p53 activity [19]. Therefore, further studies are needed to clarify the relationship between BCL11A and p53.

The relationship between BCL11A and prognosis

Survival curves in our study showed that the survival of EC decreased with the increased expression of BCL11A. Comparing the survival among three groups by the log-rank test showed that the difference was statistically significant ($P < 0.001$). The expression of BCL11A in the survival group was significantly lower than that in the deceased group ($P = 0.011$). Our results suggested that high BCL11A expression is correlated with low survival rate of EC.

However, further study using multivariate Cox regression model to analyze the influence of multiple factors on the survival rate showed that no independent variable were included in the final model and there was no significant difference among the survival of groups of different BCL11A expression levels ($P = 0.760$). In addition, no significant differences were found among other prognosis-associated factors with different BCL11A expression level ($P > 0.05$). This may result from the limited number of cases and a lot of censored data in the current study. Further randomized case-control study with large sample sizes are needed to analyze the relationship between the expression of BCL11A and the prognosis of EC.

Classification of EC based on ER/PR expression

The ER-/PR- group in the current study included mostly type II ECs, with only a small proportion of type I ECs that were poorly differentiated [G2, G2-3, G3 = 9 (12) cases]. BCL11A expression in ER-/PR- group was relatively high. The ER+/PR+ group consisted of mostly type I EC, and some mixed adenocarcinoma with only little portion of type II component. There was no typical type II EC in this group. In ER+/PR+ group, type I ECs were well differentiated [G1, G1~2 = 23 (29) cases], and BCL11A expression was low (**Table 4**). Therefore, the difference between the ER/PR classification and traditional classification occurs mainly in the poorly differentiated type I ECs, including the most controversial G3 endometrioid adenocarcinoma, for which the criteria of classification are still not clear. Our study suggested that BCL11A expression level might help with the classification.

In 2013, TCGA [15] analyzed gene and protein profiles of EC from 373 patient samples and found that there were many copy number alterations, little DNA methylation, low ER/PR expression, and many p53 mutations in uterine

Table 4. Experimental groups and traditional classification

Histological type	ER&PR- group	ER&PR+ group	Traditional classification	*P*-value
Endometrioid adenocarcinoma	12	29	I	
G1, G1~2	3	23	I	
G2, G2~3, G3	9	6	I	
Serous adenocarcinoma	10	0	II	
Clear cell adenocarcinoma	2	0	II	
Mixed adenocarcinoma	22	11	II	
Other	13	0	II	
Total	59	40	-	-
MD	0.12080±0.07762	0.04718±0.02401	-	< 0.001

serous adenocarcinoma and about 25% of high-grade endometrioid carcinomas. However, most endometrioid carcinomas had few copy number alterations and p53 mutations, but with many mutations in PTEN, CTNNB1, PIK3CA, ARID1A, KRAS and ARID5B. As a result, it was proposed that EC could be re-classified into 4 categories, including POLE ultramutated, microsatellite instability hypermutated, copy-number low and copy-number high. Classification based on genomic features may directly influence treatment decisions and guide targeted therapy. Some scholars have proposed a new classification of EC combining molecular biology and clinicopathological features, which would better predict the prognosis and therapeutic efficacy, and help with monitoring and screening [20].

The limitations of this experiment

Limitations of this study included: First, only ER+/PR+, and ER-/PR-ECs cases were included in the current study. ECs with only ER or PR expression were excluded. The study subjects did not include all types of EC. Second, BCL-11A expression in different endometrial tissues was evaluated indirectly in this study, by IHC and measurement of MD values. The method was subjective and semi-quantitatively. The study would be more objective and complete if the level of BCL11A mRNA or protein expression could be measured quantitatively, or the function of BCL11A in tumorigenesis, metastasis and prognosis could be validated in mouse or cell BCL11A gene knockout model. Third, since the number of deaths (complete data) for survival analysis was relatively small, the result of survival analysis may have bias. However, as a preliminary exploratory study, our result may still provide reference value.

Conclusion

In summary, BCL11A may play an important role in the occurrence and development of ER and PR-deficient ECs. Targeted BCL11A therapy would be a potential treatment strategy for EC patients whose steroid hormone receptor expression is absent or endocrine therapy has failed. High BCL11A expression in EC was associated with a low survival rate. BCL11A may become a prognostic factor of EC. The fact that BCL11A is overexpressed in ER/PR-EC may provide a new paradigm for EC classification and a better treatment strategy. Combining molecular biology and clinicopathological features would better predict the prognosis and therapeutic efficacy, as well as help with monitoring and screening.

Disclosure of conflict of interest

None.

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