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Original Article

Expression of glycine decarboxylase in epithelial ovarian cancers and its association with prognosis

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Abstract: GLDC is aberrantly overexpressed in numerous malignant tumors, associated with poor survival of patients, but in epithelial ovarian cancers, the expression and function of GLDC is unclear. In this study, we mainly discuss expression, distribution, and prognostic significance of GLDC in epithelial ovarian cancers. The expression of GLDC were detected by immunohistochemistry (IHC), then the staining was evaluated, the clinical and pathologic characteristics, overall survival (OS), progress free survival (PFS) were analyzed. The results indicated that GLDC expression is up-regulated in the epithelial ovarian cancers compared to benign tumor tissues. The expression of GLDC is significantly correlated with FIGO stage (P=0.018), lymph node metastasis (P=0.023), residual tumor size (P=0.020), while it isn't correlated with other clinical features. In a Kaplan Meier analysis, the higher expression of GLDC was correlated with poor OS and PFS. Therefore, GLDC may be a significant prognostic factor in epithelial ovarian cancers and useful to further clinical trials.

Keywords: Glycine decarboxylase, epithelial ovarian cancer, prognosis

Introduction

Epithelial ovarian cancer (EOC) accounts for about 80% of ovarian cancers and is the most lethal gynecologic malignancies [1]. The prognosis of EOC is poor due to its advanced stage at the time of diagnosis, the metastasis of EOC is the major causes of death [2]. However, the majority of patients with EOC are diagnosed with metastatic disease due to no effective screening tests or the appearance early symptoms [3, 4]. Approximately 75% of patients are diagnosed with advanced (stage III/IV) ovarian carcinoma, which is characterized by peritoneal or distant metastases, respectively, and for which the 5-year survival rate is 15-20%; the rate for patients diagnosed during the early stage (stage I/II) is 80-90% [5, 6]. Therefore, it is ultimately urgent to find an effective method of early diagnosis for EOC.

Glycine decarboxylase (GLDC) is an oxidoreductase, which plays an important role in amino acid metabolism [7]. The overexpression of GLDC promotes cell proliferation and their transformation to cancer cells through increasing glycine-serine metabolism and nucleotide synthesis [8, 9]. The oncogenic effect of aberrant GLDC upregulation is related to many cancer patients, high GLDC expression level is associated with higher mortality and poor survival rates in hepatocellular carcinoma (HCC) [10], non-small-cell lung carcinoma (NSCLC) [11], glioma and other cancer patients [12-14], while it's the exact opposite in hepatocellular carcinoma (HCC). The knockdown of GLDC expression in non-transformed cells does not affect cell viability, suggests the therapeutic relevance of GLDC, and GLDC as a target may have a wide therapeutic index.

In ovarian cancers, Zhang and colleagues found that GLDC was aberrantly upregulated in a set of primary tumors and 606 human cancer cells, especially ovarian and germ cell tumors through metabolomic analysis [8].

It's unclear whether aberrant expression of GLDC is associated with clinical characteriza-

tion and prognosis of epithelial ovarian cancer patients. In this study, we mainly investigated the expression levels of GLDC and its relevance to clinical significance and prognosis of epithelial ovarian cancer patients. The results obtained from this study maybe provide useful clinical data into the treatment in epithelial ovarian cancers.

Materials and methods

Human tissues

A total of 136 tissue samples including 110 epithelial ovarian cancers (EOC) and 26 benign ovarian tumors (BOT) were taken upon surgical resection in the First Affiliated Hospital of Sun Yat-sen University from 2006 to 2009. All the samples were made into paraffin-embedded tissue specimens after normal dehydration and dehydration processing. All patients selected had no liver, kidney, endocrine diseases or any other malignant diseases, and had not received radiotherapy, chemotherapy or hormonal therapy before surgical resection. The relevant clinic and pathological data included patients' age, gender; smoking index; tumor staging (TNM); histological type; regional lymph node metastasis; overall survival (OS).

Reagents and materials

Anti-GLDC antibody was purchased from Sigma Company (Sigma, St. Louis, MO), and rotary microtome and NovoLink Polymer Detection System was obtained from Leica Microsystems Company (Wetzlar, Germany). EDTA buffer (pH 8.0), PBS, 3% H_2O_2 reagent and other reagents were prepared in this laboratory.

Immunohistochemistry

Paraffin-embedded epithelial ovarian cancer and normal tissue sections were cut into 4 μm by rotary microtome and adhered into slides. The slides were dewaxed by xylene and rehydrated with a series of graded alcohols (100%, 95%, 90%, 80%, and 75% ethanol) and washed with water for three times, followed by heat-induced antigen retrieval with EDTA buffer (pH 8.0). Subsequently, the slides were blocked by 3% H_2O_2 reagent for 5 minutes, and then were stained by the NovoLink Polymer Detection System, according to the manufacturer's protocol. The main primary antibodies have been used: anti-GLDC antibody (1:100). Negative controls were generated by omitting the primary antibody.

Immunohistochemistry evaluation

The immunoreactive score (IRS) was evaluated by three independent and experienced examiners. Expression status was dichotomized using Allred score >3 as cutoff. Cytoplasmic and nuclear staining was determined, where for negative -; + for weak; ++ for moderate; +++ for strong staining. The percentage of positive tumor cells were scored as: "0" (no positive cells), "1" (10% positive cells or less), "2" (11% to 50% positive cells), "3" (51% to 75% positive cells), and "4" (more than 75% positive cells). The score of 0 and 1 is defined as the low expression group, while the score of 2 and 3 is defined as the high expression group.

Statistical analysis

All statistical analyses were analyzed by statistical software SPSS 13.0 (SPSS Inc., Chicago, USA). Differences between high and low expression were compared through X^2. Multiple linear regression analysis was used to analyze the relationship between GLDC and the factors of clinical pathology. OS and PFS were analyzed initially by Cox proportional hazard regression. The P value of <0.05 was considered statistically significant.

Results

GLDC expression in epithelial ovarian cancers

To assess the expression level of GLDC, immunohistochemistry were used in 110 cases EOC and BOT paraffin-embedded tissues. Expression status was dichotomized as negative (Allred score <3) and positive (≥3) based on statistical assessment. Positive GLDC expression was observed in 66 out of 110 (60%) in EOC, whereas positive GLDC expression was detected in 2 out of 26 (7.69%) in BOT (**Figure 1**). Compared with expression of GLDC, it was significantly higher in EOC (**Table 1**).

Expression of GLDC in relation to clinic and pathologic characteristics

The correlations between the expression of GLDC and clinical and pathologic characteristics were analyzed. According to the results of immunohistochemistry, GLDC expression was correlated with FIGO stage (I-II *vs.* III-IV,

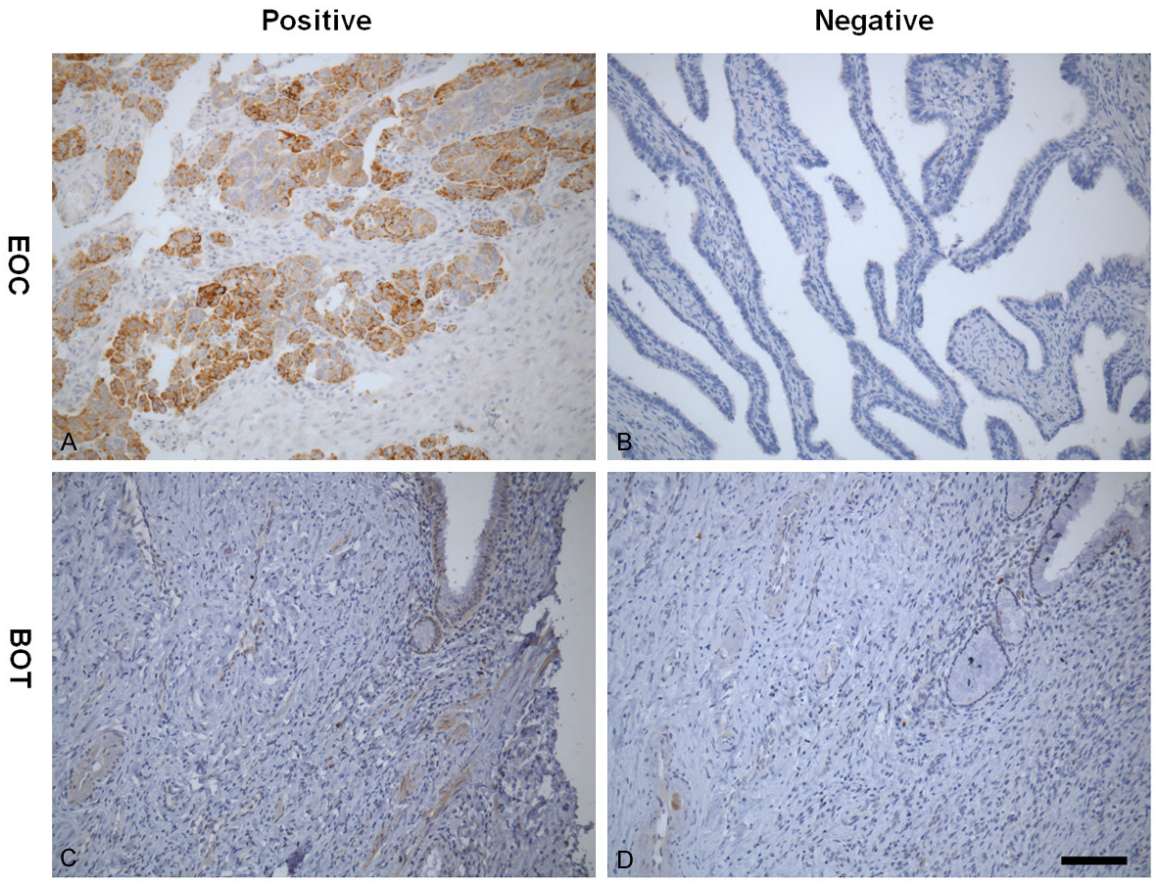

Figure 1. Immunohistochemical analyses of GLDC in EOC tissues and BOT tissues. The positive expression of GLDC was observed in the EOC tissues (A) and BOT tissues (C). The negative expression of GLDC was showed in the EOC tissues (B) and BOT tissues (D). (Bar =200 μm).

Table 1. The different analyses of the GLDC expression

Groups	Cases	GLDC expression		*P*-value
		Low (0-1+)	High (2+-3+)	
EOC	110	44	66	<0.001
Benign	26	24	2	

P=0.018), lymph node metastasis (*P*=0.023) and residual tumor size (≥1 cm *vs.* <1 cm, *P*=0.020). However, no significant association was suggested between GLDC expression and other clinical-pathologic parameters including age, menopause, histological subtype, histological differentiation, tumor size, serum CA125 and ascites cancer cells (**Table 2**).

Correlation of the expression of GLDC with OS and PFS

Previous studies reported GLDC overexpression as a poor survival factor in many cancers [8], but its prognostic role in EOC is unknown. In the present study, Kaplan-Meier survival analysis and log-rank test were used to analyze the correlation between GLDC expression with OS and FPS, and indicated that high GLDC expression in EOCs predicted poor survival (*P*=0.001, **Figure 2A**). 5-year OS rate was 28.79% (19/66) in the high GLDC expression group while it was almost 63.64% (28/44) in the low GLDC expression group (**Table 3**). We also analyzed the relationship between GLDC expression and PFS, and found that High GLDC expression patients inclined to be relapse within 5 years (*P*=0.001, **Figure 2B**). The relapse rate was 81.82% (54/66) in the high GLDC expression group, while it was 54.55% (24/44) in the low GLDC expression group.

Evaluation of risk factors for epithelial ovarian cancer patients

COX proportional hazard regression model was used to evaluate the risk factors. The clinic-

Table 2. Correlation of GLDC expression with clinic-pathologic parameters

Characteristics	n (110)	GLDC expression		Chi-square test	
		Low (0-1+) 44	High (2+-3+) 66	χ^2	*P*-value
Age (years)					
>51	54	19	35	1.025	0.311
≤51	56	25	31		
Menopause					
Yes	61	21	40	1.773	0.183
No	49	23	26		
FIGO stage					
I-II	38	21	17	5.635	0.018*
III-IV	72	23	49		
Histopathological differentiation					
Well-moderate	72	31	41	0.811	0.368
Poor	38	13	25		
Histopathological subtypes					
Serous	80	30	50	4.219	0.377
Mucinous	16	9	7		
Endometrioid	5	2	3		
Clear cell	3	2	1		
Others	6	1	5		
Lymph node metastasis					
No	71	34	37	5.191	0.023*
Yes	39	10	29		
Tumor size					
<5 cm	43	20	23	1.247	0.264
≥5 cm	67	24	43		
CA125					
≤35 U/L	22	9	13	0.009	0.922
>35 U/L	88	35	53		
Ascites cancer cell					
Positive	65	23	42	1.410	0.235
Negative	45	21	24		
Residual tumor size					
≥1 cm	22	4	18	5.455	0.020
<1 cm	88	40	48		

*$P<0.05$, statistically significance.

pathologic characteristics and GLDC expression were used as the independent variates in the univariate analysis, and the results observed that FIGO stage (I-II vs. III-IV), histologic differentiation (poor vs. well-medium), lymph node metastasis (yes vs. no), ascites cancer cells (positive vs. negative), residual tumor size (≥1 cm vs. <1 cm) and GLDC expression (high vs. low) were correlated 5-year OS and PFS (**Table 4**). Meanwhile, the multivariate analysis results showed that low GLDC expression and low FIGO stage were associated with good OS (**Table 5**) and poor PFS (**Table 6**), suggested it may be an independent risk factor.

Discussion

The integrated genomic analysis showed that epithelial ovarian cancer was a heterogeneous disease, having a variable degree of malignancy and prognosis [15]. The treatment of epithelial ovarian cancers has significant progress in the past decades, but prognosis and survival rate were still not optimistic [16, 17]. The main-

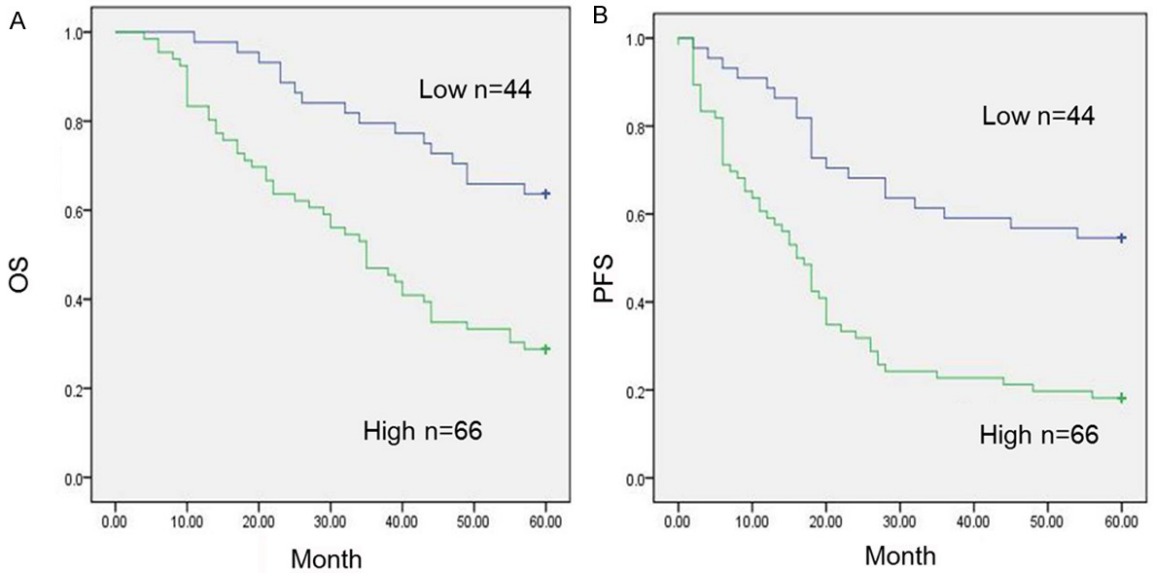

Figure 2. Evaluation of GDLC as a predictor for OS and FPS by the Kaplan-Meier (KM) plot. A: 5-year overall survival (OS) curve in different GLDC expression group. High GLDC expression predicts lower 5-year OS rate comparing with the low expression group (P<0.001). B: Progress free survival (PFS) curve in different GLDC expression group. Patients with high GLDC expression have shorter PFS (P<0.001).

Table 3. Prognostic statue of EOC patients in high and low GLDC expression groups

Groups	Cases	GLDC expression		*P*-value
		Low (0-1+)	High (2+-3+)	
Survive within 5 years				
Yes	47	28	19	0.001*
No	63	16	47	
Relapse within 5 years				
Yes	74	20	54	<0.001*
No	36	24	12	

*P<0.05, statistically significance.

ly reason is no effective method to detect epithelial ovarian cancer in the early stage. Glycine decarboxylase, also known as glycine dehydrogenase, was reported to be overexpressed in several cancers, includes NSCLC, breast cancer and EOC [8, 11, 12].

In our study, we mainly discuss the relationship between GLDC expression, clinical characterization and prognosis of EOC patients. Our results suggest the importance of evaluating GLDC immunoreactivity as they have important and distinct prognostic implications.

Our data shows that higher GLDC expression was found in EOC relative to in BOT, suggested that GLDC may be involved in EOC tumorigenesis. GLDC expression is significantly correlated with FIGO stage, lymph node metastasis and residual tumor size, but not correlated with age, menopause, histological subtype, histological differentiation, ascites cancer cell and serum CA125 level. This phenomenon suggest that GLDC not only is an prognostic marker, but also may be involved in the progress of EOC by very complicated mechanisms, but there was no more clear data about this finding now.

Recent reports showed tumoral positivity of GLDC was significantly related to shorter DFS and OS in invasive lobular breast carcinoma [18], and associated with shorter OS in breast cancer patients with brain metastasis [19]. In this study, we evaluated the relationship between survival outcome of EOC with different expression of GLDC using the Kaplan-Meier analysis. Patients with high expression GLDC were likely to have significantly shorter OS and PFS. Lymph node metastasis, FIGO stages and optimal cytoreduction surgery (residual tumor size <1 cm) are main prognostic factors for EOC patients. We performed Cox regression analysis to explore whether GLDC is a potential prognostic factors for EOC. The result showed that GLDC, lymph node metastasis, FIGO stage, histologic differentiation, residual tumor size and

Table 4. Univariate analysis of OS and PFS of EOC patients

Prognostic variables	OS		PFS	
	HR (95% CI)	*P*-value	HR (95% CI)	*P*-value
Age (>51 years *vs.* ≤51 years)	1.413 (0.861-2.320)	0.172	1.395 (0.883-2.202)	0.154
Menopause (Yes *vs.* No)	1.658 (0.992-2.770)	0.054	1.571 (0.984-2.508)	0.058
FIGO stage (I-II *vs.* III-IV)	9.044 (3.873-21.119)	<0.001	5.038 (2.732-9.290)	<0.001
Histological differentiation (Poor *vs.* Well -medium)	1.233 (1.045-1.456)	0.013	1.227 (1.051-1.432)	0.010
Histological subtype (Serous *vs.* Non-serous)	1.425 (0.787-2.583)	0.243	1.502 (0.873-2.585)	0.141
Lymph node metastasis (Yes *vs.* No)	3.225 (1.947-5.341)	<0.001	2.932 (1.836-4.682)	<0.001
Tumor size (≥5 cm *vs.* <5 cm)	1.214 (0.727-2.029)	0.458	1.412 (0.875-2.277)	0.157
CA125 (>35 U/L *vs.* ≤35 U/L)	1.577 (0.802-3.101)	0.187	1.875 (0.987-3.560)	0.055
Ascites cancer cell (Positive *vs.* Negative)	3.825 (2.099-6.971)	<0.001	2.683 (1.619-4.46)	<0.001
Residual tumor size (≥1 cm *vs.* <1 cm)	3.307 (1.921-5.694)	<0.001	3.547 (2.087-6.027)	<0.001
GLDC expression (High *vs.* Low)	2.870 (1.624-5.075)	<0.001	2.900 (1.727-4.868)	<0.001

Table 5. Multivariate analysis of the correlation between prognostic variables and OS of EOC patients

Prognostic variables	OS	
	HR (95% CI)	*P*-value
FIGO stage (I-II *vs.* III-IV)	5.001 (1.925-12.993)	0.001
Histological differentiation (Poor *vs.* Well-medium)	1.064 (0.898-1.262)	0.473
Lymph node metastasis (Yes *vs.* No)	1.280 (0.745-2.197)	0.371
Ascites (Yes *vs.* No)	1.891 (0.980-3.646)	0.151
GLDC expression (High *vs.* Low)	2.166 (1.191-3.939)	0.011
Residual tumor size (≥1 cm *vs.* <1 cm)	1.250 (0.689-2.268)	0.463

Table 6. Multivariate analysis of the correlation between prognostic variables and PFS of EOC patients

Prognostic variables	PFS	
	HR (95% CI)	*P*-value
FIGO stage (I-II *vs.* III-IV)	3.064 (1.483-6.333)	0.002
Histological differentiation (Poor *vs.* Well-medium)	1.111 (0.944-1.307)	0.205
Lymph node metastasis (Yes *vs.* No)	1.259 (0.746-2.122)	0.388
Ascites (Yes *vs.* No)	1.254 (0.695-2.265)	0.452
GLDC expression (High *vs.* Low)	2.465 (1.441-4.219)	0.001
Residual tumor size (≥1 cm *vs.* <1 cm)	1.781 (0.994-3.189)	0.052

residual tumor size correlated with patients' OS or PFS, and the multivariate analysis suggested GLDC is an independent prognostic factor.

In conclusion, our study indicated that GLDC is GLDC expression was related to clinical significance and prognosis of epithelial ovarian cancer patients. High expression of GLDC is involved in the poor outcome of patients with EOC, suggests GLDC may be an independent prognostic factor, though there still were many un-revealed questions. This prognostic maker could play an important role in stratifying patients in clinical trials through analyzing more adequate cases.

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Disclosure of conflict of interest

None.

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