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ALDH1 Expression Correlates with Favorable Prognosis in Ovarian Cancers

Bin Chang[1,3,#], **Guangzhi Liu**[1,#], **Fenxia Xue**[1], **Daniel G. Rosen**[4], **Lianchun Xiao**[2], **Xuemei Wang**[2], and **Jinsong Liu**[1]

[1]Department of Pathology The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

[2]Department of Biostatistics, The University of Texas M. D. Anderson Cancer Center, Houston, Texas, USA

[3]Department of Pathology and Laboratory of Xinjiang Endemic and Ethnic Diseases, Shihezi University School of Medicine, Shihezi, Xinjiang, China

[4]Department of Pathology, Baylor College of Medicine, Houston, Texas, USA

Abstract

Aldehyde dehydrogenase 1 (ALDH1), a detoxifying enzyme responsible for the oxidation of intracellular aldehydes, was shown to play a role in the early differentiation of stem cells, through its role in oxidizing retinol to retinoic acid. It has been shown that ALDH1 is a predictor of poor clinical outcome in breast cancer. The authors hypothesized that the level of ALDH1 expression may be correlated with the clinical outcome of patients with ovarian cancer. Immunohistochemical staining of ALDH1 expression was analyzed in 442 primary ovarian carcinomas using tissue microarray. The associations between the expression of the ALDH1 and clinical factors (diagnosis, tumor grade, stage, and clinical response to chemotherapy), as well overall and disease-free survival were analyzed. Expression of ALDH1 was found in 48.9% of the samples. Fisher's exact test suggested that high expression of ALDH1 was significantly associated with endometrioid adenocarcinoma ($P < 0.0001$), early-stage disease ($P = 0.006$), complete response to chemotherapy ($P < 0.05$) and a low serum level of CA125 ($P = 0.02$). High percentage of cells expressing ALDH1 was associated with a longer overall survival time ($P = 0.01$) and disease free survival time ($P = 0.006$) by Log rank test. In contrast to its role in breast cancer, ALDH1 was a favorable prognostic factor in ovarian carcinoma. ALDH1 therefore may play a different role in ovarian cancer than it does in breast cancer.

Page proofs, Correspondence and Requests for Reprints: Jinsong Liu, Department of Pathology, Unit 85, The University of Texas M. D. Anderson Cancer Center, 1515 Holcombe Blvd, Houston, TX 77030. Phone: 713-745-1102; Fax: 713-792-5529; E-mail: jliu@mdanderson.org..

[#]First two authors contributed equally to this work.

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Keywords

ALDH1; Ovarian Cancer; Immunohistochemistry; Prognosis

Introduction

Aldehyde dehydrogenase (ALDH) is a family of ubiquitous enzymes located in nearly all mammalian tissues, which catalyze the oxidation of aldehydes to their carboxylic acid forms (1, 2). They participate in the detoxification of acetaldehyde (1, 2), the metabolism of biogenic amines (3), corticosteroids (4) and retinoic acid (5, 6). To date, 17 isoforms of ALDH had been described (7). ALDH1 is the cytosolic isoforms. Murine and human hematopoietic stem/progenitor cells have been isolated based on their high levels of ALDH activity (8-13). ALDH activity has been used to identify stem-like subsets not only in human hematopoietic cancers but also in solid cancers (e.g., breast cancer) (14-17). A recent study by Ginestier et al. demonstrated that high ALDH activity selected for both normal and tumorigenic human mammary epithelial cells with stem/progenitor properties; expression of ALDH1 was a predictor of poor clinical outcome in breast tumors (15). However, it remains controversial that these cell surface markers can be used as the sole means to isolate cancer stem cells because of the heterogeneous nature of solid tumors (14, 18-22). Furthermore, the clinical, pathological, and immunohistochemical features of cancers associated with high expression of these markers remain unknown.

Ovarian cancer ranks as the fifth leading cause of cancer deaths among women (23). The expression of ALDH1 and its clinical significance is unknown in ovarian cancer. The authors hypothesized that the level of ALDH1 expression may be correlated with the clinical outcome of patients with ovarian cancer. The purpose of this study therefore was to evaluate the association between the expression of ALDH1 and the clinical pathologic factors (including diagnosis, tumor grade, disease stage, and clinical response to chemotherapy), as well the overall survival and disease-free survival of ovarian cancer. To do this, we retrospectively analyzed the clinical pathologic factors of 442 cases of primary ovarian cancer and subjected archived tissue specimens to microarray analysis of the expression of putative cancer stem cell marker ALDH1 by immunohistochemical staining and correlate with the clinical outcome.

Materials and Methods

Patients and clinicopathologic data

This study analyzed tumor samples from women diagnosed with primary ovarian carcinoma that had undergone initial surgery at The University of Texas M. D. Anderson Cancer Center between January 1, 1990, and December 31, 2005. Depending on the availability of representative tumor samples, data for 442 patients were obtained. The relevant clinical data were collected by retrospective review of the patients' files. Follow-up information was updated through May 2008 by reviewing medical records and the United States Social Security Index. Histopathologic diagnoses were based on World Health Organization criteria (24), tumor grading for non-serous carcinomas was based on tumor grading was based on

Gynecologic Oncology Group criteria (25-27), and disease staging was assigned according to the International Federation of Gynecology and Obstetrics staging system (28). Serous carcinomas were graded by using a two-tier system (low grade and high grade) according to the criteria proposed by Malpica et al (29).

To analyze response to primary therapy, we classified patients as responders or nonresponders. Patients who entered complete clinical remission with a normal CA125 level after chemotherapy for histologic or cytologic diagnosis of ovarian carcinoma with a treatment-free interval of ≥ 6 months were defined as responders (30). The group of nonresponders also was subdivided according to whether patients had progressive disease or recurrent disease. Progressive disease was defined as progression that occurred without disease remission observed after the initiation of treatment; Recurrent disease was defined as disease that was detected after a period of clinically documented remission that was not sustained (31, 32).

Construction of the tissue microarrays

We constructed tissue microarray blocks by taking one representative paraffin-embeded block from every patient and taking one core from morphologically representative areas of blocks as previously described (33). The use of tissue blocks and chart reviews were approved by the Institutional Review Board of The University of Texas M. D. Anderson Cancer Center.

Immunohistochemical analysis

Tissue microarray slides were subjected to immunohistochemical staining according to the manufacturer's protocol (Biocare Medical, Concord, CA). In brief, after initial deparaffinization/hydration, sections were microwaved for 15 min in 10 mM citrate buffer, pH 6.0, to unmask the epitopes. Endogenous peroxidase activity was blocked by using 3% hydrogen peroxide. Non-specific binding was blocked with background-sniper (Biocare Medical) and slides were incubated for 10 min at room temperature. The slides were then incubated overnight at 4°C with primary mouse monoclonal antibody against ALDH1 (clone 44/ALDH, 1:100 dilution; BD Biosciences, San Jose, CA USA); with a biotin-labeled secondary antibody (Universal Goat Link, Biocare Medical) for 15 min; and finally with HRP (Biocare Medical) for 15 min. Tissues were then stained for 5 min with 3,3′-diaminobenzidine (Biocare Medical). Finally, tissues were counterstained with hematoxylin, dehydrated, and mounted in DePex. Negative controls were made by replacing the primary antibody with phosphate-buffered saline. The intensely ALDH1-positive stromal cells were used as internal positive controls.

Immunohistochemical stainings for ALDH1 were analyzed by two gynecological pathologists (J.L., B.C.). Staining scored only according to cytoplasmic staining of the cancer cells. The degree of staining was quantified using a four-score grading system. Cores with <5% ALDH1-positive cells were given a score of 0, those with 5%-20% ALDH1-positive cells were given a score of 1, those with 20%-50% positive cells were scored as 2, and those with >50% positive cells were scored as 3. For the statistical analysis, cases were

divided into two groups: low expression (with scores of 0 or 1) and high expression (with scores of 2 or 3).

Statistical analysis

Fisher's exact test and logistic regression analysis were performed to evaluate the association of ALDH1 with clinical factors. The Kaplan-Meier method was used to estimate the probability of overall survival and disease-free survival, and the log rank test was used to compare the overall survival or disease-free survival between different comparison groups, such as patients with low or high ALDH1 expressions. Multivariate Cox proportional hazards regression models were fitted to to determine the significant factors associated with overall survival and disease-free survival and assess the association of ALDH1 with overall survival or disease-free survival after adjust the effect of other clinical factors. The overall survival time was computed as the time interval from the date of first biopsy to the date of death or the last follow-up date, whichever occurred first. Patients were alive on the last follow-up date were censored. The disease survival time was computed as the time period from the date of first biopsy to the date of recurrence, the date of death or the date of last follow-up, whichever occurred first. Patients alive on the last follow-up date without recurrence were censored. Results were considered statistically significant at the $P < 0.05$ level. SAS 9.1 software (SAS Institute Inc., Cary, NC) was used for the statistical analysis.

Results

Patient characteristics

The median age of the 442 patients was 60 years (range, 21-89 years). The median overall survival time was 4.0 years (95% CI: 3.5 -4.6 years), and the overall survival rates were 60% (95% CI: 0.55 -0.65) at 3 years, 42% (95% CI: 0.37 -0.47) at 5 years, and 27% (0.22 -0.32) at 10 years. The median follow-up interval was 8.0 years with a 95% confidence interval of 6.5 to 10.2 years.

ALDH1 expression and localization

Diffuse cytoplasmic staining with moderate intensity was observed in different proportion of the tumor cells. Very strong cytoplasmic and nuclear staining was observed in stromal cells. The expression in epithelial cancer cells was scored and subjected for statistical analysis. The percentage of positive cancer cells varied from <5 % to > 50% in our patient population (Fig. 1)

Association between expression of ALDH1 and clinicopathologic variables

The results of immunostaining of the tumor microarrays, organized according to clinicopathologic characteristics of the patients, are shown in Table 1. No ALDH1 was expressed (score = 0) in 226 patients (51%), 1% to 5% of the cells expressed ALDH1 in 82 patients (19%) (score also = 0), 6% to 20% of the cells expressed ALDH1 in 49 patients (11%) (score = 1), 21% to 50% of the cells expressed ALDH1 in 46 patients (10%) (score = 2), and >50% of cells expressed ALDH1 in 41 patients (9%) (score = 3). High expression of ALDH1 (>20% of cells) was associated with endometrioid adenocarcinoma (P <0.0001), early-stage disease (P =0.006) (The cut-offs for early vs late stage is I vs II- IV), and low

serum CA125 level (P =0.02). We analyzed the correlation between the expression of ALDH1 and the grade of serous carcinoma and endometrioid carcinoma separately, because of different grading systems were used in serous carcinoma and endometrioid carcinoma. No correlation was found between the expression of the ALDH1 and grade in either the serous or endometrioid carcinoma (data not shown).

The correlation of ALDH1 expression (high or low) with response to primary therapy is shown in Table 2. In total, 346 patients (78%) received postsurgical cisplatinbased treatment, either alone or in combination with other adjuvant drugs. In 46 patients (10%), cisplatin-based treatment was administered before surgical debulking surgery. Three patients (1%) received other forms of treatment (melphalan, 5-fluorouracil plus folinic acid. In 5 patients (1%), the treatment protocol was unknown. Overall, higher levels of expression of ALDH1 (>20%) were observed in the complete response group than in nonresponse group (P = 0.0002). Similar proportions of ALDH1 expression were observed in both the post-surgical cisplatin-based treatment subgroup (P =0.01 and the pre-surgical cisplatin-based treatment subgroup (P=0.04).

The multivariate logistic regression analysis suggested that ALDH1 was significantly associated with histological type and response to chemotherapy (see supplementary table 1). Endometroid carcinoma patients would be more likely to have a higher ALDH1 expression (>20%) compared with these with serous adenocarcinoma (OR=6.12, P <0.0001). Patients with progression disease and recurrent disease would be less likely to have a higher ALDH1 expression (OR=0.31, 0.45 and P =0.03 and 0.03 respectively).

Association of ALDH1 with overall survival and disease-free survival

Overall survival and disease free survival rates at 3 years, 5 years, and 10 years are shown in relation to the expression of ALDH1 in Table 3 and Table 4. At the time of this report, 88 of the 442 analyzed patients were alive without clinical evidence of ovarian carcinoma, 75 were alive with ovarian carcinoma, 262 had died of ovarian carcinoma, 15 were alive with unknown ovarian carcinoma status and 2 had been lost to follow-up which were excluded from the overall survival and disease-free survival analysis. A significant association between the expression of ALDH1 and overall survival (P <0.05) was observed. Patients who had tumors with >20% ALDH1-positive cells had better overall survival rate (P =0.01) and disease free survival rate (P =0.006) than patients who had tumors with <20% ALDH1-positive cells (Fig. 2).

The multivariate Cox proportional hazards regression analysis indicated that stage were significantly associated with overall survival and disease-free survival. Patients with stage II, III and IV would have a higher risk to be dead compared to stage I patients (HR=4.32, 7.2, 9.6 and P =0.01, 0.0002, 0.00002 respectively). Patients with stage II, III and IV would have a higher risk of event (ie, recurrence, progression or death) compared to stage I patients (HR=2.4, 5.7, 7.3 and P =0.048, <0.0001, <0.0001 respectively).

Discussion

In the current study of 442 well-characterized patients with long-term follow-up, high levels of ALDH1 expression were observed in 19% of the ovarian carcinoma samples, which correlated with endometrioid adenocarcinoma, early disease stage, complete response to chemotherapy, and low serum CA125 level and favorable survival. In our study, multivariate Cox proportional hazards regression analysis showed that the early- stage of disease was strong associated with longer overall survival and disease-free survival (P <0.0002 and $P < 0.0001$, respectively) and was a independent prognosis predicator. Although ALDH1 was not an independent predictor in multivariate analysis, high expression of ALDH1 was associated with early-stage disease (P =0.006). It gave us a clue that ALDH1 might be a potential independent prognosis predictor in ovarian cancer. Our results are contrast with the report by Ginestier et al. who demonstrated that the expression of ALDH1 was an independent predictor of poor clinical outcome in breast tumors (15). We found that high ALDH1 expression was associated longer overall survival in patients with ovarian carcinoma. ALDH1 may play a different role in ovarian cancer than it does in breast cancer.

ALDH1 has been demonstrated to be a stem cell marker in several types of malignancy (14-17). Theoretically, a high proportion of cancer stem cells in the tumor should be correlated with a poor prognosis. However, depending on the cancer site, markers used to identify stem cells from one organ may or may not be useful for identifying stem cells from other organs or tumor types (18, 34, 35). Our result, which is based on a large body of clinical material, demonstrates that ALDH1 expression is correlated with favorable clinical outcome in patients with ovarian carcinoma. It remains to be determined whether ALDH1 is associated with a stem cell or stem-like cells in human ovarian cancer.

In summary, the current results demonstrate that in contrast to its role in breast cancer, ALDH1 plays a favorable role in ovarian carcinoma and thus high expression of ALDH1 is a favorable prognostic factor in patients with ovarian cancer. ALDH1 thus may play a different role in ovarian cancer than it does in breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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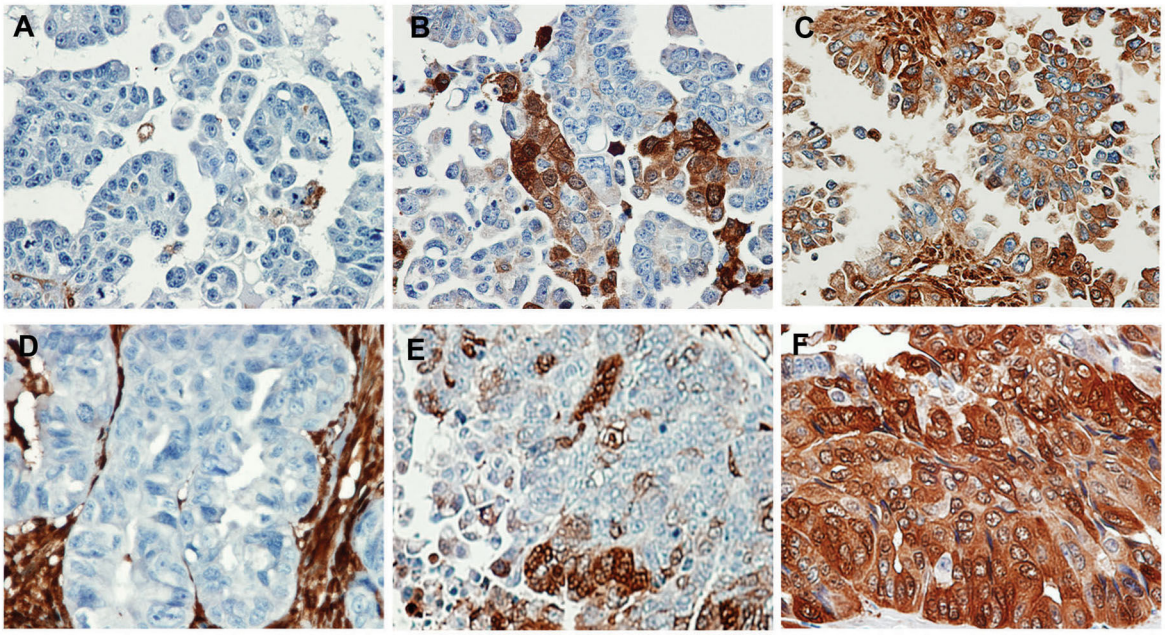

Fig. 1.

Immunoreactivity patterns of ALDH1 in ovarian serous adenocarcinomas (*A*-*C*) and endometrioid adenocarcinomas (*D*-*F*). *A*, ALDH1-negative staining in serous carcinoma. *B*, ≤ 20% serous carcinoma cells show cytoplasmic staining for ALDH1. *C*, Diffuse positive staining for ALDH1 in serous carcinoma. *D*, ALDH1-negative staining in endometrioid adenocarcinoma. *E*, ≤ 20% endometrioid carcinoma cells show cytoplasmic staining for ALDH1. *F*, Diffused positive staining for ALDH1 in endometrioid carcinoma. (Original magnification X200).

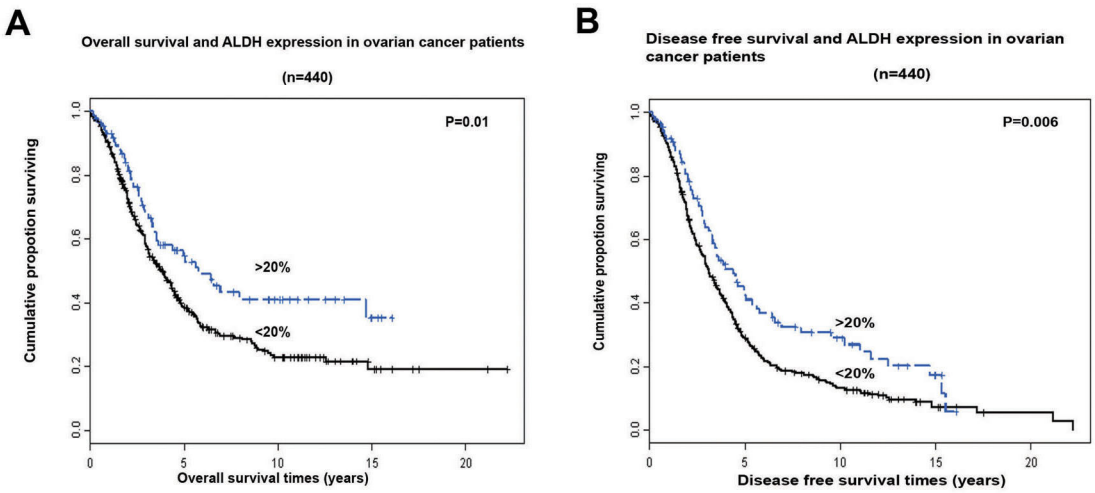

Fig. 2.

Kaplan-Meier survival curves for groups of ovarian carcinoma patients with low and high levels of ALDH1 expression. *A*, Overall survival curves in all patients with ovarian cancer (n = 440). *B*, Disease free survival curves in all patients (n = 440).

Table 1

Correlations between the Expression of ALDH and Clinicopathologic Factors

	No. of Patients (%)			
Characteristic	**≤20% ALDH-positive cells**	**> 20% ALDH-positive cells**	**Total No.**	***P*** *
Histologic type				<0.0001
Serous carcinoma	227 (85)	39 (15)	266	
Endometrioid carcinoma	15 (43)	20 (57)	35	
Mucinous carcinoma	3 (60)	2 (40)	5	
Clear-cell carcinoma	12 (86)	2 (14)	14	
MMMT	12 (70)	5 (30)	17	
Poorly differentiated carcinoma	7 (88)	1 (12)	8	
Transitional cell carcinoma	6 (100)	0 (0)	6	
Mixed-type carcinoma	75(82)	16(18)	91	
FIGO disease stage				0.006
Stage I	18 (56)	14 (44)	32	
Stage II	24 (80)	6 (20)	30	
Stage III	250 (82)	55 (18)	305	
Stage IV	60 (83)	12 (17)	72	
unknown			3	
CA125(U/ml)				
<500	55 (71)	23 (29)	78	0.02
≥500	113 (84)	22 (16)	135	
unknown			229	

MMMT: malignant mixed Mullerian tumor; FIGO: International Federation of Gynecology and

* *P* values were calculated by Fisher's exact test

Table 2

Correlation of ALDH1 Expression and Response to Primary Therapy

	No. of patients		
Response to primary therapy*	**≤ 20% ALDH1-positive cells**	**> 20% ALDH-positive cells**	**Total**
Unknown response	10	2	12
Responders			
Cisplatin-based regimens			
Postsurgery†	170	53	223
Presurgery‡	9	6	15
Other regimens	0	0	0
Unknown regimen	3	0	3
Nonresponders, progressive disease			
Cisplatin-based regimens			
Postsurgery†	84	11	95
Presurgery‡	21	4	25
Other regimens	1	0	1
Unknown regimen	1	0	1
Nonresponders, recurrent disease			
Cisplatin-based regimens			
Postsurgery†	26	2	28
Presurgery‡	6	0	6
Other regimens	2	0	2
Unknown regimen	1	0	1
No chemotherapy	11	9	20
Total	321	121	442

*P values were calculated by using Fisher's exact test (response to primary therapy, P=.0002)

†Cisplatin-based postsurgery subgroup (P=0.01).

‡Cisplatin-based presurgery subgroup (P=0.04).

Table 3

ALDH1 Expression and Overall Survival

ALDH expression	No. of Patients	Median survival (95%CI) years	Survival rate (95%CI)			*P* *
			3-Year	5-Year	10-Year	
≤ 20%	353	3.8 (3.2 , 4.4)	0.58 (0.53 , 0.64)	0.39 (0.33 , 0.45)	0.23 (0.18 , 0.29)	0.01
> 20%	87	5.8 (3.5 , NA)	0.68 (0.55 , 0.79)	0.55 (0.44 , 0.67)	0.41 (0.30 , 0.55)	

* *P* values were derived from the Log rank test.

Table 4

ALDH1 Expression and Disease Free Survival

ALDH expression	No. of Patients	Median survival (95%CI) years	Survival rate (95%CI)			*P* *
			3-Year	5-Year	10-Year	
≤ 20%	353	3.1 (2.8 , 3.7)	0.52 (0.47 , 0.57)	0.29 (0.24 , 0.34)	0.13 (0.1 , 0.18)	0.006
> 20%	87	4.4 (3.3 , 5.8)	0.64 (0.54 , 0.75	0.44 (0.34 , 0.56)	0.29 (0.2 , 0.42)	

* *P* values were derived from the Log rank test.