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ORIGINAL ARTICLE

Prospective Study

Expression of pyruvate dehydrogenase is an independent prognostic marker in gastric cancer

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Abstract

AIM: To investigate the expression and prognostic role of pyruvate dehydrogenase (PDH) in gastric cancer (GC).

METHODS: This study included 265 patients (194 male, 71 female, mean age 59 years (range, 29-81 years) with GC who underwent curative surgery at the First Affiliated Hospital of China Medical University from January 2006 to May 2007. All patients were followed up for more than 5 years. Patient-derived paraffin embedded GC specimens were collected for tissue microarrays (TMAs). We examined PDH expression by immunohistochemistry in TMAs containing tumor tissue and matched non-neoplastic mucosa. Immunoreactivity was evaluated independently by two researchers. Overall survival (OS) rates were determined using the Kaplan-Meier estimator. Correlations with other clinicopathologic factors were evaluated by two-tailed χ^2 tests or a two-tailed *t*-test. The Cox proportional-hazard model was used in univariate analysis and multivariate analysis to identify factors significantly correlated with prognosis.

RESULTS: Immunohistochemistry showed that 35.47% of total cancer tissue specimens had cytoplasmic PDH staining. PDH expression was much higher in normal mucosa specimens (75.09%; P = 0.001). PDH

expression was correlated with Lauren grade (70.77% in intestinal type *vs* 40.0% in diffuse type; $P = 0.001$), lymph node metastasis (65.43% with no metastasis *vs* 51.09% with metastasis; $P = 0.033$), lymphatic invasion (61.62% with no invasion *vs* 38.81% with invasion; $P = 0.002$), histologic subtypes (70.77% in intestinal type *vs* 40.0% in diffuse type; $P = 0.001$) and tumor-node-metastasis (TNM) stage (39% in poorly differentiated *vs* 65.91% in well differentiated and 67.11% in moderately differentiated; $P = 0.001$) in GC. PDH expression in cancer tissue was significantly associated with higher OS ($P < 0.001$). The multivariate analysis adjusted for age, Lauren classification, TNM stage, lymph node metastasis, histological type, tumor size, depth of invasion and lymphatic invasion showed that the PDH expression in GC was an independent prognostic factor for higher OS (HR = 0.608, 95%CI: 0.504-0.734, $P < 0.001$).

CONCLUSION: Our study indicated that PDH expression is an independent prognostic factor in GC patients and that positive expression of PDH may be predictive of favorable outcomes.

Key words: Pyruvate dehydrogenase; Gastric carcinoma; Tissue microarray; Prognosis; Immunohistochemical analysis

Core tip: This is the first reported study to evaluate the prognostic role of pyruvate dehydrogenase (PDH) expression in gastric cancer (GC). This study showed that reduced PDH expression was correlated with Lauren grade, lymph node metastasis, lymphatic invasion, histologic subtype and TNM stage in GC. We propose that increased PDH expression may contribute to a decrease in the proliferation and development of GC. In particular, PDH protein expression was found to positively correlate with survival in GC patients, and a high level of PDH expression was found to be associated with better overall survival in patients with resected GC. In conclusion, this study showed that PDH expression is an independent prognostic factor in gastric carcinomas.

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INTRODUCTION

Although the incidence of gastric cancer (GC) is declining, it is still ranked as the fourth most common cancer and the second leading cause of cancer-related mortality worldwide[1,2]. Despite advances in early diagnosis and therapy, metastases are a common cause of death[3,4]. Among the prognostic factors for GC that are now available, the most important is the tumor-node-metastasis (TNM) stage. However, the prognosis varies among patients of the same stage[5]. Therefore, novel molecular markers need to be defined to better identify different subsets of the disease and assist in the implementation of individualized therapeutic regimens.

The Warburg effect, also known as aerobic glycolysis, is one of the characteristics of tumor cells in which a high rate of glycolysis occurs, even in the presence of adequate oxygen[6-8]. The surprisingly high rate of glucose uptake and lactate production in tumors in the presence of oxygen led Warburg to speculate that an aberrant metabolism could be the cause of many cancers[9]. It has been a belief that the glycolytic phenotype of cancer cells is attributable to defects in mitochondrial oxidative phosphorylation (OXPHOS). However, recent results have revealed that most tumor cells have a substantial reserve capacity to produce adenosine triphosphate by OXPHOS when glycolysis is suppressed, showing that the high rate of glycolysis exhibited by most tumors is required to support cell growth rather than to compensate for defects in mitochondrial function[10]. Because reactive oxygen species are natural by-products of mitochondrial respiration, it has been proposed that the conversion of glucose to lactate may protect cancer cells from oxidative stress[11]. Therefore, taking advantage of the glycolytic characteristics of cancer cells and the activating function of mitochondrial OXPHOS may serve as a significant strategy for cancer therapy.

Pyruvate dehydrogenase (PDH) is a mitochondrial enzyme that plays a central role in aerobic energy metabolism by catalyzing the irreversible oxidation of glucose-derived pyruvate to acetyl-CoA. Acetyl-CoA then enters the tricarboxylic acid cycle, where it reacts with oxaloacetate to form citrate. In cancerous cells the inhibition of PDH activity *via* the over-expression of pyruvate dehydrogenase kinase (PDK) leads to the energetic switch from mitochondrial glucose oxidation to cytoplasmic glycolysis[12]. Therefore, PDH serves as a gate-keeper enzyme link between glycolysis and the mitochondrial citric acid cycle[13,14]. Several studies have found that the activation of PDH shifts cancer cell metabolism from glycolysis to glucose oxidation and thus decreases the mitochondrial membrane potential and lactate production, augments reactive oxygen species, and is associated with the induction of apoptosis and reduction in tumor cell proliferation without any harmful effects in normal cells[12-17]. Recent research showed that the normalization of glucose metabolism by stimulating PDH in cancer cells restored their susceptibility to anoikis and impaired their

metastatic potential[18]. However, the expression status in GC, the relation of PDH expression with progression, and the prognosis of patients remains unknown. In this study, we first examined the expression of PDH in GC and then correlated its expression with clinical pathological parameters and overall survival (OS). Our results demonstrate that the loss of PDH expression is a marker of tumor aggressiveness and that a high expression of PDH in GC may be predictive of favorable outcomes.

MATERIALS AND METHODS

Patients

The present study included 265 patients with GC who received curative surgery from January 2006 to May 2007 at the First Affiliated Hospital of China Medical University. There were 194 males and 71 females, with a mean age of 59 years (range, 29-81 years). None of the patients underwent chemotherapy or radiotherapy before surgery. Follow-up information was collected from all patients. The Institutional Review Board at the First Affiliated Hospital of China Medical University approved this study.

Ethics statement

Ethical approval for this research was obtained from the Research Ethics Committee of China Medical University, China. All patients providing tumor tissue as well as normal gastric tissue samples signed a consent form prior to surgical removal of the gastric carcinoma to allow this research to be undertaken.

Tissue samples and pathology

All patient-derived formalin-fixed and paraffin-embedded GC specimens and matched non-neoplastic mucosa (NNM) specimens (from at least 2 cm away from the carcinoma) were collected during surgical resection and archived under protocols that were approved by the Institutional Review Board of the University. The histologic diagnosis and other microscopic characteristics were confirmed by pathologists, and the TNM stage of each gastric carcinoma was evaluated according to the Union for International Cancer Control system for the extent of tumor spread[19]. The histologic architecture of the gastric carcinoma was expressed using Lauren's classification[20,21] and the World Health Organization (WHO) classification[22]. Tumor size, depth of invasion, and lymphatic invasion were also determined.

Tissue microarray and immunohistochemistry

Representative areas of solid tumors and adjacent NNM were identified in hematoxylin and eosin (HE)-stained sections of the selected cases. A 1.5 mm diameter tissue core per donor block was punched out using a 1.5 mm diameter punch and then transferred to a recipient block with a maximum of 200 cores. The sections (4 μm thick) were consecutively cut from each tissue microarray block, and HE staining was performed on the tissue microarrays (TMAs) to confirm tumor and NNM tissue. Immunohistochemical analysis was performed on the TMA sections, and pressure cooker-mediated antigen retrieval was performed in citrate buffer (pH 6.0) for 10 min. The sections were incubated with a 1:100 dilution of pyruvate dehydrogenase (C54G1) in Rabbit mAb (Cell Signaling) overnight at 4 ℃, and then incubated with goat anti-mouse or anti-rabbit Envision System Plus-HRP (Dako Cytomation) for 30 min at room temperature. After rinsing three times in PBS for 10 min each, the sections were incubated with DAB for 1 min, counterstained with Mayer's hematoxylin, dehydrated, rinsed and mounted. The same protocol with the omission of the primary antibody was used as a negative control.

Follow-up after surgery

The patients underwent close clinical observation, including chest/abdominal/pelvic computed tomographic imaging, measurement of carcinoembryonic antigen level, blood testing at 2- to 3-mo intervals, and a yearly gastroscopy. Follow-up was in accordance with National Comprehensive Cancer Network Practice Guidelines for Gastric Cancer. OS rate was defined as the interval from the initial surgery to death. The end date of follow-up for conducting the analysis was June 29, 2012.

Evaluation of immunohistochemical staining

Immunoreactivity was evaluated independently by two researchers who were blinded to the patient outcomes. The evaluation was based on the staining intensity for PDH and was scored as 0 (-) negative; 1 (+) weak; 2 (++) moderate; or 3 (+++) strong. If heterogeneity was detected by cell immunohistochemical staining, the proportion of positive cells was considered as follows: 0, negative; 1, positive in ⩽ 10% of cells; 2, positive > 10% and ⩽ 50%; 3, positive > 50% and ⩽ 80%; and 4, positive in > 80% of cells. The two scores were then multiplied, and the expression was graded as follows: negative, score = 0 (-); weak expression, score = 1-4 (+); moderate expression, score = 5-8 (++); or strong expression, score = 9-12 (+++). These specimens were divided into two groups according to their scores: 0-4 was the negative group, and 5-12 was the positive group. In the event of a discrepancy in scoring, both pathologists re-examined the slides under a microscope.

Statistical analysis

All statistical analyses were performed using SPSS 17.0 software (SPSS Inc, Chicago, IL, United States). OS rates were determined using Kaplan-Meier curves, and an event was defined as death from cancer-related causes. The log-rank test was used to identify the differences between survival curves. In univariate

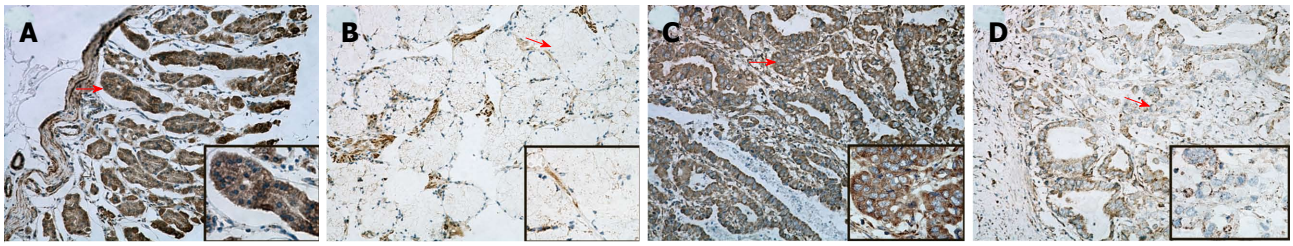

Figure 1 Immunohistochemical staining of pyruvate dehydrogenase in gastric samples. The typical diffuse cytoplasmic staining of the protein can be found in many gastric carcinoma and normal gastric tissues. A: PDH positivity was observed in the cytoplasm of NNM; B: PDH negativity was observed in NNM; C: PDH positivity was observed in the cytoplasm of well-differentiated gastric cells; D: Low expression of PDH was observed in gastric well-differentiated cancer cells. PDH: Pyruvate dehydrogenase; NNM: Non-neoplastic mucosa.

Table 1 Expression of pyruvate dehydrogenase in non-neoplastic mucosa and cancerous tissues in gastric cancer

Tissue sample	*n*	PDH							*P* value[1]
		-	+-	Total	+	++	Total	PR (%)	χ^2 test
Adjacent normal mucosa	265	46	20	66	159	40	199	75.09	0.001
Primary cancer tissue	265	50	68	118	102	45	147	55.47	

[1]Pearson χ^2 test. PDH: Pyruvate dehydrogenase.

analysis, a two-tailed χ^2 test or a two-tailed *t*-test was used for statistical comparisons. The Cox proportional-hazard model was used in univariate analysis and multivariate analysis to identify the significant factors that were correlated with prognosis. For all analyses, *P* values < 0.05 were considered significant.

The statistical methods of this study were reviewed by Wu Wei from the Statistics Teaching and Research section of China Medical University.

RESULTS

PDH expression in human GC tissue

We graded stained sections of the TMAs of GC and NNM tissue cores according to their cytoplasmic immunohistochemical staining intensity against PDH protein, and the percentage of positive cells was determined when HE staining had heterogeneity. The readable samples included 265 GC and matched NNM samples. The typical diffuse cytoplasmic staining of the protein can be found in many GC and NNM tissues, as shown in Figure 1.

Of the 265 GC tissue specimens, 147 (55.47%) showed positive cytoplasmic PDH staining (102 moderate positive and 45 strong positive), and 118 (44.53%) displayed negative staining (68 weak staining and 50 negative staining). In contrast, PDH expression was much higher in NNM specimens with positive staining in 199 (75.09%) specimens (40 strong positive and 159 moderate positive) and negative staining in 66 (24.91%) specimens (20 weak staining and 46 negative staining). A comparative analysis of the immunohistochemistry results of the TMAs indicated that PDH was differentially downregulated in the GC specimens compared with the NNM tissues (Table 1; *P* = 0001). Figure 2 shows the PDH expression level in GC and NNM tissues from the same patient. The results showed that 123 patients had PDH co-expression (GC^+/NNM^+), 24 patients had GC^+/NNM^- single expression, 76 patients had GC^-/NNM^+ single expression, and 42 patients had double-PDH negative expression.

Clinicopathological variables in 265 cases of gastric cancer

As summarized in Table 2, we found that decreased expression of PDH was significantly associated with GC Lauren grade, lymph node metastasis, lymphatic invasion, and TNM stage ($P < 0.05$), but not with age, sex, tumor size or depth of invasion ($P > 0.05$). Among the WHO histologic subtypes, the poorly differentiated subtype displayed a lower PDH expression than did the well differentiated, moderately differentiated and mucinous carcinoma subtypes ($P < 0.05$; Table 3). In addition, PDH expression was significantly inversely correlated with TNM stage and the depth of invasion of differentiated carcinomas ($P < 0.05$; data not shown) and was significantly inversely correlated with the depth of invasion, Lauren grade and TNM stage of undifferentiated carcinomas ($P < 0.05$; data not shown).

Survival analysis

The 5-year OS rate of the 265 patients with primary GC was 46% (122/265), with 143 deaths observed during the follow-up period. The median duration of follow-up was 50 mo (range, 9-78 mo). Kaplan-Meier survival curves and the log-rank test demonstrated that patients with positive expression of PDH in GC tissue had better OS than did patients with negative PDH expression in

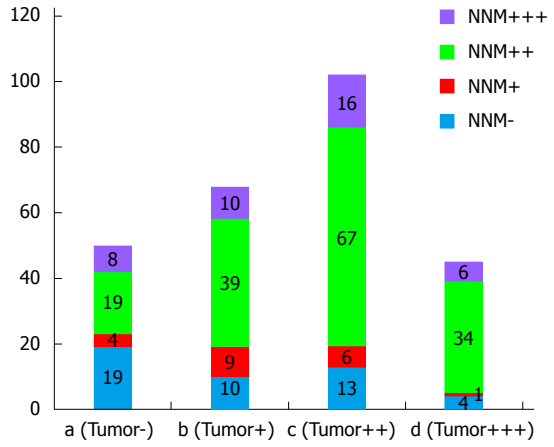

Figure 2 Relationship between pyruvate dehydrogenase expression level in cancer and non-neoplastic mucosa tissue from the same patient. The results showed that 123 patients had pyruvate dehydrogenase (PDH) co-expression (GC^+/NNM^+), 24 patients had GC^+/NNM^- single expression, 76 patients had GC^-/NNM^+ single expression, and 42 patients had double PDH negative expression; 147 cases (55.47%) showed positive PDH staining (Tumor ++ and Tumor +++) and 118 (44.53%) specimens displayed negative staining (Tumor - and Tumor +). PDH expression was much higher in the NNM tissue with positive staining in 199 (75.09%) specimens and negative staining in 66 (24.91%) specimens; $P < 0.001$. NNM: Non-neoplastic mucosa; GC: Gastric cancer.

the tumor ($P < 0.001$; Figure 3A). The 5-year survival rate of patients with positive expression was significantly higher than that of patients with negative expression (65.8% *vs* 28.0%, respectively). In addition, the expression of PDH in NNM had a predictive prognostic role ($P = 0.008$; Figure 3B). We combined the expression of PDH in GC and in NNM and then divided the patients into a co-expression group (GC^+/NNM^+), two single-expression groups (GC^+/NNM^- and GC^-/NNM^+), and a double-PDH negative group. The co-expression group had a significantly longer survival time than did the double-PDH negative group ($P < 0.001$; Figure 3C). Because GC can be classified into different subtypes, we also analyzed the prognostic value of PDH in different subtypes stratified by Lauren grade (intestinal-type and diffuse-type), histological classification (differentiated type and undifferentiated type), and TNM stage (Ⅰ-Ⅳ). The results showed that stronger PDH staining was significantly associated with better OS in each subtype of GC ($P < 0.05$; Figure 3D-K).

Multivariate analysis was performed using the Cox proportional hazards model for all of the significant variables in the univariate analysis. Table 4 shows the analysis, adjusted for age, Lauren classification, TNM stage, lymph node metastasis, histological type, tumor size, depth of invasion and lymphatic invasion covariates, and that PDH expression in GC was an independent prognostic factor for higher OS (HR = 0.608, 95%CI 0.504-0.734, $P < 0.001$).

DISCUSSION

A striking discovery was made in a tumor metabolism study in the 1920s by Warburg. The study demonstrated that, as a result of multiple adaptive mechanisms, cancer cells take up glucose at higher rates than do normal cells and produce energy primarily by aerobic glycolysis rather than by the mitochondrial oxidation of pyruvate for their energy requirements. The important function of aerobic glycolysis in tumor progression has been recognized[23,24], though the molecular mechanisms leading to this phenotype and its functional significance in cancer development remain unknown. PDH is a mitochondrial enzyme that catalyzes the conversion of pyruvate into acetyl-CoA. In tumor cells, the inhibition of PDH activity can inhibit mitochondrial OXPHOS and promote tumor aerobic

Table 2 Relationship between pyruvate dehydrogenase expression and clinicopathological features of gastric carcinomas

Clinicopathologic variable	*n*	PDH expression			
		-	+	PR (%)	*P* value[1]
	265	118	147	55.47	
Sex					0.577
Female	71	34	37	52.11	
Male	194	84	110	56.7	
Age (yr)					0.902
< 60	133	60	73	54.89	
⩾ 60	132	58	74	56.06	
Tumor size (cm)					0.347
< 4	80	32	48	60.00	
⩾ 4	185	87	98	52.97	
Depth of invasion					0.093
Tis-1	25	7	18	72.00	
T2-4	240	111	129	53.75	
Lauren grade					0.001
Intestinal type	130	38	92	70.77	
Diffuse type	135	81	54	40.00	
TNM Stage					0.010
0- Ⅰ	38	8	30	78.95	
Ⅱ-Ⅳ	227	110	117	51.54	
Lymph node metastases					0.033
Negative	81	28	53	65.43	
Positive	184	90	94	51.09	
Lymphatic invasion					0.002
Absent	198	76	122	61.62	
Present	67	41	26	38.81	

[1]Pearson χ^2 or Fisher's exact test. PR: Positive rate; PDH: Pyruvate dehydrogenase

Table 3 Association of PDH expression with different subtypes of gastric adenocarcinoma according to WHO classification

Tissue Sample	*n*	PDH				PR (%)
		-	+-	+	++	
Well-differentiated	44	6	9	12	17	65.91
Moderately differentiated	76	9	16	36	15	67.11
Poorly differentiated	100	30	31	31	8	39[1]
Mucinous	30	2	6	17	5	73.33
Signet ring cell	15	3	6	6	0	40
Total	265	50	68	102	45	55.50

[1]Compared with well-differentiated $P = 0.004$, moderately differentiated $P < 0.001$, or mucinous. *P* value obtained from Pearson χ^2 test. PDH: Pyruvate dehydrogenase.

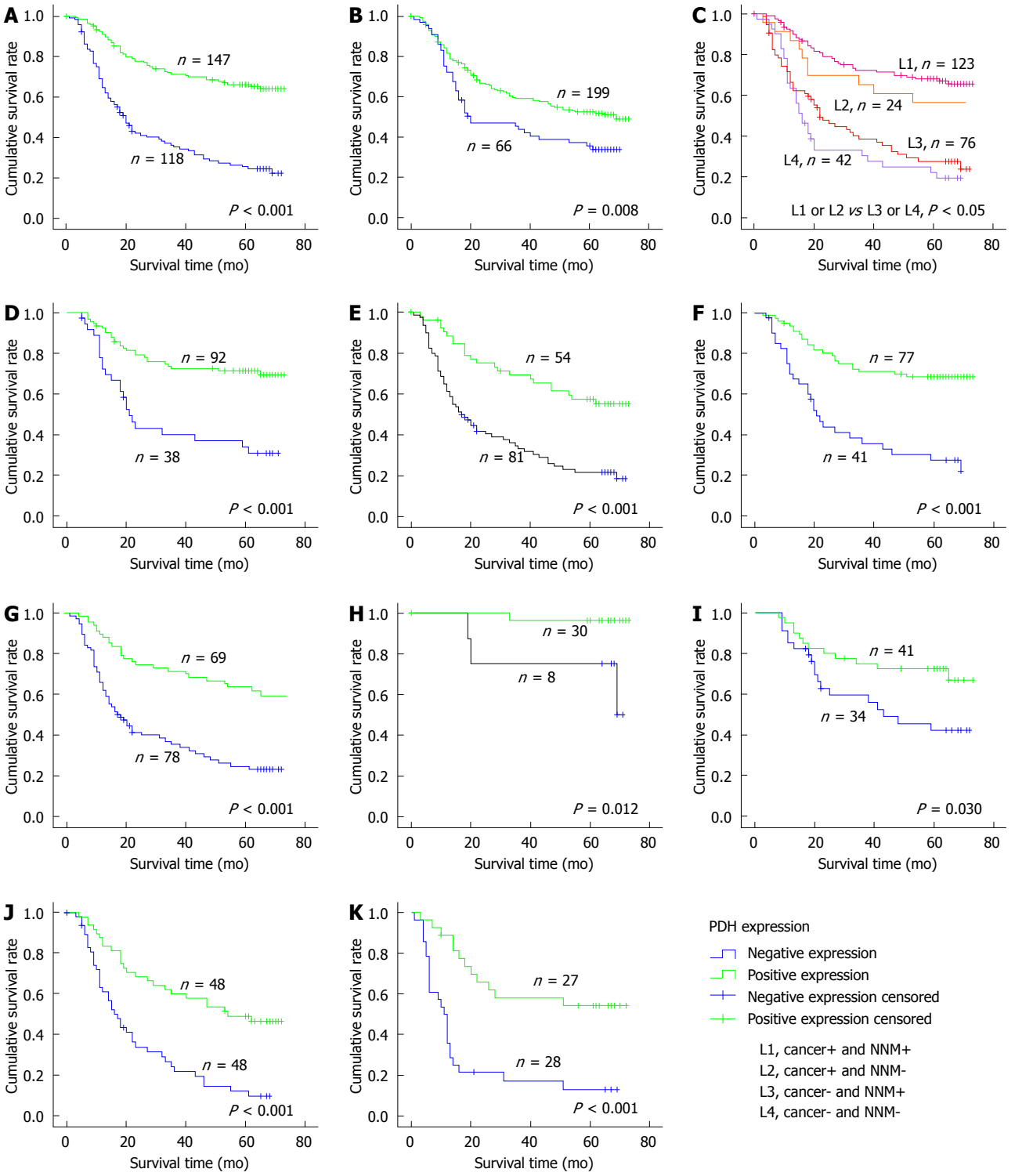

Figure 3 Correlation between pyruvate dehydrogenase expression and prognosis of gastric cancer patients. Kaplan-Meier curves for cumulative survival of patients with gastric cancer (GC) according to GC tissue pyruvate dehydrogenase (PDH) expression shows that PDH expression in GC (A), in non-neoplastic mucosa (NNM) (B) and in both GC and NNM (C) was significantly associated with better overall survival. The Kaplan-Meier curves for cumulative survival rate stratified by Lauren grade, histological type and tumor-node-metastasis (TNM) stage also show that PDH expression was significantly associated with a better overall survival in each subtype of GC: intestinal-type GC (D), diffuse-type GC (E), differentiated type GC (F), undifferentiated type GC (G), and TNM stage Ⅰ (H), Ⅱ (I), Ⅲ (J), and Ⅳ (K) subgroups.

glycolysis. Nevertheless, the expression of PDH in GC remains unknown. Therefore, we hypothesized that tumor cell inhibition of the activity of PDH and the resultant altered expression of PDH in cancer cells may represent a potential prognostic biomarker in patients who are at risk of developing metastasis or recurrence with gastric carcinoma.

To our knowledge, this is the first reported study to

Table 4 Univariate and multivariate analysis for overall survival after surgery using Cox relative risk

Variable	Univariate analysis		Multivariate analysis	
	RR (95%CI)	*P* value	RR (95%CI)	*P* value
PDH expression in tumor (positive *vs* negative)	0.552 (0.462-0.658)	< 0.001[1]	0.608 (0.504-0.734)	< 0.001[1]
PDH expression in NNM (positive *vs* negative)	0.830 (0.699-0.987)	0.035	0.869 (0.727-1.039)	0.123
Age (≥ 60 yr *vs* < 60 yr)	1.446 (1.030-2.032)	0.033	1.447 (1.010-2.073)	0.044
Tumor size (< 4 cm *vs* ≥ 4 cm)	2.297 (1.505-3.504)	< 0.001[1]	1.492 (0.956-2.329)	0.078
Depth of invasion (Tis-1 *vs* T2-4)	5.114 (1.889-13.843)	0.001[1]	1.683 (0.567-4.995)	0.348
Lauren grade (intestinal-type *vs* diffuse-type)	1.978 (1.396-2.803)	< 0.001[1]	1.574 (1.081-2.292)	0.018[1]
TNM Stage (0-Ⅰ *vs* Ⅱ-Ⅳ)	1.809 (1.504-2.176)	< 0.001[1]	1.512 (1.191-1.920)	0.001[1]
Lymph node metastasis (positive *vs* negative)	3.146 (1.989-4.977)	< 0.001[1]	1.733 (1.061-2.830)	0.028[1]
Lymphatic invasion (positive *vs* negative)	2.041 (1.424-2.924)	< 0.001[1]	1.271 (0.875-1.847)	0.208
Histological type (differentiated *vs* undifferentiated)	1.460 (1.033-2.063)	0.032	1.058 (0.667-1.678)	0.811

[1]Significant difference. RR and 95%CI were assessed using univariate and multivariate Cox regression analysis. RR: Relative risk.

investigate PDH expression *in vitro* in a large series of human GC specimens. An important finding was that PDH protein expression significantly correlated with survival in OS patients and that increased expression of PDH was found to be associated with good survival in GC patients.

We examined the expression of PDH in tumor tissue from 265 GC patients, and presented its correlation with clinicopathological parameters and patients' prognosis. Our study revealed that immunohistochemical staining of PDH was detected in GC and NNM, and it was interesting to find that PDH expression was significantly downregulated in GC specimens compared with adjacent NNM tissues. These results may be consistent with a previous study that found that aberrant metabolism could be the cause of many cancers[9]. Our study also showed that tumor tissue PDH expression was strongly inversely correlated with the following GC clinicopathologic characteristics: Lauren grade, lymph node metastasis, lymphatic invasion, histologic subtypes and TNM stage. Therefore, we propose that the loss of PDH expression may contribute to the proliferation and development of GCs. In addition, we analyzed the prognostic role of PDH on OS of patients with GC and found a significant association between PDH expression (in GC or NNM) and OS of patients, and patients with stronger PDH staining had a longer survival time. When we combined the expression of PDH in GC and NNM and divided patients into a co-expression group, two single-expression groups and a double-PDH negative group, the co-expression group patients had a much longer survival time than did the double-PDH negative group. We also analyzed the prognostic value of PDH in different subtypes stratified by TNM stage, Lauren classification and histological classification separately. The results showed that stronger PDH staining was significantly associated with better OS in each subtypes of GC. Our results suggest that the expression of PDH is an independent prognostic factor of OS and indicate that PDH might have an anticancer role in tumor development.

PDH is widely expressed in the mitochondrial matrix of mammalian cells and provides a link between glycolysis and the tri-carboxylic acid cycle by catalyzing the conversion of pyruvate into acetyl-CoA. The activity of PDH depends on the integrity of a multienzyme complex, which is comprised of PDH(E1), dihydrolipoamide acetyltransferase (E2) and dihydrolipoamide dehydrogenase (E3), and two regulatory components, PDK and PDH phosphatase[25]. PDK-1 is a Ser/Thr kinase that negatively regulates PDH activity by phosphorylating the PDHA1 subunit[26]. A study demonstrated that the mitochondrial metabolism of tumor cells is increased by the pharmacologic inhibition of PDK-1[27]. In cancer cells, lactate dehydrogenase A has been shown to play a critical role in glycolysis by converting pyruvate to lactate, and a high level of lactate is associated with a poor prognosis in a number of tumors[28]. Maintaining the glycolysis pathway may be a more important aspect of the inhibition of PDH[9,29]. Ozden *et al*[30] reported that SIRT3 interacts with PDH(A1) and directs its enzymatic activity *via* changes in protein acetylation and links glycolysis to respiration. Kikuchi *et al*[31] revealed that prolyl-hydroxylase regulates PDH activity in cells by physically interacting with the PDH complex. The above studies and our research suggested that a decrease in the quantity and quality of PDH may occur during the development of tumorigenesis. Recent research showed that stimulating PDH in cancer cells restored their susceptibility to anoikis and impaired their metastatic potential[18]. In our study, the correlation between the expression of PDH and OS in GC patients may provide important evidence that a decrease in the quantity and quality of PDH is implicated in cancer metabolism in the process of GC development. However, the mechanism remains obscure and is a subject for further study.

In conclusion, these results indicate that the expression of PDH is significantly inversely correlated with clinical pathological characteristics of GC. Moreover, the expression of PDH may be useful in predicting outcomes as a strong molecular marker in GC patients, and may be associated with a negative carcinogenic regulatory role. Nevertheless, it remains

to be determined how the expression of PDH is regulated and what the relationship is between the expression of PDH and the activity of PDH in tumor cells. In addition, our results could not explicitly explain why a certain number of patients expressed PDH in tumor tissue but not in their NNM tissue. The hypothesis that we proposed to account for this phenomenon is that normal tissues could have a lower expression of PDH when they have an abundant oxygen supply, which could not be detected by immunohistochemistry. We also do not know whether the PDH expression in NNM inhibits the growth and metastasis of the tumor cells. These biological roles of PDH in the progression of these tumors need to be further elucidated.

COMMENTS

Background

Pyruvate dehydrogenase (PDH), a mitochondrial enzyme that catalyzes the conversion of pyruvate into acetyl-CoA, serves as a gate-keeper enzyme link between glycolysis and the citric acid cycle. The inhibition of PDH activity is linked to cancer aerobic glycolysis. However, its expression in cancer has not been characterized. The purpose of this study was to clarify the expression of PDH in gastric cancer and its potential impact on the development and prognosis in gastric cancer (GC).

Research frontiers

Aerobic glycolysis is a hallmark of cancer progression. Pyruvate kinase M2 (PKM2) and lactate dehydrogenase A (LDHA) are the hotspots of aerobic glycolysis. Some studies note that the high expression of PKM2 and LDHA could promote glycolysis. The aerobic glycolysis process showed that high rates of glucose uptake and lactate production in tumors facilitated cancer proliferation. The inhibition of PDH activity is linked to the promotion of cancer aerobic glycolysis.

Innovations and breakthroughs

This is the first reported study to evaluate the prognostic role of PDH expression in cancer. The purpose of this study was to clarify the expression of PDH in GC and its potential impact on the development and prognosis in GC.

Applications

The expression of PDH may be useful in predicting outcomes in GC patients as a strong molecular marker associated with a negative carcinogenic regulatory role.

Terminology

The Warburg effect, also known as aerobic glycolysis, is one of the characteristics of tumor cells in which a high rate of glycolysis occurs even in the presence of adequate oxygen. PDH is a mitochondrial enzyme that plays a central role in aerobic energy metabolism by catalyzing the irreversible oxidation of glucose-derived pyruvate to acetyl-CoA. Acetyl-CoA then goes into the tricarboxylic acid cycle where it reacts with oxaloacetate to form citrate.

Peer-review

This is a study in which the authors analyzed the expression of PDH in gastric cancers. The results suggest that positive expression of PDH was independent prognostic factors in cancer tissue, and PDH expression was significantly associated with higher overall survival.

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