中国临床研究 Chin J Clin Res, March 2024, Vol.37, No.3

Cite as: Xia JJ, Xu JT, Guan XX. Glucose metabolism-related genes with clinicopathological characteristics and prognosis of breast cancer: an analysis based on TCGA database [J]. Chin J Clin Res, 2024,37(3):359-364.
DOI: 10.13429/j.cnki.cjcr.2024.03.007

Glucose metabolism-related genes with clinicopathological characteristics and prognosis of breast cancer: an analysis based on TCGA database

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Abstract: Objective To investigate the relationship between the expression of *LDHA, SLC16A1* and *SLC16A3* genes and pathologic features and prognosis in breast cancer. **Methods** Tissue samples from 1 060 breast cancer patients in The Cancer Genome Atlas (TCGA) were obtained. The association of *LDHA, SLC16A1* and *SLC16A3* gene expressions with clinicopathological features and prognosis of breast cancer were analyzed. Survival curve was drawn by Kaplan-Meier survival analysis, and univariable and multivariable survival prognoses were analyzed by Cox proportional hazard regression model. **Results** *LDHA* expression was associated with distant metastasis (M stage) (χ^2=5.560, *P*=0.018), estrogen receptor (ER) expression (χ^2=8.532, *P*=0.003), and human epidermal growth factor receptor 2 (HER-2) expression (χ^2=4.418, *P*=0.036); *SLC16A1* expression correlated with age (χ^2=8.040, *P*=0.005), ER expression (χ^2=17.428, *P*<0.01), and progesterone receptor (PR) expression (χ^2=5.486, *P*=0.019). *SLC16A3* expression correlated with ER expression (χ^2=22.447, *P*<0.01) and PR expression (χ^2=20.590, *P*<0.01). Patients with high expression of *LDHA* (χ^2=3.856, *P*=0.049), *SLC16A1* (χ^2=3.978, *P*=0.046) and *SLC16A3* (χ^2=5.008, *P*=0.025) had lower cumulative survival rates. *SLC16A1* (*HR*=1.894, 95%*CI:* 1.246-2.878, *P*=0.003) and *SLC16A3* (*HR*=1.769, 95%*CI*:1.009-2.847, *P*=0.019) were the independent risk factors for overall survival (OS) in breast cancer patients. **Conclusion** *LDHA, SLC16A1* and *SLC16A3* are associated with certain pathologic features and poorer prognosis of breast cancer, which may provide new prognostic indicators and therapeutic targets for breast cancer treatment.

Keywords: Breast cancer; Glucose metabolism; Lactate dehydrogenase A; Solute carrier family 16 member 1; Solute carrier family 16 member 3; Overall survival

Fund program: Social Development Project of the Jiangsu Province (BE2021741)

The incidence and mortality of breast cancer in China are gradually increasing and are expected to continue rising [1]. According to the 2020 Global Cancer Observatory, breast cancer has become the most common cancer worldwide [2]. Tumor cells accelerate the uptake and utilization of various nutrients [3]. They tend to preferentially obtain energy through anaerobic glycolysis, a phenomenon known as the Warburg effect [4]. Although the efficiency of glycolysis in producing ATP is relatively low, the rate is much higher than that of oxidative phosphorylation [5]. Moreover, the intermediate products of glycolysis play significant roles in inhibiting cell apoptosis, promoting cell biosynthesis, and generating signaling molecules [6]. The lactate produced by anaerobic glycolysis is transported outside the cell by lactate transporters, maintaining the weak acidity of the tumor microenvironment, which is more conducive to tumor growth [7-8].

The lactate dehydrogenase A (*LDHA*) catalyzes the reduction of pyruvate to lactate, a key step in glycolysis. The solute carrier family 16 members (S*LC16A*) encode monocarboxylate transporters (MCT), mainly responsible for transporting lactate generated from intracellular metabolism to the extracellular environment, preventing intracellular lactate accumulation and maintaining the acidic environment outside tumor cells. They can also transport extracellular lactate into cells to provide metabolic substances for tumor cells [9]. *SLC16A1* and *SLC16A3* encode MCT1 and MCT4, respectively. MCT1 primarily depends on the concentration of lactate and protons inside and outside the cell for lactate transport, while MCT4 mainly transports lactate produced in the glycolytic pathway out of the cells.

This study aims to analyze the expression of glucose metabolism genes in breast cancer tissues using The Cancer Genome Atlas Database (TCGA) to provide new insights into the prevention and treatment of breast cancer.

1 Materials and Methods

1.1 Source of Sample Data

Data related to breast cancer were downloaded from The Cancer Genome Atlas Database (TCGA), including two groups: the first group includes 113 samples of adjacent normal breast tissue and cancerous breast tissue,

which contain data on the expression of all gene mRNA; the second group includes 1,097 female breast cancer patients with clinical and pathological information.

The integration of the first and second groups resulted in the third group, containing clinicopathological characteristics, follow-up and death time, and mRNA expression data in 1,060 female breast cancer patients. The clinical and pathological features of data mainly include two types. One type is the features that do not need to be obtained from tumor tissue, mainly including race, age, menopausal status, and surgical method. Another type is the features that need to be obtained from tumor tissue, mainly including tumor size (T), lymph node metastasis (N), distant metastasis (M), tumor staging, distributions of breast lesion locations, and anatomical quadrants. The data also includes overall survival (OS) and their survival status of patients, with the endpoint being patient death. The total mortality was 14.06%. **[Table 1]**

Tab.1 Characteristics and mortality of 1,060 patients

Clinical characteristics	Mortality (%)	Clinical characteristics	Mortality (%)
Age		**M stage**	
⩽58 years	12.24(66/539)	**M0**	13.51 (119/881)
>58years	15.93(83/521)	**M1**	77.27 (17/22)
Race		**Mx**	8.28 (13/157)
White people	14.83(109/735)	**Tumor stage**	
Asian	51.72(30/58)	**Ⅰ**	8.89 (16/180)
Black people or others	1.65(3/182)	**Ⅱ**	10.67 (64/600)
Deletion	8.24(7/85)	**Ⅲ**	18.57 (44/237)
Menopausal state		**IV**	75.00(15/20)
Premenopausal	8.04(18/224)	**x**	50.00(6/12)
Postmenopausal	13.17(89/676)	**Deletion**	36.36(4/11)
Perimenopausal	2.63(1/38)	**ER state**	
Deletion	33.61(41/122)	**Positive**	12.84(90/701)
Surgical method		**Negative**	17.70(37/209)
Simple mastectomy	8.63(17/197)	**Deletion**	14.67(22/150)
Modified radical mastectomy	18.59(58/312)	**PR state**	
Breast tumor resection	10.00(24/240)	**Positive**	13.14(80/609)
Others	14.67(38/259)	**Negative**	16.11(48/298)
Deletion	23.08(12/52)	**Deletion**	13.73(21/153)
Margin state		**HER-2 state**	
Positive	25.33(19/75)	**Positive**	12.57(22/175)
Negative	9.70(86/887)	**Negative**	10.63(69/649)
Unclear	19.35(6/31)	**Deletion**	24.58(58/236)
Deletion	56.72(38/67)	**Distributions of breast lesions**	
T stage		**Right side**	13.52(68/503)
T1	11.87(33/278)	**Left side**	14.54(81/557)
T2	12.32(75/609)	**Tumor quadrant position**	
T3	18.80(25/133)	**Right inner upper**	9.43(5/53)
T4	40.54(15/37)	**Right inner lower**	15.38(4/26)
Tx	33.33(1/3)	**Right outer upper**	9.85(20/203)
N stage		**Right outer lower**	14.58(7/48)
N0	8.72(41/470)	**Left inner upper**	12.96(7/54)
N1	16.15(62/384)	**Left inner lower**	27.27(6/22)
N2	18.49(22/119)	**Left outer upper**	12.20(20/164)
N3	21.43(15/70)	**Left outer lower**	10.91(6/55)
Nx	52.94(9/17)	**Unclear**	17.01(74/435)

Note: x indicates unclear staging; ER, estrogen receptor; PR, progesterone receptor; HER-2, human epidermal growth factor receptor 2.

1.2 Statistical Methods

SPSS 27.0 and GraphPad Prism 9.5 were used for data processing. Data of gene expression were numerical variables, paired sample *t*-tests were used to compare gene expression in cancerous and adjacent normal tissues. A critical value was determined from 10% to 90% of the data at 10% intervals, with the minimum *P*-value corresponding to the critical value in survival analysis as the gene expression threshold. χ^2 tests were used to explore the correlation between gene expression levels and clinicopathological characteristics. Kaplan-Meier survival analysis and log-rank tests were performed to analyze differences between the groups. Cox proportional hazard models were used for univariate and multivariate analyses. $P<0.05$ was considered statistically significant.

2 Results

2.1 Differential Gene Expression

LDHA (430.55±233.15 *vs* 255.79±59.83, $t=7.692$, $P<0.01$), *SLC16A1* (31.49±35.72 *vs* 23.66±8.97, $t=2.294$, $P=0.024$), and *SLC16A3* (11.75±10.30 *vs* 3.03±2.45, $t=9.481$, $P<0.01$) were significantly upregulated in cancerous tissues compared to adjacent normal tissues in the same patient.

2.2 Correlation Between Gene Expression and Clinicopathological Characteristics

2.2.1 Correlation between *LDHA* expression and clinicopathological characteristics

LDHA expression levels showed significant differences in distant metastasis (M) staging, ER expression status, and HER-2 status ($P<0.05$), while there was no significant difference in other pathological characteristics ($P>0.05$). **[Table 2]**

2.2.2 Correlation between *SLC16A1* expression and clinicopathological characteristics

SLC16A1 expression levels showed significant differences in age, ER expression status, and PR expression status ($P<0.05$), while there was no significant difference in other pathological characteristics ($P>0.05$). **[Table 2]**

2.2.3 Correlation between *SLC16A3* expression and clinicopathological characteristics

SLC16A3 expression levels showed significant differences in ER expression status and PR expression status ($P<0.05$), while there was no significant difference in other pathological characteristics ($P>0.05$). **[Table 2]**

2.3 Correlation of ESR1 and PGR with the Above Genes

ESR1 showed a significant negative correlation with *SLC16A1* ($r=-0.230$, $P<0.01$) and *SLC16A3* ($r=-0.143$, $P<0.01$). Similarly, *PGR* exhibited a significant negative correlation with *SLC16A1* ($r=-0.123$, $P<0.01$) and *SLC16A3* ($r=-0.110$, $P<0.01$). No significant correlation was observed between *ESR1*, *PGR*, and *LDHA* expression levels. **[Figure 1]**

2.4 Survival Analysis

Kaplan-Meier survival analysis indicated that the OS of patients with high expression of *LDHA* ($\chi^2=3.856$, $P=0.049$), *SLC16A1* ($\chi^2=3.978$, $P=0.046$), and *SLC16A3* ($\chi^2=5.008$, $P=0.025$) were lower than those of patients with low expression. **[Figure 2]**

2.5 Cox Proportional Hazard Analysis

Univariable Cox regression analysis reveals that the expression levels of *SLC16A1* and *SLC16A3*, age, tumor size (T), lymph node metastasis (N), distant metastasis (M), and clinical staging influence OS in breast cancer patients ($P<0.05$). Multivariable Cox analysis shows that high expression of *SLC16A1,* high expression of *SLC16A3*, advanced age, lymph node metastasis (N1-N3), distant metastasis (M1), and clinical staging III-IV were independent risk factors for OS in breast cancer patients ($P<0.05$). Tumor size (T3-T4) was not an independent risk factor for OS in breast cancer patients ($P>0.05$). **[Table 3]**

Tab.2 Association of LDHA, SLC16A and SLC16A3 expression with clinical characteristics in 1,060 breast cancer patients (case)

Clinical characteristics	*LDHA*		χ^2 value	*P* value	*SLC16A1*		χ^2 value	*P* value	*SLC16A3*		χ^2 value	*P* value
	Low expression (*n*=878)	High expression (*n*=182)			Low expression (*n*=323)	High expression (*n*=737)			Low expression (*n*=917)	High expression (*n*=143)		

Age			0.527	0.468			8.040	0.005			0.238	0.625
≤ 58 years	266	97			143	396			469	70		
>58 years	273	85			180	341			448	73		
Menopausal state			0.010	0.92			0.250	0.617			2.235	0.135
Premenopausal	187	37			66	158			201	23		
Postmenopausal/ Perimenopausal	594	120			223	491			613	101		
Deletion	97	25			34	88			103	19		
Margin state			0.464	0.496			0.058	0.810			2.249	0.134
Positive	60	15			24	51			69	6		
Negative	737	150			272	615			761	126		
Unclear	30	1			12	19			28	3		
Deletion	51	16			15	52			59	8		
T stage			1.713	0.191			1.721	0.190			0.486	0.486
T1-T2	741	146			263	624			765	122		
T3-T4	135	35			59	111			150	20		
Deletion	2	1			1	2			2	1		
N stage			0.917	0.338			2.874	0.09			0.201	0.654
N0	384	86			129	341			404	66		
N1-N3	481	92			185	388			498	75		
Deletion	13	4			9	8			15	2		
M stage			5.560	0.018			0.101	0.751			0.049	0.826
M0	731	150			268	613			756	125		
M1	14	8			6	16			18	4		
Deletion	133	24			49	108			143	14		
Tumor stage			1.495	0.221			2.291	0.13			0.290	0.590
Ⅰ - Ⅱ	654	126			228	552			678	102		
Ⅲ-Ⅳ	207	50			88	169			220	37		
Unclear	10	2			7	5			10	2		
Deletion	7	4			0	11			9	2		
ER state			8.532	0.003			17.428	<0.01			22.447	<0.001
Positive	597	104			229	472			624	77		
Negative	160	49			37	172			159	50		
Deletion	121	29			57	93			134	16		
PR state			2.904	0.088			5.486	0.019			20.59	<0.001
Positive	514	95			193	416			546	63		
Negative	238	60			72	226			234	64		
Deletion	126	27			58	95			137	17		
HER-2 state			4.418	0.036			2.871	0.090			0.592	0.442
Positive	136	39			59	116			147	28		
Negative	548	101			179	479			560	89		
Deletion	194	42			85	142			210	26		
Distributions of breast lesions			0.011	0.917			0.326	0.568			3.15	0.076
Right side	416	87			149	354			445	58		
Left side	462	95			174	383			472	85		
Tumor quadrant position			0.844	0.839			0.846	0.839			4.564	0.207
Inner upper	91	16			31	76			96	11		

Inner lower	38	10	17	31	37	11
Outer upper	304	63	107	260	309	58
Outer lower	86	17	30	73	89	14
Deletion	359	76	138	297	386	49

Fig. 1 Heat map of gene correlation coefficients

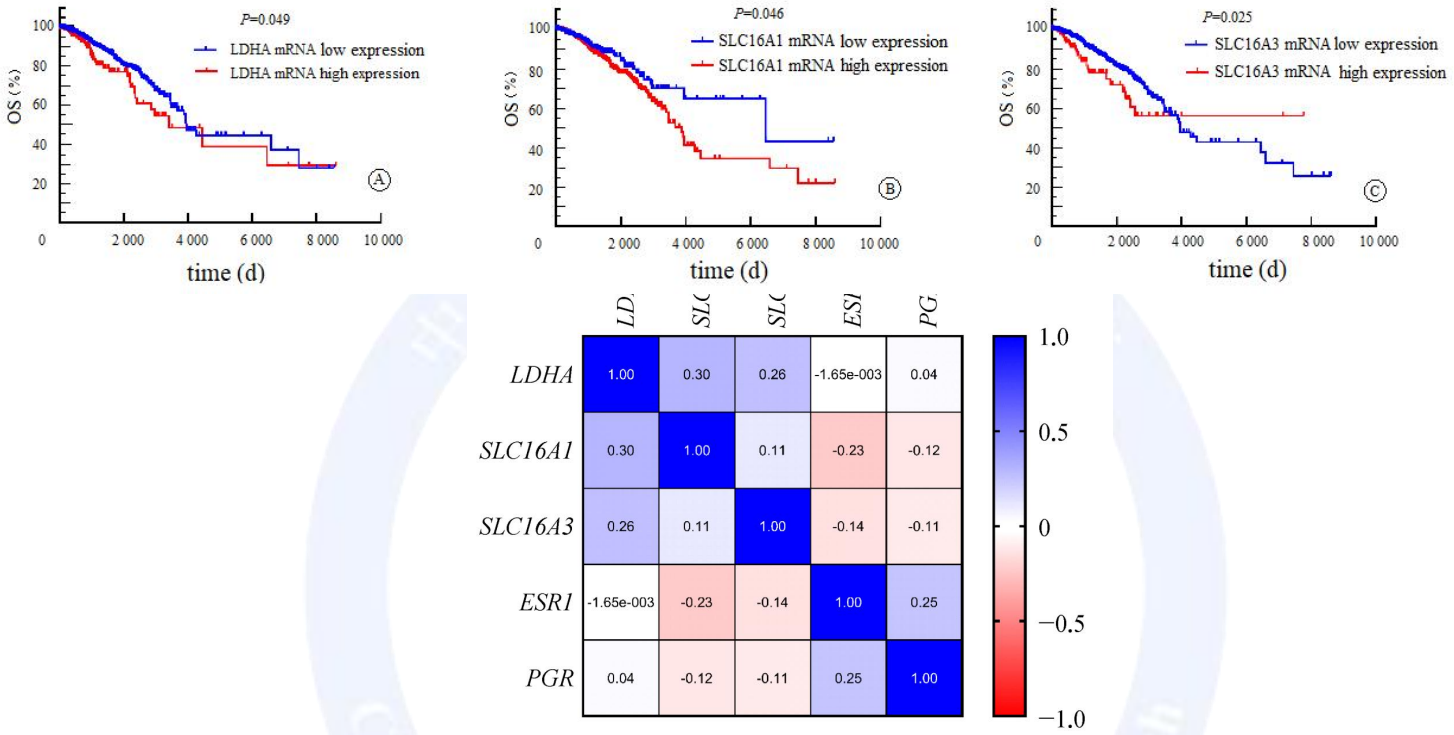

Fig.2 Kaplan Meier survival analysis of breast cancer patients with different gene mRNA expression levels

Tab.3 Univariable and multivariable Cox proportional hazard model of survival in 1,060 breast cancer patients

Clinical characteristics	Univariable Cox regression		Multivariable Cox regression	
	***HR* (95%*CI*)**	***P* value**	***HR* (95%*CI*)**	***P* value**
High expression of *SLC16A1*	1.457(1.004-2.114)	0.047	1.894(1.246-2.878)	0.003
High expression of *SLC16A3*	1.640(1.059-2.542)	0.027	1.769(1.099-2.847)	0.019
Age>58 years	1.782(1.288-2.467)	<0.001	2.014(1.398-2.903)	<0.001
T3-T4 stage	1.769(1.227-2.550)	0.002	1.016(0.612-1.687)	0.950
N1-N3 stage	2.170(1.507-3.126)	<0.001	1.616(1.033-2.527)	0.036
Distant metastasis M1	2.445(1.482-4.066)	<0.001	3.121(1.632-5.969)	<0.001
Clinical staging Ⅲ-Ⅳ	2.659(1.899-3.724)	<0.001	1.718(1.000-2.953)	0.050[a]

Note: [a] *P*=0.049,97<0.050 when the number is accurate to 5 decimal places, at the threshold of significance.

3 Discussion

Research suggested that high expression of *LDHA* in tumor tissues was associated with adverse prognosis. Knockout or inhibition of *LDHA* could impede tumor cell growth [12-13]. Zhao *et al.* [14] found a significant association between high expression of *LDHA* and high histological grade, lymph node metastasis, tumor staging of breast cancer. Negative ER expression showed higher *LDHA* expression. Fantin *et al.* [12] showed that inhibiting *LDHA* reduced the transformation of malignant tumors and delayed tumor formation. Our study confirms an association between high *LDHA* mRNA expression / distant metastasis and ER and HER-2 expression. In addition, high *LDHA* mRNA expression was associated with worse OS in patients.

Studies have shown a positive association between high expression of MCT1 and patient prognosis in non-

small cell lung cancer, head-and-neck cancer, and other cancers. The OS rate of the high *SLC16A1* expression group was significantly higher than that of the low expression group [15-16]. On the contrary, some scholars found that the high expression of *SLC16A1* was related to the adverse clinical results of urinary system tumors, primary neuroblastoma and breast cancer [17-18]. Johnson *et al.* [19] found a higher expression of MCT1 in triple negative breast cancer compared to other subtypes, and overexpression of MCT1 was associated with an increased risk of tumor growth and recurrence. In this study, breast cancer patients in the high *SLC16A1* expression group had worse OS. The difference in the above results may be due to the fact that lactate transport by MCT1 depends on the pH inside and outside the cells [10]. There are specific differences in the pH gradient inside and outside the cells of different tumors. The sample size is insufficient, which makes the statistical analysis inevitably deviate, and further sample collection may be required for verification. Our study suggests that *SLC16A1* is negatively correlated with *ESR1* and *PGR*, and higher *SLC16A1* may predict low expression of ER and PR, so that patients lose effective endocrine therapeutic targets, resulting in worse OS.

Khan *et al.* [20] treated neuroblastoma with MCT1 inhibitor, which disrupted lactate homeostasis and NADH/NAD^+ ratio of cells, inhibited the growth of cancer cells, and highly synergized with *LDHA* inhibitor to reduce cell viability. Hou *et al.* [21] found that inhibiting MCT1 could overcome the resistance of breast cancer cells to Paclitaxel. The above results showed the potential of targeting the corresponding proteins of *LDHA* and *SLC16A1* to improve the prognosis of patients.

MCT4 is highly expressed in prostate cancer, intrahepatic cholangiocarcinoma, lung cancer, bladder cancer and liver cancer, and is closely related to the proliferation, invasion and metastasis of tumor cells. Its high expression is associated with worse patient OS [22-26]. This study confirmed it. Silencing of MCT4 in prostate tumors significantly reduced cell proliferation, migration, and invasion [22]. Studies found an upregulated expression of MCT4 in breast cancer, and the higher MCT4 expression was associated with poor prognosis, immune cell infiltration and glycolysis rate-limiting enzyme [18]. *SLC16A3* is expected to become a potential prognostic indicator and target for tumor therapy to assist the treatment of breast tumors.

The results of this study showed that the expression levels of *LDHA, SLC16A1* and *SLC16A3* were higher in the ER and PR negative group. Zhao *et al.* [14] also found an increased expression of *LDHA* in the ER-negative group. *ESR1* and *PGR* were significantly negatively correlated with *SLC16A1* and *SLC16A3*. The relationship between the expression of ER, PR and the above genes needs to be further studied.

The study has some limitations. Firstly, the dataset has only a small proportion of Asian patients, which may be biased by gene expression in our country. Secondly, although TCGA database has accurate sequencing, good quality and multi-omics data [27-29], the 1,060 breast cancer samples obtained from TCGA database in this study still have insufficient data, and clinical samples can be collected later to expand the sample further. Finally, the study solely focuses on mRNA levels, and future research could benefit from incorporating other omics levels for a more comprehensive analysis. Despite these limitations, the study draws relevant conclusions.

In conclusion, *LDHA, SLC16A1* and *SLC16A3* genes are highly expressed in breast cancer tissues and negatively correlated with OS of breast cancer patients. *SLC16A1* and *SLC16A3* are independent risk factors for OS in breast cancer patients. These genes are expected to become prognostic indicators of breast cancer, which may provide a new target for the subsequent treatment of breast cancer.

Conflict of interest: None

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Submission received: 2023-11-01

·论　著·

基于 TCGA 数据库分析葡萄糖代谢相关基因与乳腺癌临床病理特性及预后相关性

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摘要：目的　探究乳酸脱氢酶 A（*LDHA*）、溶质载体家族 16 成员（*SLC16A*）*1* 及 *SLC16A3* 基因与乳腺癌病理特征及预后的关系。**方法**　获取肿瘤基因组图谱数据库（TCGA）中 1 060 位乳腺癌患者的组织样本，分析 *LDHA*、*SLC16A1* 及 *SLC16A3* 基因表达量与乳腺癌临床病理特征及预后的关联性，用 Kaplan-Meier 生存分析绘制生存曲线，Cox 比例风险回归模型进行单因素和多因素生存预后分析。**结果**　*LDHA* 表达与远处转移（M 分期）（χ^2 = 5.560，P = 0.018）、雌激素受体（ER）表达（χ^2 = 8.532，P = 0.003）、人表皮生长因子受体-2（HER-2）表达（χ^2 = 4.418，P = 0.036）相关；*SLC16A1* 表达与年龄（χ^2 = 8.040，P = 0.005）、ER 表达（χ^2 = 17.428，P<0.01）、孕激素受体（PR）表达（χ^2 = 5.486，P = 0.019）相关；*SLC16A3* 表达与 ER 表达（χ^2 = 22.447，P<0.01）、PR 表达（χ^2 = 20.590，P<0.01）相关。*LDHA*（χ^2 = 3.856，P = 0.049）、*SLC16A1*（χ^2 = 3.978，P = 0.046）和 *SLC16A3*（χ^2 = 5.008，P = 0.025）高表达患者较低表达患者累积生存率更低。*SLC16A1*（*HR* = 1.894，95%*CI*：1.246～2.878，P = 0.003）和 *SLC16A3*（*HR* = 1.769，95%*CI*：1.009～2.847，P = 0.019）是乳腺癌患者总生存时间的独立危险因素。**结论**　*LDHA*、*SLC16A1* 及 *SLC16A3* 基因与乳腺癌某些病理特征及较差的预后相关，可能为乳腺癌治疗提供新的预后指标和治疗靶点。

关键词：乳腺癌；葡萄糖代谢；乳酸脱氢酶 A；溶质载体家族 16 成员 1；溶质载体家族 16 成员 3；总生存率

中图分类号：R737.9　**文献标识码：**A　**文章编号：**1674-8182(2024)03-0359-06

Glucose metabolism-related genes with clinicopathological characteristics and prognosis of breast cancer: an analysis based on TCGA database

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Abstract: Objective　To investigate the relationship between the expression of *LDHA*, *SLC16A1* and *SLC16A3* genes and pathologic features and prognosis in breast cancer. **Methods**　Tissue samples from 1 060 breast cancer patients in The Cancer Genome Atlas (TCGA) were obtained. The association of *LDHA*, *SLC16A1* and *SLC16A3* gene expressions with clinicopathological features and prognosis of breast cancer were analyzed. Survival curve were drawn by Kaplan-Meier survival analysis, and univariable and multivariable survival prognosis were analyzed by Cox proportional hazard regression model. **Results**　*LDHA* expression was associated with distant metastasis (M stage) (χ^2 = 5.560, P = 0.018), estrogen receptor (ER) expression (χ^2 = 8.532, P = 0.003), and human epidermal growth factor receptor 2 (HER-2) expression (χ^2 = 4.418, P = 0.036); *SLC16A1* expression correlated with age (χ^2 = 8.040, P = 0.005), ER expression (χ^2 = 17.428, P < 0.01), and progesterone receptor (PR) expression (χ^2 = 5.486, P = 0.019). *SLC16A3* expression correlated with ER expression (χ^2 = 22.447, P < 0.01), PR expression (χ^2 = 20.590, P < 0.01). Patients with high expression of *LDHA* (χ^2 = 3.856, P = 0.049), *SLC16A1* (χ^2 = 3.978, P = 0.046) and *SLC*16A3 (χ^2 = 5.008, P = 0.025) had lower cumulative survival rates. *SLC16A1* (*HR* = 1.894, 95%*CI*: 1.246-2.878, P = 0.003) and *SLC16A3* (*HR* = 1.769, 95%*CI*: 1.009-2.847, P = 0.019) were the independent risk factors for overall survival in breast cancer patients.

DOI: 10.13429/j.cnki.cjcr.2024.03.007

基金项目：江苏省重点研发计划（社会发展）专项（BE2021741）

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出版日期：2024-03-20

QR code for English version

Conclusion　*LDHA*, *SLC16A1* and *SLC16A3* are associated with certain pathologic features and poorer prognosis of breast cancer, which may provide new prognostic indicators and therapeutic targets for breast cancer treatment.

Keywords: Breast cancer; Glucose metabolism; Lactate dehydrogenase A; Solute carrier family 16 member 1; Solute carrier family 16 member 3; Overall survival

Fund program: Special Project of Jiangsu Province Key Research and Development Program (Socical Development) (BE2021741)

中国乳腺癌的发病率与死亡率逐步上升,且预计呈现持续上升趋势[1]。根据 2020 年全球各类癌症登记数据显示,乳腺癌已成为全球发病率最高的肿瘤[2]。肿瘤细胞会加快对各类营养物质的摄取与转化利用[3],肿瘤细胞偏向于通过无氧酵解途径获取能量,这个现象被称为瓦博格(Warburg)效应[4]。虽然糖酵解生成三磷酸腺苷的效率较低,但速率却远远高于氧化磷酸化[5];且糖酵解的中间产物在抑制细胞凋亡、促进细胞生物合成、产生信号分子等许多方面发挥了巨大作用[6],无氧酵解所产生的乳酸经过乳酸转运蛋白转运至胞外,维持肿瘤微环境的弱酸性,更适合肿瘤的生长[7-8]。

乳酸脱氢酶 A(lactate dehydrogenase A, *LDHA*)基因编码 LDHA,它催化丙酮酸还原成乳酸,这是糖酵解的关键步骤。溶质载体家族 16 成员(solute carrier family 16 member,*SLC16A*)基因编码单羧酸转运蛋白(monocarboxylate transporter, MCT)。MCT 主要是将胞内代谢产生的乳酸转运至胞外,维持肿瘤细胞外的酸性环境;它还可将胞外的乳酸转运至胞内为肿瘤细胞提供代谢物质[9]。*SLC16A1* 和 *SLC16A3* 分别编码 MCT1 和 MCT4,MCT1(*SLC16A1* 基因编码)对于乳酸的输入和输出主要取决于细胞内外的乳酸和质子浓度[10];MCT4(*SLC16A3* 基因编码)主要作用是将糖代谢途径中产生的乳酸转运至细胞外[11]。本文用 TCGA 数据库分析乳腺癌组织中葡萄糖代谢基因的表达,为乳腺癌的预防及治疗提供新论点及思路。

1　材料与方法

1.1　*标本数据来源*　下载肿瘤基因组图谱数据库(the Cancer Genome Atlas Database, TCGA)中乳腺癌相关数据。数据为以下 2 组:第 1 组数据包括 113 例患者癌旁乳腺组织及其癌变乳腺组织样本,这些样本包含了所有基因 mRNA 表达的数据;第 2 组数据包括临床病理信息数据的 1 097 名女性乳腺癌患者资料。

第 1 组数据与第 2 组数据整合出第 3 组数据:包含临床病理特征、随访及死亡时间和基因 mRNA 表达数据的 1 060 名女性乳腺癌患者资料。数据的临床病理特征主要包括两类,一类是无需从肿瘤组织中获取的特征,主要包括:种族、年龄、绝经状态、手术方式;另一类是需要从肿瘤组织获取的特征,主要包括:肿瘤大小(T)、淋巴结转移(N)、远处转移(M)、肿瘤分期、肿瘤左右位置以及解剖象限。数据还包括患者总生存时间(overall survival, OS)和患者的生存状态,终点为患者死亡。总死亡率为 14.06%。见表 1。

表 1　1 060 例患者的临床病理特征及其死亡率
Tab. 1　Characteristics and death rates of 1 060 patients

临床特征	死亡率(%)	临床特征	死亡率(%)
年龄		M 分期	
≤58 岁	12.24(66/539)	M0	13.51(119/881)
>58 岁	15.93(83/521)	M1	77.27(17/22)
种族		Mx	8.28(13/157)
白人	14.83(109/735)	肿瘤分期	
亚洲人	51.72(30/58)	Ⅰ	8.89(16/180)
黑人或其他	1.65(3/182)	Ⅱ	10.67(64/600)
缺失	8.24(7/85)	Ⅲ	18.57(44/237)
绝经状态		Ⅳ	75.00(15/20)
绝经前	8.04(18/224)	x	50.00(6/12)
绝经后	13.17(89/676)	缺失	36.36(4/11)
围绝经期	2.63(1/38)	ER 状态	
缺失	33.61(41/122)	阳性	12.84(90/701)
手术方式		阴性	17.70(37/209)
单纯式乳房切除术	8.63(17/197)	缺失	14.67(22/150)
改良乳腺根治术	18.59(58/312)	PR 状态	
乳腺肿瘤切除术	10.00(24/240)	阳性	13.14(80/609)
其他	14.67(38/259)	阴性	16.11(48/298)
缺失	23.08(12/52)	缺失	13.73(21/153)
切缘状态		HER-2 状态	
阳性	25.33(19/75)	阳性	12.57(22/175)
阴性	9.70(86/887)	阴性	10.63(69/649)
不明确	19.35(6/31)	缺失	24.58(58/236)
缺失	56.72(38/67)	肿瘤位置	
T 分期		右侧	13.52(68/503)
T1	11.87(33/278)	左侧	14.54(81/557)
T2	12.32(75/609)	肿瘤象限位置	
T3	18.80(25/133)	右内上象限	9.43(5/53)
T4	40.54(15/37)	右内下象限	15.38(4/26)
Tx	33.33(1/3)	右外上象限	9.85(20/203)
N 分期		右外下象限	14.58(7/48)
N0	8.72(41/470)	左内上象限	12.96(7/54)
N1	16.15(62/384)	左内下象限	27.27(6/22)
N2	18.49(22/119)	左外上象限	12.20(20/164)
N3	21.43(15/70)	左外下象限	10.91(6/55)
Nx	52.94(9/17)	未明确	17.01(74/435)

注:分期中 x 表示未知;ER 为雌激素受体;PR 为孕激素受体;HER-2 为人表皮生长因子受体。

1.2　*统计学方法*　使用 SPSS 27.0、Graphpad Prism 9.5 对数据进行处理。基因表达数据属于数值变量,使用成对样本 t 检验比较癌变组织及癌旁组织中的基因表达。在数据的 10%~90%之间每隔 10 个数取一个临界值,以生存分析结果中得出最小 P 值对应的临界值作为基因的表达阈值将基因表达分为高表达组和低表达组。用 χ^2 检验分析基因的表达水平与临床病理特征的关联性。对不同组别进行 Kaplan-Meier 生存分析,绘制生存曲

线,运用 log-rank 检验分析其差异性。Cox 比例风险回归模型进行单因素与多因素分析,将差异有统计学意义的单因素进行多因素分析。P<0.05 为差异具有统计学意义。

2　结　果

2.1　基因的差异表达　同一患者的癌变组织 *LDHA*(430.55±233.15 *vs* 255.79±59.83, t=7.692, P<0.01)、*SLC16A1*(31.49±35.72 *vs* 23.66±8.97, t=2.294, P=0.024)、*SLC16A3*(11.75±10.30 *vs* 3.03±2.45, t=9.481, P<0.01)表达均高于自身的癌旁组织,差异有统计学意义。

2.2　基因表达与乳腺癌患者临床病理特征关联性

2.2.1　*LDHA* 的表达与临床病理特征的关联性　*LDHA* 表达量的高低在远处转移(M 分期)、ER 表达状态、HER-2 表达状态中差异有统计学意义(P<0.05),在其他病理特征中差异无统计学意义(P>0.05)。见表 2。

表 2　1 060 名乳腺癌患者 *LDHA*、*SLC16A* 及 *SLC16A3* 表达与临床特征的关联性　(例)

Tab. 2　Association of *LDHA*, *SLC16A* and *SLC16A3* expression with clinical characteristics in 1 060 breast cancer patients　(case)

病理特征	*LDHA*		χ^2 值	P 值	*SLC16A1*		χ^2 值	P 值	*SLC16A3*		χ^2 值	P 值
	低表达(n=878)	高表达(n=182)			低表达(n=323)	高表达(n=737)			低表达(n=917)	高表达(n=143)		
年龄												
≤58 岁	442	97	0.527	0.468	143	396	8.04	0.005	469	70	0.238	0.625
>58 岁	436	85			180	341			448	73		
绝经状态												
绝经前	187	37			66	158			201	23		
绝经后或围绝经	594	120	0.010	0.920	223	491	0.250	0.617	613	101	2.235	0.135
缺失	97	25			34	88			103	19		
切缘状态												
阳性	60	15			24	51			69	6		
阴性	737	150	0.464	0.496	272	615	0.058	0.810	761	126	2.249	0.134
不明确	30	1			12	19			28	3		
缺失	51	16			15	52			59	8		
T 分期												
T1~T2	741	146			263	624			765	122		
T3~T4	135	35	1.713	0.191	59	111	1.721	0.190	150	20	0.486	0.486
缺失	2	1			1	2			2	1		
N 分期												
N0	384	86			129	341			404	66		
N1~N3	481	92	0.917	0.338	185	388	2.874	0.090	498	75	0.201	0.654
缺失	13	4			9	8			15	2		
M 分期												
M0	731	150			268	613			756	125		
M1	14	8	5.560	0.018	6	16	0.101	0.751	18	4	0.049	0.826
缺失	133	24			49	108			143	14		
肿瘤分期												
Ⅰ~Ⅱ	654	126			228	552			678	102		
Ⅲ~Ⅳ	207	50	1.495	0.221	88	169	2.291	0.130	220	37	0.290	0.590
不明确	10	2			7	5			10	2		
缺失	7	4			0	11			9	2		
ER												
阳性	597	104			229	472			624	77		
阴性	160	49	8.532	0.003	37	172	17.428	<0.001	159	50	22.447	<0.001
缺失	121	29			57	93			134	16		
PR												
阳性	514	95			193	416			546	63		
阴性	238	60	2.904	0.088	72	226	5.486	0.019	234	64	20.590	<0.001
缺失	126	27			58	95			137	16		
HER-2												
阳性	136	39			59	116			147	28		
阴性	548	101	4.418	0.036	179	479	2.871	0.090	560	89	0.592	0.442
缺失	194	42			85	142			210	26		
肿瘤位置												
右侧乳腺	416	87	0.011	0.917	149	354	0.326	0.568	445	58	3.150	0.076
左侧乳腺	462	95			174	383			472	85		
肿瘤象限分布												
内上	91	16			31	76			96	11		
内下	38	10			17	31			37	11		
外上	304	63	0.844	0.839	107	260	0.846	0.839	309	58	4.564	0.207
外下	86	17			30	73			89	14		
缺失	359	76			138	297			386	49		

注:缺失不纳入统计分析。

2.2.2　*SLC16A1* 的表达与临床病理特征的关联性　*SLC16A1* 表达量的高低在年龄、ER 表达状态、PR 表达状态中差异有统计学意义（$P<0.05$），在其他病理特征中差异无统计学意义（$P>0.05$）。见表 2。

2.2.3　*SLC16A3* 的表达与临床病理特征的关联性　*SLC16A3* 的表达量在 ER 表达状态、PR 表达状态中差异有统计学意义（$P<0.05$），其他病理特征其表达量高低差异无统计学意义（$P>0.05$）。见表 2。

2.3　*ESR1*（编码 ER 的基因）和 *PGR*（编码 PR 的基因）与上述基因的相关性　*ESR1* 与 *SLC16A1*（$r=-0.230$，$P<0.01$）、*SLC16A3*（$r=-0.143$，$P<0.01$）呈显著负相关；*PGR* 与 *SLC16A1*（$r=-0.123$，$P<0.01$）、*SLC16A3*（$r=-0.110$，$P<0.01$）呈现显著负相关。未见到 *ESR1*、*PGR* 与 *LDHA* 表达量之间具有显著的相关性。见图 1。

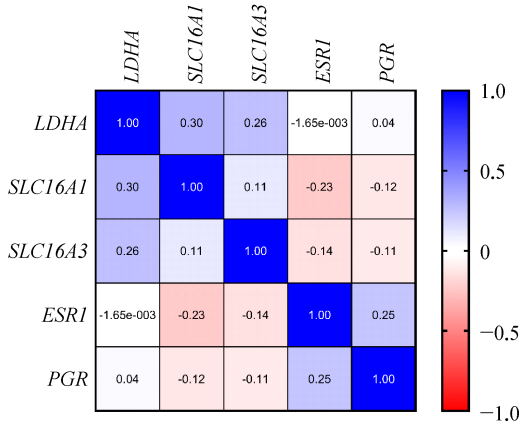


图 1　基因相关系数热图

Fig. 1　Heat map of gene correlation coefficients

2.4　生存分析　Kaplan-Meier 生存分析结果显示 *LDHA*（$\chi^2=3.856$，$P=0.049$）、*SLC16A1*（$\chi^2=3.978$，$P=0.046$）、*SLC16A3*（$\chi^2=5.008$，$P=0.025$）高表达组的累积生存率较低表达组更低。见图 2。

2.5　Cox 风险回归分析　单因素 Cox 回归分析显示，*SLC16A1* 表达量、*SLC16A3* 表达量、年龄、肿瘤大小（T）、淋巴结转移（N）、远处转移（M）及临床分期等影响患者的 OS。

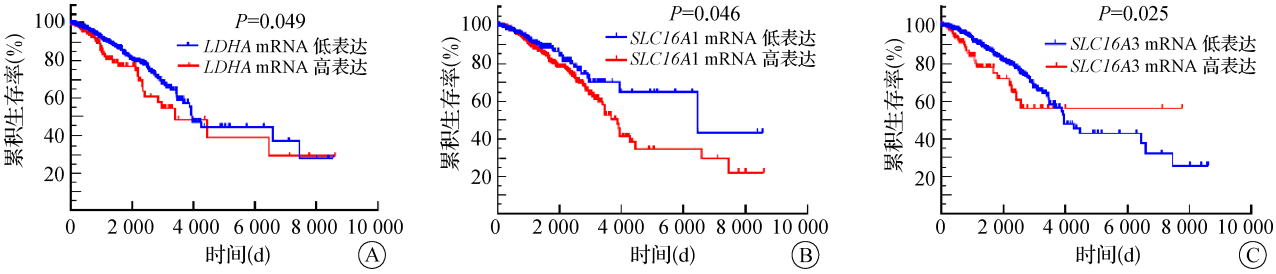
对与预后有关的单因素进行多因素 Cox 分析示，*SLC16A1* 高表达、*SLC16A3* 高表达、高龄、淋巴结转移（N1～N3）、远处转移（M1）和临床分期Ⅲ～Ⅳ期是乳腺癌患者 OS 的独立危险因素；而肿瘤大小（T3～T4）不是患者 OS 的独立危险因素。见表 3。

表 3　1 060 例乳腺癌患者生存预后影响的 Cox 单因素及多因素分析

Tab. 3　Univariable and multivariable Cox proportional hazard regression model of survival in 1 060 breast cancer patients

病理特征	单因素 Cox 回归		多因素 Cox 回归	
	HR（95%*CI*）	*P* 值	*HR*（95%*CI*）	*P* 值
SLC16A1 高表达	1.457（1.004～2.114）	0.047	1.894（1.246～2.878）	0.003
SLC16A3 高表达	1.640（1.059～2.542）	0.027	1.769（1.099～2.847）	0.019
年龄>58 岁	1.782（1.288～2.467）	<0.001	2.014（1.398～2.903）	<0.001
T3～T4 分期	1.769（1.227～2.550）	0.002	1.016（0.612～1.687）	0.950
N1～N3 分期	2.170（1.507～3.126）	<0.001	1.616（1.033～2.527）	0.036
远处转移 M1	2.445（1.482～4.066）	<0.001	3.121（1.632～5.969）	<0.001
临床分期Ⅲ～Ⅳ	2.659（1.899～3.724）	<0.001	1.718（1.000～2.953）	0.050[a]

注：a 表示保留小数点后 5 位时 $P=0.049\,97<0.050$，处于显著性临界值。



注：A 为不同 *LDHA* mRNA 表达水平的 OS，B 为不同 *SLC16A1* mRNA 表达水平的 OS，C 为不同 *SLC16A3* mRNA 表达水平的 OS。

图 2　不同基因 mRNA 表达水平乳腺癌患者的 Kaplan-Meier 生存分析

Fig. 2　Kaplan Meier survival analysis of breast cancer patients with different gene mRNA expression levels

3　讨　论

有研究表明 *LDHA* 在肿瘤组织中高表达，并与肿瘤的不良的预后有关。*LDHA* 敲除[12-13]和 *LDHA* 抑制都会抑制体外肿瘤细胞的生长[12]。赵雪可等[14]发现 *LDHA* 高表达与乳腺癌组织学高分级、淋巴结转移和肿瘤分期等相关；且 ER 阴性表现出更高的 *LDHA* 表达。Fantin 等[12]表明，抑制 *LDHA* 可减少恶性肿瘤的转化、延迟肿瘤的形成。本研究见到 *LDHA* mRNA 高表达与远处转移和 ER、HER2 表达存在关联性，并且 *LDHA* mRNA 高表达与患者更差的 OS 相关。

有研究表明在非小细胞肺癌、头颈部癌等癌症中 MCT1 高表达与患者预后呈现正相关，*SLC16A1* 高表达组的总体生存率明显高于低表达组[15-16]。相反，

有学者发现 *SLC16A1* 高表达与泌尿系统肿瘤、原发性神经母细胞瘤及乳腺癌的不良临床结果相关[17-18]。Johnson 等[19]发现三阴性乳腺癌中 MCT1 表达高于其他亚型,且 MCT1 过度表达与肿瘤生长风险增加与复发有关。在本研究中,*SLC16A1* 高表达组的乳腺癌患者有着更差的 OS。上述结果的不同可能是由于 MCT1 转运乳酸取决于细胞内外的 pH 值[10],不同肿瘤细胞内外 pH 值梯度存在一定差异,或是样本量不足,使统计分析结果出现不可避免的偏差,可能需要进一步收集样本验证。就本研究而言,可能是 *SLC16A1* 与 *ESR1*、*PGR* 呈现负相关,更高的 *SLC16A1* 可能预示着 ER、PR 低表达,使患者丧失有效的内分泌治疗靶点,导致患者更差的 OS。

Khan 等[20]用 MCT1 抑制剂处理神经母细胞瘤,破坏细胞的乳酸稳态、还原和氧化烟酰胺腺嘌呤二核苷酸(reduced and oxidized nicotinamide adenine dinucleotide, NADH/NAD^+)比率,抑制了癌细胞的生长,并且与 *LDHA* 抑制剂高度协同降低细胞活力。Hou 等[21]发现抑制 MCT1 可以克服乳腺癌细胞对紫杉醇的耐药性;上述成果显示了靶向 *LDHA* 和 *SLC16A1* 相应蛋白进而改善患者预后的潜力。

MCT4 在前列腺癌、肝内胆管癌、肺癌、膀胱癌、肝癌中高表达,且与肿瘤细胞的增殖、侵袭及转移等紧密相关,其高表达与患者更差的 OS 相关[22-26],本研究结果与其一致。Sun 等[22]证实沉默 MCT4 可以使前列腺癌细胞的增殖、迁移和侵袭能力显著降低。有研究发现 MCT4 在乳腺癌中表达上调,并且与不良预后有关,且乳腺癌中 MCT4 的表达与免疫细胞浸润和糖酵解限速酶有关[18],所以 *SLC16A3* 有望成为肿瘤治疗的一个潜在的预后指标及靶点辅助乳腺肿瘤的治疗。

本研究结果示在 ER、PR 均为阴性组中,*LDHA*、*SLC16A1* 和 *SLC16A3* 的表达量更高,赵雪可等[14]研究也表明 ER 阴性组的 *LDHA* 表达量更高,本研究结果与其一致。且 *ESR1* 和 *PGR* 与 *SLC16A1* 和 *SLC16A3* 呈现显著负相关; ER、PR 的表达与上述基因的关系有待进一步研究。

本研究存在一定的不足,首先数据中亚洲患者只占小部分,可能与我国基因表达存在偏差;其次虽然 TCGA 数据库具有精确的测序,良好质量的数据以及丰富的组学[27-29],但本研究从 TCGA 数据库获取的 1 060 例乳腺癌样本仍存在一定的数据量不足,后续可收集临床样本进一步扩大样本量;最后,本研究仅在基因 mRNA 层面进行论证,未结合其他组学层面进行研究。虽然本研究存在一定的局限性,但所得出的相关结论可为后续研究提供一定的方向。

综上所述,*LDHA*、*SLC16A1* 和 *SLC16A3* 基因在乳腺癌组织中高表达,与乳腺癌患者的 OS 呈负相关; *SLC16A1* 和 *SLC16A3* 是乳腺癌患者 OS 的独立危险因素;上述基因有望成为乳腺癌的预后指标,可能为后续乳腺癌的治疗提供新的靶点。

利益冲突　无

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收稿日期:2023-11-01　**编辑**:叶小舟

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收稿日期:2023-09-01　**编辑**:李方