Original Article

Low expression of A-kinase anchor protein 5 predicts poor prognosis in non-mucin producing stomach adenocarcinoma based on TCGA data

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Background: In the past, there were not a lot of studies on how A-kinase anchor protein 5 (AKAP5) involving in the pathogenesis and prognosis of non-mucin producing stomach adenocarcinoma (NMSA). Therefore, we studied the relationship between AKAP5 and the prognosis of NMSA and its possible mechanisms using publicly available data from The Cancer Genome Atlas (TCGA)

Methods: RNA high-throughput sequencing and clinicopathologic data of NMSA were downloaded from the TCGA. Clinical pathologic features associated with AKAP5 expression were analyzed using the chi-square and Fisher exact tests. The relationship between the overall survival (OS) and AKAP5 expression was analyzed by the Kaplan-Meier method and the Cox regression analysis. GSEA analysis was performed using the TCGA dataset.

Results: Our results indicated that the AKAP5 expression was increased in NMSA (all tumor *vs.* adjacent mucosa). Also, histologic grade, clinical stage, N classification, and survival status were significantly correlated with AKAP5 expression. Kaplan-Meier curves showed that low AKAP5 expression was associated with a poor OS among the NMSA patients (P=5.003e-05), and in the clinical stage III and IV (P=4.646e-05), TNM stage T3 (P=0.016), T4 (P=0.001), N2 (P=0.012), N3 (P=0.003), M0 (P=3.911e-05), and histological grade G3 (P=1.658e-04) subgroups. Cox regression analysis showed that reduced AKAP5 expression in NMSA is associated with age (HR =1.03, P=0.007), stage (HR =1.84 for stage I, II *vs.* stage III, IV, P=0.002) and M classification (HR =1.8 for M0 *vs.* M1, P=0.010). Gene sets related to cholesterol homeostasis, glycolysis, estrogen response late, adipogenesis, estrogen response early, notch signaling, and peroxisome were differentially enriched with the low AKAP5 expression phenotype.

Conclusions: Low expression of AKAP5 may be a potential molecular marker for predicting poor prognosis of NMSA. Besides, cholesterol homeostasis, glycolysis, estrogen response, adipogenesis, notch signaling, and peroxisome may be the key pathways regulated by AKAP5 in NMSA. It also suggested that AKAP5 might potentially have biological functions in the development of stomach adenocarcinoma.

Keywords: Stomach neoplasms; adenocarcinoma; survival analysis; A-kinase anchor protein 5 (AKAP5)

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Introduction

Gastric cancer is the sixth most common malignant tumor in the world, with the third highest mortality rate (1). Although the survival rate has reached about 50% in Japan and South Korea due to great efforts made by these countries, the global survival rate of gastric cancer is still unsatisfactory (2,3). At present, the prognosis of gastric cancer is determined through clinicopathologic classification, such as TNM staging and histopathological staging. Although many patients have the same clinical and pathological stages, their prognoses are far from the same. According to the WHO histopathological classification for gastric cancer, gastric adenocarcinoma is mainly divided into tubular adenocarcinoma, papillary adenocarcinoma, mucinous adenocarcinoma, and signet ring cell carcinoma (4). Mucinous adenocarcinoma and signet ring cell carcinoma have the characteristics of being mucin-producing in its histology. They mainly belong to the undifferentiated type in the classification of gastric cancer in Japan, which generally indicates a poor prognosis (5). The prognosis of non-mucin producing stomach adenocarcinomas (NMSA) is better, but some of them still have an outcome of death. Whether or not these patients have different biological characteristics from the patients with a good prognosis is still unclear.

A-kinase anchor protein 5 (AKAP5), also named AKAP79, is a 427 amino acid protein that functions as an anchor cAMP-dependent protein kinase (PKA) to cytoskeleton or organelle-associated proteins, that transduce cAMP signals into specific intracellular effectors. AKAP5 also regulates the beta2- adrenergic receptor signaling pathway, participation in energy metabolism synthesis (6,7). Earlier studies on how AKAP5 involving disease are few. Some research has found that AKAP5 is associated with chronic obstructive pulmonary disease, long-term depression, and diabetes, but there is little research on its relationship with malignant tumors (8-10).

In this study, we mined the data of NMSA in the stomach adenocarcinoma (STAD) collection on the Cancer Genome Atlas (TCGA) database and found that AKAP5 was significantly increased in NMSA, but low AKAP5 expression of NMSA has a significantly poorer prognosis among most clinical and pathological stages. It has excellent performance for predicting the prognosis of NMSA as a biomarker. GSEA analysis was conducted to identify the biological pathway involved in AKAP5. This study suggested that the AKAP5 gene may play a key role in the pathological process of NMSA, increasing our understanding of this disease.

Methods

RNA-sequencing patient data and bioinformatics analysis

The RNA high-throughput sequencing data and corresponding clinicopathologic data of the stomach adenocarcinomas (STAD) projects were downloaded from the TCGA. The disease type of the adenomas and adenocarcinomas was included, and other types such as cystic, mucinous, and serous neoplasms were excluded. HTSeq-FPKM workflow was used for gene expression normalization. All data were conducted using the R software (version 3.5.3).

Gene set enrichment analysis (GSEA)

GSEA was utilized to understand which biological processes are involved in the high and low expression of AKAP5, respectively. In this study, we used version 4.0 of the GSEA software downloaded from the official website (11). According to the cut-off point, the samples were divided into two phenotypes: high expression and low expression. The Signal2Noise method was used to evaluate the correlation between the expression of each gene and AKAP5; then, genes were ranked according to the correlation score from high to low. The gene set permutation was run 1000 times per analysis, and the software automatically calculated the normalized enrichment score (NES), nominal P value, and false discovery rate (FDR). Gene sets with nom P value <0.05 and FDR <0.25 were significantly enriched.

Statistical analysis

All statistical analyses were performed using R (v.3.5.3). Clinical pathologic features associated with AKAP5 high and low expression groups were analyzed using the chi-square and Fisher exact tests. The relationship between overall survival (OS) and AKAP5 expression among all NMSA patients and each clinicopathological subgroup was analyzed using the Kaplan-Meier method, using the Survival package in R. The correlations between AKAP5 expression and survival along with other clinicopathological characteristic were analyzed using univariate and multivariate Cox regression analysis. The best cut point of AKAP5 expression was determined by the maximally selected rank statistics method using survminer package in R.

Table 1 Clinical characteristic of NMSA patients organized from TCGA

Clinical characteristic	n	%
Age (y)		
≥60	233	69.6
<60	102	30.4
Gender		
Male	210	62.5
Female	126	37.5
Histologic grade		
G1	8	2.4
G2	124	37.7
G3	197	59.9
Clinical stage		
Stage I	46	14.6
Stage II	101	32.2
Stage III	133	42.4
Stage IV	34	10.8
T classification		
T1	17	5.2
T2	72	22.0
T3	156	47.6
T4	83	25.3
N classification		
N0	98	30.6
N1	88	27.5
N2	70	21.9
N3	64	20.0
M classification		
M0	300	92.9
M1	23	7.1
Survival status		
Alive	202	60.1
Dead	134	39.9
H. pylori infection		
Yes	17	12.5
No	119	87.5

NMSA, non-mucin producing stomach adenocarcinoma; TCGA, The Cancer Genome Atlas.

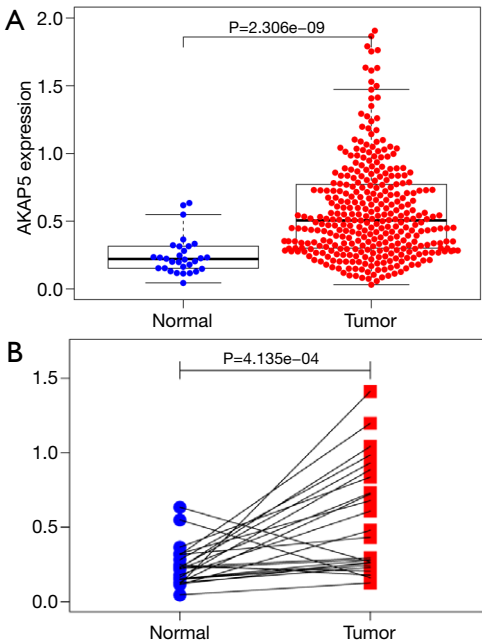

Figure 1 Differential AKAP5 expression in NMSA compared with adjacent mucosa. (A) AKAP5 expression was increased in NMSA compared with adjacent normal mucosa; (B) paired tumors and their adjacent mucosa, AKAP5 expression in NMSA was also higher than adjacent mucosa significantly). NMSA, non-mucin producing stomach adenocarcinoma.

Results

Patient characteristics

The clinical data of the 336 NMSA patients were downloaded from the TCGA database, which included patient age, gender, tumor location, histologic grade, clinical stage, TNM classification, survival status, helicobacter pylori infection (*Table 1*).

Differential AKAP5 expression in NMSA compared with adjacent mucosa

Differential expression of AKAP5 in NMSA and adjacent mucosa was performed by two independent sample Wilcoxon Rank Sum Test and paired Wilcoxon Rank Sum Test. The result showed that AKAP5 expression was increased in NMSA (all tumor *vs.* adjacent mucosa, P=2.306e-09, paired tumor *vs.* adjacent mucosa, P=4.135e-04, *Figure 1*).

Table 2 Correlation of AKAP5 expression and clinicopathologic characteristics of NMSA patients

Clinical characteristic	n	AKAP5		χ^2	P
		High	Low		
Age (y)				2.240	0.135
≥60	233	27	206		
<60	102	18	84		
Gender				2.875	0.090
Male	210	23	187		
Female	126	22	104		
Histologic grade				9.121	0.010
G1	8	0	8		
G2	124	9	115		
G3	197	36	161		
Clinical stage				9.515	0.023
Stage I	46	4	42		
Stage II	101	13	88		
Stage III	133	25	108		
Stage IV	34	0	34		
T classification				4.789	0.188
T1	17	2	15		
T2	72	8	64		
T3	156	17	139		
T4	83	17	66		
N classification				9.264	0.026
N0	98	11	87		
N1	88	5	83		
N2	70	14	56		
N3	64	12	52		
M classification					0.335
M0	300	42	258		
M1	23	1	22		
Survival status				17.937	2.3e-5
Alive	202	40	162		
Dead	134	5	129		
H. pylori infection				1.477	0.224
Yes	17	4	13		
No	119	15	104		

NMSA, non-mucin producing stomach adenocarcinoma.

Correlation between AKAP5 expression and clinicopathologic variables of NMSA

AKAP5 expression data of NMSA and their clinicopathologic information were downloaded from the TCGA. Subsequently, patients were divided into high AKAP5 expression group and low AKAP5 expression group according to the gene expression cutpoint 0.9975. The correlation between AKAP5 expression and clinicopathologic variables of NMSA is summarized in *Table 2*. Histologic grade, clinical stage, N classification, and survival status were significantly correlated with AKAP5 expression.

Low AKAP5 expression is a significant risk factor in predicting OS of NMSA

Although AKAP5 expression increased in the tumor samples, Kaplan-Meier curves showed that low AKAP5 expression was associated with a worse OS among NMSA patients (P=5.003e-05; *Figure 2*). Furthermore, low AKAP5 expression also indicated poor OS in clinical stage III and IV (P=4.646e-05), TNM stage T3 (P=0.016), T4 (P=0.001), N2 (P=0.012), N3 (P=0.003), M0 (P=3.911e-05), and histological grade G3 (P=1.658e-04). Univariate Cox regression analysis show that reduced AKAP5 expression in NMSA is associated with age (HR =1.03, P=0.007), stage (HR =1.84 for stage I, II *vs.* Stage III, IV, P=0.002) and M classification (HR =1.8 for M0 *vs.* M1, P=0.010). Univariate and multivariate Cox regression analysis showed that AKAP5 expression was an independent risk factor for OS among NMSA patients (HR =7.58, P=0.001). These results are described in *Table 3* and *Figure 3*.

GSEA

GSEA was performed to analyze which signaling pathways were activated in the AKAP5 low and high expression groups. Data sets from MSigDB Collection (h.all.v7.0.symbols) with FDR <0.25 and nom-P value <0.05 were considered to be significantly different. The most significantly enriched signaling pathways were described in *Figure 4* and *Table 4*. Gene sets related to cholesterol homeostasis, glycolysis, estrogen response late, adipogenesis, estrogen response early, notch signaling, and peroxisome were differentially enriched with the low AKAP5 expression phenotype.

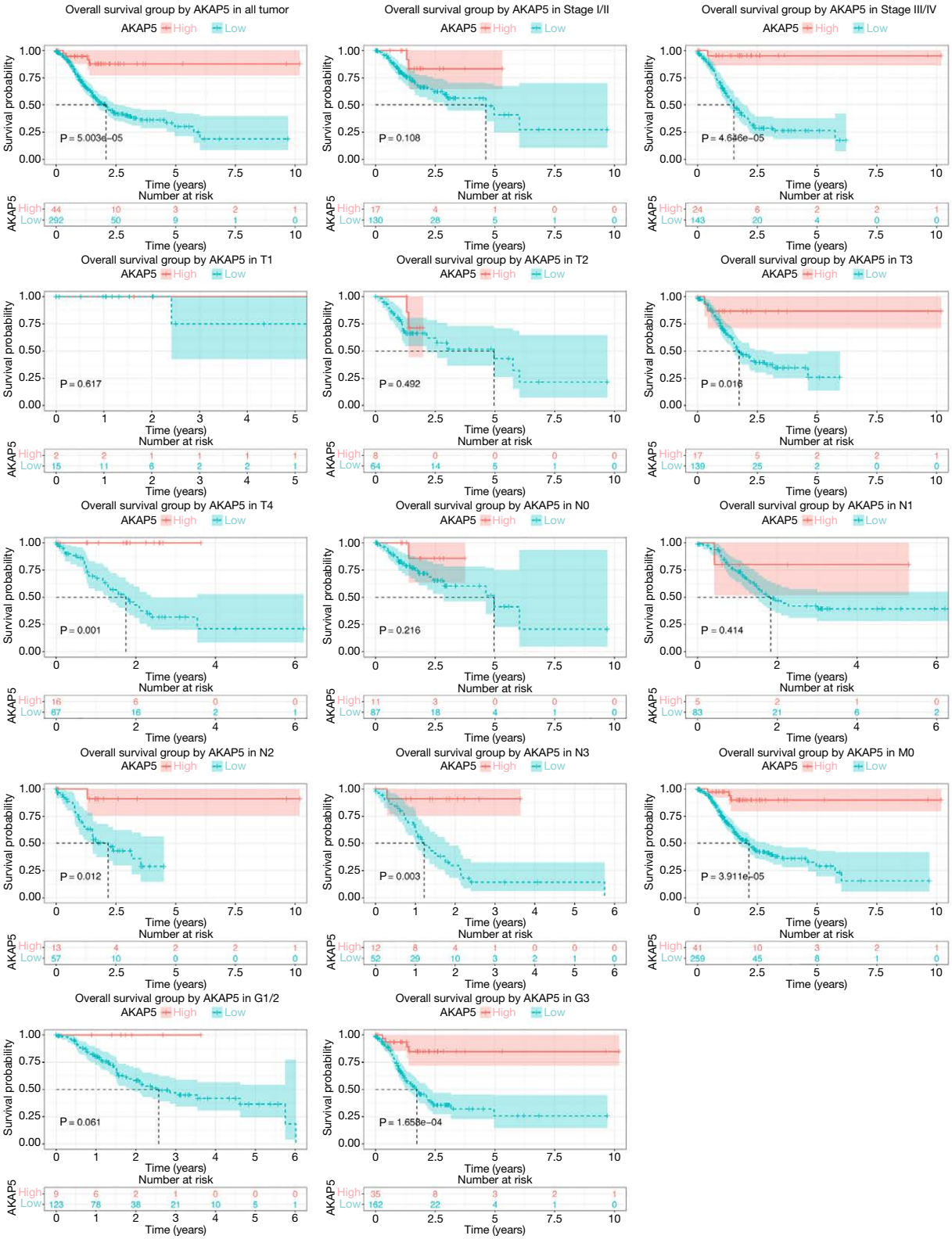

Figure 2 Kaplan-Meier curves for OS in NMSA between high and low AKAP5 expression. (A) All cases; (B,C) Kaplan-Meier curves for OS in each clinical stage subgroup; (D-L) Kaplan-Meier curves for OS in each pathological TNM classification subgroup; (M,N) Kaplan-Meier curves for OS in each histological grade subgroup. OS, overall survival; NMSA, non-mucin producing stomach adenocarcinoma.

Table 3 Univariate and multivariate COX regression analysis

Variable	Univariate analysis		Multivariate analysis	
	HR (95% CI)	P value	HR (95% CI)	P value
Age (continuous)	1.03 (1.01–1.04)	0.007	1.03 (1.01–1.05)	0.003
Gender (male *vs.* female)	1.45 (0.98–2.14)	0.061		
Histologic grade (G1 or G2 *vs.* G3)	1.23 (0.84–1.8)	0.281		
Stage (stage I or II *vs.* stage III or IV)	1.84 (1.25–2.7)	0.002	1.85 (1.09–3.13)	0.022
T (T1 or T2 *vs.* T3 or T4)	1.48 (0.94–2.32)	0.092		
N (N0 *vs.* N1 or N2 or N3)	1.76 (0.92–3.38)	0.087		
M (M0 *vs.* M1)	1.8 (1.15–2.82)	0.010	1.22 (0.66–2.24)	0.524
AKAP5 (high *vs.* low)	7.58 (2.41–23.87)	0.001	7.73 (2.45–24.38)	<0.001

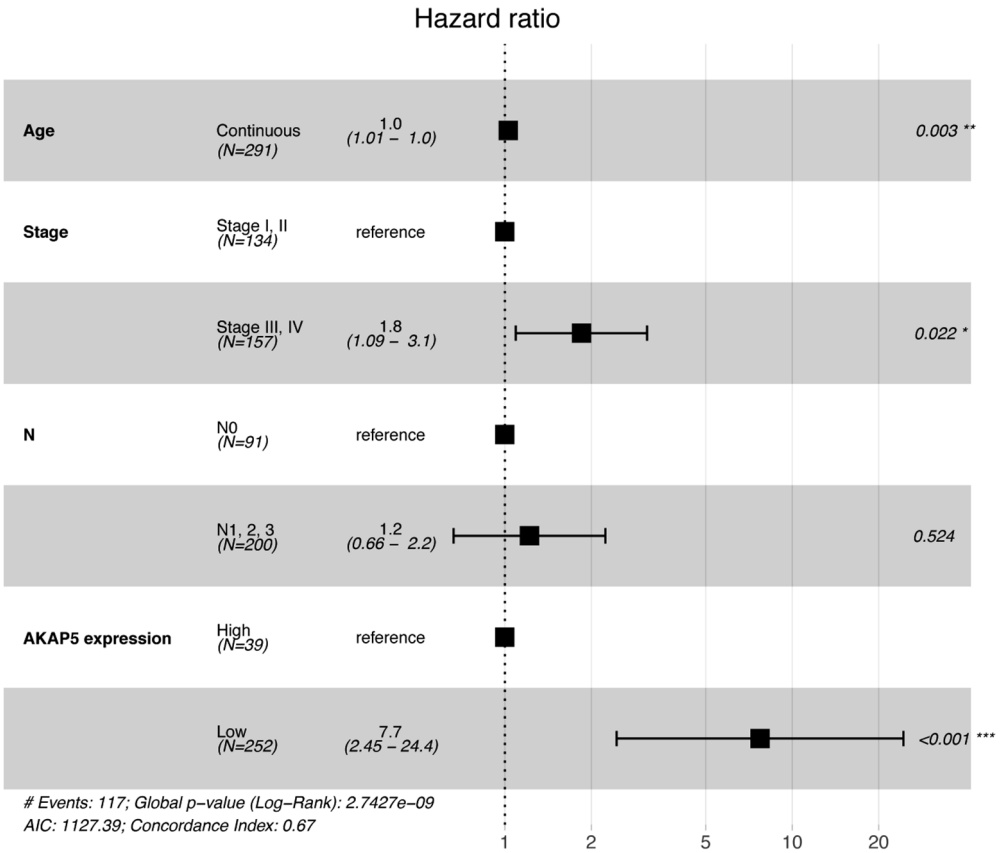

Figure 3 Forest plot of multivariate COX regression analysis.

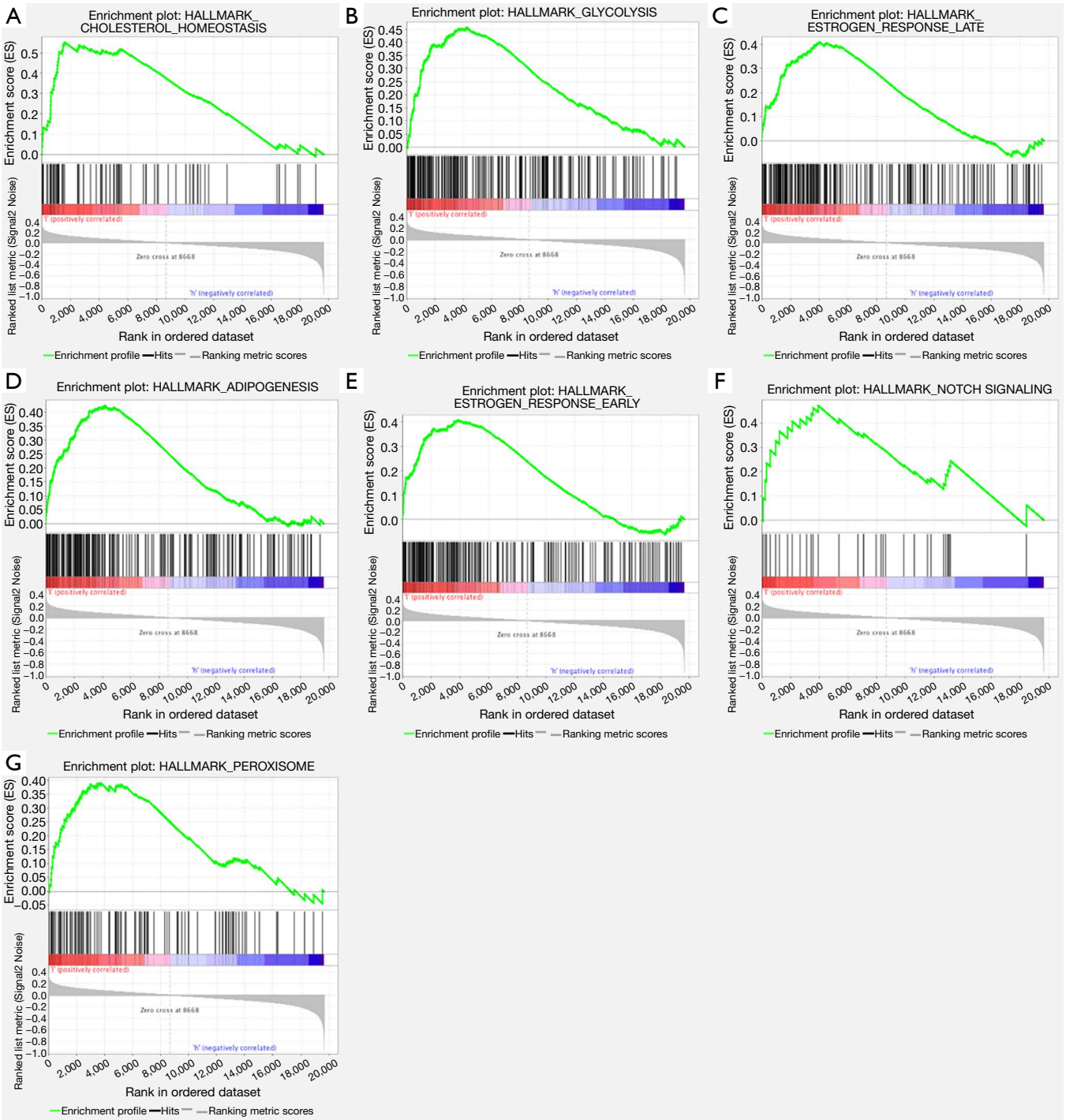

Figure 4 Significant enrichment plot of GSEA in NMSA with a low AKAP5 expression phenotype. Cholesterol homeostasis, glycolysis, estrogen response late, adipogenesis, estrogen response early, notch signaling, and peroxisome were differentially enriched with the low AKAP5 expression phenotype. GSEA, gene set enrichment analysis; NMSA, non-mucin producing stomach adenocarcinoma.

Table 4 Enrichment results of GSEA in NMSA with low AKAP5 expression phenotype

MSigDB	NES	Nom P value	FDR q value
HALLMARK_ CHOLESTEROL_ HOMEOSTASIS	1.8917518	0.00896057	0.08460237
HALLMARK_ GLYCOLYSIS	1.7547022	0.01054482	0.15448076
HALLMARK_ ESTROGEN_ RESPONSE_LATE	1.7297268	0.00154083	0.12746213
HALLMARK_ ADIPOGENESIS	1.6963805	0.01134216	0.12330247
HALLMARK_ ESTROGEN_ RESPONSE_EARLY	1.6406236	0.0184874	0.15128794
HALLMARK_NOTCH_ SIGNALING	1.6083862	0.03724395	0.15408081
HALLMARK_ PEROXISOME	1.5346892	0.0237691	0.19820438

GSEA, gene set enrichment analysis; NMSA, non-mucin producing stomach adenocarcinoma.

Discussion

As an essential protein family regulating the cAMP-PKA signaling pathway, AKAPs are directly related to the occurrence and development of carcinoma. For example, the specific polymorphism of AKAP9 is associated with the risk of breast cancer and has been found to be significantly higher in human colorectal cancer than in the adjacent tissues, as well as promoting cell proliferation, invasion, and migration (12). Mutations in the AKAP10 gene increase the risk of breast and colorectal cancer (13,14). AKAP12 expression is associated with endothelial barrier function and is speculated to have a tumor suppressor effect (15,16).

The AKAP protein family is an important regulatory protein of the cAMP-PKA signaling pathway, which is capable of anchoring the protein kinase A (PKA) regulatory subunits RI and RII to specific organelles specifically; thus, it is able to transduce the second messenger cAMP signal. Studies have shown that the cAMP-PKA pathway is closely related to the proliferation, apoptosis, and tumorigenesis of various tumor cells (such as prostate cancer, colorectal cancer, and breast cancer) (12,17-19).

The relationship between AKAP5 and the development of tumors is poorly understood; some studies have suggested there to be an indirect relationship with the development of them. AKAP5 can bind to E-cadherin and β-catenin to regulate mucosal adhesion junctions, which may be associated with tumor migration and metastasis (20). AKAP5 inhibits cell proliferation, but in smooth muscle cells rather than tumor cells (21). In breast cancer, low AKAP5 expression is more prone to metastasis and recurrence (22).

Since the role of AKAP5 in stomach adenocarcinoma has not been clarified, GSEA analysis was used to predict the pathway associated with AKAP5 in NMSA. The results showed that the low AKAP5 expression group was associated with cholesterol homeostasis, glycolysis, estrogen response, adipogenesis, notch signaling, and peroxisome. The estrogen signaling pathway has been widely studied in breast cancer, and this pathway also contributes to the oncogenesis and the advancement of gastric cancer as well. For instance, estrogen receptor (ER) α36 is highly expressed in gastric cancer and is associated with lymph node metastasis (23). The possible mechanisms by which estrogen receptors promote tumor growth include the activation of the Akt-PI3K signaling pathway by glucose-regulated protein 94 (GRP94), or promoting gastric cancer cell proliferation, differentiation, and invasion by activating the c-Src signaling pathway and increasing cyclins D1 expression, which regulates the cell cycle to promote proliferation (23-25). The activation of the Notch signaling pathway is related to the clinical progress of gastric cancer (26,27). It may promote the proliferation, migration, and invasion of gastric cancer cells by interacting with mTOR, STAT3-Twist, and other signaling pathways or inhibiting the activity of PTEN (27-29). Enhanced glycolysis is part of the Warburg effect of tumor cells, which enables gastric cancer cells to metabolize glucose into lactic acid in an aerobic environment, providing a source for cellular biosynthesis and cell division (30). This process may involve changes in key enzymes of glycolysis and mitochondrial damage, which are often related to a poor prognosis of the tumor (31-34). In addition to abnormal glucose metabolism, abnormal lipid metabolism is also observed in gastric cancer, but the specific mechanisms for this are still unclear (35). The research on the relationship between these pathways and AKAP5 is very scarce and needs further explored through experiments.

Unfortunately, the major deficiency of this study is that the research data is only from TCGA. Although the source of TCGA samples may have some limitations, TCGA is one of the best cancer databases in the world, with the largest number of sequencing data and the most comprehensive

clinical information. In a limited sample, we found that low expression of AKAP5 may be a potential molecular marker for predicting poor prognosis of NMSA. Besides, cholesterol homeostasis, glycolysis, estrogen response, adipogenesis, notch signaling, and peroxisome may be the key pathways regulated by AKAP5 in NMSA. It also suggested that AKAP5 might have a potential biological function in stomach adenocarcinoma.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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