Research Paper

The prognostic value of Cyclin-Dependent Kinase 5 and Protein Phosphatase 2A in Gastric Cancer

Jian-Xian Lin[1,2,3*], Xin-Sheng Xie[1,2,3*], Xiong-Feng Weng[1,2,3], Chao-Hui Zheng[1,2,3], Jian-Wei Xie[1,2,3], Jia-Bin Wang[1,2,3], Jun Lu[1,2,3], Qi-Yue Chen[1,2], Long-Long Cao[1,2], Mi Lin[1,2], Ru-Hong Tu[1,2], Chang-Ming Huang[1,2,3✉], Ping Li[1,2,3✉]

1. Department of Gastric Surgery, Fujian Medical University Union Hospital, Fuzhou, Fujian Province, China
2. Key Laboratory of Ministry of Education of Gastrointestinal Cancer, Fujian Medical University, Fuzhou, Fujian Province, China
3. Fujian Key Laboratory of Tumor Microbiology, Fujian Medical University, Fuzhou, Fujian Province, China

*Jian-Xian Lin and Xin-Sheng Xie contributed equally to this work and should be considered co-first authors.

✉ Corresponding authors: Ping Li, E-mail:Pingli811002@163.com; Chang-Ming Huang, E-mail: hcmlr2002@163.com; Department of Gastric Surgery, Fujian Medical University Union Hospital, No.29 Xinquan Road, Fuzhou 350001, Fujian Province, China. **Telephone:** +86-591-83363366; **Fax:** +86-591-83363366

Abstract

Purpose To discuss the relationship between the clinicopathological data, long-term survival of gastric cancer patients and different expression levels of Cyclin-Dependent Kinase 5 (CDK5) and Protein Phosphatase 2A (PP2A).

Method The expression levels of CDK5 and PP2A were detected by immunohistochemistry in specimens from 124 patients with primary gastric cancer. The correlation among the expression of CDK5 and PP2A, clinicopathological factors and prognosis was investigated.

Result The expression level of CDK5 was correlated with the TNM stage (p=0.030) and N stage (p=0.001), while the expression level of PP2A was correlated with the TNM stage and N stage (p=0.001 and p=0.004) as well as the degree of differentiation (p=0.046). The expression of CDK5 was positively correlated with the expression of PP2A in gastric cancer. Co-expression of CDK5 and PP2A is an independent prognostic factor that affected overall survival, and provided more accurate prognostic value for the overall survival of gastric cancer patients.

Conclusion The expression of CDK5 and PP2A is positively correlated in gastric cancer. Co-expression of CDK5 and PP2A was an independent prognostic factor in patients with gastric cancer.

Key words: CDK5; PP2A; prognosis; gastric cancer

Introduction

Gastric cancer (GC) is the fifth most common malignant cancer worldwide and is the third most common cause of cancer-related death [1]. China has a high incidence of gastric cancer, as more than 400,000 new cases occur every year, which account for 42% of the world's gastric cancer cases [2]. Considering that the symptoms of early gastric cancer are not highly specific, misdiagnosis and missed diagnosis may occur. Most patients are in the middle and late stages of disease at the time of their first visit to a healthcare professional, which seriously affects the treatment strategy and prognosis. This is also one of the major causes of the high overall mortality of gastric cancer. Therefore, it is of great importance to find new molecular markers that can be used to evaluate the prognosis and to develop novel therapies for gastric cancer.

CDK5 is an important serine/threonine kinase

that is expressed in many organisms. CDK5 is widely expressed in the nervous system and other tissues, and is involved in a variety of pathophysiological processes [3, 4]. In recent years, it has been suggested that CDK5 is involved in the occurrence and development of many types of malignant tumors [5]. It has been reported that activation of CDK5 can phosphorylate the Rb protein, release E2F1 into the nucleus, and thus activate the expression of downstream factors and promote the development of medullary thyroid carcinoma [6]. The inhibition of CDK5 activity can interfere with the Notch pathway, inhibit the activation of the Notch intracellular domain (NICD), and thus inhibit tumor growth [7]. In addition, CDK5 plays an important role in the proliferation, invasion and metastasis of malignant tumors such as liver cancer and prostate cancer among others [8, 9]. However, in previous studies, we found that low expression of CDK5 was associated with the overall poor survival of gastric cancer patients. The nuclear accumulation of CDK5 inhibited the proliferation and tumorigenicity of human gastric cancer cells, which suggests that CDK5 might play a role as a tumor suppressor in the carcinogenesis and development of gastric cancer [10].

PP2A is a widespread Ser/Thr protein phosphatase in eukaryotes. The structural subunit (PR65/A: 65 kDa), the regulatory subunit (B subunit: 50~130 kDa) and the catalytic subunit (PP2Ac: 36 ~ 38 kDa) form a trimer; this complex, is involved in the cell cycle, DNA replication, signal transduction, cell differentiation, malignant transformation and other cellular and biological events. PP2A was traditionally considered to be related to the occurrence and development of neurodegenerative diseases, tumors and other diseases [11-13]. Aberrant PP2A expression is associated with the occurrence and development of many malignant tumors, such as colorectal cancer, breast cancer, lung cancer and glioma [14-17]. Activation of PP2A can promote apoptosis, dedifferentiation and can inhibit the proliferation of tumor cells, and thus activation of PP2A is a potential target for the treatment of malignant tumors [18, 19]. Louis et al [20] Found that a knockout of the PP2A subunit (Ppp2r5d) in mice could affect the activities of CDK5 and GSK-3β, decrease the activity of CDK5 phosphatase and increase the activity of GSK-3β, which lead the to the development of space restricted tau disease in these knockout mice. However, the expression of CDK5 and PP2A in gastric cancer and its influence on prognosis have not been reported. Therefore, the expression of CDK5 and PP2A was detected in 124 cases of gastric cancer after radical gastrectomy. The correlation among CDK5 and PP2A expression, the clinicopathological features and prognosis was analyzed.

Materials and Methods
Human gastric tumor tissues

The gastric cancer specimens used in this study were collected from January 2013 to December 2014 in the Department of Gastric Surgery, Union Hospital of Fujian Medical University, from patients who underwent D2 lymph node dissection and gastrectomy for gastric cancer. Cases with incomplete clinical data were excluded, which resulted in 124 cases. All patients received their first diagnosis of gastric cancer and received no other treatment, such as neoadjuvant chemotherapy or chemoradiotherapy, before surgery. All diagnoses were confirmed by pathology after surgery, and each case had detailed clinicopathological data. Gastric cancer was confirmed by hematoxylin and eosin (H&E) staining in all cases. The clinicopathological data of 124 patients with GC included age, sex, size of the primary tumor, location of the primary tumor, degree of differentiation, histological type (Bormann type), depth of invasion, lymph node metastasis, vascular invasion and TNM stage (according to the TNM classification of gastric cancer (eighth edition) of the International Union against Cancer (2016)); the pathological stage of the tumor was reassessed. This study was approved by the ethics committee of Fujian Medical University Union Hospital and written consent was obtained from all patients.

Immunohistochemistry (IHC)

Paraffin sections containing sufficient formalin fixed tumor tissue were sectioned continuously at a thickness of 4 μm and were mounted on silage coated slides for immunohistochemical analysis. The slices were deparaffinized with xylene and rehydrated in 95%, 85% and 75% ethanol. Antigen retrieval was performed by subjecting the slides to high-pressure sterilization at 121°C for 2 min in 0.01 mol/L sodium citrate buffer solution (pH 6.0). Endogenous peroxidase activity was blocked by incubating the slides with 3% H_2O_2 at room temperature for 10 min. The slices were then washed in phosphate buffered saline (PBS) solution and blocked in 10% goat serum (Zhongshan Biotechnology Co, Ltd.) for 30 minutes. Next, the sections were incubated with diluted rabbit anti-human CDK5 (ab24189 diluted 1: 200.USA) or rabbit anti-human PP2Aa (ab32104n diluted 1: 150; Abcam, Cambridge, MA, USA) overnight in a humidified chamber at 4°C. After three washes in PBS, the sections were incubated with the secondary antibody conjugated to horseradish peroxidase at room temperature for 30 minutes. The signal was developed with diaminobenzidine solution, which

was followed by counterstaining in 20% hematoxylin. Finally, all slides were dehydrated and mounted on cover glass. For negative controls, antibody diluent was substituted for the primary antibody.

Evaluation of Immunohistochemistry Intensity

The IHC of tissue sections was examined by two experienced pathologists, who scored the slides according to the intensity of cell staining and the proportion of positively stained tumor cells. In the event of a discrepancy, the sample was reassessed, and a consensual scoring criterion was selected for the evaluation. CDK5 is primarily expressed in the cytoplasm and/or the nucleus of cancer cells, and the immunohistochemical staining is yellow to brown. The expression pattern of the protein in the tumor was one in which the cells were either all positive or completely negative. Therefore, the proportion of tumor cells that were stained is not available. The standard for the evaluation of CDK5 staining intensity was as follows: (a1): no staining (score of 0), (a2): weak staining (score of 1), (a3): moderate staining (score of 2) and (a4) strong staining (score of 3) (Figure 1A). For CDK5, a score ≤ 1, is considered low expression, while all other scores indicate high expression. Unlike CDK5, the expression pattern of PP2A is not all or none, and thus the standard for the evaluation of PP2A staining intensity is the same as that of CDK5. The positive proportion of stained tumor cells was scored as follows: (b5): ≤ 5% positive cells (score of 0), (b6): 6% to 25% positive cells (score of 1), (b7): 26% to 50% positive cells (score of 2), (b8): ≥ 51% positive cells (score of 3) (Figure 1B). If the total score (percentage score × intensity score) was less than 3, PP2A protein expression was considered low, but if the score was 4 or higher, PP2A protein expression was considered high.

Follow-up

All patients were followed up once every 3 months for the first 2 years and were then, followed up every six months for the next 3-5 years. The last follow-up time point was December 2017. Follow-up routine examinations, including a physical examination, laboratory tests (CA19-9, CEA and CA72-4), chest X-ray, abdominal CT, B Ultrasound, and gastroscopy were performed each year. The total survival time is defined as the time from surgery to the last follow-up, or the time of death, or the expiration of the follow-up database (e.g., lost to follow-up, death from other diseases, etc.)
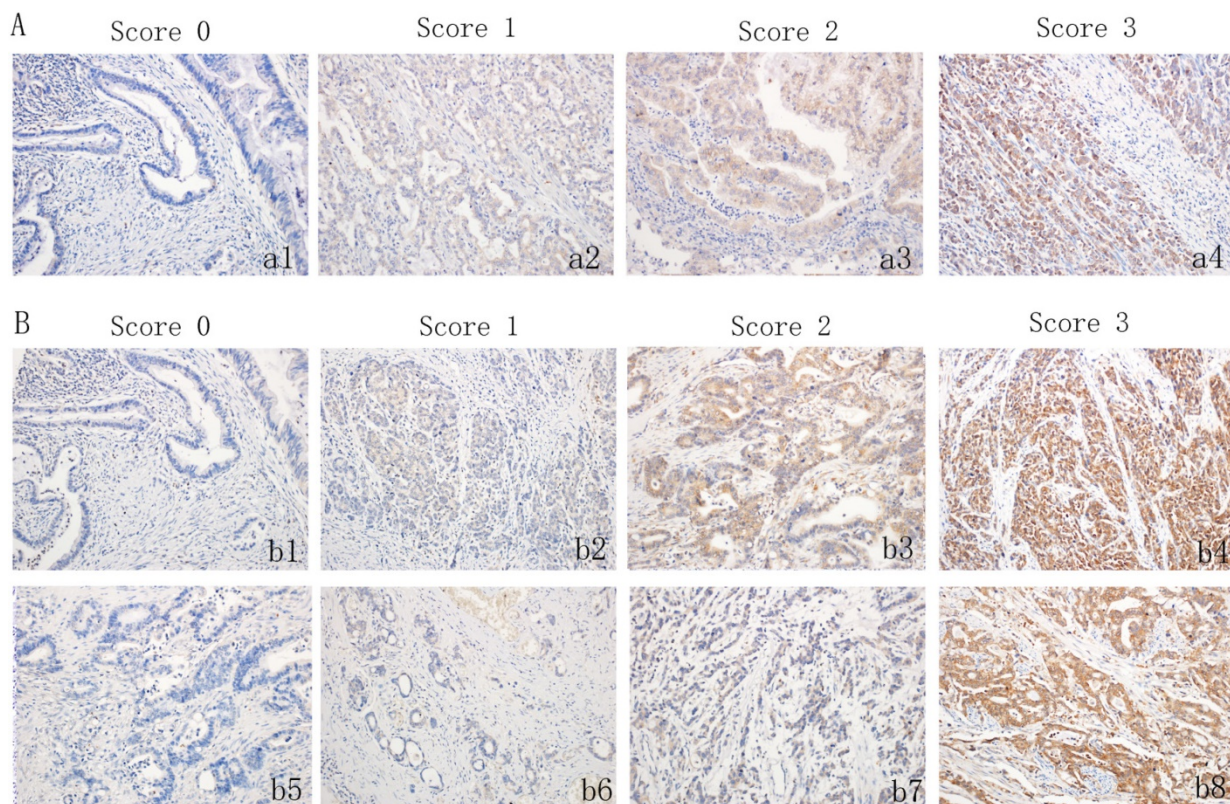

Figure 1. Immunohistochemistry staining for CDK5 and PP2A expression in gastric cancerous tissue and the criteria for immunohistochemistry scoring. (A) Intensity scores for CDK5 expression in gastric cancer tissue. (a1): no staining (score 0), (a2): weak staining (score 1), (a3): moderate staining (score 2) and (a4) strong staining (score 3). (B) Distribution score and intensity score for PP2A expression in gastric cancer tissue. (b1): no staining (score 0), (b2): weak staining (score 1), (b3): moderate staining (score 2) and (b4) strong staining (score 3). (b5): ≤ 5% positive cells (score 0), (b6): 6% to 25% positive cells (score 1), (b7): 26% to 50% positive cells (score 2), (b8): ≥ 51% positive cells (score 3).
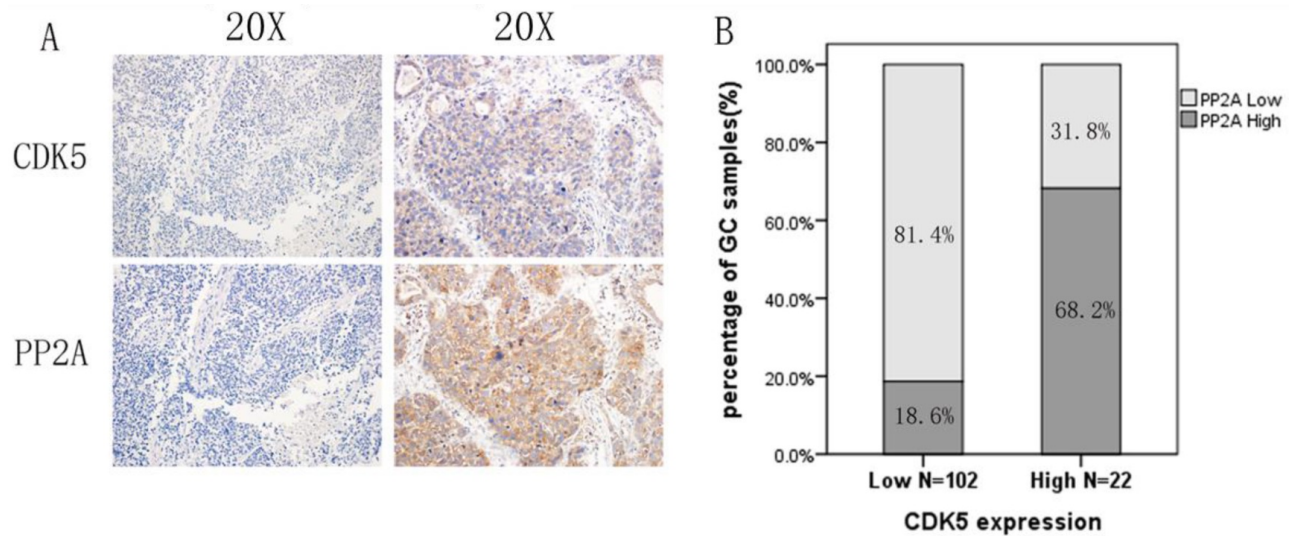
Figure 2. CDK5 is positive correlated with PP2A expression in gastric cancer. A: High CDK5 and PP2A expression in the same patient. B: The positive expression rate of PP2A was 68.2% in gastric cancer tissues with high expression of CDK5, and negative expression rate of PP2A was 81.4% in stomach tissues with low expression of CDK5.

Statistical analysis

All the data were processed by SPSS23.0 statistical software package. Appropriate test methods, such as the χ2 test or Fisher's exact test, were selected according to the type of variables and the purpose of comparison. The survival rate was calculated by the Kaplan-Meier method, and the subsequent survival curve was plotted. The log-rank test was used to compare the survival rates. Cox regression was used to analyze the independent factors that affected the prognosis. The area under the ROC curve was used to compare the prognostic ability of different indexes. The difference was statistically significant when p < 0. 05.

Results

Expression Status of CDK5 and PP2A in Gastric Cancer

Of the 124 patients with primary gastric cancer, 102 patients had low expression of CDK5 (82.2%), and 22 patients had high expression (17.8%).In addition, 90 patients had low expression of PP2A (72.6%), and 34 patients had high expression of PP2A (27.4%). Among the patients with low expression of CDK5, 81.4% showed low expression of PP2A. A significant positive correlation was observed between the expression levels of CDK5 and PP2A in gastric cancer tissue (p<0.001, Figure 2).

Relationship between the expression of CDK5 and PP2A and the Clinicopathological data of patients with gastric cancer

According to the different expression levels of CDK5 and PP2A, the correlation factor analysis showed that the expression levels of CDK5 and PP2A in gastric cancer were correlated with N stage (CDK5: p=0.001, PP2A: p=0.004) and TNM (CDK5: p=0.030, PP2A: p=0.001) stage. In addition, PP2A is also related to the differentiation level of the tumor tissue (p=0.046; Table 1). Furthermore, the expression levels of CDK5 and PP2A were also correlated with the TNM stage (p=0.008) and N stage (p=0.006; Table 2).

Prognostic value of CDK5 and PP2A expression

The median follow-up time was 28.5 months, and the 3-year overall survival rate was 70.6%.The survival analysis showed that the 3-year overall survival rate of gastric cancer patients with low expression of CDK5 was 69.9%, which was lower than that of patients with high expression of CDK5 (95.5%). This difference was statistically significant (Figure 3 A). The prognosis of gastric cancer patients with low expression of PP2A was also worse than that of patients with high expression of PP2A (68.0% vs. 91.2%, Figure 3 B). The 3-year overall survival rate of patients with low co-expression of CDK5 and PP2A was 66.5%, which was significantly lower than that of patients with high expression of CDK5 and/or PP2A (90.2%, Figure 4 A). Further analysis showed that the prognosis of patients with high expression of CDK5 and PP2A was better than that of patients with high expression of CDK5 or PP2A, and that patient with low expression of CDK5 and PP2A exhibited the worst prognosis, (Figure 4 B).

Univariate and multivariate analyses of prognosis in the entire group

A univariate analysis showed that the 3-year

overall survival rate was correlated with T stage (p=0.033), N stage (p=0.043), TNM stage (p<0.001), and the expression of CDK5 (p=0.015) and PP2A (p=0.008) in tumor tissues. The co-expression of CDK5 and PP2A in tumor tissues (p=0.004) was also demonstrated (Table 3). A multivariate analysis showed that the TNM stage (p=0.037) and the co-expression of CDK5 and PP2A (p=0.048) were independent prognostic factors in patients with gastric cancer (Table 4).

expression of CDK5 and PP2A together with TNM stage in the prediction of gastric cancer prognosis. The results showed that the area under the curve of the combination of CDK5 and PP2A (AUC: 0.639, 95%CI: 0.534-0.743, p=0.020) was larger than that of CDK5 or PP2A expression alone (CDK5: AUC: 0.599, 95%CI: 0.493-0.704, p=0.098. PP2A: AUC: 0.622, 95%CI: 0.517-0.726, p=0.041). In addition, the prognostic value of the combined expression of CDK5 and PP2A is closer to that of the TNM stage (AUC: 0.685, 95%CI: 0.591-0.780, Figure 6).

Table 1. Relationships between CDK5 and PP2A protein expressions in gastric cancer tissues and various clinicopathological variables

Variables	Total	CDK5 expression				PP2A expression			
		Low	high	X^2	P	low	high	X^2	P
Gender				0.203	0.653			0.468	0.494
Male	97	79	18			69	28		
Female	27	23	4			21	6		
Age (years)				2.184	0.139			0.018	0.894
>60	85	67	18			62	23		
≤60	39	35	4			28	11		
Tumor size(cm)				1.284	0.257			0.213	0.644
>5	47	41	6			33	14		
≤5	77	61	16			57	20		
Tumor location				1.085	0.781			0.371	0.946
Lower 1/3	53	44	9			38	15		
Middle 1/3	18	16	2			14	4		
Upper 1/3	41	33	8			29	12		
More than 1/3	22	19	3			9	3		
Bormann type				0.109	0.741			2.052	0.152
I+II type	25	20	5			21	4		
III+IV type	99	82	17			69	30		
Degree of differentiation				2.827	0.093			3.999	0.046
Well/moderate	48	36	12			30	18		
Poor and not	76	66	10			60	16		
Histological type				0.948	0.814			7.384	0.061
Papillary	58	48	10			44	14		
Tubular	36	28	8			22	14		
Mucinous	9	8	1			5	4		
Signet-ring cell	21	18	3			19	2		
Depth of invasion				2.944	0.086			0.195	0.659
T1+ T2	19	13	6			13	6		
T3+ T4	105	89	16			77	28		
Lymph node metastasis				10.288	0.001			8.376	0.004
Negative	18	10	8			8	10		
Positive	106	92	14			82	24		
TNM stage				4.714	0.030			10.957	0.001
I+II	38	27	11			20	18		
III+IV	86	75	11			70	16		
Vessel invasion				0.167	0.683			0.334	0.563
Negative	78	65	13			58	20		
Positive	46	37	9			32	14		

Table 2. Relationships between different CDK5 and PP2A protein expression status in gastric cancer tissues and various clinicopathological variables

Variables	Total	CDK5 and PP2A low	CDK5 and/ or PP2A high	χ2	P
Gender					
Male	97	62	35	1.833	0.176
Female	27	21	6		
Age (years)					
>60	85	56	29	0.135	0.713
≤60	39	27	12		
Tumor size (cm)					
>5	46	30	16	0.215	0.643
≤5	77	47	30		
Tumor location					
Lower 1/3	53	34	19	0.787	0.853
Middle 1/3	18	13	5		
Upper 1/3	41	27	14		
More than 1/3	12	9	3		
Bormann type					
I+II type	25	19	6	1.163	0.281
III+IV type	99	64	35		
Degree of differentiation					
Well/moderate	48	28	20	2.618	0.106
Poor and not	76	55	21		
Histological type					
Papillary	58	40	18	1.999	0.573
Tubular	36	22	14		
Mucinous	9	5	4		
Signet-ring cell	21	16	5		
Depth of invasion					
T1+ T2	19	12	7	0.145	0.704
T3+ T4	104	71	34		
Lymph node metastasis					
Negative	18	7	11	7.484	0.006
Positive	106	76	30		
TNM stage					
I+II	38	19	19	7.100	0.008
III+IV	86	64	22		
Vessel invasion					
Negative	78	53	25	0.098	0.755
Positive	46	30	16		

The relationship between the expression of CDK5 and PP2A and the duration of TNM stage

As shown in Figure 5, when CDK5 or PP2A expression is low, the TNM stage of gastric cancer tends to be advanced, which indicates that they are negatively correlated. We established an ROC curve to compare the expression of CDK5 alone, the

Discussion

In recent years, the diagnosis and treatment of gastric cancer have improved, but this cancer is still one of the most lethal malignant tumors. The exploration of specific biomarkers and effective therapeutic targets for gastric cancer is of great significance to

promote the early diagnosis of gastric cancer and to improve the efficacy of molecularly targeted drugs. It has been reported that CDK5 can bind to its target protein and modify that protein so that it has an important biological function. The function of CDK5 is closely related to that of other binding proteins such as p35, p39, p27 and crm-1, among others [21-23]. Recently, we used co-immunoprecipitation and mass spectrometry to search for binding proteins and potential downstream targets of CDK5. The results showed that CDK5 could bind to PP2A. Considering our work and the research of Louis et al [20], we speculate that there is a functional correlation between CDK5 and PP2A. However, no relevant studies have revealed the prognostic role of CDK5 and PP2A in gastric cancer.

In this study, immunohistochemistry was used to analyze the correlation between the expression of CDK5 and PP2A and the clinicopathological data in 124 patients with gastric cancer. It was found that the

expression of CDK5 and PP2A in tumor tissues was correlated with TNM stage. A multivariate Cox regression analysis showed that TNM stage and co-expression of CDK5 and PP2A were independent prognostic factors in gastric cancer. CDK5 is an atypical CDK, and recent studies have suggested that CDK5 is involved in the occurrence and development of many types of malignant tumors. CDK5 also plays an important role in many cancers, such as breast cancer, lung cancer, prostate cancer, multiple myeloma and pancreatic cancer. Our study found that the 3-year overall survival rate of gastric cancer patients with low expression of CDK5 was lower than that of patients with high expression of CDK5, and the difference was statistically significant ($P < 0.05$). Most patients with stage I and II disease had tumors with low expression of CDK5, while most patients with stage III and stage IV disease had tumors with high expression of CDK5. It is suggested that CDK5 may be a tumor suppressor in gastric cancer, which is consistent with our previous studies.

Figure 3. Kaplan–Meier analysis of the correlation between the expression of CDK5 and PP2A and the overall survival of gastric cancer patients. (A) Patients with low expression of CDK5 were compared with the high expression of CDK5.(B) Patients with low expression of PP2A were compared with the high expression of PP2A.

Figure 4. Kaplan–Meier analysis of the correlation between the co-expression of CDK5 and PP2A and the overall survival of gastric cancer patients.(A) Patients with low expression of both CDK5 and PP2A were compared with the rest of the patients.(B) Patients with CDK5 high and/or PP2A high expression were subject to analysis.

Several studies have shown that PP2A is a tumor suppressor: PP2A inhibits tumor genesis via down-regulation of the AKT/TSC1/RAIB/ mTOR pathway, the inactivation of c-Myc, or by antagonizing the Wnt/β-catenin signaling pathway [24]. PP2A can stabilize p53 or cd25 and can thus inhibit tumor growth/ proliferation or induce tumor cell apoptosis [25]. In this study, the prognosis of gastric cancer patients with low expression of PP2A was significantly lower than that of patients with high expression of PP2A. The difference was statistically significant. The majority of patients with stage I and stage II disease had tumors with low expression of PP2A, while those with stage III and stage IV disease had tumors with high expression of PP2A, which suggests that PP2A might play a role in the suppression of gastric cancer.

In addition, we also found a positive correlation between the expression of CDK5 and PP2A in gastric cancer. Among the gastric cancer tissues with high expression CDK5, the expression level of PP2A was higher compared with that
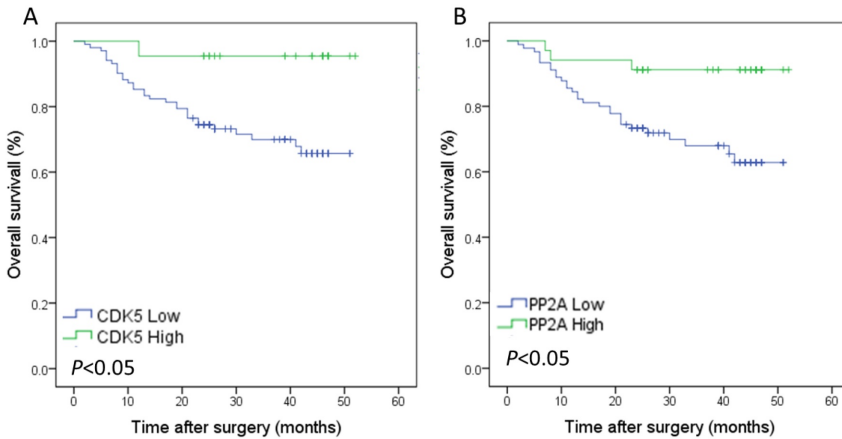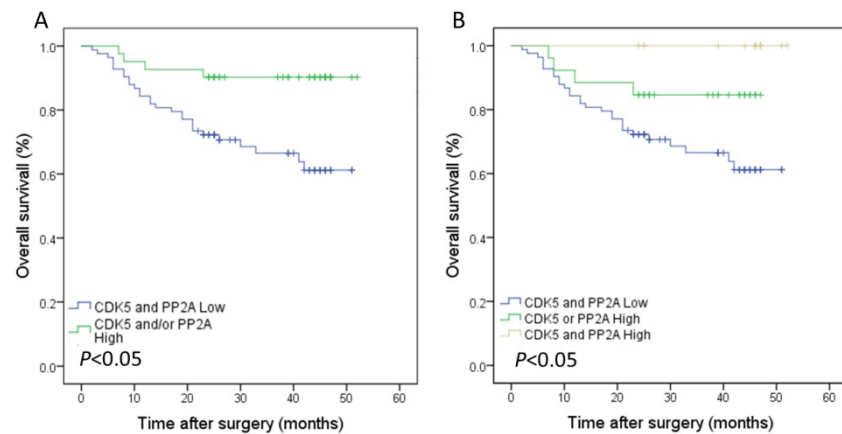
when CDK5 expression was low. The difference was statistically significant. Moreover, the prognosis of high PP2A/low CDK5 and high CDK5/ low PP2A group was worse than that of both CDK5 and PP2A high expression group, but better than that of both CDK5 and PP2A low expression group. There may be partly because of that the low expression of CDK5 correlation with poor prognostic factors (lymph node metastasis and TNM stage) and low expression of PP2A correlation with (degree of differentiation, lymph node metastasis and TNM stage). Further analysis revealed significant differences in N stage and TNM stage between patients with low expression of CDK5 and PP2A and other patients. In addition, Louis et al.[20] found that mice knocked out of the PP2A subunit (Ppp2r5d) were able to decrease the phosphatase activity of CDK5 and increase the activity of GSK-3β. Therefore, we hypothesized that their (CDK5 and PP2A) impact on prognosis may be related to the overlapping of the two tumor suppressing effects. The accuracy of the combined expression of CDK5 and PP2A in the prediction of the prognosis was better than that of CDK5 or PP2A expression alone, which indicates that the combined expression of CDK5 and PP2A had a better predictive effect on the overall survival rate of gastric cancer patients. More attention should be paid to the role of CDK5 and PP2A in gastric cancer, which requires further study.

There are still some limitations of our study. Fist, only 15 patients (11.1%) had both CDK5 and PP2A high expression, therefore, our results need to be validated in a more large-scale study. Second, we evaluated these two tumor makers only by immunohistochemical staining, and focus on the effect of expression patterns of CDK5 and PP2A on the clinicopathological characteristics and the prognosis of patients with gastric cancer. Further study for more information of the possible mechanisms for this finding is necessary in the future.

In summary, low expression of CDK5 and PP2A is closely related to poor prognosis of gastric cancer, and the expression of CDK5 and PP2A is positively correlated in gastric cancer. The co-expression of CDK5 and PP2A is an independent prognostic factor for the overall survival of patients with gastric cancer.

Table 3. Univariate analysis of the correlation between clinicopathological parameters and survival of patients with gastric cancer

Variables	3-year OS rate	Log-Rank Test	p
Gender			
Male	74.6	0.027	0.869
Female	74.1		
Age (years)			
>60	76.1	0.901	0.342
≤60	71.8		
Tumor size (cm)			
>5	63.8	2.433	0.119
≤5	81.4		
Tumor location			
Lower 1/3	77.4	3.700	0.296
Middle 1/3	81.5		
Upper 1/3	62.9		
More than 1/3	91.7		
Bormann type			
I+ II	84.0	0.896	0.344
III+IV	75.6		
Degree of differentiation			
Well/moderate	76.3	0.609	0.435
Poor and not	73.4		
Histological type			
Papillary	68.2	4.153	0.245
Tubular	83.2		
Mucinous	66.7		
Signet-ring cell	81.0		
Depth of invasion			
T1+T2	90.9	4.545	0.033
T3+T4	71.6		
Lymph node metastasis			
Negative	94.4	4.108	0.043
Positive	71.1		
TNM stage			
I+II	97.4	14.543	0.000
III+IV	64.2		
Vessel invasion			
Negative	79.0	1.293	0.256
Positive	72.1		
CDK5 expression			
Low	69.9	5.964	0.015
High	95.5		
PP2A expression			
Low	68.0	7.045	0.008
High	91.2		
CDK5/PP2A expression			
CDK5 and/or PP2A high	90.2	8.122	0.004
CDK5 and PP2A low	66.5		

Table 4. Multivariate analysis of the correlation between clinicopathological parameters and survival time of patients with gastric cancer

| Covariates	Coefficient	Standard Error	HR	95% CI for HR	p
CDK5 and PP2A expression (low/low vs. high and/or high)	-1.075	0.544	0.341	0.118-0.991	0.048
Depth of invasion (T3,T4 vs. T1,T2)	0.665	1.061	1.944	0.243-15.553	0.531
Lymph node metastasis (positive vs. negative)	-0.703	1.293	0.495	0.039-6.238	0.587
Distant metastasis (positive vs. negative)	0.437	0.642	1.548	0.440-5.446	0.496
TNM stage (stage III + IV vs. I + II)	2.717	1.301	15.138	1.183-193.739	0.037
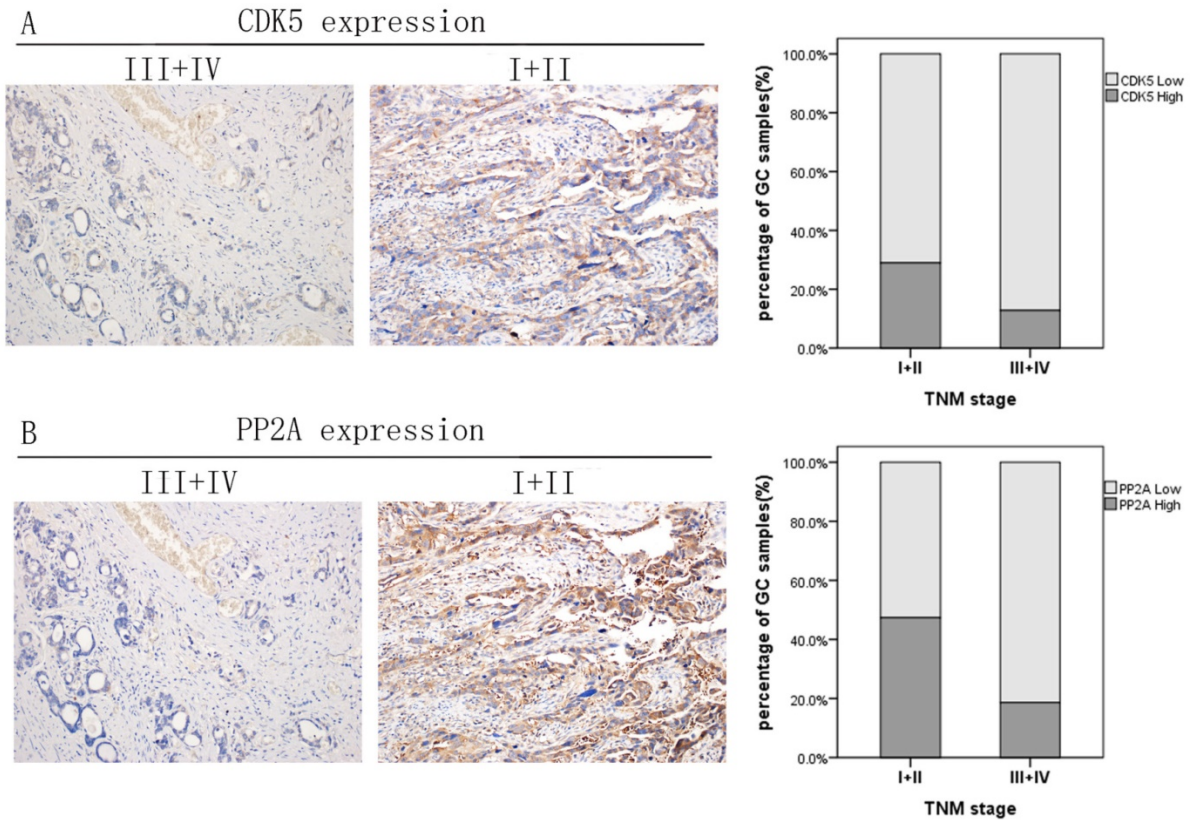
Figure 5. Expression levels of CDK5 and PP2A in gastric cancer tissues with different TNM stage. (A) Negative association of CDK5 expression with gastric cancer TNM stage. (B) Negative association of PP2A expression with gastric cancer TNM stage.
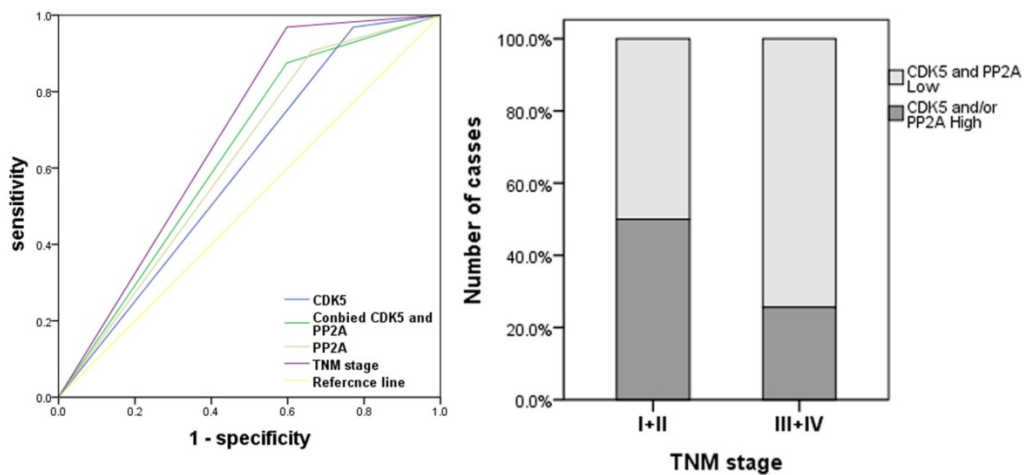

Figure 6. Receiver operating characteristic analysis of the sensitivity and specificity of the predictive value of PP2A expression model, CDK5 expression model, the combined of PP2A and CDK5 model and the TNM model. A: Co-expression of PP2A and CDK5 were significant correlated with TNM stage. B: The area under the ROC curve was 0.639 (0.534–0.743) for the co-expression of PP2A and CDK5 model, 0.599 (0.493–0.704) for the CDK5 expression model, 0.622 (0.517-0.726) for the PP2A expression model, 0.685 (0.591-0.780) for the TNM model.

Competing Interests

The authors have declared that no competing interest exists.

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