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Original Article

Clinicopathological significance of expression of CIP2A and c-myc in human gallbladder carcinoma

Song-Tao Xu[1,2*], Wen-Jing Wen[3*], Jin Zhou[4*], Jia-Xiu Liu[5*], Guo-Jian Gu[6,7]

Departments of [1]Clinical, [3]Basic Medical Science, Luohe Medical College, Luohe, Henan, P. R. China; [2]Tumor Occurrence and Prevention Research Innovation Team of Luohe, Luohe, Henan, P. R. China; [4]Department of General Surgery, The First Affiliated Hospital of Soochow University, Suzhou, Jiangsu, P. R. China; [5]Department of Medical Laboratory and Pharmacy, Jiangsu Vocational College of Nursing, Huaian, Jiangsu, P. R. China; [6]Department of Pathology, Taicang Affiliated Hospital of Soochow University, Taicang, Jiangsu, P. R. China; [7]Department of Pathology, The First People's Hospital of Taicang, Taicang, Jiangsu, P. R. China. [*]Equal contributors.

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Abstract: CIP2A (cancerous inhibitor of phosphatase 2A) and c-myc are abnormally expressed in many malignant tumors, and are involved in occurring and progressing of malignant tumors. The aim of this study is t o investigate the expression of CIP2A and c-myc in human gallbladder carcinoma (GBC) and to explore their clinical and pathological significance. The expression of CIP2A and c-myc protein was detected in 65 cases of human GBC and 19 cases of tumor-adjacent tissues by immunohistochemical method. Our results demonstrate that the positive rate of CIP2A was 64.6% in human GBC which was higher than that in tumor-adjacent tissues (26.3%), P=0.001. Patients with high CIP2A expression were significantly related to size (P=0.040), differentiation (P=0.015), TNM stage (P=0.011) and lymphatic metastasis (P=0.004). The positive rate of c-myc was 58.5% in GBC tissues, which was higher than that in tumor-adjacent tissues (15.8%), P=0.001. The positive rate of c-myc protein was significantly related to size (P=0.001), differentiation (P=0.005), TNM stage (P=0.002) and lymphatic metastasis (P=0.031). CIP2A protein was positively correlated with c-myc protein (r=0.617, P<0.001). Patients with higher CIP2A or c-myc expression had shorter overall survival time, while patients with lower CIP2A or c-myc expression had better survival time. Cox multivariate analysis showed that size, TNM stage, lymphatic metastasis, CIP2A as well as the c-myc expression were negatively correlated with overall survival of GBC (P=0.006, P=0.019, P=0.001, P=0.019 and P=0.030, respectively). In conclusion, the expression of CIP2A and c-myc are markedly related with size, differentiation, TNM stage and lymphatic metastasis of GBC. CIP2A is positively related with the expression of c-myc. To detect CIP2A and c-myc may be helpful to evaluate prognosis and infiltrative capability of GBC.

Keywords: Gallbladder carcinoma, immunohistochemistry, CIP2A, invasion, survival

Introduction

Gallbladder carcinoma (GBC) is a malignant tumour, which is a rank first in the extrahepatic biliary tract in the world [1]. Due to the absence of effective systemic therapy, surgical resection is the only effective treatment for GBC [2]. Its prognosis is poor, and the 5-year survival rate is also poor [2, 3]. GBC greatly threatens the human health. It is very important to identify prognostic factors and explore the possibility of the molecular targeted therapy for us to improve the effect of the treatment. But there has been no reliable molecular prognostic indicator of the carcinoma of gallbladder yet. Thus, determining the new, highly specific molecular markers for assessing prognosis, also as potential molecular targets for treatment, is particularly important.

CIP2A (cancerous inhibitor of phosphatase 2A), also known as KIAA1524 and p90, is located in the 3ql3.13 of chromosomes, and is highly expressed in many species of malignant tumors (such as colon cancer, breast cancer , gastric cancer cells, hepatocellular carcinoma, lung adenocarcinoma, pancreatic ductal adenocarcinoma .etc.) [4-9]. So we speculated that it was involved in the occurrence and development of tumors.

c-myc which is located in the 8q24 of chromosomes is a central transcription factor, and can promote cells' process of anti-apoptosis, differentiation, proliferation and so on. It can pro-

Table 1. Expression of CIP2A[a] and c-myc in gallbladder carcinoma and tumor-adjacent tissue tissues

Related factor	Gallbladder carcinoma tissue		Tumor-adjacent tissue		*P* value
	Negative (-)	Positive (+)	Negative (-)	Positive (+)	
CIP2A	23 (35.4)	42 (64.6)	14 (73.7)	5 (26.3)	0.003
C-myc	27 (41.5)	38 (58.5)	16 (84.2)	3 (15.8)	0.001

[a]Cancerous inhibitor of phosphatase 2A.

Table 2. Analysis of CIP2A[a] and c-myc positive expression and related factors

Related factor	N	CIP2A expression		*P* value	C-myc expression		*P* value
		Negative (-)	Positive (+)		Negative (-)	Positive (+)	
Age (year)							
≥60	36	10 (27.8)	26 (72.2)	0.153	13 (36.1)	23 (63.9)	0.323
<60	29	13 (44.8)	16 (55.2)		14 (48.3)	15 (51.7)	
Gender							
Male	22	8 (36.4)	14 (63.6)	0.906	11 (50.0)	11 (50.0)	0.322
Female	43	15 (34.9)	28 (65.1)		16 (37.2)	27 (62.8)	
Size (cm)							
<3	40	18 (45.0)	22 (55.0)	0.040	23 (57.5)	17 (42.5)	0.001
≥3	25	5 (20.0)	20 (80.0)		4 (16.0)	21 (84.0)	
Differentiation							
Well	19	11 (57.9)	8 (42.1)	0.015	13 (68.4)	6 (31.6)	0.005
Moderate+poor	46	12 (26.1)	34 (73.9)		14 (30.4)	32 (69.6)	
TNM stage							
0-I	14	9 (64.3)	5 (35.7)	0.011	11 (78.6)	3 (21.4)	0.002
II-IV	51	14 (27.5)	37 (72.5)		17 (31.4)	35 (68.6)	
Lymphatic metastasis							
Yes	27	4 (14.8)	23 (85.2)	0.004	7 (25.9)	20 (74.1)	0.031
No	38	19 (50.0)	19 (50.0)		20 (52.6)	18 (47.4)	

[a]Cancerous inhibitor of phosphatase 2A.

mote the occurrence and development of tumors [10-12]. C-myc is easily degraded by ubiquitin-protein [13, 14]. But, CIP2A can increase the protein stability of c-myc by inhibiting protein phosphatase (PP2A)-mediated dephosphorylation of c-myc at serine 62 [15].

In present study, immunohistochemical method is used to assay the expression of the CIP2A and c-myc in 65 cases of GBC, and investigate their clinical and pathological significance. They may be useful to develop an easy diagnostic and prognosis tool to monitor GBC.

Materials and methods

Patients enrolled

A total of 65 patients with GBC who accepted surgical treatment between January 2011 and January 2016 in the First People's Hospital of Taicang and 19 cases of tumor-adjacent tissues were taken as the control group. The present study was approved by the ethics committee of the First People's Hospital of Taicang, and all tissue samples were reviewed from patients with appropriate informed consent. The average age of the 65 patients was 63.1 ranging from 42 to 79 years old. None of these patients received pre-operative chemotherapy or radiotherapy. GBC patients in the experimental group were shown in **Tables 1** and **2**. TNM classification system was based on American Joint Committee on Cancer (AJCC) in 2010 [16]. B-ultrasound or CT scan was performed once at 3-month intervals after surgery. They were followed up for 3 to 60 months after surgery via the telephone.

Immunohistochemical (IHC) analysis

The expression of CIP2A and c-myc were detected by streptavidin-biotin-peroxidase complex method based on previous publication [17, 18]. In brief, Paraffin-embedded blocks were cut into 4-μm sections and baked. The specimens were deparaffinized and rehydrated, and then incubated 10 min by 3% H_2O_2. The specimens were incubated in citric acid buffer solution and boiled it until the pressure of the pressure cooker reached 0.14 MP for 1 min. Rabbit polyclonal anti-CIP2A (1:100; Abcam, Cambridge, UK) or rabbit monoclonal anti-c-myc (1:150; Santa Cruz Biotechnology, Santa Cruz, CA USA) was incubated with the speci-

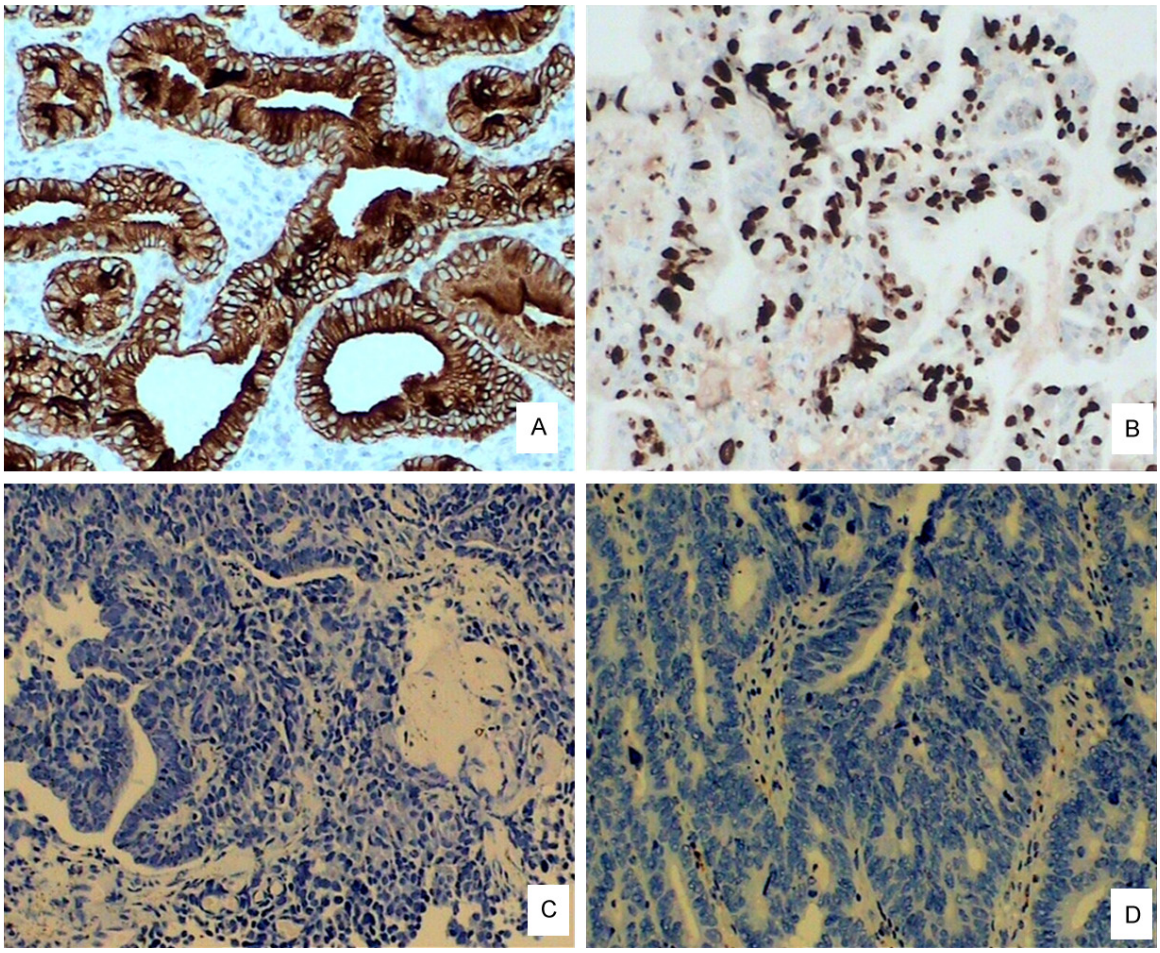

Figure 1. CIP2A were higher expressed in GBC tissues and its cytoplasm was stained brown (100×) (A). CIP2A were lower expressed in GBC tissues and tumor cells were not stained (100×) (C). C-myc were higher expressed in GBC tissues and its nucleus was stained yellow (100×) (B). c-myc were lower expressed in GBC tissues and tumor cells were not stained (100×) (D).

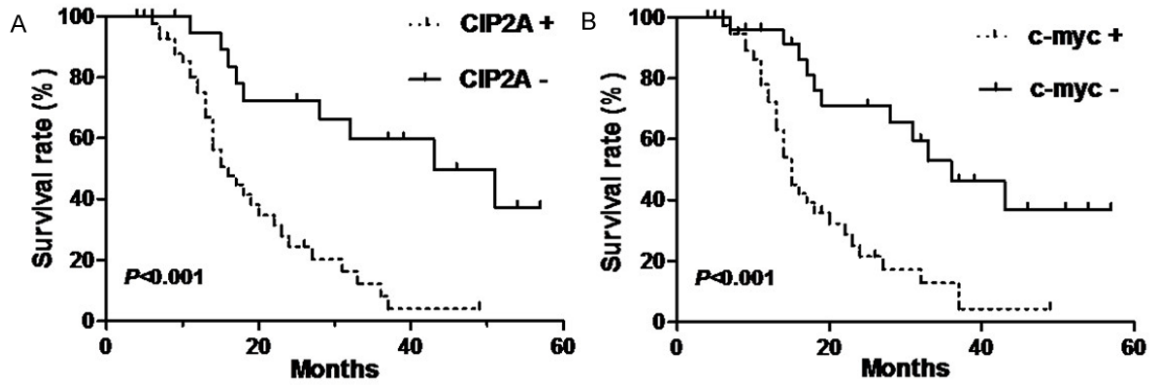

Figure 2. Kaplan-Meier survival curves of GBC patients based on CIP2A expression (A) or C-myc expression (B).

mens overnight at 4°C. after the specimens were rinsed with phosphate buffer saline (PBS), they were treated with biotinylated secondary antibody (1:250; Beyotime Institute of Biotechnology, Haimen, China), followed by further incubation with streptavidin-horseradish per-

Table 3. Correlations between CIP2A[a] and c-myc expression in gallbladder carcinoma tissues

Smad4	CIP2A		Contingency coefficien (r)	χ^2	P
	+	-			
+	34	4	0.617	24.724	<0.001
-	8	19			

[a]Cancerous inhibitor of phosphatase 2A.

oxidase complex (Beyotime Institute of Biotechnology, Haimen, China). Drop the 100 μL DAB (Beyotime Institute of Biotechnology, Haimen, China) solution to each section, and then hematoxylin stains and washes them to colorless. The CIP2A or c-myc antibody which replaced by normal non-immune serum was used as negative controls.

Evaluation of CIP2A and c-myc staining

Combined with a previous publication, the slides were examined by two independent pathologists who did not know the data of the patients. Each slide was observed five views, and 100 cells were observed in each view under 400 times magnification. According to the intensity and percentage of CIP2A and c-myc staining, their expression were defined as positive (moderate or strong, 5-100% positive cells) and negative (negative or mild, 0-4% positive cells) [19].

Statistical analysis

SAS software version 9.2 and GraphPad Prism version 5.0 were used for statistical analysis. Statistical analysis was performed with a chi-square (**Tables 1** and **2**). The correlation between CIP2A and c-myc was tested by Pearson χ^2 test. The overall survival was performed using the Kaplan-Meier method and log-rank test.

The risk factors for overall survival were calculated with Kaplan-Meier method and Cox multivariate analysis. *P* values <0.05 were considered to indicate statistically significant.

Results

Relationship between CIP2A and c-myc expression and clinicopathological parameters

The cytoplasm and/or nucleus appearing yellow or brown granules were defined as positive expression of CIP2A, and positive (**Figure 1A**), and negative (**Figure 1C**). The nucleus and/or cytoplasm appearing yellow or brown granules were defined as positive expression of c-myc, and positive (**Figure 1B**), and negative (**Figure 1D**). As was shown in **Tables 1** and **2**, the positive rate of CIP2A was 64.6% in human GBC which was higher than that in tumor-adjacent tissues (26.3%), P=0.003. High levels of CIP2A protein were significantly related to size, differentiation, TNM stage and lymphatic metastasis (P=0.040, P=0.015, P=0.011, and P=0.004, respectively). However, CIP2A expression was not associated with age and gender (P=0.153, P=0.906, respectively). The positive rate of c-myc was 58.5% in GBC tissues, which was higher than that in tumor-adjacent tissues (15.8%), P=0.001. The positive rate of c-myc was significantly related to size, differentiation, TNM stage and lymphatic metastasis (P=0.001, P=0.005, P=0.002 and P=0.031, respectively). However, c-myc protein expression was not associated with age and gender (P=0.323 and P=0.322, respectively).

Correlation between the expression of CIP2A and c-myc and their survival

The correlation was shown in **Figure 2**. Kaplan-Meier survival curves of GBC patients were based on CIP2A or c-myc expression. Patients with high CIP2A expression had significantly worse survival compared to those patients with low expression (P<0.001, log-rank test) (**Figure 2A**). Patients with high c-myc expression had worse survival compared to those patients with low expression (P<0.001, log-rank test) (**Figure 2B**).

Cox multivariate analysis showed that size, TNM stage, lymphatic metastasis, CIP2A as well as the c-myc expression were negatively correlated with overall survival of GBC (P=0.006, P=0.019, P=0.001, P=0.019 and P=0.030, respectively). These suggested that size, high stage of TNM, lymphatic metastasis, high levels of CIP2A and c-myc were independent risk factors for prognosis (**Table 4**).

Correlation between CIP2A and c-myc expression in GBC tissues and clinicopathological parameters

There was a positive correlation between CIP2A and c-myc expression in GBC tissues (r=0.617, P<0.001), as was shown in **Table 3**.

Table 4. COX analyses of different clinicopathological variables and CIP2A and c-myc expression status as predictors for overall survival in in gallbladder carcinoma tissues

Variable	Hazard ratio	95% Hazard ratio confidence limits		*P* value
Age (≥60 vs. <60)	2.742	0.913	8.235	0.072
Gender (male vs. female)	0.698	0.298	1.639	0.409
Size (≥3 vs. <3)	2.975	1.376	6.432	0.006
Differentiation (well vs. moderately-poorly)	1.004	0.393	2.568	0.993
TNM stage (0-I vs. II-IV)	5.452	1.327	22.399	0.019
Lymphatic metastasis (yes vs. no)	4.659	1.922	11.292	0.001
CIP2A (positive vs. negative)	3.600	1.237	10.475	0.019
C-myc (positive vs. negative)	2.639	1.101	6.326	0.030

Discussion

CIP2A has been found overexpressed in many human cancers [4-9]. However, its Clinicopathological significance in gallbladder carcinoma is still unknown. In this study, CIP2A expression was observed in the cytoplasm and/or nucleus, and the positive rate of CIP2A in GBC was significantly higher than that of the tumor-adjacent tissues. CIP2A expression in well differentiation was much lower than that in moderate-poor differentiation, and the higher the differentiation was, the lower the positive rate was. It suggested that CIP2A might participate in tumorigenesis of GBC. The positive rate of CIP2A was closely related to the size, TNM stage and lymphatic metastasis, which indicated that the CIP2A protein could lead to the invasion and metastasis of tumor. Many scholars believed that high expression of CIP2A tumor patients had poor prognosis. Na Liu in nasopharyngeal carcinoma research found that CIP2A high expression had shorter survival time [20]. In the study of the pancreatic cancer also found that CIP2A expression positive patients' survival rate was obviously lower than that of CIP2A expression negative patients' [21].

Therefore, CIP2A was expected to be an independent tumor prognostic factor. Our follow-up results also showed that the patients with CIP2A overexpression had unfavorable effect and the survival time was shorter than those with low CIP2A expression. Cox multivariate analysis also suggested that high CIP2A expression was negatively correlated with overall survival of GBC. It was an independent risk factor for prognosis.

As CIP2A and the tumor's proliferation, migration mechanisms and so on develop, we paid more attention to new drugs and gene therapy which were targeted at the CIP2A. Zhai et al then adopted the method of RNA interference (RNAi) to transfect osteosarcoma MG-63 cell to reduce expression of CIP2A significantly, resulting in the sharp decrease of the ability of MG-63 cell's proliferation and invasion [22]. Cantini L employed RNA interference to lead siRNA into oral cancer cells (scc25, cal25) to decrease the expression of CIP2A protein in cells, and the result was that the proliferation and invasion ability of tumor cells was significantly decreased [23]. CIP2A might be a new target for gene therapy.

In the current study, c-myc expression was observed in the nucleus and/or in cytoplasm GBC cells. It found that the positive rate of c-myc in GBC tissue cells were significantly higher than that in the tumor-adjacent tissues. C-myc expression was associated with the tumor differentiation. It suggested that c-myc might participate in tumorigenesis of GBC. The positive rate of c-myc was closely related to the size, TNM stage and lymphatic metastasis which indicated that the c-myc protein could lead to the invasion and metastasis of tumor.

Studies showed that patients with high c-myc expression had poor prognosis [24, 25].

Our study also showed that patients with high c-myc expression had significantly worse survival compared with those with low c-myc expression. The Cox multivariate analysis also suggested that high c-myc expression was an independent risk factor for prognosis. It might be helpful to consider the auxiliary diagnosis of GBC, and judge the prognosis of patients.

Our study also found that the expression of CIP2A was up-regulated, while the expression of c-myc protein in GBC was up-regulated, and they were positively correlated. CIP2A protein

was positively correlated with c-myc protein. Some studies showed that CIP2A knockdown in tumor cell lines decreased cell proliferation and growth, and reduced c-myc levels [26, 27]. It suggested that CIP2A mediates cancer progression via the c-myc signaling pathway. However, it should be verified in a large sample size of GBC patients. In future research, the method of RNAi can be used to knock down CIP2A expression, and studied on its impact on the expression of c-myc in GBC cells. This may be clarified its specific mechanism.

In conclusion, CIP2A and c-myc overexpression were closely related to tumor progression and metastasis in GBC. CIP2A and c-myc overexpression correlates to poor prognosis. CIP2A was positively correlated with c-myc levels. They may be helpful in the auxiliary diagnosis and judging the prognosis for GBC patients. If we make further research on it, it is hopeful to become the new target for gallbladder gene therapy.

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Disclosure of conflict of interest

None.

Address correspondence to: Guojian Gu, Department of Pathology, Taicang Affiliated Hospital of Soochow University, Taicang, Jiangsu, P. R. China; Department of Pathology, The First People's Hospital of Taicang, Taicang, Jiangsu, P. R. China. Tel: +86-512-53610208; Fax: +86-512-53610208; E-mail: ggj1326@163.com

References

[1] Lai CH and Lau WY. Gallbladder cancer: a comprehensive review. Surgeon 2008; 6: 101-110.

[2] Shindoh J, de Aretxabala X, Aloia TA, Roa JC, Roa I, Zimmitti G, Javle M, Conrad C, Maru DM, Aoki T, Vigano L, Ribero D, Kokudo N, Capussotti L and Vauthey JN. Tumor location is a strong predictor of tumor progression and survival in T2 gallbladder cancer: an international multicenter study. Ann Surg 2015; 261: 733-739.

[3] Carriaga MT and Henson DE. Liver, gallbladder, extrahepatic bile ducts, and pancreas. Cancer 1995; 75: 171-190.

[4] Wang HW, Yang SH, Huang GD, Lin JK, Chen WS, Jiang JK, Lan YT, Lin CC, Hwang WL, Tzeng CH, Li AF, Yen CC and Teng HW. Temsirolimus enhances the efficacy of cetuximab in colon cancer through a CIP2A-dependent mechanism. J Cancer Res Clin Oncol 2014; 140: 561-571.

[5] Laine A, Sihto H, Come C, Rosenfeldt MT, Zwolinska A, Niemela M, Khanna A, Chan EK, Kahari VM, Kellokumpu-Lehtinen PL, Sansom OJ, Evan GI, Junttila MR, Ryan KM, Marine JC, Joensuu H and Westermarck J. Senescence sensitivity of breast cancer cells is defined by positive feedback loop between CIP2A and E2F1. Cancer Discov 2013; 3: 182-197.

[6] Zhao Y, Li Y, Han J, Liu T, Guan Q, Zhao P, Guo L, Liu K and He D. Helicobacter pylori enhances CIP2A expression and cell proliferation via JNK2/ATF2 signaling in human gastric cancer cells. Int J Mol Med 2014; 33: 703-710.

[7] Hou DR, Huang AC, Shiau CW, Wang CY, Yu HC and Chen KF. Bortezomib congeners induce apoptosis of hepatocellular carcinoma via CIP2A inhibition. Molecules 2013; 18: 15398-15411.

[8] Sung WW, Wang YC, Lin PL, Cheng YW, Chen CY, Wu TC and Lee H. IL-10 promotes tumor aggressiveness via upregulation of CIP2A transcription in lung adenocarcinoma. Clin Cancer Res 2013; 19: 4092-4103.

[9] Wang L, Gu F, Ma N, Zhang L, Bian JM and Cao HY. CIP2A expression is associated with altered expression of epithelial-mesenchymal transition markers and predictive of poor prognosis in pancreatic ductal adenocarcinoma. Tumour Biol 2013; 34: 2309-2313.

[10] Arnold HK and Sears RC. Protein phosphatase 2A regulatory subunit B56alpha associates with c-myc and negatively regulates c-myc accumulation. Mol Cell Biol 2006; 26: 2832-2844.

[11] Khanna A, Bockelman C, Hemmes A, Junttila MR, Wiksten JP, Lundin M, Junnila S, Murphy DJ, Evan GI, Haglund C, Westermarck J and Ristimaki A. MYC-dependent regulation and prognostic role of CIP2A in gastric cancer. J Natl Cancer Inst 2009; 101: 793-805.

[12] Guo Z, Liu D and Su Z. CIP2A mediates prostate cancer progression via the c-Myc signaling pathway. Tumour Biol 2015; 36: 4777-4783.

[13] Sears RC. The life cycle of C-myc: from synthesis to degradation. Cell Cycle 2004; 3: 1133-1137.

[14] Gregory MA and Hann SR. c-Myc proteolysis by the ubiquitin-proteasome pathway: stabilization of c-Myc in Burkitt's lymphoma cells. Mol Cell Biol 2000; 20: 2423-2435.

[15] Junttila MR, Puustinen P, Niemela M, Ahola R, Arnold H, Bottzauw T, Ala-aho R, Nielsen C, Ivaska J, Taya Y, Lu SL, Lin S, Chan EK, Wang

XJ, Grenman R, Kast J, Kallunki T, Sears R, Kahari VM and Westermarck J. CIP2A inhibits PP2A in human malignancies. Cell 2007; 130: 51-62.
[16] In: Edge SB, Byrd DR, Compton CC, Fritz AG, Greene FL and Trotti A, editors. AJCC Cancer Staging Manual. 7th edition. New York, NY: Springer; 2010.
[17] Xu S, Gu G, Ni Q, Li N, Yu K, Li X and Liu C. The expression of AEG-1 and Cyclin D1 in human bladder urothelial carcinoma and their clinicopathological significance. Int J Clin Exp Med 2015; 8: 21222-21228.
[18] Li J, Zhang N, Song LB, Liao WT, Jiang LL, Gong LY, Wu J, Yuan J, Zhang HZ, Zeng MS and Li M. Astrocyte elevated gene-1 is a novel prognostic marker for breast cancer progression and overall patient survival. Clin Cancer Res 2008; 14: 3319-3326.
[19] Ren J, Li W, Yan L, Jiao W, Tian S, Li D, Tang Y, Gu G, Liu H and Xu Z. Expression of CIP2A in renal cell carcinomas correlates with tumour invasion, metastasis and patients' survival. Br J Cancer 2011; 105: 1905-1911.
[20] Liu N, He QM, Chen JW, Li YQ, Xu YF, Ren XY, Sun Y, Mai HQ, Shao JY, Jia WH, Kang TB, Zeng MS and Ma J. Overexpression of CIP2A is an independent prognostic indicator in nasopharyngeal carcinoma and its depletion suppresses cell proliferation and tumor growth. Mol Cancer 2014; 13: 111.
[21] Xu P, Yao J, He J, Zhao L, Wang X, Li Z and Qian J. CIP2A down regulation enhances the sensitivity of pancreatic cancer cells to gemcitabine. Oncotarget 2016; 7: 14831-14840.
[22] Zhai M, Cong L, Han Y and Tu G. CIP2A is overexpressed in osteosarcoma and regulates cell proliferation and invasion. Tumour Biol 2014; 35: 1123-1128.
[23] Cantini L, Attaway CC, Butler B, Andino LM, Sokolosky ML and Jakymiw A. Fusogenic-oligoarginine peptide-mediated delivery of siRNAs targeting the CIP2A oncogene into oral cancer cells. PLoS One 2013; 8: e73348.
[24] Han S, Kim HY, Park K, Cho HJ, Lee MS, Kim HJ and Kim YD. c-Myc expression is related with cell proliferation and associated with poor clinical outcome in human gastric cancer. J Korean Med Sci 1999; 14: 526-530.
[25] Chrzan P, Skokowski J, Karmolinski A and Pawelczyk T. Amplification of c-myc gene and overexpression of c-Myc protein in breast cancer and adjacent non-neoplastic tissue. Clin Biochem 2001; 34: 557-562.
[26] Wiegering A, Pfann C, Uthe FW, Otto C, Rycak L, Mader U, Gasser M, Waaga-Gasser AM, Eilers M and Germer CT. CIP2A influences survival in colon cancer and is critical for maintaining Myc expression. PLoS One 2013; 8: e75292.
[27] Barragan E, Chillon MC, Castello-Cros R, Marcotegui N, Prieto MI, Hoyos M, Pippa R, Llop M, Etxabe A, Cervera J, Rodriguez G, Buno I, Rifon J, Sierra J, Gonzalez M, Calasanz MJ, Sanz MA and Odero MD. CIP2A high expression is a poor prognostic factor in normal karyotype acute myeloid leukemia. Haematologica 2015; 100: e183-185.