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Clinical Significance of *PRKCI* Gene Expression in Cancerous Tissue in Patients With Gastric Cancer

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Abstract. *Background/Aim: The PRKCI gene encodes Protein kinase C iota. The overexpression of protein kinase C iota is associated with poor outcomes in patients with gastric and other cancers, but the role of the PRKCI gene in gastric cancer is not fully understood. Thus, we evaluated the clinical significance of PRKCI gene expression in gastric cancer. Materials and Methods: PRKCI mRNA expression levels in cancerous tissues and adjacent normal mucosa from 398 patients with gastric cancer were measured. Relationships between PRKCI gene expression and clinicopathological characteristics and outcomes were examined. Results: Overall survival was lower in patients with a high expression of PRKCI than in those with low expression (p=0.016). No other relationships were observed. A high PRKCI expression was found to be an independent prognostic factor (p=0.036, HR=1.44, 95%CI=1.02-2.02). Conclusion: PRKCI gene expression in cancerous tissue might be a useful prognostic factor in patients with gastric cancer after gastrectomy.*

Gastric cancer is the fifth most common cancer and the third leading cause of death from cancer worldwide (1). The prognosis for advanced gastric cancer remains poor, despite advancements in diagnostic methods, surgical techniques, and chemotherapy. Therefore, outcomes may be improved through personalized treatment using biomarkers.

The *PRKCI* gene encodes protein kinase C iota (PKCi) enzyme. The PKCi is a member of the protein kinase C family and is an oncogenic K-ras effector protein. Protein kinase C regulates various cellular functions, including cell proliferation, division, differentiation, survival, migration, and polarization (2-4). It was reported that *PRKCI* was amplified in several human cancers, including esophageal (5), lung (6), and ovarian cancer (7, 8). Additionally, the overexpression of PKCi was associated with a poor prognosis in patients with lung (6), pancreatic (9), ovarian (7), bile duct (10), prostate (11), and gastric cancer (12). In recent years, the roles of PKCi in tumorigenesis and oncogenic signaling mechanisms have been demonstrated in several cancers (2). Furthermore, it was reported that *PRKCI* and *SOX2* are co-amplified and serve a critical role in cancer stem cell biology in lung squamous cell carcinoma (13). However, the role of the *PRKCI* gene in gastric cancer has not been sufficiently revealed. The aim of this study was to reveal the clinical significance of *PRKCI* gene expression in cancerous tissue from patients with gastric cancer.

Patients and Methods

Patients and samples. We studied specimens of cancerous tissue and paired adjacent normal mucosa from the stomachs of 398 patients with gastric cancer who did not receive preoperative therapy. The patients underwent gastrectomy through either the Department of Surgery at Yokohama City University and the Gastroenterological Center,

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Key Words: Gastric cancer, protein kinase C iota, PRKCI.

Yokohama City University Medical Center and the Department of Gastrointestinal Surgery at Kanagawa Cancer Center between 2002 and 2010. Informed consent was obtained from each patient, and the Ethics Committees of the Yokohama City University (approval number: 18-7A-4) and the Kanagawa Cancer Center approved the protocol (approval number: epidemiological study-29) before the study was initiated. Each tissue sample was embedded in optimal cutting temperature compound (Sakura Finetechnical Co. Ltd., Tokyo, Japan) and immediately stored at –80˚C until use. Tissue specimens were stained with hematoxylin and eosin then histopathologically examined. Total RNA was prepared from sections of tissue that consisted of >80% cancerous cells.

RNA extraction and complementary cDNA synthesis. Total RNA isolated from cancerous tissue and adjacent normal mucosa was prepared with the use of Trizol (Gibco, Life Technology, Gaithersburg, MD, USA). cDNA was synthesized from 0.4 μg of total RNA with an iScript cDNA Synthesis Kit (Bio-Rad Laboratories, Hercules, CA, USA). Once it was synthesized, the cDNA was diluted in water to 0.2 μg/μl and stored at –20˚C until use.

Quantitative real-time reverse transcription polymerase chain reaction. The oligonucleotide primers for *PRKCI* were as follows: sense primer 5'-GCCAGGAGATACAACCAGCAC-3' and antisense primer 5'-CAAGAGCCCACCAGTCAACAC-3'. We used β-actin as the internal control. The oligonucleotide primers for β-actin were as follows: sense primer 5'-AGTTGCGTTACACCCTTTCTTGAC-3' and antisense primer 5'-GCTCGCTCCAACCGACTGC-3'. Quantitative real-time reverse transcription polymerase chain reaction was performed using iQSYBR Green Supermix (Bio-Rad Laboratories, Inc.). Reactions were carried out in a total volume of 15 μl that included: 0.2 μg of cDNA; 0.4 μM of each primer; 7.5 μl of iQ SyBR Green Supermix containing dATP, dCTP, dGTP, and dTTP at concentrations of 400 μM each; and 50 U/ml of iTag DNA polymerase. The reaction consisted of: 1) 3 min at 95˚C, 2) 40 cycles of denaturation of the cDNA for 10 seconds for *PRKCI* and for 15 seconds for β-actin at 95˚C, 3) annealing for 10 sec at 62.2˚C for *PRKCI* and for 15 sec at 60˚C for β-actin, 4) primer extension at 72˚C for 20 sec for *PRKCI* and for 30 sec for β-actin, and 5) 10 min at 72˚C. Melting curve analyses were carried out to distinguish specific from nonspecific products and primer dimmers. To evaluate specific mRNA expression in samples, a standard curve was produced for each run, measuring 3 points of the human control cDNA (Clontech Laboratories, Inc., CA, USA). The concentrations of each sample were calculated by relating its crossing point to the standard curve.

Statistical analysis. Gene expression levels between cancerous and adjacent normal mucosa were compared using the Wilcoxon test. Relationships between gene expression and potential explanatory variables, including the patient's age, patient's gender, size of the tumor, depth of invasion of the tumor, presence of lymph node metastasis, presence of distant metastasis, stage of the cancer, lymphatic invasion of cancer, venous invasion of cancer, and histological type of cancer, were evaluated with the chi-square test. Associations between *PRKCI* gene expression and survival were assessed using the Kaplan–Meier method and compared by the log-rank test. A Cox proportional-hazards model was used to perform univariate analyses and multivariate analyses to determine risk factors for gastric cancer. The optimal cutoff point for *PRKCI* was selected using the minimum *p*-value method, and the internal validity of the cutoff point was confirmed using a twofold cross-validation approach (14). All statistical analyses were performed using EZR (Saitama Medical Center, Jichi Medical University, Saitama, Japan), which is a graphical user interface for R (The R Foundation for Statistical Computing, Vienna, Austria). More precisely, it is a modified version of R commander designed to add statistical functions frequently used in biostatistics. Two-sided *p*-values were calculated, and a difference was considered statistically significant at $p<0.05$.

Table I. *Relations between PRKCI gene expression and clinicopathological factors*.

Variables	All patients (n=398)	PRKCI expression		*p*-Value
		High (n=94)	Low (n=304)	
Age (years)				0.984
<70	205	49	156	
≥70	193	45	148	
Gender				0.876
Female	119	27	92	
Male	279	67	212	
Tumor size (mm)				0.064
<65	213	42	171	
≥65	185	52	133	
Histological type				1
Well/Moderate	186	44	142	
Poor	212	50	162	
Serosal invasion				0.546
–	195	43	152	
+	203	51	152	
Lymph-node metastasis				0.679
–	119	26	93	
+	279	68	211	
Distant metastasis				0.19
–	317	70	247	
+	81	24	57	
Lymphatic invasion				0.162
–	136	26	110	
+	262	68	194	
Venous invasion				0.378
–	140	29	111	
+	258	65	193	
TNM pathological stage				0.065
I	64	13	51	
II	103	22	81	
III	150	35	115	
IV	81	24	57	

Results

PRKCI mRNA expression. There were no significant differences in *PRKCI* mRNA expression levels between the cancerous tissues (1.40±3.44) and the normal adjacent mucosa (1.33±2.71; $p=0.273$; Figure 1).

Relationship between PRKCI gene expression levels and clinicopathological features in cancerous tissue. The study

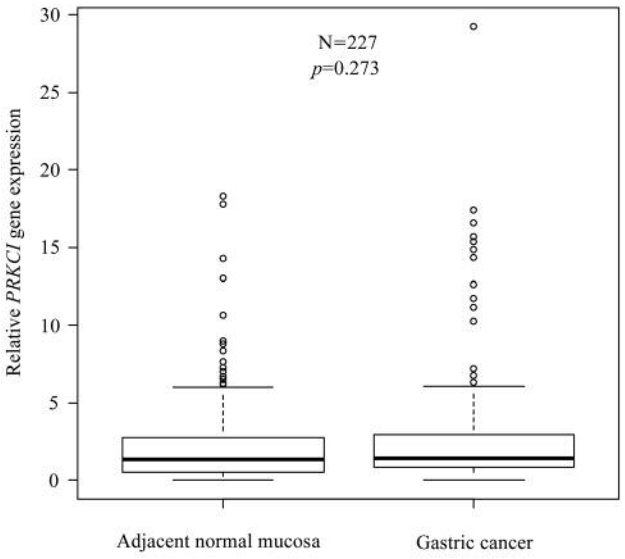

Figure 1. *Comparison of PRKCI gene expression between gastric cancerous tissue and adjacent normal mucosa.*

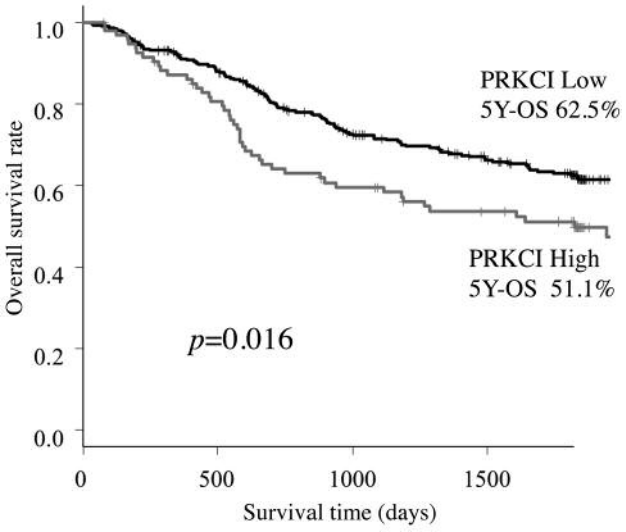

Figure 2. *Comparison of overall survival between high and low expression of the PRKCI gene.*

samples were divided into two subgroups (high expression group: n=304; low expression group: n=94) according to the expression level of *PRKCI* mRNA (cutoff point=2.83). The relationships between these subgroups and clinicopathological features were examined, and no significant relationships were found (Table I).

Relationship between PRKCI mRNA expression levels and patient outcomes. The 5-year overall patient survival rate was significantly lower in the high *PRKCI* expression group than in the low expression group (51.1% *vs*. 62.5%, respectively; p=0.016; Figure 2).

Univariate and multivariate analyses of the relationship of clinicopathological factors and PRKCI mRNA expression levels with overall survival. Through univariate Cox regression analyses, high expression of the *PRKCI* gene, patient's gender, size of the tumor, serosal invasion, lymph node metastasis, distant metastasis, lymphatic invasion, and venous invasion were selected as significant factors of the overall survival of patients with gastric cancer. Multivariate analysis found that high expression of the *PRKCI* gene, serosal invasion, lymph node metastasis, lymphatic invasion, and venous invasion were independent prognostic factors in patients with gastric cancer (Table II).

Discussion

In this study, we evaluated expression levels of *PRKCI* mRNA in cancerous and adjacent normal mucosa. We then examined the relationships between these expression levels, clinicopathological factors and overall survival in patients with gastric cancer after surgery to reveal the clinical significance of *PRKCI* mRNA expression in cancerous tissue.

First, we compared expression levels of *PRKCI* mRNA in cancerous tissue and adjacent normal mucosa. Several previous studies have compared expression levels of *PRKCI* mRNA in various cancerous tissues and adjacent normal tissues (6, 9, 11). The overexpression of *PRKCI* mRNA was reported in many types of cancer (2), while significant overexpression of *PRKCI* mRNA was not detected in bladder cancer and brain cancer (2, 15, 16). Our results agreed with the latter findings: expression levels of *PRKCI* mRNA were not significantly higher in 227 specimens of cancerous tissue compared to paired adjacent normal mucosa.

We next examined the relationship between the expression of *PRKCI* and clinicopathological features. A previous retrospective cohort study reported that high expression of *PRKCI* significantly corelated with curability of the cancer, depth of the tumor, stage of the cancer, and peritoneal dissemination of the cancer (17). Another retrospective cohort study of PKCi expression level showed that high PKCi expression was significantly associated with diffuse type and recurrence of cancer (12). However, in our study, there was no significant relationship between the expression level of *PRKCI* mRNA and clinicopathological features.

We then assessed the relationship between *PRKCI* mRNA expression levels in cancerous tissues and outcomes in patients with gastric cancer. Elevated PKCi expression was previously shown to be associated with decreased survival in patients with lung (6), bile duct (10), ovarian (18), prostate (11), and gastric cancer (12). In our study, 5-year

Table II. *Uni- and multivariate analysis of clinicopathological factors for overall survival.*

Factors	Number of patients	Univariate		*p*-Value	Multivariate		*p*-Value
		HR	95%CI		HR	95%CI	
Age (years)							
<70	205	1					
≥70	193	1.12	0.82-1.52	0.47			
Gender							
Female	119	1			1		
Male	279	1.63	1.14-2.35	0.008	1.18	0.81-1.72	0.4
Tumor size (mm)							
<65	213	1			1		
≥65	185	1.49	1.09-2.02	0.012	0.87	0.63-1.21	0.4
Histological type							
Well/Moderate	186	1					
Poor	212	1.27	0.93-1.73	0.14			
Serosal invasion							
–	195	1			1		
+	203	3.02	2.16-4.22	<0.001	1.65	1.14-2.40	0.009
Lymph-node metastasis							
–	119	1			1		
+	279	3.9	2.46-6.17	<0.001	2.04	1.19-3.49	0.009
Distant metastasis							
–	317	1			1		
+	81	5.25	3.82-7.23	<0.001	3.43	2.43-4.85	<0.001
Lymphatic invasion							
–	136	1			1		
+	262	2.54	1.74-3.69	<0.001	1.28	0.87-1.88	0.2
Venous invasion							
–	140	1			1		
+	258	2.24	1.56-3.21	<0.001	1.3	0.85-1.99	0.23
PRKCI expression							
Low	304	1			1		
High	94	1.51	1.08-2.11	0.017	1.45	1.03-2.04	0.031

survival was significantly lower in the high-*PRKCI* expression group than in the low-*PRKCI* expression group. We found that a High level of *PRKCI* gene expression was a significant independent predictor of 5-year survival in patients with gastric cancer.

The mechanism through which *PRKCI* gene expression is associated with poor prognosis of gastric cancer patients after gastrectomy remains unclear. Various studies have suggested that three main factors are involved. First, a high expression of the *PRKCI* gene activates Rac family small GTPase 1 (Rac1) and matrix metallopeptidase 10 (MMP10); Rac1 is mediated by Ras; MMP10 induces epithelial–mesenchymal transition to promote cancer cell proliferation and invasion and may be associated with a poor prognosis (19-21). Second, it is reported that high expression of the *PRKCI* gene is closely related to cancer chemoresistance because it inhibits apoptosis. *PRKCI* promotes nuclear factor kappa B (NFkB) expression and inhibits apoptosis by inducing BCL2 apoptosis regulator (Bcl2) expression by NFkB expression (22, 23). Lastly, *PRKCI* gene expression might promote immune suppressive environments that lead to a poor prognosis of human cancers. An *in vivo* study in a mouse model of ovarian cancer showed that a high expression of *PRKCI* corelates with a high expression of Yes associated protein (YAP1) and a low infiltration of cytotoxic T cells (24). Further, YAP1 has been shown to induce immune suppression in prostate tumors in mice through the recruitment of myeloid-derived suppressor cells (MDSCs) and suppression of CD8+ T cells (25).

There are several limitations in this study. First, this study examined *PRKCI* mRNA expression in cancerous tissues. It is necessary to examine both mRNA expression and protein expression using the same specimen to determine the clinical utility of a protein as a biomarker. Second, there is the problem of heterogeneity in cancerous tissue. The sample from which the mRNA was extracted was 5 mm^2 of cancerous tissue from the stomach that included the deepest part of the tumor but did not completely represent the entire tumor.

In conclusion, *PRKCI* gene expression in cancerous tissues in the stomach may be a useful prognostic marker in patients with gastric cancer.

Conflicts of Interest

The Authors have no conflicts of interest to declare regarding this study.

Authors' Contributions

Itaru Hashimoto and Takashi Oshima made substantial contributions to conception and design. Itaru Hashimoto, Kentaro Sakamaki, Naohide Oue, Yayoi Kimura, Yukihiko Hiroshima, Kentaro Hara, Yukio Maezawa, Kazuki Kano, Toru Aoyama, Takanobu Yamada, Naoto Yamamoto, Takashi Ogata, Hiroyuki Ito, Manabu Shiozawa, Soichiro Morinaga, Yasushi Rino, Wataru Yasui, Munetaka Masuda, Yohei Miyagi And Takashi Oshima made substantial contributions to collection of data, or analysis and interpretation of data and have been involved in drafting the article or revising it critically for important intellectual content. Itaru Hashimoto and Takashi Oshima have given final approval of the version to be submitted. All Authors read and approved the final manuscript.

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References

1 Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA and Jemal A: Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin *68*: 394-424, 2018. PMID: 30207593. DOI: 10.3322/caac.21492

2 Murray NR, Kalari KR and Fields AP: Protein Kinase Cι Expression and Oncogenic Signaling Mechanisms in Cancer. J Cell Physiol *226*: 879-887, 2011. PMID: 20945390. DOI: 10.1002/jcp.22463

3 Reyland ME: Protein kinase C isoforms: Multi-functional regulators of cell life and death. Front Biosci *14*: 2386-2399, 2009. PMID: 19273207.

4 Rosse C, Linch M, Kermorgant S, Cameron AJM, Boeckeler K and Parker PJ: PKC and the control of localized signal dynamics. Nat Rev Mol Cell Biol *11*: 103-112, 2010. PMID: 20094051. DOI: 10.1038/nrm2847

5 Yang YL, Chu JY, Luo ML, Wu YP, Zhang Y, Feng YB, Shi ZZ, Xu X, Han YL, Cai Y, Dong JT, Zhan QM, Wu M and Wang MR: Amplification of PRKCI, located in 3q26, is associated with lymph node metastasis in esophageal squamous cell carcinoma. Genes Chromosomes Cancer *47*: 127-136, 2008. PMID: 17990328. DOI: 10.1002/gcc.20514

6 Regala RP, Weems C, Jamieson L, Khoor A, Edell ES, Lohse CM and Fields AP: Atypical protein kinase Cι is an oncogene in human non-small cell lung cancer. Cancer Res *65*: 8905-8911, 2005. PMID: 16204062. DOI: 10.1158/0008-5472.CAN-05-2372

7 Eder AM, Sui X, Rosen DG, Nolden LK, Cheng KW, Lahad JP, Kango-Singh M, Lu KH, Warneke CL, Atkinson EN, Bedrosian I, Keyomarsi K, Kuo W, Gray JW, Yin JCP, Liu J, Halder G and Mills GB: Atypical PKCι contributes to poor prognosis through loss of apical-basal polarity and Cyclin E overexpression in ovarian cancer. Proc Natl Acad Sci *102*: 12519-12524, 2005. PMID: 16116079. DOI: 10.1073/pnas.0505641102

8 Zhang L, Huang J, Yang N, Liang S, Barchetti A, Giannakakis A, Cadungog MG, O'Brien-Jenkins A, Massobrio M, Roby KF, Katsaros D, Gimotty P, Butzow R, Weber BL and Coukos G: Integrative genomic analysis of protein kinase C (PKC) family identifies PKCι as a biomarker and potential oncogene in ovarian carcinoma. Cancer Res *66*: 4627-4635, 2006. PMID: 16651413. DOI: 10.1158/0008-5472.CAN-05-4527

9 Scotti ML, Bamlet WR, Smyrk TC, Fields AP and Nicole R M: Protein kinase C Iota is required for pancreatic cancer cell transformed growth and tumorigenesis. Cancer Res *70*: 2064-2074, 2010. PMID: 20179210. DOI: 10.1158/0008-5472.CAN-09-2684

10 Li Q, Wang JM, Liu C, Xiao BL, Lu JX and Zou SQ: Correlation of aPKC-iota and E-cadherin expression with invasion and prognosis of cholangiocarcinoma. Hepatobiliary Pancreat Dis Int *7*: 70-75, 2008. PMID: 18234642.

11 Ishiguro H, Akimoto K, Nagashima Y, Kojima Y, Sasaki T, Ishiguro-Imagawa Y, Nakaigawa N, Ohno S, Kubota Y and Uemura H: aPKC lamda/iota promotes growth of prostate cancer cells in an autocrine manner through transcriptional activation of interleukin-6. Proc Natl Acad Sci *106*: 16369-16374, 2009. PMID: 19805306. DOI: 10.1073/pnas.0907044106

12 Takagawa R, Akimoto K, Ichikawa Y, Akiyama H, Kojima Y, Ishiguro H, Inayama Y, Aoki I, Kunisaki C, Endo I, Nagashima Y and Ohno S: High Expression of atypical protein kinase C λ/ι in gastric cancer as a prognostic factor for recurrence. Ann Surg Oncol *17*: 81-88, 2009. PMID: 19774416. DOI: 10.1245/s10434-009-0708-x

13 Justilien V, Walsh MP, Ali SA, Thompson EA, Murray NR and Fields AP: The PRKCI and SOX2 oncogenes are coamplified and cooperate to activate hedgehog signaling in lung squamous cell carcinoma. Cancer Cell *25*: 139-151, 2014. PMID: 24525231. DOI: 10.1016/j.ccr.2014.01.008

14 Mazumdar M, Smith A and Bacik J: Methods for categorizing a prognostic variable in a multivariable setting. Stat Med *22*: 559-571, 2003. PMID: 12590414. DOI: 10.1002/sim.1333

15 Lee J, Kotliarova S, Kotliarov Y, Li A, Su Q, Donin NM, Pastorino S, Purow BW, Christopher N, Zhang W, Park JK and Fine HA: Tumor stem cells derived from glioblastomas cultured in bFGF and EGF more closely mirror the phenotype and genotype of primary tumors than do serum-cultured cell lines. Cancer Cell *9*: 391-403, 2006. PMID: 16697959. DOI: 10.1016/j.ccr.2006.03.030

16 Sanchez-Carbayo M, Socci ND, Lozano J, Saint F and Cordon-Cardo C: Defining molecular profiles of poor outcome in patients with invasive bladder cancer using oligonucleotide microarrays. J Clin Oncol *24*: 778-789, 2006. PMID: 16432078. DOI: 10.1200/JCO.2005.03.2375

17 Kashihara H, Shimada M, Kurita N, Iwata T, Sato H, Kozo Y, Miyatani T, Chie T and Noriko M: Protein kinase Cι is a new prognostic factor in gastric cancer. Surg Today *45*: 759-764, 2014. PMID: 25108825. DOI: 10.1007/s00595-014-1010-5

18 Weichert W, Gekeler V, Denkert C, Dietel M and Hauptmann S: Protein kinase C isoform expression in ovarian carcinoma correlates with indicators of poor prognosis. Int J Oncol *23*: 633-639, 2003. PMID: 12888898.

19 Khosravi-Far R, Solski PA, Clark GJ, Kinch MS and Der CJ: Activation of Rac1, RhoA, and mitogen-activated protein kinases is required for Ras transformation. Mol Cell Biol *15*: 6443-6453, 1995. PMID: 7565796. DOI: 10.1128/mcb.15.11.6443

20 Qiu RG, Chen J, Kirn D, Mc Cormick F and Symons M: An essential role for rac in ras transformation. Nature *374*: 457-459, 1995. PMID: 7700355. DOI: 10.1038/374457a0

21 Murray NR, Jamieson L, Yu W, Zhang J, Gökmen-Polar Y, Sier D, Anastasiadis P, Gatalica Z, Thompson EA and Fields AP: Protein kinase Cι is required for Ras transformation and colon carcinogenesis *in vivo*. J Cell Biol *164*: 797-802, 2004. PMID: 15024028. DOI: 10.1083/jcb.200311011

22 Murray NR and Fields AP: Atypical protein kinase Cι protects human leukemia cells against drug-induced apoptosis. Am J Pathol *272*: 27521-27524, 1997. PMID: 9346882. DOI: 10.1074/jbc.272.44.27521

23 Lu Y, Jamieson L, Brasier AR and Fields AP: NF-κB/RelA transactivation is required for atypical protein kinase Cl-mediated cell survival. Oncogene *20*: 4777-4792, 2001. PMID: 11521190. DOI: 10.1038/sj.onc.1204607

24 Sarkar S, Bristow CA, Dey P, Rai K, Perets R, Ramirez-Cardenas A, Malasi S, Huang-Hobbs E, Haemmerle M, Wu SY, McGuire M, Protopopov A, Jiang S, Liu JF, Hirsch MS, Chang Q, Lazar AJ, Sood AK, Drapkin R, DePinho R, Draetta G and Chin L: PRKCI promotes immune suppression in ovarian cancer. Genes Dev *31*: 1109-1121, 2017. PMID: 28698296. DOI: 10.1101/gad.296640.117

25 Wang G, Lu X, Dey P, Deng P, Wu CC, Jiang S, Fang Z, Zhao K, Konaparthi R, Hua S, Zhang J, Li-Ni-Ngtapia EM, Kapoor A, Wu CJ, Patel NB, Guo Z, Ramamoorthy V, Tieu TN, Heffernan T, Zhao D, Shang X, Khadka S, Hou P, Hu B, Jin EJ, Yao W, Pan X, Ding Z, Shi Y, Li L, Chang Q, Troncoso P, Logothetis CJ, McArthur MJ, Chin L, Alan Wang Y and Depinho RA: Targeting YAP-dependent MDSC infiltration impairs tumor progression. Cancer Discov, 2016. PMID: 26701088. DOI: 10.1158/2159-8290.CD-15-0224

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