The Role of Activation-induced Cytidine Deaminase Expression in Gastric Adenocarcinoma

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Abstract. *Backround: Gastric adenocarcinoma is one of the most common malignant tumors and the leading cause of malignancy-related death worldwide. Studies have reported overexpression of activation-induced cytidine deaminase (AID) and protein kinase c iota (PKCi) proteins showing involvement in the regulation of carcinogenesis. In the present study, we investigated the expression of AID and PKCi in patients with gastric adenocarcinoma and determined the correlation between these proteins. Materials and Methods: This study was conducted between September 2009 and September 2010 on a total of 59 patients with gastric adenocarcinoma at the Tokushima University Hospital. AID, PKCi and mutated p53 protein expressions were evaluated by immunohistochemistry in gastric adenocarcinoma. Results: High AID and PKCi expression was significantly ($p<0.05$) associated with poorly-differentiated gastric adenocarcinoma. In addition, PKCi expression was significantly correlated with clinicopathological findings such as a lymph node metastasis, and venous and lymphatic invasion ($p<0.05$). Furthermore, AID expression was significantly correlated with PKCi and mutated p53 protein expression in gastric adenocarcinoma ($p<0.05$). Conclusion: High AID and PKCi expressions were significantly correlated with poorly-differentiated gastric adenocarcinoma.*

Gastric adenocarcinoma is one of the most common malignant tumors and the leading cause of malignancy-related death worldwide (1). Its 5-year survival rates are approximately 20% in most countries of the world (2, 3), excluding Japan. Tsubono *et al*. reported 5-year survival rates for gastric cancer being 60% in Japan (4).

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Activation-induced cytidine deaminase (AID) is a member of the apolipoprotein B mRNA editing enzyme (APOBEC), which plays a crucial role in DNA breakage through de-amination of cytosines into uracils. However, the overexpression or persistent expression of AID protein was correlated with chronic inflammation through nuclear factor-kappa B (NF-κB) in hepatitis and gastritis (5, 6). Constitutive expression of AID also caused the development of liver tumors with the morphological characteristics of hepatocellular carcinoma (7). The expression of AID was not detected in non-cancerous lung cells, it was detected in lung cancer cells (8), which shows that AID is aberrantly expressed in primary lung cancer cells. In general, the above studies show AID expression is common in several cancer types.

PKCi protein plays different roles in epithelial cell functions, such as in cell polarity (9-11), cell survival (12), and cell growth (11). Moreover, PKCi is involved in promoting tumorigenicity and metastasis of human esophageal cancer (13). Among the PKC isozymes, only atypical *PKCi* has been shown to function as a proper oncogene (14, 15), and as such, is an attractive target for gastric adenocarcinoma. Both AID and PKCi expressions were observed in different cancer tissues, from that we hypothesized that these proteins might be positively correlated with each other.

p53 is a tumor-suppressor gene which plays a crucial role in growth suppression of cancer, apoptosis and DNA repair (16). Mutated p53 (mp53) can accumulate at high concentration in the nuclei of tumor cells (17), and its dysfunction may affect the biological events in cancer cells, which could lead to aggressive carcinogenesis. Futhermore, mp53 was detected in primary human gastric cancer (18).

In general AID is induced by inflammation and is involved in various types of human carcinogenesis. Abnormal expression of AID, as well as PKCi, has been reported in different types of cancer. However, the correlation between AID and PKCi remains unknown. Therefore, increasing knowledge about AID and understanding its correlation with PKCi, as well as mp53, might allow for stratification of the prognosis of various cancer types and consideration of

whether targeting these proteins is beneficial for patients with adenocarcinoma. In the present study we, performed immunohistochemistry in gastric tumor tissues with the aim of a better comprehension of the correlation between AID expression with PKCi, as well as mp53, expression, in gastric adenocarcinoma and also the clinicopathological correlations with the expression of these proteins.

Patients and Methods

We enrolled a total of 59 (13 male, and 46 female) patients surgically-resected for gastric adenocarcinoma at the Tokushima University Hospital between September 2009 and September 2010. The age of the study participants ranged from 40 to 87 years, with a mean age of 62 years. The clinicopathological parameters were obtained from the pathological reports, including tumor differentiation, lymph node metastasis, and TNM stage, and all data were reviewed and confirmed by experienced pathologists.

Immunohistochemistry. The sample processing and immunohistochemistry procedures were performed following standard immunohistochemical staining protocols. In brief, sections were cut with thickness of 4 μm, de-paraffinized in xylene, and dehydrated in descending ethanol concentration. Endogenous peroxidase activity was blocked by 10 min of incubation with 0.3% hydrogen peroxidase in 50% of methanol. Antigen retrieval was performed by using a multifunctional microwave histoprocessor at 100˚C and by using a microwave heating in citrate buffer (pH 6.0) for 24 min. We used a protein block (serum-free, code x0909; Dako, Glostrup, Denmark) for blocking non-specific antigen of AID for 10 min. Sections were incubated for 60 min at ambient temperature with primary antibody and were washed with phosphate buffered saline (PBS) three times for 5 min. Immunohistochemical staining was completed using a monoclonal mouse antibody against AID (ZA001, catalog no.39-250, dilution 1:100; Invitrogen, Zymed Laboratories, San Francisco, CA, USA), PKCi (Mat.Number 610176, dilution 1:100, BD Biosciences) and human p53 (clone DO-7, code no. M 7001; dilution 1:100; Dako).

After washing with PBS, sections were incubated for 60 min at ambient temperature with second antibody of the detection reagent (code K5027, Glostrup, Denmark). Diaminobenzidine tetrahydrochloride was used as the chromogen. Finally, sections were counter-stained with Mayer's hematoxylin.

Immunohistochemistry evaluation. For positive control of AID, we used tonsillar tissue and lymph nodes, and negative controls were performed by omitting the primary antibody. The mean percentage of positive tumor cells was determined using an Image System (Nikon Digital Camera, DXM1200F, Gotenba, Shizuoka, Japan).

Cytoplasmic AID expression was evaluated by summing the staining percentage and intensity scores. The staining percentage was assigned to one of the following categories: 0= no staining, 1= up to 5% of cells stained, 2= 5%-10% of cells stained, 3= 10%-25% of cells stained, 4= 25%-50% of cells stained, 5= more than 50% of cells stained. The staining intensity was assigned as: 0=no expression, 1+= weak expression, 2+= strong expression. The cytoplasmic expression levels of AID were classified as low (score ≤4) and high (score ≥5) (19).

p53 protein immunohistochemistry staining was considered positive when nuclear staining was 10% or more (20).

Table I. *Patients' characteristics*.

Clinicopathological variable	Enrolled patients
Gender M/F	25/34
Age (years) ≤ 70/ ≥ 71	41/18
Invasion T 1,2/ T 3,4	48/11
Lymph node metastasis –/+	37/22
Peritoneal metastasis –/+	53/6
Stage I,II/III,IV	42/17
Venous invasion, –/+	38/21
Lymphatic invasion –/+	38/21
Differentiated/undifferentiated	14/59

M/F: Male/female.

PKCi was scored according to a previous method as follows: 0, no staining; 1+, weak; 2+, moderate intensity; and 3+, strong intensity. Scores of 0 and 1+ were defined as negative, scores of 2+ and 3 were defined as positive (21). Figure 1 shows representative images of immunohistochemistry.

Statistical analysis. The *p*-value of overall and disease-free survival was denied by using Kaplan Meier analysis with JMP10 software (SAS Campus Drive, Cary, NC). Information from the laboratory analysis and patients were entered into Stat. View 5.0 software (SAS Campus Drive, Cary, NC) and statistical analyses were performed using Student's *t*-test, the chi-square test. A *p*-value of less than 0.05 was considered statistically significant.

Results

Relationship between AID expression in the cancerous lesion of gastric adenocarcinoma and clinicopathological findings. Patients' clinicopathological characteristics are summarized in Table I.

The relationship between AID expression and the clinicopathological characteristics, such as tumor differentiation, age, gender, tumor stage, and venous or lymphatic invasion were evaluated as shown in Table II. AID was significantly correlated with poorly-differentiated gastric adenocarcinoma (p=0.01). However, there was no significant correlation between AID expression and age, gender, stage, TNM classification, nor venous or lymphatic invasion.

Correlation between PKCi expression and clinicopathological findings in gastric adenocarcinoma. The correlation of PKCi expression and the clinicopathological characteristics is examined in Table III. The positive expression of the PKCi protein was significantly correlated with lymph node metastasis, venous invasion, lymphatic invasion and poorly-differentiated gastric adenocarcinoma (p<0.05).

Correlation of AID, PKCi and mp53 protein expressions in gastric adenocarcinoma. In this study, 47 (80%) cases of

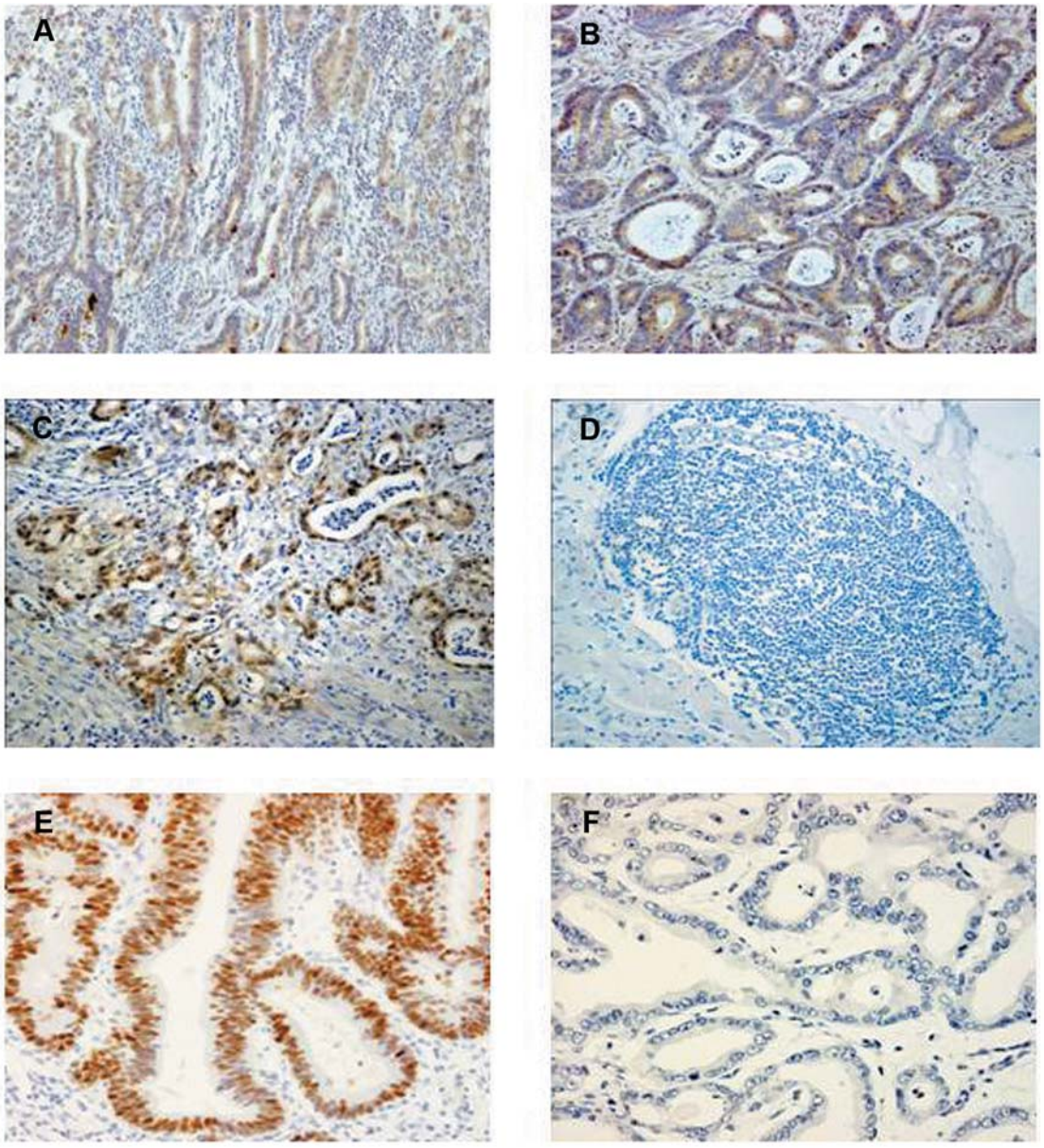

Figure 1. *Representative histological features of gastric adenocarcinoma by activation-induced cytidine deaminase (AID) immunostaining. A: AID protein score 7, high expression. B: AID protein score 3, low expression. C: Positive protein kinase c iota (PKCi) expression. D: Negative PKCi expression. E: Positive nuclear expression of p53 protein. F: Negative expression of p53 protein.*

AID-high and 12 (20%) of AID-low expression in the carcinoma of gastric adenocarcinoma were examined. There were 40 (68%) positive and 19 (32%) negative cases of PKCi protein expression, which was significantly positively-correlated with AID protein (Table II) (p=0.01). In addition, 39 (66%) mp53-positive and 20 (34%) mp53-negative cases were observed, which correlated with AID protein expression significantly in gastric adenocarcinoma (Table II) (p=0.045).

Survival rates of patients according to AID and PKCi expression in gastric adenocarcinoma. Overall survival was evaluated in 59 patients and disease-free survival was evaluated in 51 patients who underwent resection; for disease-free survival, patients with stage IV disease were excluded. Median follow-up time was 36 months, with a range of 4 to 46 months. As shown in Figure 2A there was no significant difference, but there was tendency (p=0.12) for better 4-year overall survival in the patients' group with

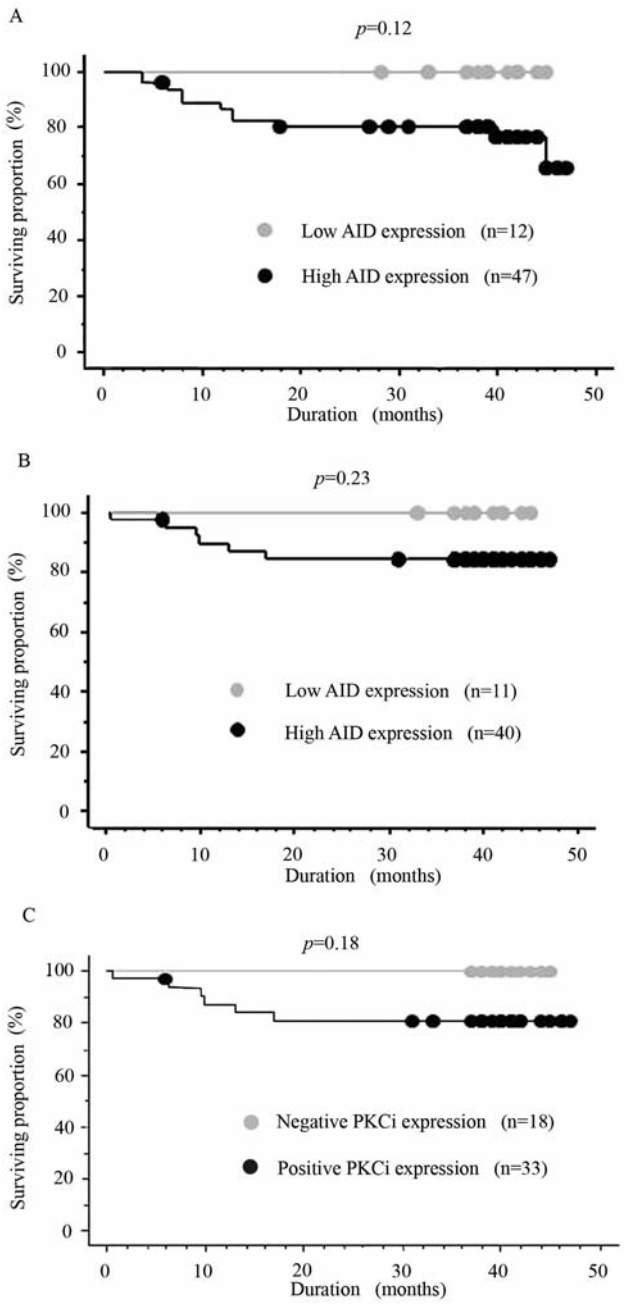

Figure 2. *A: Overall survival curve according to activation-induced cytidine deaminase (AID) protein expression in gastric adenocarcinoma. B: Disease-free survival curve according to AID protein expression in gastric adenocarcinoma. C: Disease-free survival according to protein kinase c iota (PKCi) protein expression in gastric adenocarcinoma.*

low AID expression. The disease-free survival of AID expression was 85% in the high- and 100% low-AID groups at 4 years (p=0.23) (Figure 2B). Disease-free survival by PKCi-positive and -negative expression (80% and 100%, respectively 3-year) is shown in Figure 2C (p=0.18).

Table II. *Correlation between activation-induced cytidine deaminase (AID) expression and clinicopathological findings in gastric adenocarcinoma.*

Factor	High expression group (n=47)	Low expression group (n=12)	p-Value
Gender M/F	31/16	7/5	0.62
Age (years) ≤70/ ≥71	33/14	7/5	0.43
Invasion T 1,2/ T 3,4	38/9	10/2	0.84
Lymph node metastasis –/+	29/18	8/4	0.75
Peritoneal metastasis –/+	42/5	11/1	0.81
Stage I,II/III,IV	29/18	8/4	0.75
Venous invasion –/+	25/22	7/5	0.75
Lymphatic invasion –/+	23/24	8/4	0.27
Differentiated/undifferentiated	27/20	2/10	0.01
PKCi (–/+)	12/35	8/4	0.01
mp53 (–/+)	13/34	7/5	0.045

M/F: Male/female; PKCi: protein kinase C iota; mp53: mutated p53.

Table III. *Correlation between protein kinase C iota (PKCi) expression in gastric adenocarcinoma and clinicopathological findings.*

Factor	Positive expression group (n=39)	Negative expression group (n=20)	p-Value
Gender M/F	13/26	12/8	0.61
Age (years) ≤ 70/ ≥ 71	24/15	17/3	0.06
Invasion T 1,2/ T 3,4	31/8	17/3	0.6
Lymph node metastasis –/+	21/18	16/4	0.049
Peritoneal metastasis –/+	35/4	18/2	0.97
Stage I, II/III, IV	27/12	15/5	0.64
Venous invasion –/+	23/16	15/5	0.01
Lymphatic invasion –/+	23/16	15/5	0.01
Differentiated/undifferentiated	14/25	15/5	0.01

M/F: Male/female.

Discussion

The present study examined AID and PKCi expression in patients surgically-resected for gastric adenocarcinoma, and these results were compared to clinicopathological characteristics.

The expression of AID has been mentioned in non-B-cells, including gastric epithelial cells, human hepatocytes, biliary cells, and colonic epithelial cells (5, 7, 22, 23). These studies have suggested that AID is a genomic mutator. Its aberrant expression was detected in several types of cancer, such as hepatocellular carcinoma, cholangiocarcinoma and colon cancer (7, 22, 23). We revealed here that high AID expression was significantly correlated with poorly-differentiated gastric adenocarcinoma.

Previously, PKCi was shown to be a key signaling component involved in the regulation of normal cell proliferation, differentiation, and cell polarity (9-12, 24). This kinase localizes to the apical domain of epithelial cells, its role is establishing cell polarity (9).

PKCi is oncogenic in several types of cancer. This study investigated the relationship between PKCi and clinicopathological characteristics, and the correlation of AID and PKCi protein expression in gastric adenocarcinoma. In previous studies, overexpression of PKCi was observed in cholangiocarcinoma, and in lung, ovarian, breast, and gastric cancer (15, 25-28). Positive expression of the PKCi protein was found here to be significantly correlated with lymph node metastasis, venous and lymphatic invasion, and poorly-differentiated gastric adenocarcinoma. Takagawa *et al*. reported that high expression of PKCi was significantly correlated with lymph node metastasis in gastric cancer (28). The *PKCi* gene was identified as a human oncogene (26, 29).

In the present study, we found a significant correlation between AID and PKCi expressions. We can speculate that these proteins may influence each other and promote carcinogenesis.

In another study, *Helicobacter pylori* infection induced transient activation of aPKC (30, 31), which is required for NF-κB activation (32). It has been reported that AID expression was activated through the NF-κB activation in human gastric epithelial cells and hepatocellular carcinoma (5, 7).

In addition, we explored the strong correlation between AID and mp53 protein in gastric adeocarcinoma. Aberrant expression of AID protein promotes accumulation of nucleotide alterations in the *p53* gene and its overexpression in human gastric cancer (5, 33). *p53* mutation has been found in well-differentiated adenocarcinoma (34). An *in vitro* study showed the overexpression of AID induces a mutation of *p53* gene in gastric cells (7). Some studies reported the frequency of *p53* alteration in gastric cancer, 18%-58% had *p53* mutation, and *p53* overexpression occured in 26%-65% of gastric adenocarcinomas (35, 36).

We found a tendency for a high expression of AID protein to correlate with a lower rate in gastric adenocarcinoma. In our study, positive expression of PKCi protein was related to lower rate of disease-free survival in gastric adenocarcinoma, which was comparable to the findings of Takagawa *et al*. whereby aPKC λ/i overexpression was a strong prognostic marker for gastric cancer recurrence (28).

Conclusion

High AID and PKCi expressions were significantly correlated with poorly-differentiated gastric adenocarcinoma.

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References

1 Jemal A, Siegel R, Ward E, Murray T, Xu J, Smigal C and Thun MJ: Cancer statistics, 2006. CA Cancer J Clin *56*: 106-130, 2006.

2 Cunningham SC, Kamangar F, Kim MP, Hammoud S, Haque R, Maitra A, Montgomery E, Heitmiller RE, Choti MA, Lillemoe KD, Cameron JL, Yeo CJ and Schulick RD: Survival after gastric carcinoma resection: Eighteen-year experience at a single institution. J Gastrointest Surg *9*: 718-725, 2005.

3 Faycal J, Bessaguet C, Nousbaum JB, Cauvin JM, Cholet F, Bideau K, Robaszkiewicz M and Gouerou H: Epidemiology and long term survival of gastric carcinoma in the French district of Finistere between 1984 and 1995. Gastroenterol Clin Biol *29*: 23-32, 2005.

4 Tsubono Y and Hisamichi S: Screening for gastric cancer in Japan. Gastric Cancer *3(1)*: 9-18, 2000.

5 Matsumoto Y, Marusawa H, Kinoshita K, Endo Y, Kou T, Morisawa T, Azuma T, Okazaki IM, Honjo T and Chiba T: *Helicobacter pylori* infection triggers aberrant expression of activation-induced cytidine deaminase in gastric epithelium. Nat Med *13*: 470-476, 2007.

6 Kou T, Marusawa H, Kinoshita K, Endo Y, Okazaki IM, Ueda Y, Kodama Y, Haga H, Ikai I and Chiba T: Expression of activation-induced cytidine deaminase in human hepatocytes during hepatocarcinogenesis. Int J Cancer *120(3)*: 469-476, 2007.

7 Endo Y, Marusawa H, Kinoshita K, Morisawa T, Sakurai T, Okazaki IM, Watashi K, Shimotohno K, Honjo T and Chiba T: Expression of activation-induced cytidine deaminase in human hepatocytes *via* NF-κB signaling. Oncogene *26(38)*: 5587-5595, 2007.

8 Shinmura K, Igarashi H, Goto M, Tao H, Yamada H, Matsuura S, Tajima M, Matsuda T, Yamane A, Funai K, Tanahashi M, Niwa H, Ogawa H and Sugimura H: Aberrant expression and mutation-inducing activity of AID in human lung cancer. Ann Surg Oncol *18(7)*: 2084-2092, 2011.

9 Ohno S: Intercellular junctions and cellular polarity: The PAR-aPKC complex, a conserved core cassette playing fundamental roles in cell polarity. Curr Opin Cell Biol *13*: 641-648, 2001.

10 Etienne-Manneville S and Hall A: Cell polarity: PAR6, aPKC and cytoskeletal crosstalk. Curr Opin Biol *1*: 67-72, 2003.

11 Moscat J and Diaz-Meco MT: The atypical protein kinase Cs. Functional specificity mediated by specific protein adapters. EMBO Rep *1*: 399-403, 2001.

12 Jamieson L, Carpenter L, Biden TJ and Fields AP: Protein kinase C iota activity is necessary for BCR-ABL-mediated resistance to drug-induced apoptosis. J Biol Chem *274*: 3927-3930, 1999.

13 Liu SG, Wang BS, Jiang YY, Zang TT, Shi ZZ, Yang Y, Yang YL, Wang XC, Lin DC, Zhang Y, Yang H, Cai Y, Zhan QM and Wang MR: Atypical protein kinase Ci (PKCi) promotes metastasis of esophageal squamous cell carcinoma by enhancing resistance to anoikis *via* PKCi-SKP2-AKT pathway. Mol Cancer Res *9(4)*: 390-402, 2011.

14 Regala RP, Weems C, Jamieson L, Khoor A, Edell ES, Lohse CM and Fields AP: Atypical protein kinase C iota is an oncogene in human non-small cell lung cancer. Cancer Res *65(19)*: 8905-8911, 2005.

15 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 WL, Gray JW, Yin JC, Liu J, Halder G and Mills GB: Atypical PKC iota contributes to poor prognosis through loss of apical-basal polarity and cyclin E overexpression in ovarian cancer. Proc Natl Acad Sci USA *102(35)*: 12519-12524, 2005.

16 Hollstein M, Sidransky D, Vogelstein B and Harris CC: *p53* mutations in human cancers. Science *253*: 49-53, 1991.

17 Karim S and Ali A: Correlation of p53 overexpression and alteration in *p53* gene detected by polymerase chain reaction-single strand conformation polymorphism in adenocarcinoma of gastric cancer patients from India. World J Gastroenterology 15(11): 1381-1387, 2009.

18 Tamura G, Kihana T, Nomura K, Terada M, Sugimura T and Hirohashi S: Detection of frequent *p53* gene mutations in primary gastric cancer by cell sorting and polymerase chain reaction single-strand conformation polymorphism analysis. Cancer Res 51(11): 3056-3058, 1991.

19 Goto A, Hirahashi M, Osada M, Nakamura K, Yao T, Tsuneyoshi M, Takayanagi R and Oda Y: Aberrant activation-induced cytidine deaminase expression is associated with mucosal intestinalization in the early stage of gastric cancer. Virchows Arch *458(6)*: 717-724, 2011.

20 Gonzales-Angulo AM, Sneige N, Buzdar AU, Valero V, Kau SW, Broglio K, Yamamura Y, Hortobagyi GN and Cristofanilli M: *p53* expression as a prognostic marker in inflammatory breast cancer. Clin Cancer *10*: 6215-6221, 2004.

21 Ishiquro H, Akimoto K, Nagashima Y, Kagawa E, Sasaki T, Sano JY, Takagawa R, Fujinami K, Sasaki K, Aoki I, Ohno S, Kubota Y and Uemura H: Coexpression of aPKCλ/i and IL-6 in prostate cancer tissue correlated with biochemical recurrence. Cancer Sci *102(8)*: 1576-1581, 2011.

22 Komori J, Marusawa H, Machimoto T, Endo Y, Kinoshita K, Kou T, Haga H, Ikai I, Uemoto S and Chiba T: Activation-induced cytidine deaminase links bile duct inflammation to human cholangiocarcinoma. Hepatology *47*: 888-896, 2008.

23 Endo Y, Marusawa H, Kou T, Nakase H, Fujii S, Fujimori T, Kinoshita K, Honjo T and Chiba T: Activation-induced cytidine deaminase links between inflammation and the development of colitis-associated colorectal cancers. Gastroenterology *135*: 889-898, 2008.

24 Suzuki A, Ishiyama C, Hashiba K, Shimizu M, Ebnet K and Ohno S: aPKC kinase activity is required for the asymmetric differentiation of the premature junctional complex during epithelial cell polarization. J Cell Sci *115*: 3565-3573, 2002.

25 Regala RP, Weems C, Jamieson L, Copland JA, Thompson EA and Fields AP: Atypical protein kinase C I plays a critical role in human lung cancer cell growth and tumorigenicity. J Biol Chem *280*: 31109-31115, 2005.

26 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.

27 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(1): 70-75, 2008.

28 Takagawa R, Akimoto K, Ichikawa Y, Akiyama H, Kojima Y, Ishiquro H, Inayama Y, Aoki I, Kunisaki C, Endo I, Nagashima Y and Ohno S: High expression of atypical protein kinase C λ/i in gastric cancer as a prognostic factor for recurrence. Ann Surg Oncol 17: 81-88, 2010.

29 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 PKC iota as a biomarker and potential oncogene in ovarian carcinoma. Cancer Res 66: 4627-35, 2006.

30 Allen LA and Allgood JA: Atypical protein kinase C-zeta is essential for delayed phagocytosis of *Helicobacter pylori*. Curr Biol 12(20): 1762-6, 2002.

31 Win HY and Acevedo-Duncan M: Atypical protein kinase C phosphorylates IKKαβ in transformed non-malignant and malignant prostate cell survival. Cancer Lett 270: 302-311, 2008.

32 Dominguez I, Sanz L, Arenzana-Seisdedos F, Diaz-Meco MT, Virelizier JL and Moscat J: Inhibition of protein kinase C zeta subspecies blocks the activation of an NF-κB-like activity in *Xenopus laevis* oocytes. Mol Cell Biol 13: 1290-1295, 1993.

33 Kim CJ, Song JH, Cho YG, Cao Z, Kim SY, Nam SW, Lee JY and Parks WS: Activation-induced cytidine deaminase expression in gastric cancer. Tumour Biol 28: 333-9, 2007.

34 Fenoglio-Preiser CM, Wang J, Stemmermann GN and Noffsinger A: TP53 and gastric carcinoma: A review. Hum Mutat 21: 258-270, 2003.

35 Poremba C, Yandell DW, Huang Q, Little JB, Mellin W, Schmid KW, Bocker W and Dockhorn-Dworniczak B: Frequency and spectrum of *p53* mutations in gastric cancer--a molecular genetic and immunohistochemical study. Virchows Arch 426(5): 447-55, 1995.

36 Monig SP, Eidt S, Zirbes TK, Stippel D, Baldus SE and Pichlmaier H: *p53* expression in gastric cancer: Clinicopathological correlation and prognostic significance. Dig Dis Sci 42(12): 2463-2467, 1997.

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