Int J Clin Exp Pathol 2016;9(5):5635-5641
www.ijcep.com /ISSN:1936-2625/IJCEP0024024

Original Article

CREB-binding protein expression and the correlation with clinical aspects of oral squamous cell carcinoma

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Received January 14, 2016; Accepted March 24, 2016; Epub May 1, 2016; Published May 15, 2016

Abstract: Background: The CREB-binding protein (CBP) is a member of the histone acetyltransferase family of transcriptional coactivators that regulate the chromosomal infrastructure and mediate the combination of transcription factors and DNA. However, the clinical significance of CBP expression in oral squamous cell carcinoma (OSCC) and its correlation with patients' prognoses remain unclear. Materials and methods: CBP expression in 276 patients with OSCC was detected using tissue microarrays, and the associations between nuclear CBP expression and the clinical parameters of OSCC patients were evaluated. Results: Nuclear CBP expression was observed in 182 patients (68.2%), and high nuclear CBP expression was associated with a more receded clinical stage (P = 0.031) and smaller tumor size (P = 0.007) but not associated with positive lymph node metastasis or distal metastasis. Conclusion: Our results revealed that the loss of CBP nuclear expression in OSCC samples can predict the progression of OSCC patients in Taiwan.

Keywords: CREB-binding protein, OSCC, tissue microarrays, clinical stage

Introduction

Oral squamous cell carcinoma (OSCC) is a common cancer worldwide. Its incidence is increasing rapidly every year in Asian countries, including in Taiwan. In addition to alcohol and tobacco consumption, chewing betel quid is the main reason for the increased prevalence of OSCC in this region [1]. OSCC is characterized by a high degree of local invasiveness and a high rate of metastasis, which increase the death rate among these patients [2, 3]. Despite extensive research, the 5-year mortality rate of oral cancer remains approximately 50%, with no significant decrease worldwide [4]. Therefore, identifying a reliable biomarker for prediction of metastasis and prognosis of OSCC is crucial.

Abnormal regulation of the chromatin structure may lead to aberrant gene expression and cancer development [5]. CREB-binding protein (CBP) and its paralog, E1A-binding protein (p300), are members of the histone acetyltransferase (HAT) family of transcriptional coactivators [6, 7]. They play a crucial role in the mechanisms of transcriptional activation. Relaxation of chromatin through their intrinsic HAT can regulate multiple biological activities such as cell proliferation, differentiation, metastasis, and apoptosis [8]. Several studies have suggested that CBP and p300 have tumor relevance because they regulate the activities of tumor-related proteins such as p53 and NF-κB [9, 10] and control the modification of nucleosomal histones that govern epigenetic expression and silence several tumor-related genes [11, 12]. CBP and p300 expression is associated with a poor prognosis in small-cell lung cancer; Gao et al. reported that the overall survival rate of patients with CBP- and p300-positive tumors was significantly lower than that of patients with CBP- and p300-negative tumors [13]. Another study also indicated that CBP is highly expressed in lung cancer cells and tumor tissues [14]. CBP and p300 downregulation revealed atargetable function in the survival and invasion of glioma and prostate cancer cells [15, 16]. However, the clinical significance

Table 1. Patient characteristics

Characteristics	Total (%)
Total number of patients	267
Age (year)	
Mean ± SD	54.99 ± 11.13
Gender	
Male	253 (94.8%)
Female	14 (5.2%)
Cancer location	
Buccal mucosa	108 (40.4%)
Tongue	91 (34.2%)
Gingiva	33 (12.4%)
Palate	14 (5.2%)
Floor of Mouth	10 (3.7%)
Others	11 (4.1%)
Clinical stage	
I	51 (19.1%)
II	56 (21.0%)
III	30 (11.2%)
IV	130 (48.7%)
T classification	
T1	65 (24.3%)
T2	83 (31.1%)
T3	20 (7.5%)
T4	99 (37.1%)
N classification	
N0	172 (64.4%)
N1	32 (12.0%)
N2	59 (22.1%)
N3	4 (1.5%)
M classification	
M0	265 (99.3%)
M1	2 (0.7%)
Grade	
Well	44 (16.5%)
Moderate, poor	223 (83.5%)

of CBP expression in OSCC remains unclear. Therefore, the present study investigated CBP expression and clinicopathologic features in surgically resected OSCC patients for identifying patients with increased risks of cancer recurrence and providing a theoretical basis for further clinical prevention of OSCC.

Materials and methods

Patients and tissue microarray

In this study, we collected 276 OSCC patients who underwent treatment at Changhua Christian Hospital, (Changhua, Taiwan) between 2000 and 2006 as previously described [17]. Before commencement of this study, approval was obtained from the Institutional Review Board of Changhua Christian Hospital and informed written consent to participate in the study was obtained from each person.

Immunohistochemical staining

OSCC TMA block slides were deparaffinized in xylene, rehydrated through a series of decreasing dilutions of alcohol and distilled water, and washed with phosphate-buffered saline as previously described [18]. Then, the slides were incubated with anti-CREB-binding protein antibody (Abcam; ab10490) in a dilution of 1:100. Expression of CBP was assessed semi-quantitatively based on the staining intensity by two pathologists, who blinded to clinical outcome, scoring coded sections under a light microscope independently. The intensity of staining was scored as negative (score 0), weak (score 1 +), and strong (score 2 +), respectively.

Statistical analysis

Statistical analyses were performed with the SPSS statistical software 17.0 (SPSS Inc., Chicago, IL, USA). Demographic data including age, six, clinical stage, T classification, N classification, M classification, differentiation, the continuous variables were presented by mean ± standard deviation; the categorical variables were presented by numbers (%). A *P*-value of less than 0.05 was regarded as statistically significant.

Results

Table 1 lists the clinicopathologic characteristics of patients with OSCC. Weenrolled 267 patients (253 male patients; mean age = 54.99 ± 11.13 y, range = 44-66 y) and analyzed their conditions. The cancers were located at the buccal mucosa (*n* = 108), tongue (*n* = 91), gingiva (*n* = 33), palate (*n* = 14), floor of the mouth (*n* = 10), and other locations (*n* = 11). According to the American Joint Committee on Cancer system, the tumors were classified into TNM stages I (*n* = 51), II (*n* = 56), III (*n* = 30), and IV (*n* = 130).

Nuclear CBP expression was detected by immunohistochemistry. Representative examples of tumors demonstrating overall negative (score:

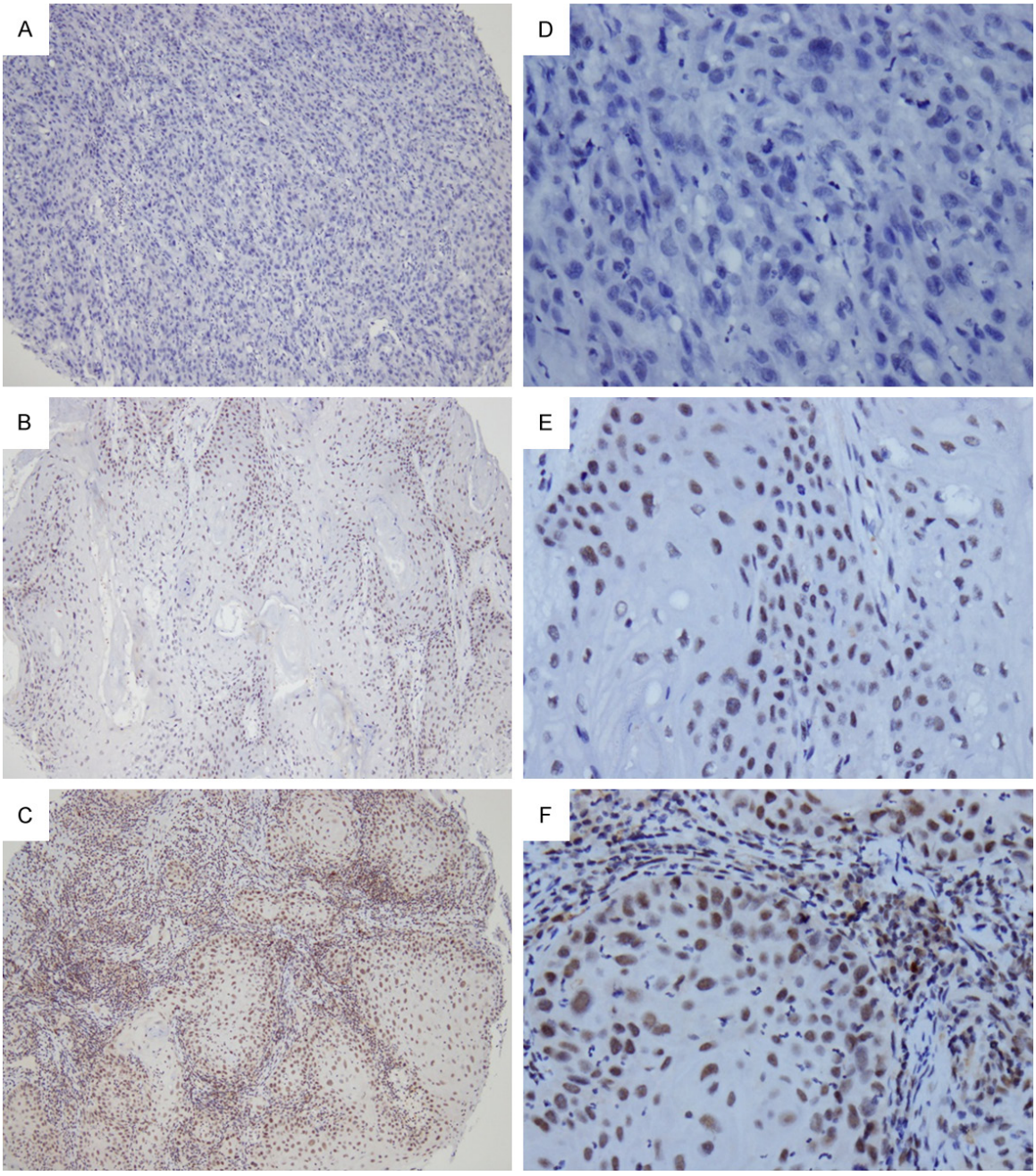

Figure 1. CREB-binding protein (CBP) in primary oral cancer. Tissue microarrays of primary oral squamous cell carcinomas (OSCCs) (276) were immunohistochemically analyzed for CBP. A and D. No detectable CBP (0). B, E. Weak expression levels (1 +). C, F. Strong expression levels (2 +). A-C. Low-power field (100 ×); D-F. High-power field (400 ×).

0), low (score: 1), and high CBP (score: 2) expression are illustrated in **Figure 1**.

Table 2 depicts the relationships between selected clinicopathologic factors and CBP expression. CBP immunohistological stains were classified according to the level of nuclear CBP expression into 2 groups, weak (score: 0) and strong (score: 1 and 2). A higher CBP expression was significantly associated with a more receded clinical stage (P = 0.031) and smaller tumor size (P = 0.007). However, the results revealed no significant association between CBP expression and patient age, sex, lymph node metastasis, or distal metastasis (**Table 2**).

Table 2. Patient characteristics regarding CBP expression

Characteristics	No. of patients (%)		*P* value
	CBP (weak)	CBP (strong)	
Total number of patients	85 (31.8)	182 (68.2)	
Age (year)			
< 55	51 (60.0)	93 (51.1)	0.174
≥ 55	34 (40.0)	89 (48.9)	
Gender			
Male	81 (95.3)	172 (94.5)	0.788
Female	4 (4.7)	10 (5.5)	
Cancer location			
Buccal mucosa	32 (37.6)	76 (41.8)	0.654
Tongue	32 (37.6)	59 (32.4)	
Gingiva	12 (14.2)	21(11.5)	
Others	9 (10.6)	26 (14.3)	
Clinical stage			
I + II	26 (30.6)	81 (44.5)	0.031*
III + IV	59 (69.4)	101 (55.5)	
T classification			
T1 + T2	37 (43.5)	111 (61.0)	0.007*
T3 + T4	48 (56.5)	71 (39.0)	
N classification			
N0	52 (61.2)	120 (65.9)	0.449
N1 + 2 + 3	33 (38.8)	62 (34.1)	
M classification			
M0	83 (97.6)	180 (100)	0.101
M1	2 (2.4)	0 (0)	
Grade			
Well	14 (16.5)	30 (16.5)	0.998
Moderate, poor	71 (83.5)	152 (83.5)	

*$P < 0.05$.

Table 3 illustrates the relationships between selected clinicopathologic factors and CBP expression in patients aged < 55 years. The results revealed that higher CBP expression was significantly associated with a more receded clinical stage ($P = 0.020$) and smaller tumor size ($P = 0.021$); no significant associations between CBP expression and patient age, sex, lymph node metastasis, or distal metastasis were observed. **Table 4** illustrates that CBP expression had no significant correlation with clinicopathologic factors in patients aged ≥ 55 years.

Discussion

Oral cancer is a fatal disease and has the fourth highest mortality of malignancy among Taiwanese males. The relatively high prevalence of oral cancer in Taiwan is due mainly to the prevalence of chewing betel quid [19]. Oral cancer arises from several anatomic sites within the oral cavity, with the tongue and buccal mucosa being the most common sites in Taiwanese patients [20]. Despite advances in cancer diagnosis and treatment, the prognosis of OSCC remains dismal. Most OSCC patients die of recurrence or metastasis. The present study detected CBP expression in tumor tissues by using immunohistochemistry, revealing that high CBP expression in patients with OSCC is significantly associated with clinical stage and tumor size.

The chromosomal infrastructure is essential for gene control, determining both the active and repressed states. Turning the correct genes on and off is crucial. Histones and chromatin components play a crucial role in this decision-making process [21]. CBP and p300 are transcriptional coactivators and members of the HAT family. In addition, by regulating the chromosomal infrastructure, they mediate the combining of transcription factors and DNA. Several studies have demonstrated that CBP and p300 play a crucial role in regulating cell proliferation, differentiation, and apoptosis [22, 23]. High CBP expression upregulates tumor growth and predicts a poor prognosis in patients with lung cancer. Studies have also reported that CBP and p300 are associated with the tumorigenesis of various malignancies including colorectal, breast, hepatocellular, and non-small cell lung carcinomas [24-27]. Ianculescu et al. reported that CBP and p300 promoted prostate cancer progression, which could be blocked by siRNA [28]. CBP and p300 also promoted cancer progression in colon cancer cell lines with microsatellite instability [29]. However, our results revealed that nuclear CBP expression was associated with an obstructed clinical stage and tumor size in patients with OSCC (**Table 2**). These findings suggest that CBP may act as a tumor suppressor in patients of OSCC. CBP and p300 can promote cell proliferation and cancer development under specific conditions; however, they are also crucial for the transactivation function of p53, BRCA1, and FOXO3, which are all critical tumor suppressors [30-32]. In the

Table 3. Patient characteristics regarding CBP expression in the young patient (age < 55)

	No. of patients (%)		
Characteristics	CBP (weak)	CBP (strong)	*P* value
Total number of patients	51 (35.4)	93 (64.6)	
Gender			
Male	49 (96.1)	88 (94.6)	0.698
Female	2 (3.9)	5 (5.4)	
Cancer location			
Buccal mucosa	21 (41.2)	35 (37.6)	0.417
Tongue	18 (35.3)	34 (36.6)	
Gingiva	8 (15.7)	9 (9.7)	
Others	4 (7.8)	15 (16.1)	
Clinical stage			
I + II	14 (27.5)	44 (47.3)	0.020*
III + IV	37 (72.5)	49 (52.7)	
T classification			
T1 + T2	21 (41.2)	57 (61.3)	0.021*
T3 + T4	30 (58.8)	36 (38.7)	
N classification			
N0	29 (56.9)	62 (66.7)	0.243
N1 + 2 + 3	22 (43.1)	31 (33.3)	
Grade			
Well	10 (19.6)	18 (19.4)	0.971
Moderate, poor	41 (80.4)	75 (80.6)	

*$P < 0.05$.

Table 4. Patient characteristics regarding CBP expression in the older patient (age ≥ 55)

	No. of patients (%)		
Characteristics	CBP (weak)	CBP (strong)	*P* value
Total number of patients	34 (27.6)	89 (72.4)	
Gender			
Male	32 (94.1)	84 (94.4)	0.955
Female	2 (5.9)	5 (5.6)	
Cancer location			
Buccal mucosa	11 (32.4)	41 (46.1)	0.460
Tongue	14 (41.1)	25 (28.1)	
Gingiva	4 (11.8)	12 (13.5)	
Others	5 (14.7)	11 (12.3)	
Clinical stage			
I + II	12 (35.3)	37 (41.6)	0.525
III + IV	22 (64.7)	52 (58.4)	
T classification			
T1 + T2	16 (47.1)	54 (60.7)	0.173
T3 + T4	18 (52.9)	35 (39.3)	
N classification			
N0	23 (67.6)	58 (65.2)	0.795
N1 + 2 + 3	11 (32.4)	31 (34.3)	
Grade			
Well	4 (11.8)	12 (13.5)	0.800
Moderate, poor	30 (88.2)	77 (86.5)	

present study, the tumor-suppressive function of CBP both in vitro and in vivo supported our clinical data: (1) CBP possibly induces an imbalance in the expression of oncogenes and tumor-suppressor genes by the deregulation of histone acetylation [33], (2) CBP dysfunction alters the normal acetylation pattern of several cancer-related nonhistone substrates causing malignant transformation [34-36], (3) p53 acetylated and activated by CBP can inhibit cell growth [37], and (4) CBP may strengthen DNA damage signals by inhibiting tumor cell growth [38]. p53 is as a tumor suppressor and plays a crucial role in regulating cell-cycle progression and apoptosis. Inactivation of the p53 pathway accounts for the most common molecular defects in human cancers [39]. Previous studies have reported that p53 downregulation through CBP enhances tumorigenesis [40]. Jin et al. also demonstrated that a histone deacetylase inhibitor, DWP0016, induced p53 acetylation, which benefited from the upregulation of the coactivators, CBP and p300, to inhibit cell growth in glioblastoma cells [37]. Therefore, CBP has a dual functional property, depending on the cellular environment. Previous studies have reported that p53 is associated with tumorigenesis; activation of p53 expression is a potential strategy for anticancer treatment in head and neck squamous cell carcinoma. Therefore, the correlation between CBP and p53 may provide a useful prognostic marker in OSCC diagnostics.

We conducted an immunohistochemical analysis and observed that nuclear CBP expression was associated with an obstructed clinical stage and tumor size in patients with OSCC. In addition, CBP expression was not associated with poor overall survival. We could not study the relationship between CBP expression and poor overall survival. Therefore, further research with additional patient information is warranted to conclusively determine the usefulness of nuclear CBP in OSCC diagnostics and to clarify the downstream mechanisms involved in controlling the biological behavior of OSCC via histone-modifying molecules.

Acknowledgements

This study was supported by a research grant from National Science Council, Taiwan (NSC96-2628-B-040-021-MY3 and NSC102-2314-B-040-008-MY3) and Chung Shan Medical University Hospital, Taiwan (CSH-2015-C-015; CSH-2015-E-001-Y2).

Disclosure of conflict of interest

None.

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References

[1] Chiba I. Prevention of Betel Quid Chewers' Oral Cancer in the Asian-Pacific Area. Asian Pac J Cancer Prev 2001; 2: 263-269.

[2] Tanaka T. Chemoprevention of oral carcinogenesis. Eur J Cancer B Oral Oncol 1995; 31B: 3-15.

[3] Petersen PE. Oral cancer prevention and control--the approach of the World Health Organization. Oral Oncol 2009; 45: 454-460.

[4] Kantola S, Parikka M, Jokinen K, Hyrynkangs K, Soini Y, Alho OP and Salo T. Prognostic factors in tongue cancer-relative importance of demographic, clinical and histopathological factors. Br J Cancer 2000; 83: 614-619.

[5] Popovic R and Licht JD. Emerging epigenetic targets and therapies in cancer medicine. Cancer Discov 2012; 2: 405-413.

[6] Bannister AJ and Kouzarides T. The CBP co-activator is a histone acetyltransferase. Nature 1996; 384: 641-643.

[7] Ogryzko VV, Schiltz RL, Russanova V, Howard BH and Nakatani Y. The transcriptional coactivators p300 and CBP are histone acetyltransferases. Cell 1996; 87: 953-959.

[8] Goodman RH and Smolik S. CBP/p300 in cell growth, transformation, and development. Genes Dev 2000; 14: 1553-1577.

[9] Avantaggiati ML, Ogryzko V, Gardner K, Giordano A, Levine AS and Kelly K. Recruitment of p300/CBP in p53-dependent signal pathways. Cell 1997; 89: 1175-1184.

[10] Cras A, Politis B, Balitrand N, Darsin-Bettinger D, Boelle PY, Cassinat B, Toubert ME and Chomienne C. Bexarotene via CBP/p300 induces suppression of NF-kappaB-dependent cell growth and invasion in thyroid cancer. Clin Cancer Res 2012; 18: 442-453.

[11] Zhao X and Benveniste EN. Transcriptional activation of human matrix metalloproteinase-9 gene expression by multiple co-activators. J Mol Biol 2008; 383: 945-956.

[12] Wang F, Zhang R, Wu X and Hankinson O. Roles of coactivators in hypoxic induction of the erythropoietin gene. PLoS One 2010; 5: e10002.

[13] Gao Y, Geng J, Hong X, Qi J, Teng Y, Yang Y, Qu D and Chen G. Expression of p300 and CBP is associated with poor prognosis in small cell lung cancer. Int J Clin Exp Pathol 2014; 7: 760-767.

[14] Tang Z, Yu W, Zhang C, Zhao S, Yu Z, Xiao X, Tang R, Xuan Y, Yang W, Hao J, Xu T, Zhang Q, Huang W, Deng W and Guo W. CREB-binding protein regulates lung cancer growth by targeting MAPK and CPSF4 signaling pathway. Mol Oncol 2016; 10: 317-29.

[15] Santer FR, Hoschele PP, Oh SJ, Erb HH, Bouchal J, Cavarretta IT, Parson W, Meyers DJ, Cole PA and Culig Z. Inhibition of the acetyltransferases p300 and CBP reveals a targetable function for p300 in the survival and invasion pathways of prostate cancer cell lines. Mol Cancer Ther 2011; 10: 1644-1655.

[16] Xu LX, Li ZH, Tao YF, Li RH, Fang F, Zhao H, Li G, Li YH, Wang J, Feng X and Pan J. Histone acetyltransferase inhibitor II induces apoptosis in glioma cell lines via the p53 signaling pathway. J Exp Clin Cancer Res 2014; 33: 108.

[17] Lin SH, Lin YM, Yeh CM, Chen CJ, Chen MW, Hung HF, Yeh KT and Yang SF. Casein kinase 1 epsilon expression predicts poorer prognosis in low T-stage oral cancer patients. Int J Mol Sci 2014; 15: 2876-2891.

[18] Ko CP, Yang LC, Chen CJ, Yeh KT, Lin SH, Yang SF, Chen MK and Lin CW. Expression of myeloid zinc finger 1 and the correlation to clinical aspects of oral squamous cell carcinoma. Tumour Biol 2015; 36: 7099-7105.

[19] Kao SY and Lim E. An overview of detection and screening of oral cancer in Taiwan. Chin J Dent Res 2015; 18: 7-12.

[20] Ho PS, Ko YC, Yang YH, Shieh TY and Tsai CC. The incidence of oropharyngeal cancer in Taiwan: an endemic betel quid chewing area. J Oral Pathol Med 2002; 31: 213-219.

[21] Wolffe AP. Chromatin remodeling: why it is important in cancer. Oncogene 2001; 20: 2988-2990.

[22] Brasacchio D, Noori T, House C, Brennan AJ, Simpson KJ, Susanto O, Bird PI, Johnstone RW and Trapani JA. A functional genomics screen identifies PCAF and ADA3 as regulators of human granzyme B-mediated apoptosis and Bid cleavage. Cell Death Differ 2014; 21: 748-760.

[23] Guo W, Lu J, Dai M, Wu T, Yu Z, Wang J, Chen W, Shi D, Yu W, Xiao Y, Yi C, Tang Z, Xu T, Xiao X, Yuan Y, Liu Q, Du G and Deng W. Transcriptional

coactivator CBP upregulates hTERT expression and tumor growth and predicts poor prognosis in human lung cancers. Oncotarget 2014; 5: 9349-9361.
[24] Chen LC, Kurisu W, Ljung BM, Goldman ES, Moore D 2nd and Smith HS. Heterogeneity for allelic loss in human breast cancer. J Natl Cancer Inst 1992; 84: 506-510.
[25] Takahashi K, Kudo J, Ishibashi H, Hirata Y and Niho Y. Frequent loss of heterozygosity on chromosome 22 in hepatocellular carcinoma. Hepatology 1993; 17: 794-799.
[26] Duriez C, Schmitz A, Fouchet P, Buecher B, Thuille B, Lerebours F, Leger R, Boman F, Flejou JF, Monges G, Paraf F, Bedossa P, Sabourin JC, Salmon RJ, Laurent-Puig P, Thomas G and Olschwang S. [Localization of a tumor suppressor gene distal to D22S270 in colorectal cancers]. Gastroenterol Clin Biol 1997; 21: 358-364.
[27] Hou X, Li Y, Luo RZ, Fu JH, He JH, Zhang LJ and Yang HX. High expression of the transcriptional co-activator p300 predicts poor survival in resectable non-small cell lung cancers. Eur J Surg Oncol 2012; 38: 523-530.
[28] Ianculescu I, Wu DY, Siegmund KD and Stallcup MR. Selective roles for cAMP response element-binding protein binding protein and p300 protein as coregulators for androgen-regulated gene expression in advanced prostate cancer cells. J Biol Chem 2012; 287: 4000-4013.
[29] Ionov Y, Matsui S and Cowell JK. A role for p300/CREB binding protein genes in promoting cancer progression in colon cancer cell lines with microsatellite instability. Proc Natl Acad Sci U S A 2004; 101: 1273-1278.
[30] Watts GS, Oshiro MM, Junk DJ, Wozniak RJ, Watterson S, Domann FE and Futscher BW. The acetyltransferase p300/CBP-associated factor is a p53 target gene in breast tumor cells. Neoplasia 2004; 6: 187-194.
[31] Ogiwara H and Kohno T. CBP and p300 histone acetyltransferases contribute to homologous recombination by transcriptionally activating the BRCA1 and RAD51 genes. PLoS One 2012; 7: e52810.
[32] Wang F, Marshall CB, Li GY, Yamamoto K, Mak TW and Ikura M. Synergistic interplay between promoter recognition and CBP/p300 coactivator recruitment by FOXO3a. ACS Chem Biol 2009; 4: 1017-1027.
[33] Nagy Z and Tora L. Distinct GCN5/PCAF-containing complexes function as co-activators and are involved in transcription factor and global histone acetylation. Oncogene 2007; 26: 5341-5357.
[34] Gu W and Roeder RG. Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. Cell 1997; 90: 595-606.
[35] Zhao LY, Liu Y, Bertos NR, Yang XJ and Liao D. PCAF is a coactivator for p73-mediated transactivation. Oncogene 2003; 22: 8316-8329.
[36] Cohen HY, Lavu S, Bitterman KJ, Hekking B, Imahiyerobo TA, Miller C, Frye R, Ploegh H, Kessler BM and Sinclair DA. Acetylation of the C terminus of Ku70 by CBP and PCAF controls Bax-mediated apoptosis. Mol Cell 2004; 13: 627-638.
[37] Jin H, Liang L, Liu L, Deng W and Liu J. HDAC inhibitor DWP0016 activates p53 transcription and acetylation to inhibit cell growth in U251 glioblastoma cells. J Cell Biochem 2013; 114: 1498-1509.
[38] Yan G, Eller MS, Elm C, Larocca CA, Ryu B, Panova IP, Dancy BM, Bowers EM, Meyers D, Lareau L, Cole PA, Taverna SD and Alani RM. Selective inhibition of p300 HAT blocks cell cycle progression, induces cellular senescence, and inhibits the DNA damage response in melanoma cells. J Invest Dermatol 2013; 133: 2444-2452.
[39] Brown CJ, Lain S, Verma CS, Fersht AR and Lane DP. Awakening guardian angels: drugging the p53 pathway. Nat Rev Cancer 2009; 9: 862-873.
[40] Mazza D, Infante P, Colicchia V, Greco A, Alfonsi R, Siler M, Antonucci L, Po A, De Smaele E, Ferretti E, Capalbo C, Bellavia D, Canettieri G, Giannini G, Screpanti I, Gulino A and Di Marcotullio L. PCAF ubiquitin ligase activity inhibits Hedgehog/Gli1 signaling in p53-dependent response to genotoxic stress. Cell Death Differ 2013; 20: 1688-1697.