PCAF Modulates PTEN Activity**

The PTEN protein has a single catalytic domain possessing both lipid phosphoinositol and protein phosphatase activities. The lipid phosphoinositol phosphatase activity is essential for PTEN to block the cell cycle in the G1 phase and thereby to suppress tumor formation and progression (Cantley, L. C., and Neel, B. G. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 4240 – 4245), although the mechanisms governing PTEN activity under normal and neoplastic growth conditions remain unclear. Here, we report that PTEN interacts physically and functionally with PCAF, a histone acetyltransferase that regulates gene transcription through interaction with p300/CBP and various sequence-specific transcription factors (Nakatani, Y. (2001) Genes Cells 6, 79 – 86). Expression of PCAF results in increased acetylation of lysine residues (Lys^{125} and Lys^{128}) within the catalytic cleft of PTEN, a structure essential for phosphatidylinositol 3,4,5-trisphosphate specificity (Lee, J. O., Yang, H., Georgescu, M. M., Di Cristofano, A., Maehama, T., Shi, Y., Dixon, J. E., Pandolfi, P., and Pavletich, N. P. (1999) Cell 99, 323 – 334). The acetylation of PTEN caused by PCAF expression depends on the presence of growth factors. Reduction of endogenous PCAF activity using shRNA results in a loss of PTEN acetylation in response to growth factors and restores the ability of PTEN to down-regulate phosphatidylinositol 3-kinase signaling and to induce G_{1} cell cycle arrest. The retention of phosphatidylinositol 3-kinase/AKT signaling and cell cycle regulatory activities of acetylation-resistant PTEN K125R and K128R mutants in the presence of enforced PCAF expression suggest a causal relationship. Together, these findings indicate a mechanism of PTEN regulation that forges a link between distinct cancer-relevant pathways central to the control of growth factor signaling and gene expression.

The PTEN (phosphatase and tensin homolog deleted on chromosome 10) tumor suppressor gene is frequently mutated in diverse tumor types including those of endometrium, breast, prostate, lung, and brain (4). Germ line mutations of PTEN cause Cowden disease, an autosomal dominant hamartoma syndrome with an increased risk of developing tumors in a variety of tissues (4, 5). PTEN has been shown to play a crucial role in the regulation of cell migration, growth, and apoptosis (6 – 8). These functions are mediated by its lipid phosphatase activity, which is specific for the 3’ position of PI(3,4,5)P_{3} and phosphatidylinositol 3,4-bisphosphate (9), leading to inhibition of PI3-kinase signaling and subsequent inactivation of the Akt pathway. PTEN has also been shown to dephosphorylate tyrosine residues on FAK and Shc proteins (10).

The regulation of PTEN in normal and pathophysiological settings is an area of active investigation. Structurally, the PTEN protein consists of an amino-terminal phosphatase domain and a carboxyl-terminal domain, which is subdivided into C2, phosphorylation, and PDZ binding domains. The C2 domain lends itself to regulation of PTEN function by contributing to membrane localization, and the phosphorylation domain controls protein stability as governed by casein kinase II-directed phosphorylation (11 – 13). Given the constitutive nature of casein kinase II activity, other more tightly controlled mechanisms of regulation of PTEN function would be predicted. To address this issue, we searched for PTEN-interacting proteins by analyzing cellular protein complexes containing PTEN using tandem affinity purification coupled with mass spectrometry. One candidate was the histone acetyltransferase, PCAF (p300/CBP-associated factor), which associated with PTEN at endogenous levels in cells and whose expression caused acetylation of PTEN, inhibition of PTEN regulation of PI3K signaling, and inhibition of PTEN-regulated cell cycle arrest.

**EXPERIMENTAL PROCEDURES**

Cell Culture, Transfection, and Retrovirus Infection—HEK293T and Pten<sup>−/−</sup> MEFs were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% (v/v) fetal bovine serum at 37 °C with 5% CO_{2}. Cells were transfected by Lipofectamine 2000 (Invitrogen) following the manufacturer’s

---

* This work was supported in part by Scholar Awards for cancer research from the Kimmel Foundation and the V Foundation (to F. B. F.), Grant CA95616 from the National Cancer Institute (to W. K. C., R. M. B., F. B. F., and R. A. D.), and by a Fellow Award from the National Foundation for Cancer Research (to W. K. C.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

† This article was selected as a Paper of the Week.

‡ To whom correspondence should be addressed. Tel.: 858-534-7819; Fax: 858-534-7750; E-mail: fburnari@ucsd.edu.

---

The abbreviations used are: PI(3,4,5)P_{3}, phosphatidylinositol 3,4,5-trisphosphate; PI3K, phosphatidylinositol 3-kinase; MEF, mouse embryonic fibroblast; GFP, green fluorescent protein; MSCV, murine stem cell virus; HAT, histone acetyltransferase; shRNA, short hairpin RNA; EGF, epidermal growth factor.
recommended procedure. Pten−/− MEFs were infected with Pten- and PCAF-coding retroviruses produced in 293T cells. Various Pten mutants were constructed in enhanced GFP (EGFP) and MSCV vectors using PCR-based mutagenesis with Pfu Turbo DNA polymerase. Mammalian expression vectors for wild-type and mutant PCAF were described previously (14, 15).

**Antibodies and Immunoblotting Analysis**—Total Akt (#9272), phosphoserine-473 Akt (#9277), and anti-acetylated lysine (#9441) antibodies were purchased from Cell Signaling. Pten antibody (A2B1) was purchased from Santa Cruz Biotechnology, and PCAF polyclonal antibody was a kind gift from Dr. Yoshihiro Nakatani, Dana-Farber Cancer Institute.

**Immunoprecipitation**—293T cells were transfected with the appropriate combination of plasmids using Lipofectamine 2000 or treated with 50 ng/ml of EGF or 10% serum for the indicated time points, then harvested and extracted in lysis buffer containing 50 mM Tris-HCl (pH 7.5), 150 mM NaCl, 1 mM EDTA, and 0.5% Nonidet P-40. Lysates were cleared by centrifugation at 15,000 g for 20 min at 4 °C and analyzed by SDS-PAGE. For immunoprecipitation, lysates were incubated with anti-FLAG or anti-GFP antibody-conjugated beads (Sigma and Covance, respectively) for 4 h at 4 °C. The immunoprecipitates were washed four times with lysis buffer and then subjected to immunoblotting.

**Microscopy for Localization**—Images were acquired on a DeltaVision deconvolution microscope (Applied Precision) equipped with a Coolsnap CCD camera (Roper Scientific). 293T cells seeded on coverslips were transfected with the appropriate combination of plasmids and subsequently fixed with 0.4% paraformaldehyde in phosphate-buffered saline followed by microscopic analysis.

**In Vitro Acetylation Assay**—In vitro expressed GST-PCAF proteins (Upstate) were incubated for 1 h at 30 °C with 5 μg of GST, GST-Pten, and GST-PTEN K125R mutant in HAT assay buffer containing 50 mM Tris-HCl (pH 8.0), 50% glycerol, 0.5 mM dithiothreitol, and 0.1 mM [14C]acetyl-CoA or 0.2 mM acetyl-CoA. Completed reactions were subjected to autoradiography or used for PTEN phosphatase assay.

**Lipid Phosphatase Assay**—In vitro acetylated GST-PTEN and GST-PTEN K125R mutant proteins (300 ng) were assayed for lipid phosphatase activity against PI(3,4,5)P3 (Echelon Biosciences) essentially as described previously (16). Released phosphate was detected colometrically with Biomol green (Biomol Research Laboratories) and quantitated with a GeniosPro plate reader (Tecan).

**Suppression of PCAF Expression by shRNA**—Three shRNA plasmids for PCAF-directed knockdown were constructed in the pSuper vector and contained the following sequences:
Cell Cycle Analysis—Pten−/− MEFs were infected with Ectropic virus containing MSCV-hyg-PTEN and pBabe-PCAF and selected with hygromycin and puromycin, respectively. Cells were washed once with phosphate-buffered saline, fixed in 70% ethanol, stained with propidium iodide (25 μg/ml) (Sigma), and incubated for 30 min at 37 °C with RNase A (20 μg/ml). The DNA content of the cells was then evaluated by flow cytometry (FACSort, Becton Dickinson). Linear red fluorescence (FL2) was analyzed.

RESULTS

PTEN and PCAF Interact in Vivo—To identify PTEN interacting proteins, tandem affinity purification coupled with mass spectrometry was used to isolate and analyze PTEN-containing complexes. FLAG-hemagglutinin-NH2-terminal-tagged PTEN was expressed in 293T cells and purified by successive FLAG and hemagglutinin immunoprecipitations. Subsequently PTEN-associated proteins were analyzed by mass spectrometry, resulting in the identification of the histone acetyltransferase, PCAF, as a member of the complexes. The validity of the candidacy of PCAF was also suggested by a yeast two-hybrid screen of human and mouse cDNA libraries with the carboxyl-terminal region of PTEN (amino acids 186–401) that encompasses the regulatory phosphorylation domain. One candidate cDNA recovered, KIAA1343, exhibits structural similarity to the transcriptional adapter protein, hADA2, a molecule associated with PCAF in vivo (17, 18).

PTEN Acetylation and Enzymatic Function

CAGACTCCTGGGAATAGTA, ACCTGTGGTTGAAGGC-TCT, and TTGCGCTTTTCTTACGGCG. These constructs were mixed and transfected into 293T cells with Lipofectamine 2000.

FIGURE 3. The NH2-terminal region of PTEN is acetylated in vivo. a, 293T cell lysates were precipitated with anti-PTEN or control IgG antibody followed by immunoblotting for acetylated PTEN with anti-acetyl-lysine antibody. b, lysates treated with the histone deacetylase inhibitor, trichostatin A (TSA), were immunoprecipitated with anti-acetyl-lysine antibody or mouse IgG followed by anti-PTEN immunoblotting. c, lysates of 293T cells cotransfected with GFP-PTEN or GFP-PTEN186C and wild-type or HAT domain mutant PCAF constructs (Δ579–608 and Δ609–624) were precipitated with anti-GFP, and acetylated GFP-PTEN was detected by anti-acetyl-lysine immunoblotting. The filter was reprobed with anti-GFP to determine immunoprecipitation efficiency.

FIGURE 4. PCAF mediates acetylation of PTEN lysines 125 and 128. a, evolutionarily conserved NH2-terminal PTEN lysines are shown in red. Lys125 has been found mutated in glioblastoma (34). Lys125 and Lys128 are located in the catalytic core domain. b, 293T cell lysates cotransfected with various PTEN constructs mutated at conserved lysines and with PCAF or empty vector were immunoprecipitated with anti-PTEN antibody followed by anti-acetyl-lysine immunoblotting. Efficiency of PTEN immunoprecipitation was assessed by reprobing with anti-PTEN. c, wild-type PTEN or acetylation mimicking glutamine mutant (125/8Q) fusion proteins were reacted with recombinant PCAF and [14C]acetyl-CoA followed by autoradiographic detection of acetylated PTEN. Equal amounts of reacted GST-PTEN were verified by Coomassie staining of the membrane (lower panel). d, GST-PTEN or -K125R mutant was reacted with recombinant PCAF followed by assessment of PTEN 3'-phosphoinositol phosphatase activity using PI(3,4,5)P3 as a substrate. WT, wild-type.
PTEN Acetylation Increases in Response to PCAF—we next determined whether the expression of PCAF results in the acetylation of PTEN. First, endogenous PTEN was immunoprecipitated and then immunoblotted with an anti-acetyl-lysine antibody, revealing that PTEN is acetylated at steady state (Fig. 3a). Correspondingly, immunoblotting detected PTEN in anti-acetyl-lysine immunoprecipitates (Fig. 3b). Furthermore, the acetylation level of endogenous PTEN increased upon exposure of cells to tricostatin A, an inhibitor of Class 1 and 2 HDACs (20) (Fig. 3b), leading us to conclude that the acetylation of PTEN in vivo is a dynamic process. We then tested whether PCAF expression affects the level of PTEN acetylation. Enforced PCAF expression resulted in enhanced acetylation of wild-type PTEN (Fig. 3c) but not the PTEN 186C truncation mutant, a finding consistent with the possibility that one or more of the lysine residues from positions 1–186 were acetylated in response to PCAF expression.

Acetylation of PTEN Lysines 125 and 128 in Response to PCAF Regulates Enzymatic Activity—An interspecies comparison of PTEN amino acid sequences shows that lysine residues 125 and 128 are evolutionarily conserved (with the exception of the substitution of arginine for lysine at the first position in Saccharomyces cerevisiae) (Fig. 4a). To determine whether these lysine residues were the targets of acetylation caused by PCAF expression, we constructed mutant PTEN alleles in which non-acetylatable arginines were substituted for lysines 125 and 128 (K125R, K128R, and K125R/8R). A K80R allele was also generated since mutation at this position has been found in a human glioblastoma tumor (5) and a K144R allele, which is not evolutionarily conserved, was constructed to serve as a potential negative control. When coexpressed with PCAF, the K125R and K128R alleles of PTEN exhibited reduced acetylation, as compared with wild-type or other arginine substitution mutants of PTEN (Fig. 4b). That these modifications can be directly mediated by PCAF was demonstrated by showing that PCAF directly acetylated PTEN, but not a K125/8Q mutant, in an in vitro acetylation assay (Fig. 4c). These data indicate that lysines 125 and 128 of PTEN are preferentially acetylated by PCAF; it is also possible that other lysine residues are sequentially modified by PCAF following the initial acetylation of Lys125 and Lys128.

PCAF has an established role in regulating gene transcription by acetylating histones and various transcription factors, including p53 (2). Of relevance to this report is the observation that PCAF-related histone acetyltransferases, such as p300/CBP, have also been shown to modify and regulate the function of cytosolic proteins such as importin-α7 (21). These observations led us to conduct a series of experiments designed to assess the biochemical and functional impact of acetylation on PTEN activity. Since PCAF caused the acetylation of two lysine residues within the catalytic site of PTEN, we postulated that PCAF might alter the lipid phosphatase activity of PTEN that is responsible for regulating the activation of Akt. Consistent with this idea, an in vitro lipid phosphatase assay showed that PCAF inhibited 45% of PTEN activity but only 19% of acetylresistant K125R activity (Fig. 4d).
Akt Activation Is Regulated by PTEN Acetylation in Response to PCAF—When PCAF was coexpressed with wild-type PTEN in 293T cells, we observed a marked increase in Akt phosphorylation (Fig. 5a). This allowed an assessment of the ability of various PTEN mutants to modulate the phosphorylation levels of endogenous Akt in cells grown under conditions of growth factor exposure (Fig. 5, b and c). Consistent with results described above, expression of wild-type PTEN and the K125R and K128R mutants led to a decrease in the level of phosphorylated Akt in 293T cells and in Pten−/− MEFs, while other PTEN mutants were compromised for this activity (Fig. 5, b and c). Neither the K125/128Q mutant, which mimics acetylated PTEN, nor PCAF alone were able to decrease phospho-Akt levels (Fig. 5, b and c). Taken together, these results indicate that PCAF-mediated acetylation of PTEN inhibits its activity in the regulation of the PI3K/AKT pathway.

The Ability of PTEN to Regulate G1 Arrest Is Dependent on PCAF—PTEN inhibition of Akt activation has been reported to elicit cell cycle arrest (8) and to modulate cellular responses to growth factor stimulation (9). This led us to test whether PCAF could inhibit these PTEN-mediated activities. First, wild-type PTEN or the K125R and K128R mutants were expressed in Pten−/− MEFs in the absence of PCAF (Fig. 6). Each resulted in similar G1 cell cycle arrests (78.0, 73.9, and 70.0% G1, respectively, compared with 56.2% G1 for empty vector-infected cells). Alleviation of G1 arrest occurred when PCAF was coexpressed with wild-type PTEN (54.3% G1). This relief of the arrest was not observed when PCAF was coexpressed with the acetylation-resistant, lipid phosphatase-competent PTEN mutants, K125R and K128R (Fig. 6; 73.5 and 73.9% G1, respectively). The double K125/128Q mutant, was unable to cause a G1 arrest (54.9% and 59.4% G1, respectively).

Growth Factor-driven Cellular Akt Activation Is Modulated by the Presence of PTEN and PCAF—We then analyzed PTEN acetylation status when 293T cells were treated with serum or EGF (Fig. 7a). PTEN acetylation and its interaction with PCAF were enhanced with serum and growth factor treatment. Correspondingly, when PCAF is reduced by shRNA knockdown, PTEN is poorly acetylated (Fig. 7b). Moreover, this diminution...
of acetylation corresponds to an increased ability of PTEN to down-regulate PI3K signaling, as reflected by a reduction in Akt phosphorylation (Fig. 7c). These data indicate that PTEN function is inhibited when it is acetylated by PCAF and that this promotes G1/S transition through activation of the PI3K pathway.

**DISCUSSION**

The results presented here are consistent with PCAF-mediated acetylation providing regulated inactivation of PTEN catalytic activity. One possible mechanism for this is that modification of lysine residues within the catalytic pocket may interfere with substrate binding. However, Lys125 and Lys128 are located in the flexible catalytic domain P-loop structure (3), which suggests that the addition of small acetyl groups would not physically impede interaction with substrate. Alternatively, acetylation of these lysine residues might cause the loss of a positive charge in the catalytic cleft known to be required for selectivity of the negatively charged PI(3,4,5)P3 substrate, as well as its orientation within the cleft (3).

It is interesting to note that the yeast two hybrid screen identified KIAA1343 as a PTEN-interacting partner. This raises the possibility that it might act as a bridge between PTEN and PCAF and that its modulation might affect that interaction. While this has not been directly tested, KIAA1343 did not appear in the tandem affinity purification/mass spectrometry complexes. Moreover, 293T cells express very little KIAA1343 and they are responsive to manipulations of the PTEN and PCAF interaction. Whether this points the way toward cell type specificity of the complexes, or was the fortunate consequence of the presence in the yeast two hybrid assay of the endogenous PCAF homolog, GCN5, is an area requiring investigation.

Phosphorylation of p300/CBP by cyclin E/cdk2 has been shown to stimulate its HAT activity at the G1/S boundary (22). It is possible that PCAF may be similarly activated by cell cycle responses to extracellular cues, such as growth factor signaling, and then it in turn regulates PTEN activity by acetylation. This is consistent with our observations that PCAF knockdown reduced phospho-Akt levels when cells were stimulated with growth factor or serum, and that PCAF decreases the percent of cells in the G1 phase in PTEN-reconstituted Pten−/− MEFs. Recent investigations have shown that nuclear-localized PTEN coincides with G0-G1 phases of the cell cycle, while cytosolic-localized PTEN is responsible for regulating apoptosis (23–25). Our results extend these observations and suggest that PCAF-mediated acetylation of nuclear PTEN, as initiated by growth stimulation, results in the attenuation of PTEN phosphatase activity and promotion of cell cycle progression.

It has been reported that expression of HATs, including PCAF, correlates with cell transformation as the expression of PCAF is up-regulated in c-Myc-transduced endothelial cells (26) and GCN5L2, which belongs to the PCAF family of HATs, is overexpressed in H-RAS-transformed fibroblasts (27). High levels of p300/CBP protein in clinical biopsies of prostate cancer correlate with large tumor size and forced reduction of p300 expression in prostate cancer cell lines results in reduced proliferation (28). Mutation of CBP and other HATs can occur in various genetic diseases (29–31) and primary tumors (32), although PCAF has not been found to be mutated during astrocytic tumor progression (33). Another possibility is that mutations causing an increase in PCAF protein expression or activity occur in cancers with less frequently occurring incidences of PTEN mutation. Alternatively, mutation of other histone acetylases that function together with PCAF may contribute to PCAF-dependent pathology. For example, chromosomal translocation of p300 and CBP has been shown to cause hematological malignancies due to defects in cell cycle progression and apoptosis (32).

Thus, regulation of enzymatic activity by acetylation may be a novel and dynamic mechanism for regulating cellular proliferation. Here, we describe an instance in support of this notion by demonstrating inhibition of the lipid phosphatase activity of the PTEN tumor suppressor by PCAF, through specific acetylation of evolutionarily conserved, catalytic domain lysine residues required for selectivity, and engagement of PI(3,4,5)P3.

**REFERENCES**

1. Cantley, L. C., and Neel, B. G. (1999) Proc. Natl. Acad. Sci. U. S. A. 96, 4240–4245
2. Nakatani, Y. (2001) Genes Cells 6, 79–86
3. Lee, J. O., Yang, H., Georgescu, M. M., Di Cristofano, A., Maehama, T., Shi, Y., Dixon, J. E., Pandolli, P., and Pavletich, N. P. (1999) Cell 99, 323–334
4. Steck, P. A., Pershouse, M. A., Jasser, S. A., Yung, W. K., Lin, H., Ligon, A. H., Langford, L. A., Baumgard, M. L., Hattier, T., Davis, T., Frye, C., Hu, R., Swedlund, B., Teng, D. H., and Tavtigian, S. V. (1997) Nat. Genet. 15, 356–362
5. Eng, C. (2003) Hum. Mutat. 22, 183–198
6. Tamura, M., Gu, J., Matsumoto, K., Aota, S., Parsons, R., and Yamada, K. M. (1998) Science 280, 1614–1617
7. Furnari, F. B., Lin, H., Huang, H. S., and Caveness, W. K. (1997) Proc. Natl. Acad. Sci. U. S. A. 94, 12479–12484
8. Furnari, F. B., Huang, H. J., and Caveness, W. K. (1998) Cancer Res. 58, 5002–5008
9. Maehama, T., and Dixon, J. E. (1999) Trends Cell Biol. 9, 125–128
10. Larsen, M., Tremblay, M. L., and Yamada, K. M. (2003) Nat. Rev. Mol. Cell. Biol. 4, 700–711
11. Maehama, T., Taylor, G. S., and Dixon, J. E. (2001) Annu. Rev. Biochem. 70, 247–279
12. Vazquez, F., Ramaswamy, S., Nakamura, N., and Sellers, W. R. (2000) Mol. Cell. Biol. 20, 5010–5018
13. Torres, J., Rodriguez, J., Myers, M. P., Valiente, M., Graves, J. D., Tonks, N. K., and Pulido, R. (2003) J. Biol. Chem. 278, 30652–30660
14. Yang, X. J., Ogryzko, V. V., Nishikawa, J., Howard, B. H., and Nakatani, Y. (1996) Nature 382, 319–324
15. Puri, P. L., Sartorelli, V., Yang, X. J., Hamamori, Y., Ogryzko, V. V., Howard, B. H., Kedes, L., Wang, J. Y., Graessmann, A., Nakatani, Y., and Leverero, M. (1997) Mol. Cell 1, 35–45
16. Maehama, T., Taylor, G. S., Slama, J. T., and Dixon, J. E. (2000) Anal. Biochem. 279, 248–250
17. Ogryzko, V. V., Kotani, T., Zhang, X., Schiltz, R. L., Howard, T., Yang, X. J., Howard, B. H., Qin, J., and Nakatani, Y. (1998) Cell 94, 35–44
18. Yamagoe, S., Kanno, T., Kanno, Y., Sasaki, S., Siegel, R. M., Lenardo, M. J., Humphrey, G., Wang, Y., Nakatani, Y., Howard, B. H., and Ozato, K.
PTEN Acetylation and Enzymatic Function

(2003) Mol. Cell. Biol. 23, 1025–1033
19. Lachyankar, M. B., Sultana, N., Schonhoff, C. M., Mitra, P., Poluha, W., Lambert, S., Quesenberry, P. J., Litofsky, N. S., Recht, L. D., Nabi, R., Miller, S. J., Ohta, S., Neel, B. G., and Ross, A. H. (2000) J. Neurosci. 20, 1404–1413
20. Brunet, A., Sweeney, L. B., Sturgill, J. F., Chua, K. F., Greer, P. L., Lin, Y., Tran, H., Ross, S. E., Mostoslavsky, R., Cohen, H. Y., Hu, L. S., Cheng, H. L., Jedrychowski, M. P., Gygi, S. P., Sinclair, D. A., Alt, F. W., and Greenberg, M. E. (2004) Science 303, 2011–2015
21. Bannister, A. J., Miska, E. A., Gorlich, D., and Kouzarides, T. (2000) Curr. Biol. 10, 467–470
22. Ait-Si-Ali, S., Ramirez, S., Barre, F. X., Dhkissi, F., Magnaghi-Jaulin, L., Girault, J. A., Robin, P., Knibiehler, M., Pritchard, L. L., Ducommun, B., Trouche, D., and Harel-Bellan, A. (1998) Nature 396, 184–186
23. Chung, J. H., and Eng, C. (2005) Cancer Res. 65, 8096–8100
24. Chung, J. H., Ginn-Pease, M. E., and Eng, C. (2005) Cancer Res. 65, 4108–4116
25. Liu, J. L., Sheng, X., Hortobagyi, Z. K., Mao, Z., Gallick, G. E., and Yung, W. K. (2005) Mol. Cell. Biol. 25, 6211–6224
26. Menssen, A., and Hermeking, H. (2002) Proc. Natl. Acad. Sci. U. S. A. 99, 6274–6279
27. Zuber, J., Tchernitsa, O. I., Hinzmann, B., Schmitz, A. C., Grips, M., Hellriegel, M., Sers, C., Rosenthal, A., and Schafer, R. (2000) Nat. Genet. 24, 144–152
28. Debes, J. D., Sebo, T. J., Lohse, C. M., Murphy, L. M., Haugen de, A. L., and Tindall, D. J. (2003) Cancer Res. 63, 7638–7640
29. Steffan, J. S., Bodai, L., Pallos, J., Poelmann, M., McCampbell, A., Apostol, B. L., Kazantsev, A., Schmidt, E., Zhu, Y. Z., Greenwald, M., Kurokawa, R., Housman, D. E., Jackson, G. R., Marsh, J. L., Thompson, L. M., Spasic-Boskovic, O., Gohler, H., Waner, E. E., and Bates, G. P. (2001) Nature 413, 739–743
30. Petrij, F., Giles, R. H., Dauwerse, H. G., Saris, J. J., Hennekam, R. C., Masuno, M., Tommerup, N., van Omnen, G. J., Goodman, R. H., Peters, D. J., and Breuning, M. H. (1995) Nature 376, 348–351
31. Steffan, J. S., Kazantsev, A., Spasic-Boskovic, O., Greenwald, M., Zhu, Y. Z., Gohler, H., Wanker, E. E., Bates, G. P., Housman, D. E., and Thompson, L. M. (2000) Proc. Natl. Acad. Sci. U. S. A. 97, 6763–6768
32. Guyther, S. A., Batley, S. J., Linger, L., Bannister, A., Thorpe, K., Chin, S. F., Daigo, Y., Russell, P., Wilson, A., Sowter, H. M., Delhanty, J. D., Ponder, B. A., Kouzarides, T., and Caldas, C. (2000) Nat. Genet. 24, 300–303
33. Nishimori, H., Nishikawa, R., Fujimaki, T., Nakagomi, T., Matsutani, M., Huang, H. J., and Cavenee, W. K. (2001) J. Neurooncol. 46, 17–22
34. Bonneau, D., and Longy, M. (2000) Hum. Mutat. 16, 109–122