Published OnlineFirst June 8, 2010; DOI: 10.1158/1541-7786.MCR-09-0458

Molecular Cancer Research

Enhanced Expression of PCAF Endows Apoptosis Resistance in Cisplatin-Resistant Cells

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Abstract

Histone acetyltransferase (HAT) regulates transcription. We have previously shown that two HAT genes, *Clock* and *Tip60*, are overexpressed, and upregulate glutathione biosynthesis and the expression of DNA repair genes in cisplatin-resistant cells. To better understand the mechanism of HAT-related drug resistance, we investigated the role of another HAT gene, *p300/CBP-associated factor* (*PCAF*), and found that *PCAF* was also overexpressed in cisplatin-resistant cells and endowed an antiapoptotic phenotype through enhanced E2F1 expression. PCAF-overexpressing cells showed enhanced expression of E2F1 and conferred cell resistance to chemotherapeutic agents. Downregulation of PCAF decreased E2F1 expression and sensitized cells to chemotherapeutic agents. Moreover, knockdown of PCAF induced G_1 arrest and apoptosis. These results suggest that PCAF is one of pleiotropic factors for drug resistance and seems to be critical for cancer cell growth. *Mol Cancer Res; 8(6); 864–72. ©2010 AACR.*

Introduction

Drug and apoptosis resistance are two sides of the same coin. The treatment of cancer cells with chemotherapeutic agents might activate signal transduction pathways and modulate the expression of genes that are involved in antiapoptotic or apoptotic functions. However, the molecular mechanisms of apoptosis resistance have not been studied in cisplatin-resistant cells. We have extensively studied mechanisms involved in cisplatin resistance (1, 2). Several mechanisms are involved in the acquisition of cisplatin resistance (3), which include reduced drug accumulation (4, 5), increased production of cellular thiol (6, 7) and augmented DNA repair activity (8, 9). We have recently reported that two histone acetyltransferases (HAT), Clock and Tip60, are overexpressed in cisplatin-resistant cells (10, 11). Clock regulates glutathione biosynthesis by activating ATF4 and induces multidrug resistance (10). Tip60 is a Clock target gene and modulates the expression of DNA repair genes (11). Thus, these HATs are directly involved in drug resistance. To better understand the mechanism of HAT-dependent drug resistance, we focused on another HAT gene, *p300/CBP-associated factor* (*PCAF*).

PCAF is a transcription cofactor with intrinsic HAT activity (12). In addition to acetylating histones, PCAF can interact with and acetylate many other proteins involved in transcription. It has been reported that PCAF has a dual function in cell viability. PCAF induced cell cycle arrest and/or apoptosis by regulating the function of tumor suppressor p53 (13) and apoptosis mediators p73 (14) and Bax (15). Interestingly, a transcriptional factor, E2F1, is acetylated and stabilized by PCAF in response to DNA damage (16). Therefore, we investigated the expression of E2F1 as an important mediator of PCAF-regulating cell viability or apoptosis resistance and observed the overexpression of E2F1 in cisplatin-resistant cells. To our knowledge, this is the first report of the involvement of PCAF/E2F1 pathway in drug resistance.

Materials and Methods

Cell culture

Human prostate cancer PC3, epidermoid cancer HeLa, and bladder cancer T24 cells were cultured in Eagle's MEM. Human lung cancer A549 cells were cultured in RPMI 1640. Media were purchased from Nissui Seiyaku and contained 10% fetal bovine serum. The cisplatin-resistant P/CDP6 and HeLa/CP4 cells were derived from PC3 and HeLa cells, as previously described (17), and were 63- and 23-fold, respectively, more resistant to cisplatin than their parental cells (18). All cell lines were maintained in a 5% CO_2 atmosphere at 37°C.

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doi: 10.1158/1541-7786.MCR-09-0458

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Antibodies and drugs

Antibodies against PCAF, E2F1, Survivin, and HAT1 were purchased from Santa Cruz Biotechnology. Antibodies against caspase-3, cleaved caspase-3, caspase-7, cleaved caspase-7, and cleaved poly ADP ribose polymerase were purchased from Cell Signaling Technology. Antibodies against SirT1 were purchased from Epitomics. Anti-p73α antibody was purchased from Wako Pure Chemical Industries, Ltd. Anti–β-actin antibody was purchased from Sigma. Cisplatin and 5-fluorouracil were purchased from Sigma. Adriamycin was a kind gift from Kyowa Hakko Kogyo Co., Ltd. Oxaliplatin and 7-ethyl- 10-hydroxycamptothecin (SN-38) were kind gifts from Yakult Co. Ltd. H_2O_2 was purchased from Nacalai Tesque.

Plasmid construction

To obtain the full-length complementary DNA (cDNA) for human PCAF, PCR was carried out on a SuperScript cDNA library (Invitrogen) using the following primer pairs (single underlining indicates the start codon and stop codon): ATGTCCGAGGCTGGCGGGGC and TCACTTGTCAATTAATCCAGCTTCC for PCAF. This PCR product was cloned into the pGEM-T easy vector (Promega). To construct a plasmid expressing hemagglutinin (HA)-tagged PCAF, NH_2-terminal HA-tagged PCAF cDNA was ligated into a pcDNA3.1 vector (Invitrogen).

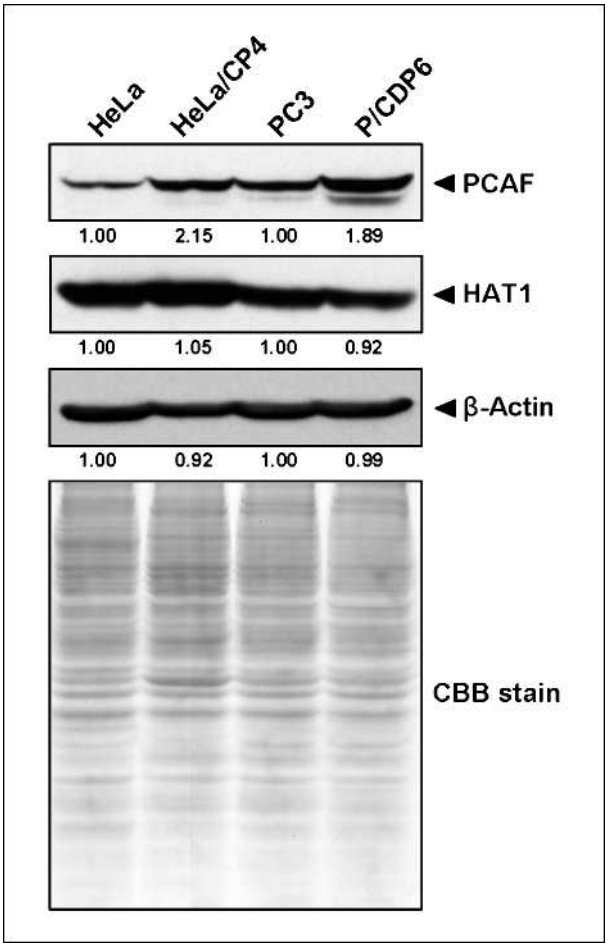

FIGURE 1. Cellular expression of PCAF in cisplatin-resistant cell lines. Whole-cell lysates (100 μg) of cisplatin-resistant cell lines (HeLa/CP4 or P/CDP6) or parent cell lines (HeLa or PC3) were subjected to SDS-PAGE, and Western blotting was done using the indicated antibodies. Immunoblotting of β-actin is shown as a loading control. The relative intensity is shown under each blot. Gel staining with Coomassie Brilliant Blue (CBB) is also shown.

Cloning of stable transfectants

The cloning of stable transfectant was done as previously described (19). Briefly, PC3 cells were transfected with pcDNA3.1-HA PCAF with Superfect reagent and cultured with 500 μg/mL hygromycin for 15 to 20 days. The resulting colonies were isolated, and the cellular expression level of HA-PCAF in each clone was investigated by Western blotting with the anti-HA antibody.

Western blotting

Whole-cell lysates were prepared as previously described (10, 20). The indicated amounts of whole-cell lysates or nuclear extract were separated by SDS-PAGE and transferred to polyvinylidene difluoride microporous membranes (Millipore) using a semidry blotter. The blotted membranes were treated with 5% (w/v) skimmed milk in 10 mmol/L Tris, 150 mmol/L NaCl, and 0.2% (v/v) Tween 20, and incubated for 1 hour at room temperature with the primary antibody. The antibodies and dilutions used were as follows: 1:1,000 dilution of anti-PCAF, 1:5,000 dilution of anti-HAT1, 1:1,000 dilution of anti–caspase-3, 1:1,000 dilution of anti–cleaved caspase-3, 1:1,000 dilution of anti–caspase-7, 1:1,000 dilution of anti–cleaved caspase-7, 1:1,000 dilution of anti–cleaved poly ADP ribose polymerase, 1:1,000 dilution of anti-E2F1, 1:1,000 dilution of anti-Survivin, 1:5,000 dilution of anti-SirT1, 1:1,000 dilution of anti-p73α, 1:5,000 dilution of anti-HA, and 1:5,000 dilution of anti–β-actin. The membranes were then incubated for 45 minutes at room temperature with a peroxidase-conjugated secondary antibody, visualized using an enhanced chemiluminescence kit (GE Healthcare Bio-Science), and the images were obtained by image analyzer (LAS-4000 mini, Fujifilm, Tokyo, Japan).

Knockdown analysis using small interfering RNAs

The following double-stranded RNA 25-bp oligonucleotides were commercially generated as follows (Invitrogen): 5′-UUUCCAAAGAGCCUUCAACCACAGG-3′ (sense) and 5′-CCUGUGGUUGAAGGCUCUUUGGAAA-3′ (antisense); PCAF small interfering RNA (siRNA) #1, 5′-UUUAGCUCACAUCCCAUUAAAGUGG-3′ (sense) and 5′-CCACUUUAAUGGGAUGUGAGCUAAA-3′ (antisense); PCAF siRNA #2, 5′-AUAUCCUGGAGCUUCUGUUCUCUUC-3′ (sense) and 5′-GAAGAGAACAGAAGCUCCAGGAUAU-3′ (antisense); PCAF siRNA #3, 5′-AAAGUUCUCCGAAGAGUCCACGGCU-3′ (sense) and 5′-AGCCGUGGACUCUUCGGAGAACUUU-3′ (antisense); E2F1 siRNA. Transfection of siRNA was done as

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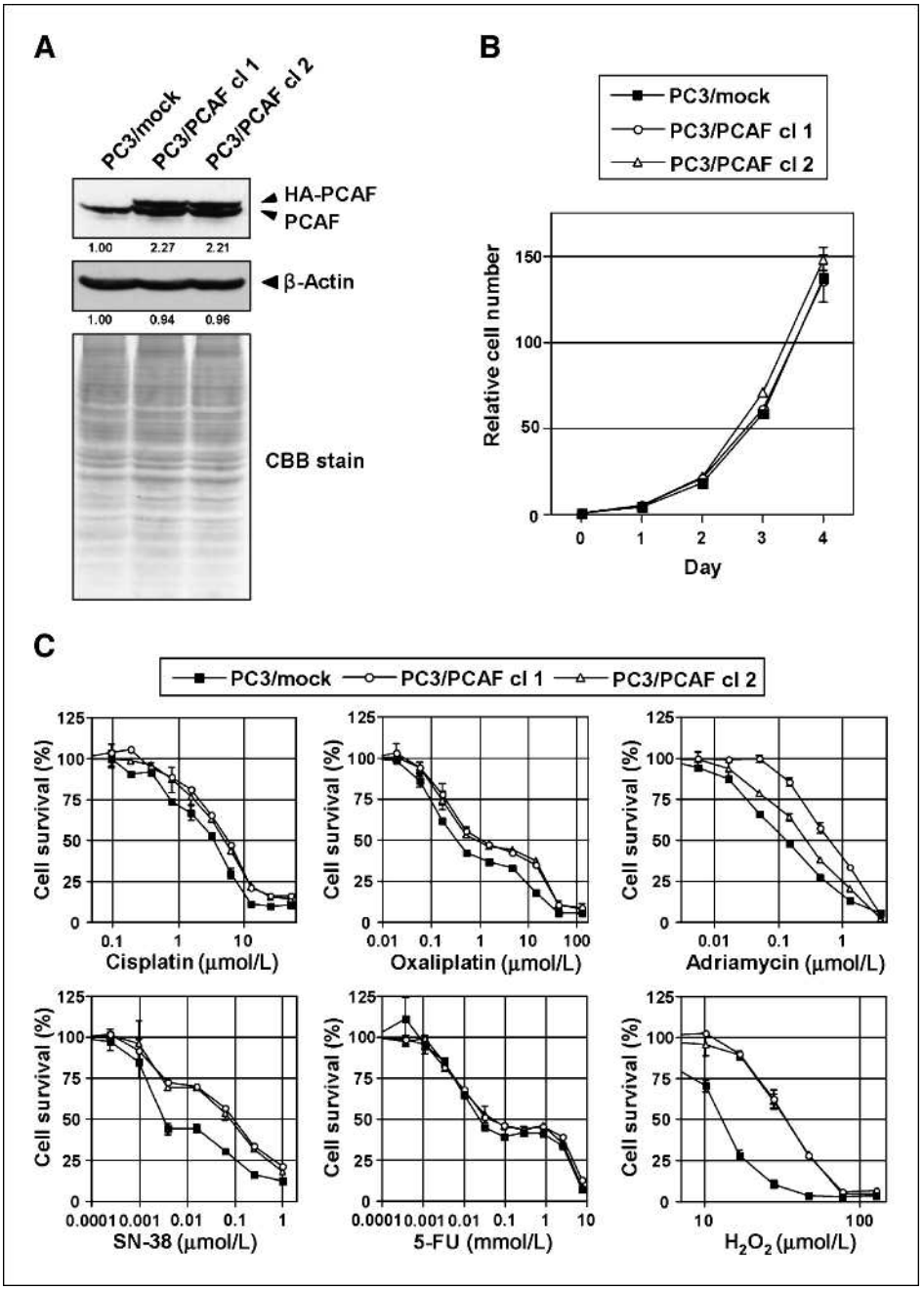

FIGURE 2. PCAF overexpression induces multidrug resistance. A, whole-cell lysates (100 μg) of PCAF-overexpressing cell lines (PC3/PCAF cl 1 and cl 2) or a control cell line (PC3/mock) were subjected to SDS-PAGE, and Western blotting was done using the indicated antibodies. Immunoblotting of β-actin is shown as a loading control. The relative intensity is shown under each blot. Gel staining with CBB is also shown. B, PC3, PC3/PCAF cl 1, or cl 2 cells (2.0×10^4 cells) were seeded onto 12-well plates and were counted daily. The cell number on day 0 corresponded to 1. Points, mean of at least three independent experiments; bars, SD. C, 1.0×10^3 PCAF-overexpressing cell lines or a control cell line were seeded onto 96-well plates. The next day, the indicated concentrations of the drugs were applied. After 48 h, cell survival was analyzed with a WST-8 assay. Cell survival in the absence of drugs corresponded to 100%. Points, mean of at least three independent experiments; bars, SD.

previously described (10, 20). Briefly, 250 pmol of siRNA and 5 μL of lipofectamine mixture were combined with 3.0×10^5 PC3 cells in 500 μL of culture medium and incubated for 20 minutes at room temperature. All cells were seeded into 35-mm dishes containing 2 mL culture medium and were harvested after culture for 72 hours for Western blotting, as described above. PC3 cells (1.0×10^3) were used in the WST-8 assay; 1.0 to 4.0×10^2 PC3 cells were used in colony formation assay; and 2.0×10^4 PC3, A549, or T24 cells were used in the cell proliferation assay as described below.

Cytotoxicity analysis

For the water-soluble tetrazolium salt (WST-8) assay, 1.0×10^3 PC3/mock, PC3/PCAF cl 1, cl 2, or PC3 cells transfected with siRNA, as described above were seeded onto 96-well plates. The next day, the indicated concentrations of the drugs were applied. After 48 hours, the surviving cells were stained with TetraColor ONE (Seikagaku Corp.) for 1 to 2 hours at 37°C. The absorbance was then measured at 450 nm. For the colony formation assay, 1.0×10^2 PC3 cells transfected with control siRNA, 2.0×10^2 PC3 cells transfected with PCAF siRNA #1, or 4.0×10^2 PC3 cells

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transfected with PCAF siRNA #2, as described above were seeded onto 35-mm dishes with 2 mL of culture medium. The next day, the indicated concentrations of the drugs were applied. After 7 days, the number of colonies was counted.

Cell proliferation assay

PC3, A549, or T24 cells (2.0×10^4 cells) transfected with siRNA, as described above, were seeded onto 12-well plates. The cells were harvested with trypsin and counted daily with a Coulter-type cell size analyzer (CDA-500, Sysmex). PC3 cells (2.0×10^4 cells) transfected with the dilution series of siRNA, as described above, were counted on the second day.

Flow cytometry

PC3 cells (3.0×10^5) transfected with siRNA, as described above, were seeded onto six-well plates and cultured for 48 hours. The cells were harvested, washed twice with ice-cold PBS supplemented with 0.1% bovine serum albumin, and fixed in 70% ethanol. After washing twice with ice-cold PBS, the cells were resuspended in PBS with 0.1% bovine serum albumin, incubated with RNase (Sigma), and stained with propidium iodide (Sigma). The cells were analyzed using an EpicsXL-MCL flow cytometer (Beckman Coulter).

Statistical analysis

The protein expression levels were assessed numerically using a Multi Gauge Version 3.0 (Fujifilm, Tokyo, Japan). Pearson's correlation was used for statistical analysis, and significance was set at the 5% level.

Results

Enhanced expression of PCAF in cisplatin-resistant cells

We have previously shown that two HATs, Clock and Tip60, are overexpressed in cisplatin-resistant cells and are involved in drug resistance (10, 11). HATs are categorized into two families, MYST (MOZ, YBF2/SAS3, SAS2, and Tip60) and GNAT (Gcn5-related N-acetyltransferases). Clock and Tip60 are both members of the MYST family. Therefore, we investigated the expression of the GNAT family in cisplatin-resistant cells. As shown in Fig. 1, cellular PCAF, but not HAT1, was overexpressed

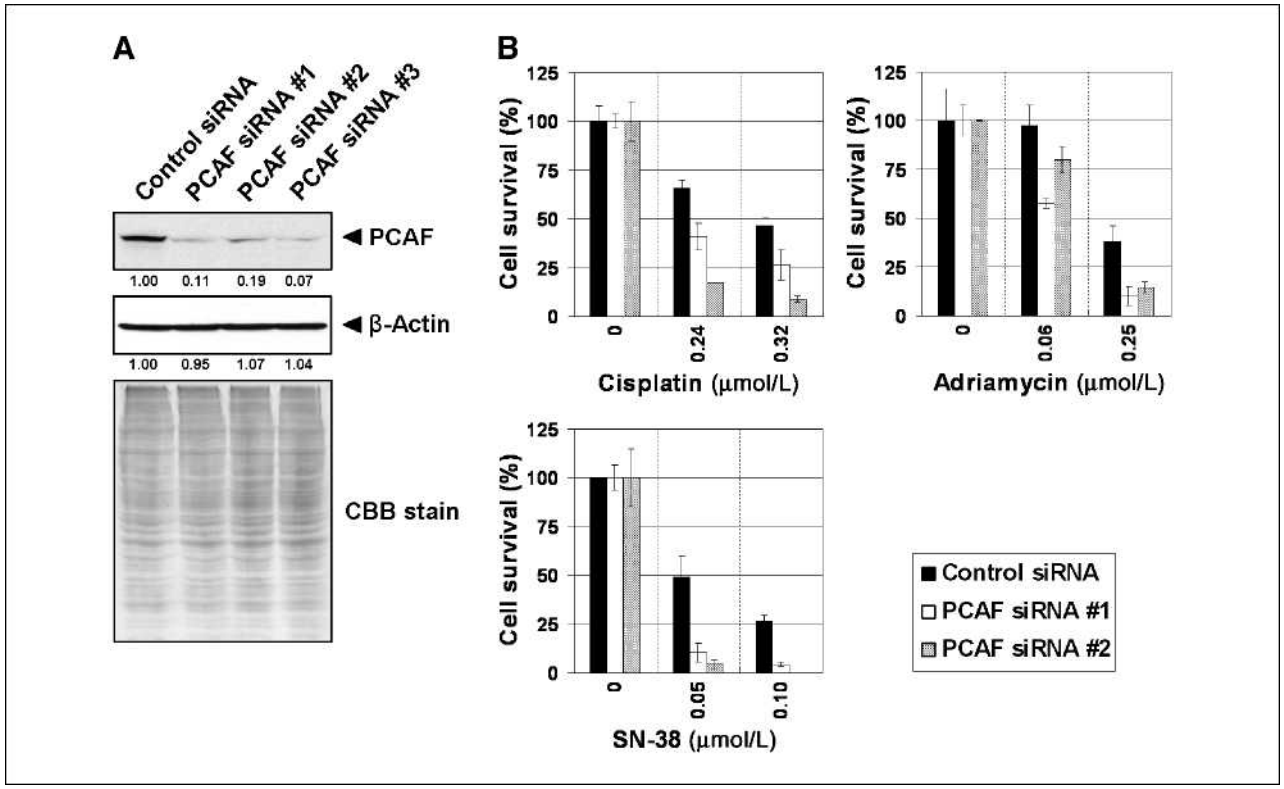

FIGURE 3. Downregulation of PCAF sensitized cells to chemotherapeutic agents. A, PC3 cells were transiently transfected with 250 pmol of control siRNA, or PCAF siRNA #1, #2, or #3. After 48 h, whole-cell lysates (100 μg) were subjected to SDS-PAGE, and Western blotting was done using the indicated antibodies. Immunoblotting of β-actin is shown as a loading control. The relative intensity is shown under each blot. Gel staining with CBB is also shown. B, PC3 cells transfected with control siRNA, or PCAF siRNA #1 or #2 were seeded onto 35-mm dishes. The next day, the indicated concentrations of the drugs were applied. After 7 d, the number of colonies was counted. Cell survival in the absence of drugs corresponded to 100%. Columns, mean of at least three independent experiments; bars, SD.

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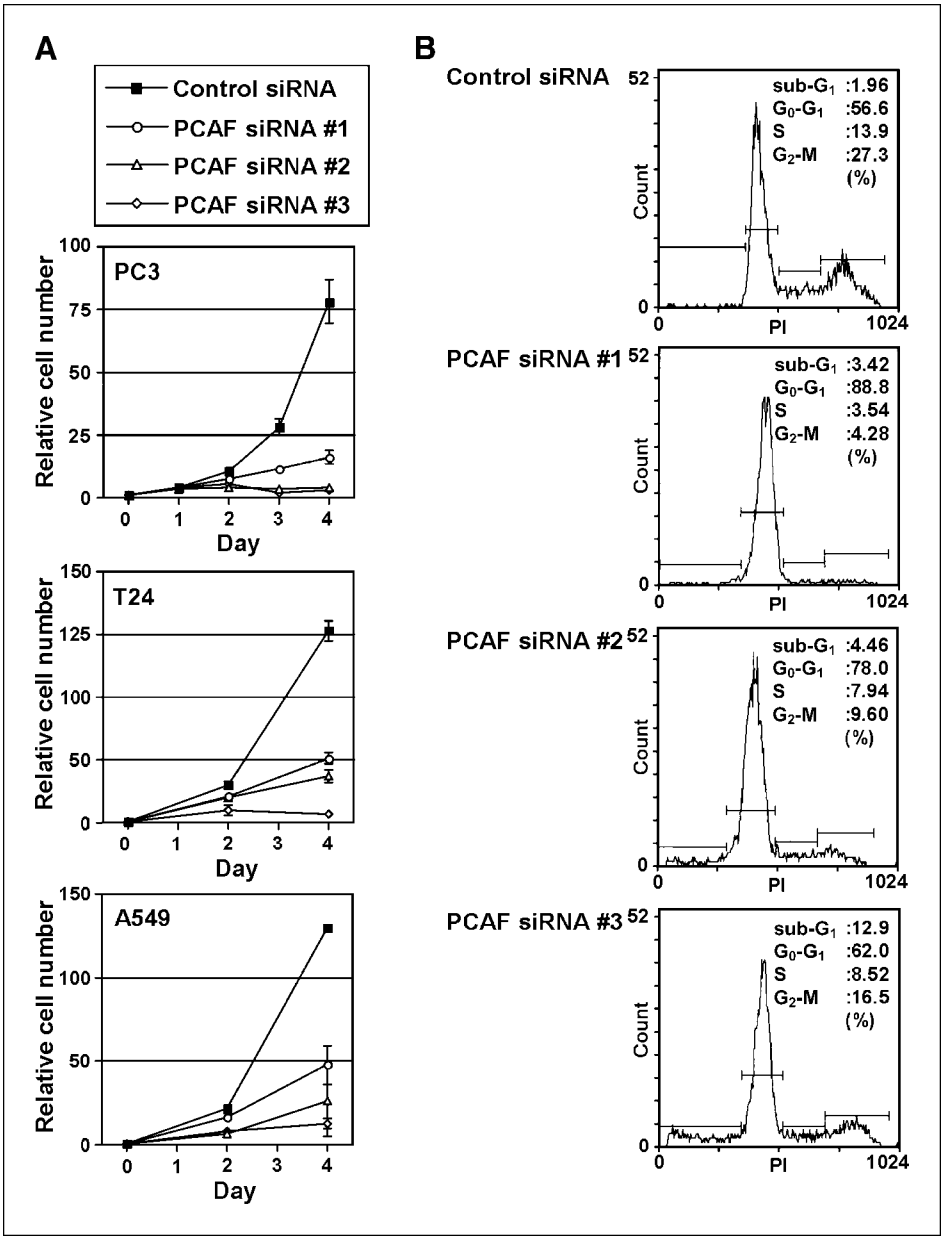

FIGURE 4. PCAF expression is indispensable for cancer growth. A, PC3, A549, or T24 cells, transfected with 250 pmol of control siRNA, or PCAF siRNA #1, #2, or #3 were seeded onto 24-well plates and counted daily or every 2 d. The cell number on day 0 corresponded to 1. Points, means of at least three independent experiments; bars, SD. B, PC3 cells were transfected as in A. After 48 h, the cells were stained with propidium iodide and analyzed by fluorescence-activated cell sorting. The cell cycle fraction is shown at the top right of each graph.

in two independent cisplatin-resistant cells, HeLa/CP4 and P/CDP6, in comparison with their parental cells.

PCAF-overexpressing cells showed multidrug resistance

To investigate whether PCAF expression is involved in drug resistance, we first established stable transfectants to overexpress PCAF in human prostate cancer PC3 cells. Two stable transfectants, PC3/PCAF cl 1 and cl 2, showed ~2.2-fold higher expression of PCAF than that of the vector-alone transfectant, PC3/mock (Fig. 2A). The growth rates of these cells were almost similar to PC3/mock (Fig. 2B). The PCAF-overexpressing cell lines showed increased resistance to cisplatin, oxaliplatin, Adriamycin, SN-38, and hydrogen peroxide (H_2O_2), but not to 5-fluorouracil (Fig. 2C). These results indicate that PCAF-overexpressing cell lines showed multidrug resistance or apoptosis resistance.

Downregulation of PCAF-sensitized cells to chemotherapeutic agents

To access whether PCAF is involved in the apoptosis-resistant phenotype, PCAF-knockdown cells were treated with anticancer agents and analyzed for cell death by the WST-8 assay. Unexpectedly, knockdown of PCAF expression did not decrease the survival rate (data not shown). One possible explanation is that knockdown of PCAF

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expression take a time to change cellular sensitivity to drugs. Then, colony formation assay was done. As shown in Fig. 3, downregulation of PCAF decreased survival rates of colonies against cisplatin, Adriamycin, and SN-38.

Induction of G_1 arrest and apoptosis by PCAF downregulation

Next, we analyzed the effect of PCAF downregulation on cell growth using p53-null PC3 cells, lung cancer A549 cells with wild-type p53, and bladder cancer T24 cells with mutant p53. As shown in Fig. 4A, knockdown of PCAF expression significantly induced cell growth retardation in these cell lines. Knockdown of PCAF expression also induced growth retardation of P/CDP6, HeLa, and HeLa/CP4 cells (data not shown). Furthermore, the cell cycle profile showed that knockdown of PCAF expression in PC3 cells induced either G_1 arrest or apoptosis (Fig. 4B). Both siRNA #1 and #2 mainly induced G_1 arrest, and siRNA #3 induced apoptosis. To confirm these results, we examined whether reducing PCAF expression can induce the activation or execution of apoptosis using siRNA #3. Knockdown of PCAF expression significantly activated and cleaved caspase-3 and caspase-7, and poly ADP ribose polymerase in PC3 cells (Fig. 5). Similar results were observed when HeLa cells were used (data not shown).

PCAF regulates E2F1 expression

It has been shown that PCAF is required for the stabilization and accumulation of E2F1 and is involved in E2F1-dependent apoptosis in response to DNA damage (16). Therefore, we analyzed E2F1 expression in cisplatin-resistant cells and PCAF-overexpressing cells. E2F1 expression was significantly upregulated in cisplatin-resistant cells (Fig. 6A). Moreover, stable transfectants overexpressing PCAF showed a 12-fold higher expression of E2F1 protein compared with control cells (Fig. 6B). Knockdown of PCAF expression also reduced the level of E2F1 protein (Figs. 5B and 6C). Similarly, an antiapoptotic gene, *Survivin*, was upregulated in cisplatin-resistant cells and PCAF-overexpressing cells, but a proapoptotic gene, *p73*, was not (Fig. 6A and B). The deacetylase SirT1, binds to E2F1 and inhibits the PCAF-E2F1-p73 apoptotic pathway (21, 22), and was upregulated in PCAF-overexpressing cells (Fig. 6B). To confirm our hypothesis that PCAF regulates antiapoptotic function in cancer via E2F1, we investigated whether E2F1 certainly involved in drug sensitivity. Downregulation of E2F1 sensitized cells to cisplatin, Adriamycin, and SN-38 (Fig. 7).

Discussion

In this study, we provide insight into the function of PCAF in drug resistance. Here, we found that PCAF expression was upregulated in cisplatin-resistant cells (Fig. 1). Interestingly, PCAF-overexpressing cells showed resistance not only to cisplatin but also to other chemotherapeutic agents, suggesting that PCAF overexpression is not specific to cisplatin-resistant cells (Fig. 2C). Furthermore, downregulation of PCAF sensitized cancer cells to chemotherapeutic agents (Fig. 3). To rule out the multidrug resistance phenotype, we investigated the expression of several ABC transporters. However, we did not observe enhanced expression of the ABC transporters in PCAF-overexpressing cells (data not shown). To understand the molecular mechanism of PCAF-dependent apoptosis resistance, we investigated genes related to tumor cell survival in cisplatin-resistant cells and PCAF-overexpressing cells. E2F1 has an antiapoptotic function (23-25) and is acetylated and stabilized by PCAF (16). As expected, E2F1 expression was upregulated in cisplatin-resistant cells and

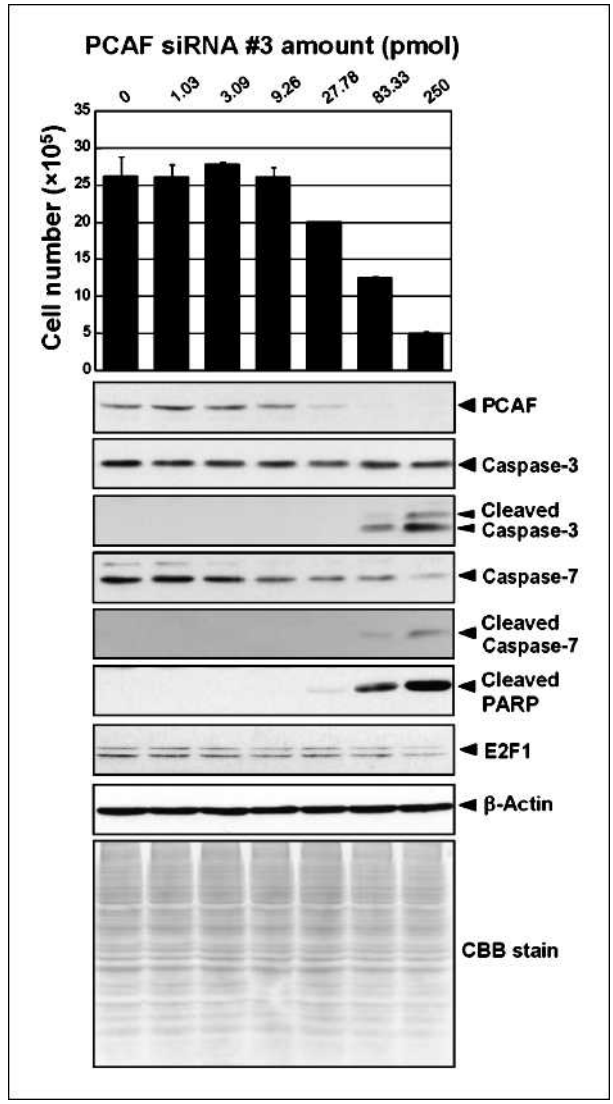

FIGURE 5. Downregulation of PCAF induced apoptosis. PC3 cells were transiently transfected with the dilution series of PCAF siRNA #3. After 48 h, the cells were counted; whole-cell lysates (100 μg) were subjected to SDS-PAGE; and Western blotting was done using the indicated antibodies. Immunoblotting of β-actin is shown as a loading control. The relative intensity is shown under each blot. Gel staining with CBB is also shown.

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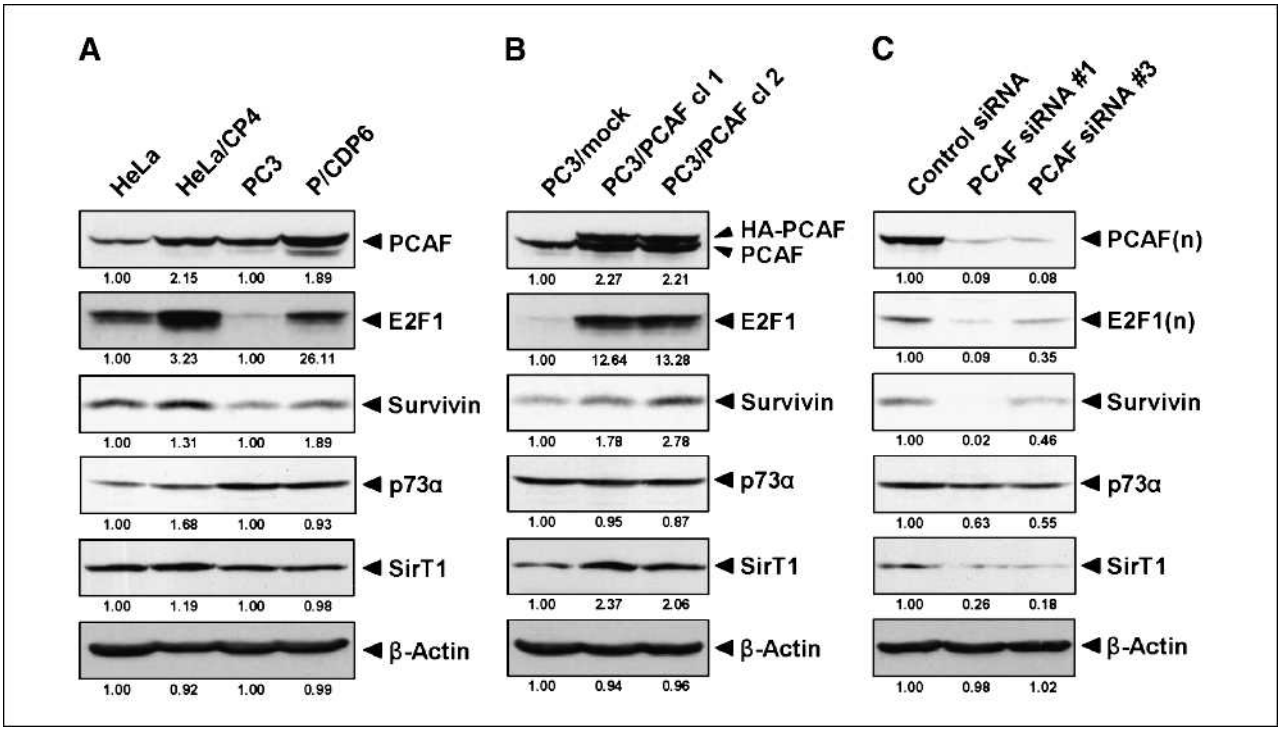

FIGURE 6. PCAF expression induced antiapoptosis genes by regulating E2F1 expression. A to C, whole-cell lysates (100 μg) and nuclear extracts [100 μg, PCAF(n) and E2F1(n) in C] of cisplatin-resistant cell lines (HeLa/CP4 or P/CDP6), parent cell lines (HeLa or PC3), PCAF-overexpressing cell lines (PC3/PCAF cl 1 and cl 2), a control cell line (PC3/mock) or PC3 cells transfected with control siRNA, or PCAF siRNA #1 or #3 as described in (Figs. 1, 2A, and 4A)respectively were subjected to SDS-PAGE, and Western blotting was done using the indicated antibodies. Immunoblotting of β-actin is shown as a loading control. The relative intensity is shown under each blot.

PCAF-overexpressing cells (Fig. 6A and B). Moreover, downregulation of E2F1 sensitized cancer cells to chemotherapeutic agents (Fig. 7). These results suggest that E2F1 might be involved in antiapoptosis. Survivin is a prosurvival gene inhibiting apoptosis, and it has been shown that E2F1 bound to the Survivin promoter and induced its transcription in rat embryonic fibroblasts (26). The expression of Survivin was upregulated in cisplatin-resistant cells

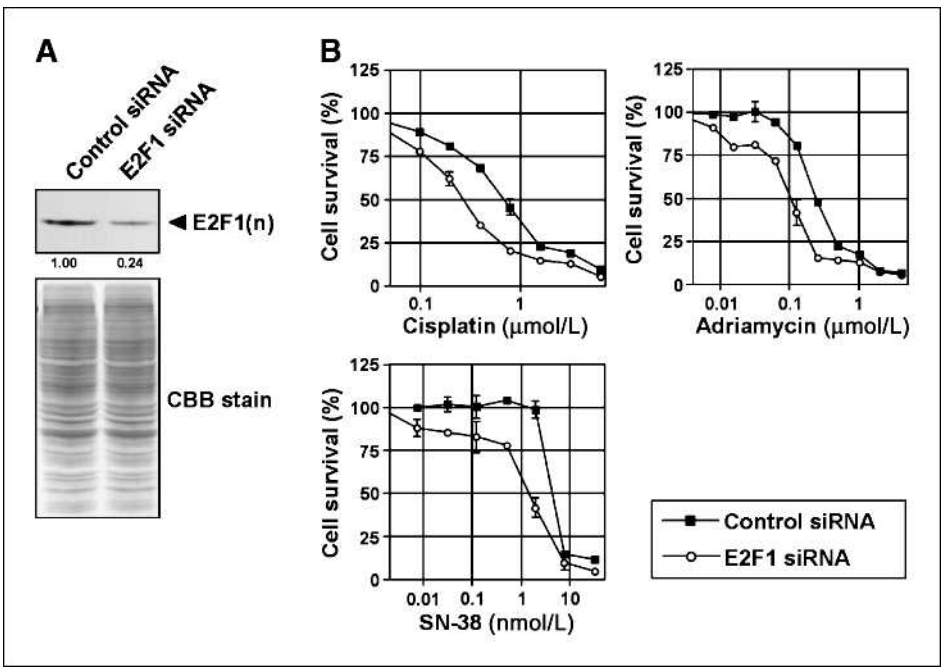

FIGURE 7. Downregulation of E2F1 sensitized cells to chemotherapeutic agents. A, PC3 cells were transiently transfected with 250 pmol of control siRNA or E2F1 siRNA. After 48 h, nuclear extracts (100 μg) were subjected to SDS-PAGE, and Western blotting was done using the indicated antibodies. The relative intensity is shown under each blot. Gel staining with CBB is also shown. B, 1.0×10^3 PC3 cells, transfected as in A, were seeded onto 96-well plates. The next day, the indicated concentrations of the drugs were applied. After 48 h, cell survival was analyzed with a WST-8 assay. Cell survival in the absence of drugs corresponded to 100%. Points, mean of at least three independent experiments; bars, SD.

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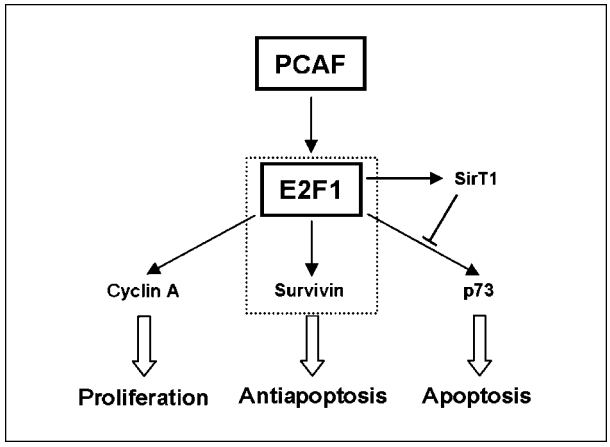

FIGURE 8. PCAF/E2F1 pathways enable cancer cells to acquire apoptosis resistance. PCAF stabilizes E2F1. E2F1 may contribute to apoptosis resistance by transcriptional induction of target genes such as cyclin A, Survivin and SirT1.

and PCAF-overexpressing cells (Fig. 6A and B). These findings indicate that PCAF might induce Survivin expression through E2F1 and induce an antiapoptotic phenotype.

Downregulation of PCAF induced cell growth retardation due to cell cycle arrest and apoptosis (Figs. 4 and 5), indicating that PCAF is a potential target for cancer treatment. These results are consistent with the reports that knockdown of PCAF inhibited tumorigenesis and tumor progression in nude mice (27), and inhibitors of PCAF HAT activity decreased cell proliferation (28, 29). In addition, E2F1 expression was decreased by the downregulation of PCAF (Fig. 6C). Because PCAF can stabilize the E2F1 protein (16), downregulation of PCAF might lead to the destabilization of the E2F1 protein. E2F1 has a well-known function in promoting cell cycle progression by regulating pRB (30, 31). Thus, downregulation of E2F1 might induce cell cycle arrest. Furthermore, it is consistent with the function that cyclin A, which promotes the cell cycle G_1-S and G_2-M transitions and is regulated by E2F1 (31), was decreased in addition to decreased E2F1 expression (data not shown). Although downregulation of PCAF also induced apoptosis, we could not determine whether cell cycle arrest resulted in apoptosis or not. Because both PCAF and E2F1 have proapoptotic functions, they should not be involved in this process directly.

Downregulation of PCAF induced cell growth retardation in p53-null, p53-mutated, and wild-type p53 cells (Fig. 4A), suggesting that PCAF reduced cell viability in a p53-independent manner. Although it has been shown that PCAF induces apoptosis in a p53-dependent/independent manner, the growth rate of PCAF-overexpressing cells is broadly similar to that of control cells (Fig. 2B). Because PCAF-overexpressing cells were established from p53-null PC3 cells, apoptosis might not be induced. Alternatively, Survivin or other genes might negatively regulate apoptosis. The growth of cisplatin-resistant cells is very slow but viable, although PCAF expression is upregulated. P/CDP6 cells are p53-null cells, but HeLa/CP4 cells are mutant-type p53 cells. This suggests that, in cisplatin-resistant cells and PCAF-overexpressing cells, the PCAF-inducing apoptosis system may be abolished, regardless of p53 expression, or suppressed by an antiapoptotic gene such as Survivin. It has been shown that E2F1 can activate the expression of proapoptotic genes (30, 32-36). However, we did not observe increased expression of the proapoptotic gene *p73*, which is an E2F1 target gene, in either cisplatin-resistant cells or PCAF-overexpressing cells (Fig. 6A and B). It has been reported that SirT1 represses E2F1-dependent p73 promoter activity and apoptosis (21, 22). SirT1 expression was upregulated in PCAF-overexpressing cells (Fig. 6B), suggesting that SirT1 might negatively regulate the E2F1-dependent p73-apoptotic pathway. In cisplatin-resistant cells, SirT1 expression was not increased (Fig. 6A), indicating that E2F1-dependent apoptosis system might be out of control of SirT1 and regulated by other antiapoptotic genes such as Survivin. These results suggest that PCAF/E2F1 pathways enable cancer cells to acquire apoptosis resistance as shown in Fig. 8.

The functional coordination of HATs and histone deacetylase (HDAC) is important for gene expression, DNA repair, cell cycle, and apoptosis. HDAC inhibitors can induce cell cycle arrest, differentiation, and apoptosis. Inhibitors of HDAC are a promising target for cancer chemotherapy. Because PCAF downregulation induces cell cycle arrest and apoptosis, we believe that HAT inhibitors are also promising agents for cancer chemotherapy. PCAF downregulation and HDAC inhibitors can both induce apoptosis in cancer cells, indicating that inducing an imbalance in cellular acetylation of proteins might be critical for apoptosis induction.

Collectively, this study is the first report of PCAF-dependent antiapoptosis in relation to drug resistance. Furthermore, PCAF seems to be an indispensable component of cancer cell survival. PCAF is one of pleiotropic factors for drug resistance and might be a potential target of cancer therapy.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Acknowledgments

We thank S. Takasaki, S. Mifune, and S. Tabata for their technical assistance.

Grant Support

KAKENHI (17016075), a University of Occupational and Environmental Health Grant for Advanced Research, and The Vehicle Racing Commemorative Foundation.

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Received 10/14/2009; revised 03/30/2010; accepted 05/11/2010; published OnlineFirst 06/08/2010.

Published OnlineFirst June 8, 2010; DOI: 10.1158/1541-7786.MCR-09-0458

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Mol Cancer Res 2010;8:864-872. Published OnlineFirst June 8, 2010.