Inhibition of the Acetyltransferases p300 and CBP Reveals a Targetable Function for p300 in the Survival and Invasion Pathways of Prostate Cancer Cell Lines

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Abstract

Inhibitors of histone deacetylases have been approved for clinical application in cancer treatment. On the other hand, histone acetyltransferase (HAT) inhibitors have been less extensively investigated for their potential use in cancer therapy. In prostate cancer, the HATs and coactivators p300 and CBP are upregulated and may induce transcription of androgen receptor (AR)-responsive genes, even in the absence or presence of low levels of AR. To discover a potential anticancer effect of p300/CBP inhibition, we used two different approaches: (i) downregulation of p300 and CBP by specific short interfering RNA (siRNA) and (ii) chemical inhibition of the acetyltransferase activity by a newly developed small molecule, C646. Knockdown of p300 by specific siRNA, but surprisingly not of CBP, led to an increase of caspase-dependent apoptosis involving both extrinsic and intrinsic cell death pathways in androgen-dependent and castration-resistant prostate cancer cells. Induction of apoptosis was mediated by several pathways including inhibition of AR function and decrease of the nuclear factor kappa B (NF-kB) subunit p65. Furthermore, cell invasion was decreased upon p300, but not CBP, depletion and was accompanied by lower matrix metalloproteinase (MMP)-2 and MMP-9 transcriptions. Thus, p300 and CBP have differential roles in the processes of survival and invasion of prostate cancer cells. Induction of apoptosis in prostate cancer cells was confirmed by the use of C646. This was substantiated by a decrease of AR function and downregulation of p65 impairing several NF-kB target genes. Taken together, these results suggest that p300 inhibition may be a promising approach for the development of new anticancer therapies. Mol Cancer Ther; 10(9); 1644–55. ©2011 AACR.

Introduction

The histone acetyltransferases (HAT) CBP and p300 are important coactivators favoring transcription. Their involvement in various pathologic processes has been extensively studied in the past (1). In fact, CBP and p300 are known as functional paralogues and their HAT domains show sequence identity of more than 90% (2). Both proteins are fundamental coactivators of a large number of transcription factors by remodeling chromatin. Moreover, p300 and CBP can bind not only to target proteins and regulate DNA binding affinity, transcriptional activation, protein–protein interactions, and stability of transcription factors but also to other cellular proteins by acetylation (3). For that reason, HATs are also named lysine acetyltransferases (KAT; ref. 4).

In cancer, the role of p300 and CBP is not clear and may depend on the physiologic background of the tumor. The fact that p300 is targeted by viral oncoproteins and is often found mutated or in a truncated form in breast, colorectal, and pancreatic cancers, indicate that p300 may act as a classical tumor suppressor (5). In prostate cancer, however, p300 and CBP clearly have oncogenic potential. Both p300 and CBP are coactivators of the androgen receptor (AR), the latter driving progression of prostate cancer by the regulating action of dihydrotestosterone (6). Acetylation of AR has been shown to enhance coactivator
protein downregulation with specific short interfering RNAs (siRNA) and (ii) chemical inhibition of HAT/KAT activity of p300/CBP with the above-mentioned compound.

Materials and Methods

Cell culture and authentication, transfections, and treatments

All cell lines were cultured in RPMI containing 10% fetal calf serum (FCS) and 1% antibiotics and GlutaMAX (Invitrogen). LAPC-4 cells were supplemented with 100 nmol/L dihydrotestosterone. Cell line authenticity was confirmed in August 2010 by short tandem repeat analysis following the procedure by Parson and colleagues (21). Lipofectamine 2000 transfections were done in serum- and antibiotics-free medium with 50 nmol/L siRNA according to the manufacturer’s protocol (Invitrogen). Target sequence for p300 was published previously (13). siControl and siCBP (On-target Plus Smart Pools) were purchased from Dharmacon (THP Medical Products Vertriebs GmbH). Six hours after transfection, medium was changed to full growth conditions. Cells were harvested 72 hours posttransfection. Because C646 was inhibited by serum (Supplementary Fig. S1), treatment with the chemical inhibitors was done for 24 hours in serum-free HITES medium (RPMI medium supplemented with 10 nmol/L hydrocortisone, 10 nmol/L estradiol, 5 μg/mL insulin, 100 μg/mL transferrin, and 30 nmol/L sodium selenite).

Western blot

Western blot was done as described before (22). For p300 and CBP, 3% to 8% Tris/acetate gels and for p65, p50, and Bcl-xL, 4% to 12% Bis/Tris gels were used. Antibodies were purchased from Santa Cruz Biotechnologies (p300 C-20, CBP A-22, α-tubulin), Cell Signaling (p65, p50), Chemicon/Millipore (glyceraldehyde-3-phosphate dehydrogenase), and New England Biolabs (Bcl-xL).

Proliferation assays

Cells were incubated for the last 16 hours with 37 kBq/well ³H-thymidine, and DNA was measured as described before (22).

Apoptosis assays

Cells were seeded in 6-well plates and transfected with siRNA or treated with C37 or C646 on the next day as described earlier. Cells were harvested and centrifuged. For flow cytometry, cell pellets were resuspended in propidium iodide (PI) buffer (0.2% Triton X-100, 2 ng/mL Na-citrate, and 0.1 mg/mL PI), and cell cycle distribution was measured with a FACSCalibur flow cytometer (Becton Dickinson). For caspase 3, 7, 9, and 8/10 activity assays, cell pellets were resuspended in 50 μL of water, and 5 μL of the cell suspension was mixed together with 20 μL of PBS and 25 μL of the respective 2-fold substrate (Caspase-Glo 3/7, 8, 9; Promega). Another 5 μL of the cell suspension was used to quantify...
protein concentration by the Bradford method. Luminescence was measured after 20 minutes with Chameleon 5025, and values were normalized to protein amount. In Solution caspase 8 (extrinsic pathway) or 9 (intrinsic pathway) inhibitors were purchased from Calbiochem (VWR International) and used at a concentration of 2 nmol/L. Expression of phosphatidylserine on cell surfaces was corroborated using the phycoerythrin Annexin V Apoptosis Detection Kit I (Becton Dickinson) following the manufacturer’s protocol. Cell populations were analyzed with a FACSCalibur flow cytometer.

Prostate-specific antigen measurements
Cells were incubated in serum-free medium for the last 24 hours before harvesting. Prostate-specific antigen (PSA) concentration was determined on an Advia Centaur XP Immunoassay System (Siemens). Cells were trypsinized and counted with a Casy cell counter (Scharfe System). PSA concentrations were normalized to cell number.

Quantitative PCR
Quantitative PCR (qPCR) was done as described before (22). TaqMan Primer/Probe mixes for p65, p50, Bcl-xl, and matrix metalloproteinase (MMP)-2 and MMP-9 were purchased from Applied Biosystems. SYBR Green primer mixes for p300 and CBP were published previously (23).

Scratch (wound healing) and Boyden chamber assays
Scratch and Boyden chamber assays were conducted as described before (24). For invasion assays, inserts were coated with Matrigel (Becton Dickinson) diluted 1:3 with serum-free medium.

Zymography
Cells were transfected as described earlier and after 2 days, serum-free medium was added for the last 24 hours. Supernatant was collected and concentrated using Vivaspin 500 (VWR International) to approximately 50 μL. Protein was quantified by the Bradford method, and equal amounts of protein were loaded onto 10% Gelatin-Zymograms (Invitrogen). Gels were stained with Coomassie blue and decolorized until clear bands indicating proteinase activity were visible.

Chromatin immunoprecipitation assays
Chromatin immunoprecipitations (ChIP) of p65 was done with the ChIPAb+NFXb (RelA) antibody/primer set together with the EZ-Magna ChIP G Kit (both from Millipore), according to the manufacturer’s instructions. AR ChIP was done on LNCaP and LAPC-4 cells that were starved for 2 days in RPMI containing 5% charcoal-stripped FCS. AR binding was induced with 1 nmol/L R1881 together with C37 or C646 treatment for 4 hours. Cells were then fixed with 1% formaldehyde, lysed, and sonicated to shear DNA. Immunoprecipitation was done with a mixture of anti-AR (Cell Signaling) and anti-AR (PG-21; Upstate/Millipore), and Protein A Sepharose CL-4B beads (GE Healthcare) overnight at 4°C, followed by 4 wash steps. Cross-linking was reversed by proteinase K digestion at 56°C to 65°C for 4 hours, and DNA was purified with the ChIP DNA Clean & Concentrator Kit (Zymo Research). SYBR Green qPCR was done with the following primer pair of the PSA enhancer region: forward: 5′-GGG GTT TGT GCC ACT GGT GAG-3′; reverse: 5′-GGG AGG CAA TTC TTC ATG GTT C-3′. Values were normalized to input controls taken before the immunoprecipitation step.

Statistical analysis
Student’s t test was used to assess significant differences between siControl or C37-treated groups and the indicated treated group (unless identified otherwise in the figure legend) and were encoded as follows: *, P < 0.05; **, P < 0.01; ***, P < 0.001.

Results
Specific downregulation of p300 by siRNA reduces proliferation and induces apoptosis
Inhibition of p300 and CBP was carried out by siRNA transfections and was confirmed to be efficient both in the castration-resistant cell line PC3 and in the androgen-sensitive cell line LNCaP 3 days after transfection (Fig. 1A). qPCR showed reduced mRNA levels of p300 and CBP at 24, 48, and 72 hours after transfection and confirmed specificity of siRNAs (Supplementary Fig. S2). To test whether inhibition of p300/CBP has antiproliferative effects on prostate cancer cells, we measured 3H-thymidine incorporation on transfected PC3 and LNCaP cells (Fig. 1B). In PC3 cells, depletion of both p300 and CBP resulted in a decreased proliferation, whereas LNCaP showed only a significant decrease after p300 downregulation. Moreover, decreased proliferation correlated with reduced PSA secretion in LNCaP cells, indicating a loss of transcriptional activity of the AR (Fig. 1C). Decreased 3H-thymidine incorporation can be a consequence of increased apoptosis. Therefore, we measured cell cycle distribution after staining the cells with PI (Fig. 1D). Quantification of the sub-G1 peak revealed that downregulation of p300 leads to an increase of apoptosis in both cell lines. Surprisingly, downregulation of CBP did not lead to an increase of apoptosis in either cell line. We concluded that expression of p300, but obviously not of CBP, is essential for the survival of PC3 and LNCaP cells.

Induction of apoptosis by p300 depletion involves both extrinsic and intrinsic pathways
To determine whether induction of apoptosis by p300 depletion is a caspase-dependent mechanism, we measured activities of the extrinsic initiator caspases 8 and 10, the intrinsic initiator caspase 9, and the executioner caspases 3 and 7 (Fig. 2A). Downregulation of p300 led to a 13.8-fold and 4.2-fold increase in caspase 3/7 activity in PC3 and LNCaP, respectively. Again, downregulation...
of CBP had no effect on caspase 3/7 activity. Moreover, both extrinsic and intrinsic apoptotic pathways were activated to the same extent after p300 depletion (Fig. 2A). We confirmed the involvement of the extrinsic pathway by using specific inhibitors of caspases 8 and 9 (Fig. 2B). Indeed, inhibition of the extrinsic pathway by caspase 8 inhibitor led to a significant reduction in caspase 3/7 activity after p300 depletion in both cell lines. Repression of the intrinsic pathway resulted only in a minor reduction in caspase 3/7 activity. These findings show that apoptosis is induced primarily via the extrinsic pathway.

**Downregulation of p300 induces p65 degradation**

Constitutive activation of NF-κB is a widely observed phenomenon in several cancer types, including prostate cancer, as NF-κB regulates a variety of apoptotic antagonists (25). We hypothesized that in the absence of p300,
proper signaling of NF-κB is inhibited, thereby rendering the prostate cancer cells sensitive to apoptotic stimuli. We analyzed expression levels of the 2 main NF-κB subunits p65 (Rel A) and p50 after treatment with specific siRNAs for p300 and CBP. Indeed, in p300-depleted cells, the protein level of p65 was decreased and this reduction was accompanied by the appearance of a higher-molecular-weight band (Fig. 3A). Moreover, mRNA levels of p65 were not affected significantly (Fig. 3A), which led to the conclusion that degradation rate of p65 is probably increased after p300 downregulation. Analysis of p50 showed slight upregulation of protein levels in both p300-depleted PC3 and p300- or CBP-depleted LNCaP (Fig. 3B), whereas p50 mRNA levels were not changed (Fig. 3B). Taken together, these data indicate that upon p300 depletion, NF-κB signaling is impaired through p65 degradation.

Inhibition of p300 decreases the invasive capacity of prostate cancer cells through an MMP-2- and MMP-9–dependent mechanism

The metastatic cascade is a well-regulated molecular process underlining different steps, including epithelial-mesenchymal transition, invasion, resistance to anoikis, angiogenesis, transport through vessels, and outgrowth of secondary tumors (26). Because of the interaction of p300/CBP with a large number of pathways, we tested whether the 2 coactivators also interfere with metastagogenesis. Indeed, in scratch assays, p300- or CBP-depleted PC3 cells showed impaired wound healing (Fig. 4A). A reduced migration was confirmed after p300 or CBP downregulation by measuring transition of PC3 and LNCaP cells through 8-μm pores of a poly(ethylene terephthalate) membrane in Boyden chambers assays (Fig. 4B). The same Boyden chambers were coated with Matrigel and used to measure invasion (Fig. 4C). Interestingly, only p300 depletion resulted in a significant reduction of invasiveness in both cell lines, showing again that p300 and CBP can regulate different cellular processes. MMPs are enzymes that degrade, among others, collagen and gelatin, thereby regulating the tumor microenvironment. It has been shown that MMP-2 and MMP-9 are expressed in prostate cancer (27, 28). We used gelatin-zymography to measure the activity of MMP-9. PC3 cells showed a reduced protease activity after p300 depletion. This was corroborated with a reduced transcription of the MMP-9 gene (Fig. 4D). The mRNA levels of MMP-2, a known activator of pro-MMP-9 (29), were also significantly decreased upon sip300 transfection. Interestingly, MMP-2 and MMP-9 mRNA expressions in LNCaP were nearly undetectable (data not shown). Reduced invasion capacity of LNCaP cells was supported by a diminished number of cells undergoing migration when comparing coated and uncoated Boyden chamber assays (Fig. 4B and C). Taken together, we conclude that both CBP and p300 play a role in regulating motility of prostate cancer cells. However, by regulating the expression of MMP-2 and MMP-9, p300 seems to be most critical in impacting the molecular pathways of invasion.
The chemical p300 inhibitor C646 induces apoptosis in androgen-sensitive and castration-resistant prostate cancer cell lines by interfering with AR and NF-κB pathways

To support our findings of reduced survival by inhibiting p300 with the siRNA approach, we tested whether chemical inhibition of p300 would also lead to these effects. The compound C646 specifically inhibits the acetyltransferase activities of p300 and CBP (20), whereas C37 is an analogue control compound that lacks acetyltransferase inhibitory properties (Supplementary Fig. S3). We tested the ability of C646 to induce apoptosis in 2 androgen-independent cell lines, PC3 and Du145, and 2 androgen-sensitive cell lines, LNCaP and LAPC-4. In caspase 3/7 activity assays, both PC3 and Du145, and in particular LNCaP, showed an increase of apoptosis after treatment with 10 and 20 μmol/L C646 but were insensitive to the control compound C37 (Fig. 5A). Interestingly, LAPC-4 showed only a marginal increase of caspase 3/7 activity at the highest concentration. For this reason, 20 μmol/L C646 was used in subsequent experiments. Apoptosis induction was confirmed by Annexin V staining of C646-treated cells (Fig. 5B). Moreover, an induction of caspase 8/10 and 9 activity after C646 treatment could be observed, showing again an involvement of both extrinsic and intrinsic pathways after inhibition of p300 (Supplementary Fig. S4). Next, we analyzed whether AR and NF-κB pathways were affected after treatment with C646. In LNCaP and LAPC-4, PSA secretion was markedly reduced after treatment with 20 μmol/L C646 (Fig. 6A). However, chromatin binding of AR was not
affected by C646, suggesting that acetylation of AR is not a prerequisite for its DNA binding activity (Supplementary Fig. S5). Furthermore, decreased expression levels of p65 were observed in all cell lines (Fig. 6B), which was associated with a decreased binding of p65 at the IkBa promoter (Fig. 6C). Bcl-xL, an antiapoptotic member of the Bcl-2 family, which is regulated by NF-κB, was also decreased in all cell lines except LAPC-4, giving a possible explanation.
for the low sensitivity of LAPC-4 to apoptotic induction by C646 (Fig. 6B). Moreover, both MMP-2 and MMP-9 mRNA expressions were significantly decreased in PC3 cells, showing that C646 may also interfere with cell invasion (Fig. 6D). Altogether, these results show that chemical inhibition of HAT/KAT function of p300/CBP leads to the induction of apoptosis via distinct molecular pathways.

Discussion

Differential functions of p300 and CBP

In the cellular processes of induction of apoptosis and invasion, we found differential functions of p300 and CBP by using specific siRNAs. In the past, differential properties of p300 and CBP have been found in various...
cellular pathways. For example, Kawasaki and colleagues found that p300, but not CBP, is needed for retinoic acid–induced differentiation of embryonal carcinoma F9 cells whereas both proteins were required for the induction of apoptosis and G1 arrest (30). Furthermore, multilineage defects in hematopoietic differentiation were found in mice with a monoallelic inactivation of the CBP gene.

However, these pathologies could not be observed in p300 heterozygous mice, suggesting that a full complement of CBP, but not of p300, is required for normal hematopoietic differentiation (31). For more examples on differential roles of p300 and CBP, we refer to an interesting review by Kalkhoven (1). Recently, a genome-wide ChIP-Seq has been conducted on cell cycle–synchronized...
cells with specific antibodies against p300 or CBP (32). Interestingly, significant differences in the levels and binding targets of both proteins were observed. Among processes differentially regulated by p300/CBP binding were also cell death and cell adhesion pathways. Taken together, those studies support our findings of differential effects of p300 and CBP.

**Induction of apoptosis by p300 inhibition through multiple pathways**

Because it is known that p300 and CBP interfere with multiple pathways, we considered that induction of apoptosis is not restricted to one pathway. The AR is of particular importance in LNCaP and LAPC-4 cells that will stop growing after androgen depletion (33, 34). Knockdown of p300 decreased PSA secretion, which is an indicator of diminished AR activity. AR-regulated transcription may be impaired because of the lack of p300 as an important coactivator of AR. Furthermore, during prostate cancer progression from androgen dependence to castration resistance, cross-talk between transduction pathways plays an important role in the ligand-independent activation of the AR (8). For example, it has been shown that IL-6 activation of AR-dependent genes in the absence of androgens is mediated by p300 (13). Thus, a combined treatment of AR blockade (e.g., bicalutamide) for ligand-dependent and p300 inhibition for ligand-dependent and -independent activation of the AR could be of potential interest.

In the second pathway, we found that p300 depletion leads to a decreased p65 level, apparently through increased turnover of the protein. This is in line with the results of a previous study, in which deacetylation of lysine 310 of p65 led to Set9-mediated methylation of p65 at lysines 314 and 315, which, in turn, resulted in polyubiquitination and proteasomal degradation of chromatin-associated p65 (18). Although we were not able to identify the nature of the higher-molecular-weight band recognized by the p65 antibody in Fig. 3A, it seems to be linked to the absence of p300 rather than to the inhibition of acetyltransferase activity of p300, as it was not observable after treatment with C646. Constitutive activation of NF-κB can be found in many prostate cancer cell lines and frequently correlates with AR downregulation (35). It was proposed that NF-κB might compensate for the lack of androgen-induced AR activity by activating the expression of several AR target genes (35). Indeed, this possibility was shown in LNCaP cells, where NF-κB activated the expression of PSA (36). Thus, compromised NF-κB signaling can confer a decrease in NF-κB- and AR-responsive genes, resulting in a lack of activated prosurvival pathways and rendering prostate cancer cells susceptible to apoptotic induction. Interestingly, degradation of p65 after p300 downregulation could also be seen in LNCaP cells that do not show constitutively activated NF-κB signaling (37). This correlated also with a lower apoptotic rate when comparing LNCaP to PC3 cells (Figs. 1D and 2A). Thus, p65 downregulation might be less important in LNCaP cell growth effects.

The involvement of the extrinsic pathway in induction of apoptosis after p300 inhibition was shown by the use of caspase 8/10 activity assays and inhibitors of caspase 8 and/or 9. It is well known that the activation of the extrinsic pathway turns on the intrinsic pathway by the action of Bid (38), whereas transactivation of the extrinsic pathway by the intrinsic pathway has not been shown. Therefore, high caspase 9 activity could be induced by cross-talk with the extrinsic pathway. On the other hand, we have also found deregulation in the AR- and NF-κB signaling pathways, leading to a lack of proproliferative stimuli. Hence, deregulation of intracellular pathways sensitizes cells to apoptosis induction. We therefore hypothesize that both intrinsic and extrinsic pathways contribute to programmed cell death after p300 inhibition. Interestingly, HDAC inhibitors also activate both apoptotic pathways (19), although it seems that in this case the intrinsic one has a superior role over the extrinsic pathway.

**Decrease of invasion by p300 inhibition**

Inhibition of tumor cell dissemination is of particular interest in prostate cancer, as most patients die from metastatic lesions rather than from the primary tumor. In addition to the proapoptotic effect of p300 inhibition, we found a decrease in cell migration and invasion. In fact, this reduction in migration and invasion is certainly also due to the increase of apoptotic cells. However, because we found that p300 inhibition decreases expression of MMP-2 and MMP-9, we conclude that p300 also interferes, as a distinct event, with the cellular pathways that regulate invasion. Interestingly, CBP depletion also led to a decrease in migration, but not invasion, in either cell line. Thus, we concluded that both p300 and CBP are important for the regulation of migration, whereas only p300 is essential for invasion. Moreover, MMP-2 and MMP-9 are known targets of NF-κB regulation (39). It has been shown that MMP-9 is downregulated in PC3 cells that have been modified to have low NF-κB activity by the introduction of a mutant form of IκBα (40). Hence, the decrease in expression levels of p65 after p300 inhibition may lead to lower NF-κB activity and MMP-9 expression. On the other hand, the high activity of NF-κB in untreated PC3 cells can explain the elevated expression of MMP-9, whereas in LNCaP cells, which have low NF-κB activity, MMP-2 and MMP-9 were only faintly expressed. Because p300 inhibition could still decrease LNCaP invasion, we deduce that p300 also regulates other pathways important for invasion.

**Potential of chemical p300 inhibition**

In addition to downregulation of p300/CBP by specific siRNAs, we have used the small molecule C646, which has been shown to specifically inhibit the HAT/KAT domain of p300 and CBP (20). C646 is a competitive inhibitor with a Ki of 400 nmol/L and is the most potent
p300/CBP inhibitor in live cells (20). We could observe similar effects of C646 on caspase activity, PSA secretion, and p65 expression levels compared with cells transfected with p300 siRNA. This led to the conclusion that apoptosis induction is dependent on the inhibition of HAT/KAT function of p300. Moreover, the 4 examined cell lines showed varying sensitivity to C646, which leads to the conclusion that the effects of C646 might be cell type, time, and dose dependent. Several other p300/CBP HAT inhibitors are known, such as the phytoextract curcumin (41). Indeed, it has been shown that curcumin could induce apoptosis and potentiate TNF-α-induced apoptosis and suppress NF-κB activation in DU145 and LNCaP cells (42). However, the role of curcumin as an acetyltransferase inhibitor has not been investigated in that study. Another example with p300/CBP HAT inhibiting abilities is plumbagin (43), which induces apoptosis and inhibits invasion of prostate cancer cells by several mechanisms including blocking of DNA-binding ability of NF-κB (44). Again, in this context, the role of plumbagin as acetyltransferase inhibitor was not analyzed. In this sense, we provide a possible functional link between the anticancer properties of the above-mentioned plant extracts and their p300/CBP HAT inhibiting properties.

Overall, our study shows that siRNA-mediated down-regulation of p300 (but not of CBP) and its chemical inhibition by the small molecule C646 led to induction of caspase-dependent apoptosis in several androgen-dependent and castration-resistant prostate cancer cells. Furthermore, p300 depletion led to a decrease of migration and invasion and may thus inhibit tumor cell dissemination. Therefore, targeting p300 by HAT inhibitors may be a promising approach in therapy for prostate cancer.

Disclosure of Potential Conflicts of Interest

P.A. Cole owns equity in Acylin Therapeutics as a cofounder. D.J. Meyers and P.A. Cole are advisors for Acylin Therapeutics, and P.A. Cole is also a SAB member in this company.

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