p300-mediated Acetylation of Human Transcriptional Coactivator PC4 Is Inhibited by Phosphorylation*

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The human positive coactivator 4 (PC4) acts as a general coactivator for activator-dependent transcription, the activity of which is regulated negatively by phosphorylation. We report here that PC4 can be acetylated specifically by another coactivator, p300. Interestingly, phosphorylation of PC4 by casein kinase II inhibits the p300-mediated acetylation. Mass spectral analysis revealed that there are at least two lysine residues acetylated in PC4, as a result of which its DNA binding activity is stimulated.

Human positive coactivator 4 (PC4)† was isolated from a mammalian cofactor activity, upstream stimulatory activity, independently by two different groups. It mediates activator-dependent transcription by RNA polymerase II, apparently through interactions with the transcriptional activator and basal transcription machinery (1, 2). PC4 binds double-stranded DNA in a sequence-independent manner. The regions required for the binding and for coactivation overlap in PC4. However, the coactivator function also depends on its ability to interact with the preinitiation complex (1, 3). Presumably both DNA binding and interaction with general transcription factors (predominantly TATA box-binding protein and TFIIA) are involved in coactivation by PC4. Recently, it was reported that PC4 binds tightly to melted double-stranded and single-stranded DNA through its novel C-terminal fold. It has been demonstrated that interactions of this unique C-terminal domain with the melted DNA repress transcription that can be attenuated by TFIIH and phosphorylation of PC4 (4—6).

PC4 is subjected to in vivo phosphorylation events that negatively regulate its coactivator function and its interactions with the activator and TATA box-binding protein/TFIIA (2, 7). Phosphorylation also inhibits double-stranded DNA binding but not the single-stranded DNA binding (3). Mutation and mass spectrometric analyses suggest that phosphorylation of PC4 in vivo is mediated by casein kinase II (CKII), and it is restricted to seven serine residues between 2 and 28 at the N terminus (7). Interestingly 95% of the total cellular PC4 is phosphorylated and thus inactive in vivo, whereas only 5% is in the nonphosphorylated active form.

Among the different human PCs, PC1/Poly (ADP-ribose) polymerase, PC3/topoisomerase I, PC4, PC52, high mobility group protein 1 (HMG-1), and HMG-2 are relatively abundant nuclear proteins that display somewhat generalized, sequence-independent DNA binding properties and are involved in diverse nuclear processes besides RNA polymerase II-mediated transcription (reviewed in Refs. 8 and 9). Thus it raises the possibility that PC4 may be a chromatin protein having transcriptional coactivator function.

The reversible acetylation of nucleosomal histones and presumably non-histone chromatin proteins plays a significant role in chromatin-mediated transcription regulation. The idea that histone acetylation is related causally to transcriptional activation has received solid support from the discovery that a number of transcriptional coactivators have histone acetyltransferase (HAT) activity. These include GCN5 and PCAF, p300 and CBP, nuclear receptor coactivators SRC1 and ACTR, and TATA box-binding protein-associated factor TAF1250 and HIV-1-tat interactive protein, TIP60 (10, 11). Among these HATs, the HAT activity of yeast GCN5 and human p300 has been shown to be directly involved in chromatin-mediated transcriptional activation (12, 13). However, histones are not the only substrates of HAT proteins. For example, CBP/p300 can acetylate p53, resulting in an enhancement of its DNA binding activity. CBP/p300 also can acetylate basal transcription factors such as TFIIIEβ and TFIIIF, the roles of which are not known (14, 15). It is known that HMG proteins also are reversibly acetylated in vivo. In duck erythrocytes, two acetylation sites in HMG-1 and HMG-14 and three sites in HMG-17 were identified (16). Recently it has been reported that PCAF is the enzyme responsible for the acetylation of HMG-17 at position 2. Apparently binding of HMG-14 and HMG-17 to nucleosome cores inhibits the PCAF-mediated acetylation of histone H3. Thus the presence of HMG-17 affects the ability of PCAF to acetylate chromatin, whereas the acetylation of HMG-17 reduces its binding affinity to chromatin (17). CBP and PCAF can also acetylate HMG-1(Y) either in solution or in the context of the enhanceosome (18). Acetylation of HMG-1(Y) by CBP but not by PCAF decreases its DNA binding activity and results in enhanceosome destabilization and disassembly. However, both CBP and PCAF HAT activities are required for activation, whereas only CBP HAT activity is required for postinduction turnover of interferon-β expression. Thus it seems acetylation of HMG protein is an important means of regulating transcription or biological function of them. Because PC4 very closely resembles HMG proteins, it was not too hard to imagine that PC4 also would be substrate for at least one of the several histone acetyltransferases.
In support of this possibility we demonstrate that PC4 can be acetylated specifically by p300 among the different HATs tested. Mass spectral analysis and acetylation of recombinant PC4 revealed that there are two lysine residues that are acetylated by p300. Most interestingly, we found that phosphorylation of PC4 by CKII inhibits the p300-mediated acetylation of PC4. However, acetylation does not influence phosphorylation of PC4. Furthermore, acetylation of PC4 stimulates its double-stranded DNA binding activity. These findings may open a new chapter in the understanding of PC4 function in vivo.

EXPERIMENTAL PROCEDURES

Purification of Recombinant Proteins—Recombinant PC4 was expressed in Escherichia coli and purified as described elsewhere (19). Briefly, the clear bacterial lysate was passed through a heparin-Sepharose column, and the bound protein was eluted with BC buffer (20 mM Tris-HCl, pH 7.9, at 4 °C, 20% (v/v) glycerol, 10 mM β-mercaptoethanol, 0.2 mM EDTA, 0.5 mM phenylmethylsulfonyl fluoride, 0.1% Nonidet P-40) containing 500 mM KCl. The peak protein fractions containing PC4 were pooled and chromatographed onto a 1-ml phosphocellulose P11 column. FLAG epitope-tagged Gal4 and p300 HAT domain (amino acids 1195–1810) also were expressed in E. coli and immunopurified on M2-agarose as described previously (20). His-tagged nucleosome assembly protein 1 (NAP1) was purified with Ni2+-nitrilotriacetic acid (Qiagen). FLAG epitope-tagged full-length PCAF and His-tagged full-length p300 were expressed and purified by infection of SF21 cells with recombinant baculoviruses followed by affinity chromatography of whole-cell extracts on M2-agarose and Ni2+-nitrilotriacetic acid column as described elsewhere (21, 22).

Purification of Human Core Histones—Human core histones were purified from HeLa nuclear pellet as described previously (23). HAT Assay—HAT assays were performed as described elsewhere (23). Indicated amounts of proteins (see figure legends) were incubated at 30 °C for 30 min in a 30-μl final reaction volume consisting of 50 mM Tris-HCl, pH 8.0, 10% (v/v) glycerol, 1 mM dithiothreitol, 1 mM phenylmethylsulfonyl fluoride, 0.1 mM EDTA, pH 8.0, 10 mM sodium butyrate, and 0.5 μl of 3.3 Ci/mmol [3H]acetyl Coenzyme A (acetyl-CoA). The reaction mixture then was blotted onto P-81 filter paper. Radioactive counts were recorded on a Wallac 1409 liquid scintillation counter. To visualize the radiolabeled acetylated protein, the reaction products were precipitated with 25% trichloroacetic acid, washed with ice-cold acetone, and resolved electrophoretically on 15% polyacrylamide gel. Gels were stained and/or autoradiographed. The extent of phosphorylation was confirmed by analyzing the protein on 15% acid-urea-polyacrylamide gel. The acetylated protein was dialyzed against water before being subjected to mass spectral analysis. Electrospray ionization mass spectral analysis was done in an HP:1100 machine using acidified water (pH 3.0). The solvent flow rate used was 0.03 ml/min. Nitrogen gas was used for drying and nebulization.

In Vitro Phosphorylation of PC4—In the phosphorylation reaction, 0.25 μg of the recombinant PC4 was incubated for 30 min at 30 °C in the phosphorylation buffer (50 mM HEPES-K+, pH 7.6, 125 mM NaCl, 10 mM MgCl2, 6% (v/v) glycerol, 5 mM dithiothreitol, and 0.5 mM phenylmethylsulfonyl fluoride) containing 5 mM ATP with 10 milliunits of rat liver CKII in a total volume of 20 μl. For large scale purification of phosphorylated PC4, the reaction volume was scaled up to 1000 μl and concentrated to a final volume of 100 μl using a 10K cutoff Centricon concentrator (Amicon). To determine the effect of acetylation on phosphorylation, the acetylated PC4 (0.25 μg) was subjected to in vitro phosphorylation using 1 μCi of [γ-32P]ATP and 1 mM cold ATP. To visualize the phosphorylated proteins, the reaction products were precipitated with 25% trichloroacetic acid, washed with ice-cold acetone, and resolved electrophoretically on 15% polyacrylamide gel. Gels were stained and/or autoradiographed. The extent of phosphorylation was quantitated using a Fuji phosphorimaging analyzer.

Electrophoretic Mobility Shift Assay—The electrophoretic mobility shift assay was carried out essentially as described previously (3) with some modifications. The sequence of the oligonucleotide comprising of HIV-1 core promoter sequences upstream of the initiator region of the adenovirus major late promoter (5′-CCCTCAAGTCTGATATATAAGGACGTGCTTTTGTGCGCTCTCACTCTTTCGCCCATCGC-3′) was used for the assays. The indicated amounts of different proteins were incubated with 40 fmol of either double-stranded labeled oligonucleotide for 30 min at 30 °C in a buffer containing 10 mM Tris-HCl, pH 7.4, 5% (v/v) glycerol, 1 mM dithiothreitol, 1 mM EDTA, pH 8.0, 0.4 M KCl, and 0.1% Nonidet P-40. The reaction mixtures then were resolved on a 6% native polyacrylamide gel at 130 V in TGE buffer (25 mM Tris, 100 mM glycine, and 10 mM EDTA, pH 8.0) for 3 h. The gels were dried and autoradiographed. Quantitation of the DNA-protein complex was carried out using a Fuji phosphorimaging analyzer.

Mass Spectral Analysis of PC4—For the mass spectral analysis of PC4, the protein was acetylated by FLAG epitope-tagged recombinant p300 HAT domain (amino acids 1195–1810). In a typical reaction mixture, 30 μg of PC4 and 3000 HAT domain was incubated in the presence of 50 μl acetyl-CoA at 37 °C for 1.5 h. To have the efficient acetylation, p300 and acetyl-CoA were added at every 30-min interval. The reaction volume was scaled up to 1000 μl and then concentrated to 100 μl using a 10K cutoff Centricon concentrator (Amicon). Acetylation of protein was confirmed by analyzing the protein on 15% acrylamide gel. The acetylated protein was dialyzed against water before being subjected to mass spectral analysis. Electrospray ionization mass spectral analysis was done in an HP:1100 machine using acidified water (pH 3.0). The solvent flow rate used was 0.03 ml/min. Nitrogen gas was used for drying and nebulization.

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fig. 1. Purified proteins used in different experiments. A, lane 1, broad range marker (Bio-Rad); lane 2, 2.3 μg of His-tagged mouse NAP1; lane 3, 2 μg of human core histones; lane 4, 1 μg of FLAG epitope-tagged Gal4 DNA-binding domain; lane 5, 0.8 μg of purified recombinant human PC4. B, baculovirus expressed full-length His-tagged p300 (lane 1) and FLAG epitope-tagged PCAF (lane 2), 0.5 μg of each protein was analyzed on 8% polyacrylamide gel and visualized by Coomassie Blue staining. C, authenticity of PC4 verified by Western blotting. The protein was resolved by 15% SDS-PAGE and subjected to either staining (lane 1) or Western blotting (lane 2).
RESULTS AND DISCUSSION

To test whether PC4 could be acetylated by known HATs, full-length His$_6$-tagged p300 (21) and FLAG epitope-tagged PCAF (22) from respective baculovirus-infected Sf21 cells (Fig. 1B) were purified. The native recombinant human PC4 (19), Gal4 DNA-binding domain, and the nucleosome assembly protein 1 (NAP1) (23) also were purified from E. coli for this purpose. The highly purified human core histones were isolated from HeLa nuclear pellet (Fig. 1A) (23). The Gal4 DNA-binding domain and NAP1 were used in the protein acetyltransferase assay as negative controls. The human core histones were included as positive controls in all the assays. The authenticity of the purified human PC4 was checked by Western blotting using polyclonal antibodies (Fig. 1C).

The reaction mixtures containing equivalent amounts of either p300 or PCAF as normalized by filter binding assay using highly purified human core histones (Fig. 2A) and the indicated amount of proteins (see figure legends) were incubated. C, substrate and enzyme requirements. Solution HAT assay products processed as above after incubation of various combinations of PC4, full-length p300, and [3H] acetyl-CoA are shown.

The present results demonstrate clearly that PC4 is acetylated specifically by p300 among the different HATs we have tested. In addition to PCAF, the equivalent HAT activity of GCN5 (short form) (25) and TIP60 (11) also could not acetylate PC4 under the identical conditions (data not shown). There are several non-histone proteins that are substrates of p300 and can be acetylated also by PCAF. These include p53, TFIIB, TFIIF, and HMG-17 (15, 17). However, HMG-14, which is related closely to HMG-17, can be acetylated only by p300 but not PCAF at the nucleosomal binding domain similar to what we report for PC4. It would be interesting to find out the mechanisms behind this p300 specificity of PC4 acetylation.

To find out the number of lysine residues that are getting acetylated in PC4, an acetylation reaction was carried out using purified FLAG epitope-tagged, recombinant p300 HAT PC4 (22) from respective baculovirus-infected Sf21 cells (Fig. 1B) were purified. The native recombinant human PC4 (19), Gal4 DNA-binding domain, and the nucleosome assembly protein 1 (NAP1) (23) also were purified from E. coli for this purpose. The highly purified human core histones were isolated from HeLa nuclear pellet (Fig. 1A) (23). The Gal4 DNA-binding domain and NAP1 were used in the protein acetyltransferase assay as negative controls. The human core histones were included as positive controls in all the assays. The authenticity of the purified human PC4 was checked by Western blotting using polyclonal antibodies (Fig. 1C).

The reaction mixtures containing equivalent amounts of either p300 or PCAF as normalized by filter binding assay using highly purified human core histones (Fig. 2A) and the indicated amount of proteins (see figure legends) were incubated. C, substrate and enzyme requirements. Solution HAT assay products processed as above after incubation of various combinations of PC4, full-length p300, and [3H] acetyl-CoA are shown.
To obtain the complete acetylation of PC4, the reaction was performed at 37 °C for a longer time, and the HAT domain and acetyl-CoA were added every 30 min (see "Experimental Procedures"). The complete acetylation was confirmed by analyzing the acetylated protein on 15% acid-urea-polyacrylamide gel (data not shown). The acetylated protein then was dialyzed thoroughly against water and subjected to electrospray ionization mass spectral analysis. As shown in Fig. 3A, unmodified mock control protein (treated with p300 HAT domain without acetyl-CoA) gave a major peak with a molecular weight of 14,265, confirming the identity of native PC4 as described previously (7). The acetylated protein showed a peak of 14,346 (Fig. 3B). The mass difference between the acetylated and the unmodified proteins suggests that there are at least two lysine residues getting acetylated by p300.

Isolation of native PC4 from HeLa nuclear extract showed 95% of the protein present as the heavily phosphorylated form in vivo (7). The phosphorylation negatively regulates PC4-mediated transcriptional coactivator activity. Presumably, phosphorylation imposes a structural change in PC4 which in turn may effect p300-mediated acetylation of PC4. To investigate this possibility, PC4 was phosphorylated to saturation levels in vitro by casein kinase II as depicted in Fig. 4A. The optimum conditions for this complete phosphorylation was standardized for 0.25 μg of PC4, 10 milliunits of casein kinase II, and 5 mM ATP (Fig. 4A, compare lanes 1 and 4). Consistent with our prediction, we found that indeed phosphorylation of PC4 modulates the acetylation negatively as of any other functional consequence of the phosphorylation. In an in vitro acetylation reaction, an equivalent amount of unmodified PC4 subjected to a mock-phosphorylation reaction (without ATP) was acetylated efficiently in a p300- and [3H]acetyl-CoA-dependent manner, whereas phosphorylated PC4 was not acetylated at all (Fig. 4B).
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compare lanes 2 and 4). This interesting result tempted us to find out what happens in the reverse consequences, i.e. how acetylation of PC4 influences its phosphorylation. To address this question, PC4 was acetylated in vitro with p300 and cold acetyl-CoA as described under “Experimental Procedures.” The acetylation of PC4 was confirmed by mass spectral analysis of the acetylated protein as described in Fig. 3. The acetylated protein then was subjected to an in vitro phosphorylation reaction by casein kinase II (Fig. 4C) and [γ-32P]ATP. We found that both acetylated and unacetylated PC4 was phosphorylated efficiently by CKII (Fig. 4C, lanes 1 and 5 versus lane 6). The quantitation of phosphorylation by phoshorimaging analysis showed that acetylation of PC4 has no effect on phosphorylation under the present reaction condition.

Phosphorylation of substrates or the enzyme (HAT) itself may be one of the key regulators of acetylation of histones and non-histone proteins. Phosphorylation of CBP by cyclin E-Cdk2 in the C-terminal region enhances its activity almost 5-fold (26). Probably phosphorylation induces a structural change in CBP that leads to the activation of acetylation function. Similarly phosphorylation of ATF-2 (27), a transcription factor that stimulates CRE-dependent transcription, enhances its intrinsic HAT activity, whereas GCN5-HAT activity is inhibited by Ku-DNA-dependent protein kinase complex-mediated phosphorylation (28). On the other hand phosphorylation of histone H3 stimulates acetylation (10-fold) by GCN5 (29). Recently it was reported that phosphorylation of p53 enhances its acetylation, which consequently enhances its DNA binding ability as well as the repair activity (14, 30). The negative regulation of acetylation upon the phosphorylation of the substrate is somewhat unique for PC4. As per our knowledge there is no report yet in which phosphorylation of a substrate inhibits acetylation. PC4 has a serine-rich acidic domain at the N terminus followed by a lysine-rich domain that is linked to a unique single-stranded DNA-binding domain (4–6). It may be possible that the phosphorylation of serine residues in the serine-rich acidic domain may induce a conformational change in PC4 that masks the acetylation sites in or around the lysine-rich domain, resulting in a complete abolition of acetylation. This possibility needs to be addressed further by detailed structural studies using site-directed mutagenesis followed by NMR spectroscopy or X-ray crystallography. However, because acetylation does not affect the phosphorylation of PC4, it may be assumed that acetylation of PC4 does not lock it in an active form. At this juncture it is difficult to predict how these two posttranslational modifications (acetylation and phosphorylation) are regulated in vivo to manifest PC4 function. Most likely there are few other proteins having phosphatase as well as deacetylase activity that also are involved in the regulation of PC4 function in the cell.

The negative effect of PC4 phosphorylation on acetylation suggests its functional consequence for acetylation. Because phosphorylation also prevents double-stranded DNA binding, which is correlated directly to its positive coactivator function, it is important to examine how acetylation affects the DNA binding ability of PC4. To address this possibility gel-mobility shift assays were done using a 60-base pair-long oligonucleotide comprising the HIV-1 core promoter sequences upstream of the initiator region of the adenovirus major late promoter with phosphorylated PC4 and acetylated PC4. The DNA binding of unmodified PC4 showed cooperativity with increasing concentration of PC4, yielding an uncompact complex (Fig. 5, lanes 2-6). Although 0.25 µg of unmodified PC4 produce a fairly good amount of complex, the equivalent amount of phosphorylated PC4 could not bind to the DNA (compare lanes 3 and 9). Interestingly, the similar amount of acetylated PC4 (by p300) enhances the double-stranded DNA binding significantly as compared with the equivalent amount (0.25 µg) of unmodified protein (compare lanes 3 and 7), whereas the addition of p300 only did not stimulate the DNA binding (compare lanes 3 and 8). It is to be noted that to achieve a similar amount of complex, nearly 3-fold more unmodified protein was needed as compared with the acetylated proteins (compare lanes 6 and 7). This experiment was repeated independently five times, and the average enhancement of DNA binding upon acetylation was found to be 40% (±5%) based on the phosphorimaging analysis quantitation.

In the present study we observe that a relatively very high amount of PC4 (0.3 µg) is required to get the proper PC4-DNA complex, which is consistent with the previous reports. The uncompact nature of the complex indicates the nonspecific binding of PC4. Although the stimulation of DNA binding by PC4 upon acetylation is not dramatic, it was consistent and very significant for the positive cofactor activity of PC4. Because the double-stranded DNA binding activity was shown to be correlated directly to the coactivation, presumably acetylation also will enhance the transcription. Our results show that phosphorylation that prevents the double-stranded DNA binding also inhibits the acetylation. Thus it is quite possible that phosphorylation-mediated negative regulation of PC4 function operates through two different pathways: first, it prevents the double-stranded DNA binding, direct interaction with TFIIA and TATA box-binding protein complex, and interaction with activators, and second, it inhibits the acetylation. It is tempting to speculate that this phosphorylation and acetylation balance ultimately regulates the PC4 function in vivo, where acetylation would be more relevant under the nucleosomal context.

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