A Signaling Role of Histone-binding Proteins and INHAT Subunits pp32 and Set/TAF-Iβ in Integrating Chromatin Hypoacetylation and Transcriptional Repression*

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Various post-translational modifications of histones significantly influence gene transcription. Although un- or hypoacetylated histones are tightly linked to transcriptional repression, the mechanisms and identities of chromatin signal transducer proteins integrating histone hypoacetylation into repression in humans have remained largely unknown. Here we show that the mammalian histone-binding proteins and inhibitor of acetyltransferases (INHAT) complex subunits, Set/template-activating factor-Iβ (TAF-Iβ) and pp32, specifically bind to unacetylated, hypoacetylated, and represively marked histones but not to hyperacetylated histones. Additionally, Set/TAF-Iβ and pp32 associate with histone deacetylases in vitro and in vivo and repress transcription from a chromatin-integrated template in vivo. Finally, Set/TAF-Iβ and pp32 associate with an endogenous estrogen receptor-regulated gene, EBI, in the hypoacetylated transcriptionally inactive state but not with the hyperacetylated transcriptionally active form. Together, these data define a novel in vivo mechanistic role for the mammalian Set/TAF-Iβ and pp32 proteins as transducers of chromatin signaling by integrating chromatin hypoacetylation and transcriptional repression.

Post-translational modifications of histone tails including acetylation, methylation, ubiquitination, sumoylation, and phosphorylation (as well as the lack thereof) have been tightly linked to gene regulation and other chromatin-based processes (1–5). Accordingly, a combinatorial presence of histone modifications referred to as the histone code has been suggested to provide specific binding sites for proteins involved in the chromatin-signaling network (1–3). Consistent with both the histone code hypothesis and signaling network model, many bromodomain-containing proteins, including histone acetyltransferases/co-activators and BRD4, associate preferentially with hyperacetylated histones, which are key components of transcriptionally active chromatin (6–8). This allows the propagation of the active state by maintaining robust acetylation of chromatin and possibly stabilizing coactivation complexes. On the other hand, methylation of lysine 4 of histone H3, however, causes the histone deacetylase (HDAC) complex from chromatin (12, 13).

Hypoacetylation of histones H3 and H4 is tightly linked to repressed chromatin domains in eukaryotic organisms including yeast, Drosophila, and humans (14). In yeast, a transcriptionally repressive protein complex, known as the Sir4 complex, has an affinity for hypoacetylated histones and is associated with histone deacetylase (HDAC) activity. It is proposed that the histone deacetylase subunit of the Sir complex, known as Sir2, first deacetylates histones, and the resulting hypo- or unacetylated histones subsequently are bound by the Sir3 subunit (15–17). However, the identity of signaling proteins in higher eukaryotes that specifically “translate” the code of the repressive/hypoacetylated state of histones/chromatin is largely unknown. Should such transducer proteins exist in humans, they should associate with “repressive” histone-modifying activities, they must be able to bind to histones, and the robustness of binding should be sensitive to the extent of acetylation. Additionally, such transducer proteins should have a direct transcriptional repressive function and should preferably be released from transcriptional activity of promoters. We have previously identified Set (also known as TAF-Iβ) and pp32 as subunits of the INHAT complex with “histone masking” activity, where binding of these proteins to histones prevents their acetylation by transcriptional coactivators (18). Here we show that Set/TAF-Iβ and pp32 have the properties to transduce the code of un- or hypoacetylated chromatin into transcriptional repression in higher eukaryotes.

MATERIALS AND METHODS

Histone Peptide Binding Assays—[35S]Methionine-labeled pp32 and Set/TAF-Iβ were synthesized using pCMX constructs in a coupled transcription-translation system (Promega) and incubated with 0.5 μg of biotin-conjugated histone tail peptides (Upstate Biotechnology, Inc., or kindly provided by Dr. M. Lazar) for 30 min at room temperature in buffer containing 150 mM KCl, 20 mM Tris-HCl (pH 7.6), 5 mM MgCl2, 1 mM dithiothreitol, 10 μg/ml bovine serum albumin, and 0.5% Nonidet P-40. Equal amounts of streptavidin-conjugated beads (Upstate Biotechnology, Inc.) were added and incubated for 1 h at 4 °C. After extensive washing, the bound proteins were separated by SDS-PAGE and visualized by a phosphorimaging device.

Total Histone Binding Assays—Histones were isolated from control HeLa cells or cells grown in 10 mM sodium butyrate using an acid

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30850 This paper is available on line at http://www.jbc.org
INHAT Links Histone Hypoacetylation to Repression

30851

extraction protocol as described (39). Acetylation of isolated histones was verified by Western blotting with anti-acetyl lysine antibody (Santa Cruz Biotechnology). Equal amounts of histones were incubated with [35S]methionine–labeled in vitro translated pp32, Set/TAF-Iβ, TAF-Io, or p300 (amino acids 1062–1143) for 30 min at room temperature in 150 mM KCl, 20 mM Tris-HCl (pH 7.6), 5 mM MgCl2, 1 mM dithiothreitol, 10 μg/ml bovine serum albumin, and 0.5% Nonidet P-40. Anti-histone antibody (MAB3422, Chemicon) was added, and the reactions were incubated for 30 min at room temperature. Protein G–agarose beads were added, and the reactions were incubated for 30 min at room temperature. After extensive washing, the bead-bound proteins were separated by SDS-PAGE and visualized by a phosphorimaging device.

Histone Peptide Pull-down Assays—HeLa cell nuclear extract was incubated with equal amounts of biotinylated histone H3 peptide (Upstate Biotechnology, Inc.) for 30 min at room temperature. Streptavidin–coated beads were added, and the reactions were incubated for 1 h at 4 °C. After extensive washing, the bead-bound proteins were separated by SDS-PAGE and analyzed by Western blot. The antibodies used were anti-pp32 (a kind gift of Dr. G. Pasternack, Johns Hopkins University, Baltimore, MD), anti-Set/TAF-Iα and anti-HP1 and HP1β (Upstate Biotechnology, Inc.).

Co-immunoprecipitation—Co-immunoprecipitation was carried out essentially as described by Hong and Chakravarti (32). Antibodies against HDAC1, HDAC2 (Cell Signaling) were used for immunoprecipitation followed by Western blotting with anti-pp32 or anti-Set/TAF-I antibodies.

GST Pull-down and Histone Deacetylation Assays—Recombinant GST fusion proteins were incubated with HeLa nuclear extract at 4 °C for 3 h and collected on glutathione beads with extensive washing. The bead-bound precipitates were then incubated with [3H]labeled acetylated histones in HDAC assay buffer (20 mM Tris-HCl (pH 8.0), 150 mM NaCl, 10% glycerol) for 2 h at 37 °C. The reaction was stopped by the addition of stop buffer (1× HCl, 0.16 M acetic acid). Released [3H] was extracted by ethyl acetate and counted in a scintillation counter.

Luciferase Assays—A (Gal4×4)-5′-TK-luciferase plasmid was stably transfected into 293T cells as described previously (22). The cells were seeded in 48-well plates and transfected using LipofectAMINE 2000 (Invitrogen) with pCMX-GAL4, pCMX-GAL4-pp32, or pCMX-GAL4-Set/TAF-Iα (50, 100, 200, or 300 ng) (six replicates each). Forty-eight h after transfection, the cells were harvested and lysed for luciferase assays (Promega).

Chromatin Immunoprecipitation (ChIP) Assays—ChIP was carried out as described in the protocols from Upstate Biotechnology, Inc. Briefly, 10-cm plates of MCF7 cells were transfected with 10 μg of Myc epitope-tagged pp32 or Set/TAF-Iβ (cloned into pDNA3.1/Myc-His vector, Invitrogen) using LipofectAMINE 2000. Four h after transfection, the medium (containing 10% fetal bovine serum) was replaced with medium supplemented with 5% charcoal-stripped serum and grown for 48 h. Cells were harvested and processed according to the protocol provided by Upstate Biotechnology, Inc. The lysates were immunoprecipitated with anti-Myc antibody (Sigma) or anti-acetylated histone H4 antibody (Upstate Biotechnology, Inc.), and the immunoprecipitates were collected and eluted and their cross-links reversed. The DNA was purified using the Qiagen PCR purification kit and used in PCR reactions with primers specific for the EB1 gene (35): EB1-A, 5′-AGG TTA GGC GAT CTT CGG GCA-3′; EB1-B, 5′-CAG ACC AAA CTT CCA CGC CAG-3′.

RESULTS AND DISCUSSION

Set/TAF-Iβ and pp32, along with TAF-Iα (a protein nearly identical to Set/TAF-Iβ) have been co-isolated by several groups (including ours as subunits of the INHAT complex) and have been implicated in multiple physiologically important chromatin-based pathways including apoptosis, mRNA stability, nucleosome assembly, and transcription (18–25, 37). We and others (18, 20, 22–25) have shown previously that TAF-Iα, Set/TAF-Iβ, and pp32 bind to histones and regulate transcription. Because Set/TAF-Iβ and TAF-Iα are identical, except for a short N-terminal portion, we focused our experiments on pp32 and Set/TAF-Iβ only.

To begin to examine the possibility that Set/TAF-Iβ and pp32 have the properties required to mediate the transcriptional repression associated with unmodified/hypoacetylated histones, we tested the critical property that Set/TAF-Iβ and pp32 may bind with different affinities to unacetylated versus acetylated histones. To investigate this possibility, we employed biotin-conjugated covalently modified histone H3 and H4 tail peptides (Fig. 1). We used histone modifications that have been associated with repressed or condensed chromatin (Fig. 1, marked by filled circles) (9–11, 15, 26), active chromatin (marked by open circles) (1–3, 7, 8, 27), or in the case of dimethyl-K4 histone H3, both (marked by a bull’s-eye) (28–30). As expected, and consistent with our previously published histone binding data, both pp32 and Set/TAF-Iβ associated strongly with unmodified histone H3 and H4 tails (Fig. 1, a and b). Importantly, this association is highly dependent on the modification state of the histone tail. In addition to unmodified histone H9 and H4 tail peptides, both Set/TAF-Iβ and pp32 bound strongly to histone H3 tail peptides methylated at lysine 9 or phosphorylated at serine 10, all modification states known to be associated with transcriptionally silent or condensed chromatin. Hyperacetylated histones are tightly linked to transcriptional activation. Consistent with that view and the proposed roles of both pp32 and Set/TAF-Iβ in transcriptional repression, acetylation of lysine residues on the histone H3 or H4 tail greatly weakened or abolished the ability of pp32 and Set/TAF-Iβ to associate with histone tails. In general, the robustness of binding is highly dependent on the extent of acetylation. For example, acetylation of a single lysine, such as histone H3 lysine 9 or lysine 14, reduced binding only modestly, but acetylation of both residues completely prevented the association of pp32 and Set/TAF-Iβ (Fig. 1a). These results demonstrate that these two proteins preferentially associate with un- or hypoacetylated histones. Consistent with this property, pp32 failed to bind to a histone H3 tail peptide, both phosphorylated at serine 10 and acetylated at lysine 14, a mark for active chromatin (Fig. 1a) (27). Similarly pp32 and Set/TAF-Iβ bound to unmodified histone H4 peptides and failed to bind tetraacetylated histone H4 peptides (Fig. 1b).

Because Set/TAF-Iβ and pp32 bound to unmodified/hypoacetylated histone tails, we next investigated its binding properties to differentially acetylated intact histones isolated from cells. To show that Set/TAF-Iβ and pp32 bind to native histones in an acetylation-sensitive manner, we isolated total histones from control or sodium butyrate (an HDAC inhibitor)-treated cells and utilized these in comparative binding assays. In vitro labeled pp32 and Set/TAF-Iβ, individually or together with TAF-Iα, showed significantly stronger binding to hypoacetylated histones isolated from nontreated cells when compared with their binding to histones isolated from treated cells (Fig. 1c, panels I–III). Unlike Set/TAF-Iβ and pp32, a bromodomain-containing region of p300 associated with both of the histone modification states with a preference for hyperacetylated histones, indicating the specificity of binding (Fig. 1c, panel IV). The concentration and acetylation status of the histones isolated from the cells used in this study was verified (Fig. 1c, panel V).

We then incubated HeLa cell nuclear extracts with biotinylated histone tail peptides to determine whether endogenous Set/TAF-Iβ and pp32 also show a binding specificity for hypoacetylated or repressively marked histones. Endogenous Set/TAF-Iβ and pp32, as well as TAF-Iα, were strongly retained by unmodified and methyl-K9 histone H3 tails but did not associate detectably with acetyl-K9 histone H3 tails (Fig. 1d). These interactions are specific because the control protein HP1β bound to methyl-K9 histone H3 only. However, unlike the HP1 protein, in which histone binding requires the presence of a specific tail modification (methyl-K9 histone H3) (9–11), the ability of Set/TAF-Iβ and pp32 to bind histones appears to require
the absence of a particular modification (lysine acetylation), with repressive modifications (methylation, phosphorylation) having no apparent negative effect on binding. Together, these results indicate that Set/TAF-Iβ and pp32 associate with histones in an acetylation-sensitive manner.

In yeast, the histone deacetylase Sir2 binds to the silencer protein Sir3, which also binds to hypoacetylated histones to establish and maintain transcriptional repression (15–17). Therefore, we reasoned that Set/TAF-Iβ and pp32 might associate with one or more HDACs to assist in perpetuating the repressed/hypoacetylated state established by the action of initial chromatin-recruited HDACs. To determine whether Set/TAF-Iβ and pp32 function in a similar manner and associate with mammalian HDACs, we carried out co-immunoprecipitation experiments. Using HeLa cell nuclear extracts and antibodies against HDACs 1 and 4–7 (class I and II HDACs), we consistently detected an interaction between Set/TAF-Iβ and HDAC1 but not HDACs 4–7, indicating the specificity of this interaction (Fig. 2a, and data not shown).

To demonstrate the recruitment of functional HDAC activity and the general nature of HDACs associated with INHAT subunits, we performed “on beads” histone deacetylase assays using material associated with GST-pp32 in a pull-down experiment (Fig. 2b). GST-pp32 pulled down ~40-fold greater HDAC activity from HeLa cell nuclear extracts than GST alone. The addition of trichostatin A, a class I and II HDAC inhibitor, completely inhibited the pp32-associated HDAC activity, whereas the addition of nicotinamide, a class III HDAC inhibitor, had only a negligible effect, indicating the specificity of the association. Moreover, a truncated version of GST-pp32 (AC2, amino acids 1–150), previously shown to be defective in the inhibition of activated transcription (23), did not associate with endogenous HDAC activity. Although the precise nature of the HDAC-containing complex requires further characterization, these results together indicate that Set/TAF-Iβ and pp32 associate with class I and/or II (but not class III) HDAC activities.

Association with HDACs and un- or hypoacetylated/repressively marked (but not hyperacetylated) histones provides a plausible mechanism for Set/TAF-Iβ and pp32 to mediate transcriptional repression signals by un- or hypoacetylated histones. As mentioned previously, proteins that transduce the repressive code of histones should be able to directly repress transcription when targeted to a promoter in vivo. In yeast, the Tup1 repressor protein binds to hypoacetylated histones and directly represses transcription (31). To determine whether Set/TAF-Iβ and pp32 are capable of directly repressing transcription, we targeted the Gal4-DNA binding domain (Gal4-DBD) fusions of pp32 and Set/TAF-Iβ to the promoter of a stable chromosomally integrated luciferase reporter gene. This stable reporter cell line has previously been utilized to demonstrate transcriptional repression by Gal4-thyroid receptor,
INHAT Links Histone Hypoacetylation to Repression

Set/TAF-Iβ and pp32 associate with HDACs. a, HeLa nuclear extract was immunoprecipitated with anti-HDAC1 antibody or control IgG and immobilized on protein G-Sepharose beads. After washing, the immunoprecipitated (IP) proteins were separated by SDS-PAGE and analyzed by Western blotting (WB) with the Set/TAF-Iβ antibody as indicated. b, GST pull-downs were performed using GST-tagged pp32, GST alone, or GST-pp32AC2 and HeLa nuclear extract. HDAC assays were performed using the pulled down material or 10% input, including trichostatin A or nicotinamide where indicated. The values given are fold counts released per min (CPM) over GST alone. TSA, trichostatin A.

Gal4-RevErb, and Gal4-PCNA (32, 33). The results of our experiments revealed that chromatin targeting of both pp32 and Set/TAF-Iβ repressed transcription in a dose-dependent manner in vivo (Fig. 3, a and b). These results indicate that Set/TAF-Iβ and pp32, when targeted to a promoter, have the ability to act as direct repressors of chromatin-integrated gene transcription.

To show that Set/TAF-Iβ and pp32 mediate transcriptional repression by hypoacetylated histones in intact cells, it was critical to demonstrate that they associate with hypoacetylated (but not hyperacetylated) chromatin in vivo. However, because of the paucity of known targets and appropriate antibodies, it had been difficult to identify in vivo targets of Set/TAF-Iβ and pp32. Nuclear hormone receptors provide an ideal system to study transcriptional regulation, because unliganded or antagonist-bound receptors are associated with the transcriptionally inactive state of genes, whereas ligand-bound receptors activate transcription (34). Accordingly, it has been demonstrated that, in the absence of 17β-estradiol, the promoters of transcriptionally inactive estrogen-responsive genes, including EB1, are hypoacetylated, whereas addition of the ligand causes promoter hyperacetylation and transcriptional activation (35, 36). This, in addition to our observations that Set/TAF-Iβ and pp32 associate with hypo-, but not hyperacetylated, histones in vitro, prompted us to examine by ChIP their presence at the estrogen hormone-responsive endogenous EB1 gene promoter.

MCF7 cells transfected with Myc epitope-tagged pp32 or Set/TAF-Iβ were treated with 17β-estradiol or solvent. ChIP with a Myc antibody revealed that both pp32 and Set/TAF-Iβ were present at the endogenous promoter of the estrogen target gene EB1 in untreated cells (Fig. 3c). More importantly, hormone treatment of the cells led to the significant release of pp32 and Set/TAF-Iβ from the promoter (Fig. 3c, compare lanes 5 and 6 with 7 and 8). Although the input levels remained constant, the observable difference in promoter-associated Set/TAF-Iβ and pp32 upon hormone treatment also served as a critical internal control. Moreover, control IgG failed to immunoprecipitate the promoter DNA (not shown). In a parallel experiment and consistent with published results, we confirmed by ChIP that the EB1 promoter remains hypoacetylated in untreated cells but is hyperacetylated in cells treated with 17β-estradiol (Fig. 3d, compare lanes 6 and 8). These results, by providing a link between the histone acetylation status of the EB1 promoter and its occupancy by Set/TAF-Iβ and pp32, indicate that these proteins are part of the in vivo transcriptional machinery involved in regulating this estrogen-responsive promoter.

Although hypoacetylated histones are tightly linked to transcriptional repression, the in vivo mechanism for such repression in humans has remained largely unknown. Our results uncovered an in vivo role for the INHAT subunits and histone-binding proteins Set/TAF-Iβ and pp32 as components of the chromatin-signaling network that translate the transcriptionally repressive “code” of histones. Set/TAF-Iβ and pp32 associate in vitro and in vivo preferentially with histones in the hypoacetylated and repressively marked state. Furthermore, the robustness of binding is dictated by the extent of histone acetylation. We present evidence that Set/TAF-Iβ and pp32 are associated with class I and/or II (but not class III) HDAC activity. Finally, we show that Set/TAF-Iβ and pp32 are able to directly repress transcription and associate with a promoter specifically in the hypoacetylated state in vivo. This, in addition to their histone binding and HDAC association properties, places them in an ideal position to transduce the transcriptionally repressive signals of hypoacetylated histones in humans.

Here we suggest an in vivo role for Set/TAF-Iβ and pp32 in integrating histone hypoacetylation and the transcriptionally inactive state in humans by using an estradiol-responsive promoter as an example. In the presence of activating amounts of the ligand estradiol, the promoter is hyperacetylated and therefore prevents the association of a significant quantity of TAF-Iβ and pp32 but promotes the association of bromodomain-containing proteins, including transcriptional coactivators/histone acetyltransferases (Fig. 3, d and e). In the inactive state, the promoter is hypoacetylated and permissive to occupancy by Set/TAF-Iβ and pp32 (35, 36) (Fig. 3, c–e). The HDAC activity associated with Set/TAF-Iβ and pp32 may help deacetylate chromatin to further establish the hypoacetylated state, which is subsequently occupied by Set/TAF-Iβ and pp32 (Fig. 3e). The concerted action of HDACs and Set/TAF-Iβ and pp32, by a mechanism functionally similar to that of the yeast Sir complex, reinforces the occupancy of the hypoacetylated promoter by Set/TAF-Iβ and pp32 via a feed forward mechanism, which maintains the transcriptionally inactive state (Fig. 3e). This is also similar to a feed forward mechanism recently described for the SMRT corepression protein (38). We have identified previously Set/TAF-Iβ and pp32 as subunits of the INHAT complex with histone masking activity, where binding of these proteins to histones prevents their acetylation by transcriptional coactivators (Fig. 3e) (18). Consistent with our proposed model, it is conceivable that Set/TAF-Iβ and pp32 first establish the inactive state of the target genes by the rapid deacetylation of hyperacetylated histones carried out by their associated HDACs. Once histones are deacetylated, Set/TAF-Iβ
and pp32 tightly associate with them and maintain repression by their histone masking as well as direct repression function (Fig. 3e).

In conclusion, this study defines novel in vivo functions of Set/TAF-Iβ and pp32 as mammalian proteins that can potentially mediate transcriptional repression by unmodified or hypoacetylated histones. Future studies investigating additional target genes, as well as pp32- and Set/TAF-Iβ-interacting proteins, will enable us to more precisely define the cellular role these proteins play in transcriptional repression and the mechanisms involved. In addition, we predict that the analysis of other previously known histone-binding proteins may reveal important information on their roles as signal transducer proteins in chromatin-based processes, including histone deposition, DNA replication, apoptotic DNA fragmentation, and transcription.

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