Acetylated Sp3 Is a Transcriptional Activator*

Sudhakar Ammanamanchi§, James W. Freeman§, and Michael G. Brattain¶

From the |Department of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Buffalo, New York 14263 and the Department of Medicine, The University of Texas Health Science Center, San Antonio, Texas 78229

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The Sp gene family consists of four members, which are referred to as Sp1–Sp4. Sp1, Sp2, and Sp4 are known to be activators of gene transcription, whereas Sp3 can be an activator or a repressor (1). Sp1 and Sp3 proteins contain two glutamine-rich activation domains at the N terminus and a highly conserved zinc finger region at the C terminus. Sp1 and Sp3 transcription factors bind to the same DNA sequence (consensus GC box) with similar affinities in many gene promoters (2). Unlike Sp1, Sp3 contains an inhibitory domain between the second glutamine-rich activation domain and zinc finger region (3). The repressor function of Sp3 has been attributed to a charged amino acid triplet (KEE) in the inhibitory domain (3). The lysine in this triplet has been reported to undergo acetylation, and it was suggested that acetylation silences Sp3 activity because mutation of this lysine residue stimulates Sp3 activity (4). However, later work (5) from the same lab indicated sumo modification of the same lysine residue silences Sp3 activity leading to reconsider the role of Sp3 acetylation on its activity. Consequently, we have addressed the functional role of Sp3 acetylation using transforming growth factor-β (TGF-β) receptor type II promoter as a target in these studies and demonstrated that acetylation stimulates but does not silence Sp3 activity.

TGF-β plays a significant role in the growth inhibition of most normal epithelial and some cancer cells. TGF-β mediates its biological affects through cell surface receptors known as type I (RI) and type II (RII) (6). Because RI and RII are required for TGF-β-mediated growth inhibition, loss of either receptor contributes to TGF-β resistance, loss of TGF-β tumor suppressor activity, and subsequent tumor formation and progression (7–9). TGF-β resistance due to methylation of the RI promoter or RI promoter repression by Sp1 deficiency was reported in gastric and colon cancer cells (10, 11). Mutational inactivation of the RII gene in genetic syndromes of gastric and colon carcinoma has identified the RII gene as a tumor suppressor (8, 12, 13). Transcriptional repression of RII due to reduced binding of nuclear proteins to the RII promoter in keratinocytes, pancreatic cancer cells, and breast cancer cells has been shown as a cause for TGF-β resistance (14–16). Ectopic RI and RII expression in RI- and RII-deficient cells led to restoration of TGF-β response and reversal of malignancy in breast and colon cancer cells (7, 9). Thus, the loss of transcriptional control of RII expression appears to have a significant role in determining the malignant phenotype of a broad variety of types of cancer cells.

The RII promoter has been characterized (17). The RII promoter lacks a distinct TATA box, is GC-rich, and depends upon the Sp1 transcription factor for the initiation of transcription. The RII promoter contains two consensus Sp1 sites (-25 bp and -143 bp relative to the transcription start site). MCF-7 breast cancer and MIA PaCa-2 pancreatic cancer cells are resistant to growth inhibition by TGF-β because of reduced transcription of RII. This was partly due to reduced/low levels of Sp1 expression in these cells (15, 16). Subsequently, we showed that unmodified Sp3 acts as a transcriptional repressor of RII in MCF-7L cells (18) and DNA methyltransferase inhibitor, 5 azacytidine induces RII expression in cancer cells through a combination of increased Sp1 and decreased Sp3 protein levels/activities (19). We now report that treatment of MCF-7L breast cancer cells with the histone deacetylase inhibitor trichostatin A (TSA) induces acetylation of Sp3 in addition to accumulation of acetylated histones H3 and H4 in association with RII promoter DNA. Acetylation of transcription factors such as p53, E2F1, Myo D, and EKLF has been shown to enhance transcriptional potency and affect protein-protein in

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§ To whom correspondence should be addressed: Dept. of Pharmacology and Therapeutics, Roswell Park Cancer Institute, Elm and Carlton Strs., Buffalo, NY 14263. Tel.: 716-845-3557; Fax: 716-845-4437; E-mail: michael.brattain@roswellpark.org.

¶ The abbreviations used are: TGF-β, transforming growth factor; TSA, trichostatin A; RII, receptor type II; HAT, histone acetyltransferase; ChIP, chromatin immunoprecipitation; Luc, luciferase; CAT, chloramphenicol acetyltransferase; TLC, thin layer chromatography; HDAC, histone deacetylase.

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Cell Culture—MCF-7E, MCF-7L breast, and MIA PaCa-2 pancreatic cancer cells were grown in McCoy’s 5A medium supplemented with 10% fetal bovine serum (Sigma), amino acids, antibiotics, pyruvate, and vitamins (Invitrogen). Cultures were maintained at 37 °C in a humidified atmosphere of 5% CO2. Wherever indicated MCF-7E, MCF-7L, and MIA PaCa-2 cells were treated for 24 h with 100 ng/ml of TSA.

Chromatin Immunoprecipitation (ChIP) Assay—MCF-7L and MIA PaCa-2 cells were plated at a density of 4 × 106 cells/15-cm dish and incubated overnight at 37 °C in a humidified atmosphere of 5% CO2. Wherever indicated MCF-7E, MCF-7L, and MIA PaCa-2 cells were treated for 24 h with 100 ng/ml of TSA.

Immunoprecipitation and Western Blot Analysis—Nuclear extracts were obtained from control and TSA-treated MCF-7L breast cancer cells. Equal amounts of nuclear extracts were immunoprecipitated with rabbit anti-human Sp3 polyclonal antibody (Upstate Biotechnology). Immunocomplexes were resolved by 7.5% SDS-PAGE and then blotted with pan-acetyl lysine or goat anti-human Sp3 antibodies (Santa Cruz Biotechnology).

Transfections and Luciferase Assay—The RII (−219 bp RII-Luc) promoter-luciferase reporter construct was used to determine RII promoter activity (21). The RII-Luc construct and control null vector without RII promoter insert (pG52) were transiently transfected into MCF-7L breast cancer cells using the FuGENE 6 method (Roche Applied Science) with a β-galactosidase plasmid for normalization (18). Cells were treated with 100 ng/ml of TSA 4 h following transfection. Cells were harvested at 24 h following TSA treatment, and promoter activities were determined using a commercial luciferase assay (Luciferase Assay System, Promega). To analyze the ectopic Sp3 effects in the presence and absence of TSA, Sp3-deficient MCF-7E cells were transfected with RII promoter-luciferase reporter or pGL2 control vector without RII promoter and CMV-Sp3 cDNA along with β-galactosidase plasmid for normalization. Cells were treated with TSA 4 h following transfection. Cells were harvested at 24 h following TSA treatment, and promoter activities were determined. To determine the effects of histone acetyltransferase p300 on Sp3-mediated RII promoter activity, wild type p300 (CMV-p300) or HAT domain-deleted mutant p300 (CMV-p300ΔHAT) along with RII-Luc plasmid were transfected into MCF-7L cells. Cells were harvested 48 h following transfection, and luciferase activity was determined following normalization to β-galactosidase.

Fig. 1. TSA induces accumulation of acetylated histones H3 and H4 in chromatin associated with the RII gene. Chromatin fragments from cells cultured with and without TSA for 24 h were immunoprecipitated with antibody to acetylated histones H3 and H4 or control normal rabbit serum (NRS). PCR primers for the RII and actin gene promoters were used to amplify the DNA isolated from the immunoprecipitated chromatin as described under “Experimental Procedures.”

Fig. 2. TSA induces RII promoter activities. MCF-7L cells were transiently transfected with the RII-Luc reporter vector or control vector without RII promoter (pGL2) along with β-galactosidase plasmid for normalization of transfection efficiency as described under “Experimental Procedures.” Cells were treated with TSA 4 h following transfection. Cells were harvested at 24 h following TSA treatment, and luciferase activity was determined and presented as relative units.

EXPERIMENTAL PROCEDURES
The above constructs were transiently transfected into MCF-7L cells using the FuGENE 6 method (Roche Applied Science). For normalization of transfection efficiency, β-galactosidase plasmid was co-transfected into the cells. Cells were treated with TSA 4 h following transfection. Cells were harvested at 24 h following TSA treatment, and CAT assays were performed as described under “Experimental Procedures.” CAT assay results were analyzed by TLC, and the TLC plate was quantitated directly using an alpha imager system.

RESULTS AND DISCUSSION

TSA Induces Accumulation of Acetylated Histones in Chromatin Associated with the RII Gene—TGF-β receptors RI and RII are essential for TGF-β-mediated growth suppression of normal epithelial and some cancer cells. TGF-β resistance due to loss of expression of RI or RII has been linked to tumor formation and progression (7–9). Ectopic RII expression in receptor-deficient cancer cells reduced tumorigenicity in athymic nude mice, thus indicating the role of RII as a tumor suppressor (7, 8). MCF-7L breast and MIA PaCa-2 pancreatic cancer cells acquire resistance to growth inhibition by TGF-β due to reduced transcription of RII (15, 16). Recent studies (16, 19, 20, 23, 24) indicated DNA methylation and histone deacetylation controls Sp3 function.}

FIG. 3. Mutant GC box RII construct blocks TSA-mediated promoter activity. MCF-7L cells were transiently transfected with the −47 RII-CAT construct containing either a wild type or mutated GC box along with a β-galactosidase plasmid for normalization of transfection efficiencies as described under “Experimental Procedures.” Cells were treated with TSA 4 h following transfection. Cells were harvested at 24 h following TSA treatment, and CAT assays were performed as described under “Experimental Procedures.” CAT assay results were analyzed by TLC, and the TLC plate was quantitated directly using an alpha imager system.

FIG. 4. Sp1/Sp3 associates with histone deacetylase activity. The Sp1/Sp3-associated histone deacetylase activity was precipitated from MCF-7L nuclear extracts using agarose-conjugated Sp1, Sp3, or control IgG antibodies as described under “Experimental Procedures.” The deacetylase activity associated with the precipitated complexes was assessed by the ability to remove an acetyl group from an acetylated substrate. Once the substrate gets deacetylated, it reacts with the developer to produce a fluorophore detectable on a fluorometric reader. In the presence of TSA, the deacetylase activity is inhibited.
lation as modes of inactivation of several genes. ChIP analysis was used to examine the effect of HDAC inhibition on the acetylation of histones H3 or H4 associated with the RII gene promoter. Chromatin fragments from cells cultured with or without TSA for 24 h were immunoprecipitated with antibodies to acetylated histones H3 or H4. DNA from the immunoprecipitate was isolated, and PCR using RII promoter primers was performed (Fig. 1). Accumulation of RII with highly acetylated histones H3 and H4 was observed in TSA-treated MCF-7L and MIA PaCa-2 cells in comparison to untreated control cells. The accumulation of acetylated histones H3 and H4 indicated histone deacetylation was involved in the transcriptional repression of RII. The TSA effect on RII is selective because the β-actin gene was not affected. The transcription of RII promoter may be repressed by a compact chromatin structure, which is maintained by increased HDAC activity in MCF-7L cells.

TSA Effects Are Mediated by a GC Box on the RII Promoter—TSA-treated MCF-7L cells showed enhanced RII mRNA expression (data not shown). To determine whether the enhanced RII expression levels following TSA treatment were due to increased RII transcription we analyzed RII promoter activities using an RII promoter-luciferase reporter construct in control and TSA-treated MCF-7L cells. The RII promoter exhibited enhanced activity in the presence of TSA (Fig. 2). The RII promoter lacks a distinct TATA box and is highly GC-rich. It contains two GC boxes at −25 bp and −143 bp relative to the transcription start site, which have been characterized as Sp1-binding sites (17). We have shown previously that the GC box at −25 bp is critical for RII promoter activity in MCF-7L cells (15). This site also mediates the transcriptional repression of RII by Sp3 (22). To determine whether the TSA effects are mediated through this GC box on the RII promoter, we analyzed the activities of wild type (−47 bp RII-CAT) and mutant GC box (−47 bp Spm RII-CAT) RII promoter constructs in control and TSA-treated MCF-7L cells. Although the activity of the wild type GC box RII promoter was up-regulated in the presence of TSA, the mutant GC box RII construct was not modulated, thus confirming that TSA effects are mediated through this GC box (Fig. 3).

Effect of TSA on Sp1 and Sp3 Binding Affinities and Their Association with HDAC1 and p300—We previously reported (15, 16) that MCF-7L and MIA PaCa-2 cells express reduced levels of Sp1 protein. In addition MCF-7L cells express high levels of Sp3 protein, which acts as a transcriptional repressor of RII (18). Inhibition of DNA methylation by 5 azacytidine induced RII expression through a combination of increased Sp1 and decreased Sp3 binding affinities (19). To determine whether the TSA-mediated RII expression is through modulation of Sp1 and Sp3 binding affinities, we carried out electrophoretic mobility shift assays on control and TSA-treated MCF-7L nuclear extracts using 32P-labeled consensus Sp1 oligonucleotide. Both the control and TSA-treated MCF-7L nuclear extracts showed the high Sp3 binding and low Sp1 binding pattern we had previously observed in these cells (18). This indicated TSA treatment did not enhance transcription through modulation of Sp1 and Sp3 binding affinities (data not shown). ChIP analysis using Sp1/Sp3 antibodies also did not show any change in the Sp1/Sp3-associated RII promoter DNA in TSA-treated MCF-7L cells (data not shown). Consequently, TSA mediates RII promoter activities by a mechanism other than alteration of the DNA binding activities of Sp1 and Sp3. This data is consistent with several other reports indicating

**Fig. 5.** TSA induces acetylation of Sp3. Nuclear extracts from control and TSA-treated MCF-7L cells were immunoprecipitated with rabbit anti-human Sp3 polyclonal antibody, and the immunoprecipitates were resolved by 7.5% SDS-PAGE, transferred to a nitrocellulose membrane, and probed with rabbit anti-human pan-acetyl lysine antibody or goat anti-human Sp3 polyclonal antibody. Ac Sp3, acetylated Sp3.

**Fig. 6.** Ectopic Sp3 affects RII promoter activity. The RII promoter-Luc reporter or control PGL2 vector without RII promoter and CMV-Sp3 vector along with a β-galactosidase plasmid was transiently transfected into Sp3-deficient MCF-7E cells. Cells were treated with TSA 4 h following transfection. Cells were harvested 24 h following TSA treatment, and luciferase activity was determined following normalization to β-galactosidase.
Histone acetyltransferase p300 stimulates RII promoter activity.

The RII promoter-Luc reporter and wild type or mutant p300 (CMV-p300 or CMV-p300ΔHAT) was transiently transfected along with a β-galactosidase plasmid for normalization into MCF-7L cells as described under “Experimental Procedures.” Cells were harvested at 48 h following transfection, and luciferase activity was determined following normalization to β-galactosidase.

Histone deacetylase inhibitors induce the expression of target genes without altering the Sp1/Sp3 binding affinities (23–25). The mechanism of RII induction by TSA may involve modifications of Sp1 and/or Sp3 proteins, alterations in their interaction with other proteins, or modulation of proteins directly or indirectly interacting with Sp1 and/or Sp3. Co-immunoprecipitation experiments using Sp1/Sp3 and HDAC1/p300 antibodies indicated that Sp1 as well as Sp3 interacts with HDAC1 and p300. However, these interactions were not affected by TSA, thus ruling out alterations in the association of Sp1/Sp3 and HDAC1/p300 as a cause for RII induction in MCF-7L cells. The transcription of RII promoter may be repressed by a compact chromatin structure, which is maintained by increased HDAC activity in MCF-7L cells. Thus, we hypothesized that TSA was acting by inhibiting HDAC enzymatic activity associated with Sp1 and Sp3.

Sp1/Sp3 Associates with Histone Deacetylase Activity—To test whether Sp1/Sp3 associates with an active histone deacetylase, we immunoprecipitated endogenous Sp1/Sp3 from MCF-7L nuclear extracts using anti-Sp1 and anti-Sp3 or control IgG antibodies. The precipitated complexes were tested for their ability to deacetylate an acetylated histone substrate (Fig. 4). We showed that Sp1 as well as Sp3 associate with deacetylase activity, and this activity is abolished when the deacetylase inhibitor TSA is included in the deacetylation reaction, suggesting that the histone deacetylase activity associated with Sp1 and Sp3 is completely sensitive to TSA. TSA treatment suppresses the Sp1/Sp3-associated HDAC activity leading to a local disruption of the nucleosome structure of the RII promoter by acetylation of histones H3 and H4. It is interesting to note that TSA induced RII expression in MCF-7L cells without decreasing Sp3 binding, because we have previously reported that Sp3 acts as a transcriptional repressor of RII in these cells (18). One plausible reason may be that unmodified Sp3 acts as a transcriptional repressor, and TSA-mediated Sp3 modification may convert Sp3 into transcriptional activator.

Sp3 Acetylation and RII Promoter Activity—The lysine residue in the inhibitory domain of Sp3 was shown to be susceptible to acetylation, and it was hypothesized that acetylation silences Sp3 activity (4). However, it was later reported that sumo modification of the same lysine residue of Sp3 silences Sp3 activity (5). Consequently, the functional role of Sp3 acetylation was unclear. We previously reported that unmodified Sp3 acts as a transcriptional repressor of RII in MCF-7L cells (18). To determine whether TSA-mediated Sp3 acetylation is involved in the transcriptional activation of RII, we analyzed the acetylation status of Sp3 using a pan-acetyl lysine antibody in control and TSA-treated MCF-7L cells. TSA induced acetylation of Sp3 in MCF-7L cells (Fig. 5). Sp3 expression levels were used to normalize protein. Acetylation of transcription factors such as p53, E2F1, Myo D, and EKLF has been shown to enhance transcriptional potency and affect protein-protein interactions (4). We have previously shown (18) that RII-positive MCF-7E breast cancer cells express Sp1 protein but were Sp3-deficient. To confirm that the TSA-mediated Sp3 modification affects RII promoter activity, we have analyzed effects of ectopic expression of Sp3 on the RII promoter activity in control and TSA-treated, Sp3-deficient MCF-7E breast cancer cells. Although ectopic Sp3 repressed RII promoter in the absence of TSA, Sp3 stimulated RII promoter activity in the TSA-treated cells (Fig. 6). Histone acetyltransferase p300 has been reported to acetylate Sp3 protein (4). Because MCF-7L cells express high levels of Sp3 and the protein was shown to repress RII promoter activity, we wanted to ascertain if histone acetyltransferase p300 was able to stimulate Sp3 transactivation of the RII promoter. We co-transfected wild type CMV-p300 or HAT domain deleted mutant p300 vector (CMV-p300ΔHAT) along with the RII promoter-luciferase construct in MCF-7L cells and analyzed the RII promoter activities (Fig. 7). The wild type p300 stimulated Sp3-mediated RII promoter activity but not the acetyltransferase activity null p300 mutant. This result suggests that p300 acts as a co-activator of Sp3 and/or possibly the acetylation activity of p300 is involved in the acetylation of Sp3 and the concomitant activation of RII promoter. Histone acetyltransferase p300 but not PCAF has been shown to acetylate Sp3 protein (4). PCAF has been shown to associate with NF-Y in the transcriptional activation of RII (27). It was also shown that binding to the GC box by Sp1/Sp3 was influenced by the presence of an intact NF-Y-binding site on the RII promoter (22). Consequently, it is plausible that p300-mediated Sp3 acetylation as well as PCAF and NF-Y association contributes to RII expression in TSA-treated MCF-7L cells. This is the first report indicating that acetylation turns Sp3 from a transcriptional repressor to transcriptional activator.
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