Tip60 Is a Nuclear Hormone Receptor Coactivator*

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The androgen receptor (AR) is a member of the nuclear hormone receptor superfamily. Recent work in this field has been focused upon defining the mechanisms of transcriptional control exacted by members of this superfamily. Using a COOH-terminal region of the human AR in a yeast two-hybrid screen, we have identified Tip60 as an AR-interacting protein. In this report, we show that Tip60, which was originally identified as a coactivator for the human immunodeficiency virus Tat protein, can enhance AR-mediated transactivation in a ligand-dependent manner in LNCaP and COS-1 cells. In addition, our experiments show that Tip60 can also enhance transactivation through the estrogen receptor and progesterone receptor in a ligand-dependent manner; thus identifying Tip60 as a nuclear hormone receptor coactivator. Our studies also demonstrate that Tip60 co-immunoprecipitates with the full-length AR in vitro and that, in our system, Tip60 enhances transactivation to levels observed with the coactivators steroid receptor coactivator 1, p300, and CREB-binding protein. The importance of such proteins in enhancing nuclear hormone receptor-mediated transcriptional activation is widely accepted, and this work suggests that Tip60 may have an equally important role to play.

The AR is a member of the nuclear hormone receptor superfamily of ligand-dependent transcription factors. In the nucleus, the ligand-activated receptors bind to their cognate response elements in or near promoter regions of target genes to positively or negatively regulate gene expression (reviewed in Ref. 1). The mechanism by which specific modulation of target gene expression is achieved by nuclear receptors (NRs) is not clearly defined. Early research indicated that there might be factors common to different receptors required for efficient transcriptional activation. This was demonstrated by the observation that different ligand-bound steroid receptors affected components of the pre-initiation complex and that this is likely to be mediated by hyperacetylated histones with stabilized pre-initiation complexes and that this is likely to be mediated by hyperacetylated histones with stabilized pre-initiation complexes and that this is likely to be mediated by hyperacetylated histones with stabilized pre-initiation complexes and that this is likely to be mediated by hyperacetylated histones with stabilized pre-initiation complexes.

Recent work investigating the progesterone receptor (PR) has shown that when bound by ligand, it exists in stable ternary complexes with SRC-1 and TIF-2 (20). Such complexes may exist with other NRs, enhancing the potential for diverse interaction upon ligand binding. In addition, many coactivators have been shown to interact with one another, such as CBP/PCAF (21), SRC-1/CBP (22), SRC-1/p300 (23), and SRC-1/PCAF (11). Also, multiple NR-interacting domains have been identified in certain coactivators such as SRC-1 (24). The multiplicity of such protein interactions therefore suggests that maximal transcriptional activation is likely to require the targeted coupling of hyperacetylated histones with stabilized pre-initiation complexes and that this is likely to be mediated by multimeric, coactivating, HAT-containing protein complexes. The observed complexity of gene expression may be reflected in the composition of these higher-order, activating complexes.

In this study, we sought to identify AR-interacting proteins in an attempt to dissect the mechanism by which the AR exerts transcriptional control. Due to the multitude of potential interacting proteins, we utilized the yeast two-hybrid system (25). This led to the identification of the Tat-interacting protein (Tip60) as an AR-interacting protein. Tip60 was originally reported as a human coactivator for the human immunodeficiency virus type 1-encoded Tat protein (26), and more recent
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work has shown that it is a member of a related genes involved in transcriptional regulation (27). Subsequently, we demonstrated that Tip60 acts as a ligand-dependent coactivator for the AR, PR, and ER (estrogen receptor). The level of enhancement observed is comparable to that of SRC-1, p300, and CBP in our system, and, taken together, these results suggest that Tip60 is potentially an important member of the NR coactivator family.

**EXPERIMENTAL PROCEDURES**

**Yeast Two-hybrid Screening**

Residues 559–918 of the hAR (GenBank accession number m23263) containing the DNA and ligand binding domains were amplified by PCR from pGEM5zf-AR (a gift from S. Liao, University of Chicago, Chicago, IL) using primers GGACTCTGAGAATCTGACACTATTCTTT and GTGTCTGTGCTCCTGCTGGA and subcloned into pB7-7 via Xba I sites. This fragment was released by NdeI-BamHI restriction of pB7-7-hAR559–918 and subcloned downstream of the GAL4 DNA binding domain (DBD) in pAS2-1 (CLONTECH). pAS2-1-hAR559–918 was transformed into the yeast strain J69-4A (a gift from P. James, University of Wisconsin). J69-4A is an improved two-hybrid strain with a GAL4 reporter gene that serves to test transcriptional activators (28). The subsequent tryptophan-positive strain was transformed with 50 μg of a human brain cDNA GAL4 activation domain fusion library constructed in pACT2 (CLONTECH). 200,000 transformants were plated onto media lacking tryptophan, leucine, and histidine. 200,000 cDNA clones in the presence of the GAL4DBD:hAR559–918 fusion were plated onto media lacking tryptophan, leucine, and histidine. The activity observed was compared to the presence of the DBD alone. After sequencing and examination of the GenBank TM database, we determined that one interacting clone was encoded by a 1.7-kb DNA fragment with a 96% identity to Tip60 (GenBank accession number u40989), which maintained the reported open reading frame for Tip60 (25). Sequence alignment revealed that the identified clone began 70 residues downstream of the NH2 terminus. Subsequent two-hybrid screens in our laboratory have identified full-length Tip60 cDNA as an interacting clone, suggesting that the 70 residues absent from our construct did not significantly interfere with the interaction. All Tip60 constructs used in this work are derived from the original 1.7-kb clone.

**Analysis of Tip60-AR Interaction Using the Yeast Two-hybrid System**

pAS2-1-hAR constructs were co-transformed with pACT2tip60 or pACT2 into J69-4A according to the manufacturer’s guidelines (CLONTECH). Subsequent Trp-positive, Leu-positive colonies were inoculated in triplicate into selective media and grown at 30°C overnight in the presence or absence of 1 μM DHT. Samples were diluted to an A600 of 0.2 and re-grown to an A600 of 0.6–0.8. Samples were divided into three 1-ml aliquots. Cells were recovered by centrifugation at 14,000 rpm for 5 min, washed once with buffer Z (0.1 M sucrose, 0.5 M potassium phosphate, pH 7.0, 10 mM KCl, and 10 mM MgSO4) and resuspended in 800 μl of buffer Z containing 21 μl of β-mercaptoethanol. 10 μl of 0.1% SDS were added, followed by 50 μl of chloroform. Samples were vortexed for 1 min and placed at 30°C, and 200 μl of o-nitrophenyl-β-D-galactopyranoside (4 mg/ml in buffer Z) were added. Reactions were timed and terminated upon observing an obvious yellow color or after 1 h via the addition of 500 μl of 1 M Na2CO3. A405 of the samples was determined, and activity was calculated as follows: (A405 × 1000/A600 × time). All assays were performed in triplicate and repeated at least three times. hAR fusion proteins for these experiments were constructed as follows: hAR559–918 was constructed as described above. Additional constructs were amplified by PCR using the following primer combinations: hAR1–150 (pLTCAGAGATCGCGAAGTCGCTGGA – pGL3-GLS) and hAR559–918 (pLTCAGAGATCGCGAAGTCGCTGGA – pGL3-GLS). hAR1–150 was constructed using a 5′ Bgl II site of pCDNA3. The following mammalian expression plasmids were used: pCMV, pCMV5, and pCMV5-hAR. The reaction was terminated via the addition of 50 μl of 1 M Na2CO3, A405 values were obtained using a MS9000 plate reader (Dynatech), and activity was calculated as described above. Transfections were performed in triplicate and repeated at least three times.

**In Vitro Interaction of AR and Tip60**

Templates were prepared using a Gene цен kit (Anachem) and resuspended in RNase-free distilled H2O. An in vitro coupled transcription and translation kit (T7-TNT; Promega) was used according to the manufacturer’s instructions. After completion of the 95-min reaction, samples were combined equally on ice, as indicated. 1 ml of immunoprecipitation buffer (50 mM Tris, pH 7.5, 150 mM NaCl, 0.2 mM Na3VO4, 0.5% Nonidet P-40, 1 mM phenylmethylsulfonl fluoride, 1 mM dithiothreitol, 25 μg/ml leupeptin, 25 μg/ml aprotinin, and 25 μg/ml pepstatin) was added to each sample, mixed, and incubated on ice for 30 min. 20 μl of protein G-Sepharose (PGS) pre-washed with the immunoprecipitation buffer were added to each sample and incubated for an additional 4 h at 4°C with rotation to remove any proteins that interacted non-specifically with PGS. PGS was removed by centrifugation at 14,000 rpm for 3 min. The supernatant was incubated with 2.5 μg of penta-His antibody (Qiagen) overnight at 4°C with rotation. 20 μl of PGS were added to each sample and incubated at 4°C for an additional 60 min. PGS antibody conjugates were recovered by centrifugation at 14,000 × g for 3 min, resuspended in 1 ml of buffer B (PBS, 0.2% Triton X-100, and 350 mM NaCl), and re-spun. Samples were resuspended in 1 ml of buffer B (PBS and 0.2% Triton X-100), re-spun, and resuspended in SDS sample buffer. Samples were resolved on 10% polyacrylamide gels at 200 V for 45 min with equal loading. The gel was fixed for 30 min (10% propionic acid and 10% acetic acid), soaked in Amplify (Amersham Pharmacia Biotech) for 30 min, dried under vacuum, and exposed an x-ray film for 4–24 h at –70°C. Templates used were pG77-7bAR1–918 and full-length Sap1a in pAS4 (a gift from A. D. Sharrocks, Newcastle University). pRSET-C-Tip60 was constructed via excision of a BamHI fragment from pACT2tip60 utilizing a BamHI site in the 3’ untranslated region of Tip60 cDNA and cloned in-frame with the hexa-His tag of pRSET-C (R&D Systems). Orientation was determined via restriction analysis and confirmed by sequencing.

**Transient Transfections of COS-1 and LNCaP Cells**

**COS-1 Cells**—Cells were cultured for at least 48 h before transfection in Dulbecco’s modified Eagle’s medium (Life Technologies, Inc.) supplemented with 10% fetal calf serum that had been stripped of steroids by treatment with dextran-coated charcoal. Cells were routinely grown to 60–80% confluence, washed, removed, and seeded at a density of 5 × 105 cells/ml in fresh medium in 35-mm wells (Corning). After 20 h, cells were transfected once with second medium containing a portion of Tip60, a Nuclear Hormone Receptor Coactivator

**LNCaP Cells**—These cells were routinely subcultured in RPMI 1640 medium (Life Technologies, Inc.) supplemented with 10% fetal calf serum. Cells were seeded at 1 × 105 cells/well in 35-mm wells at least 24 h before transfection. For studies examining the ER and PR, cells were cultured in phenol red-free RPMI 1640 medium supplemented with 10% dextran-coated charcoal-fetal calf serum. Cells were transfected using Lipofectin for a period of 8 h and washed, and medium containing vehicle or steroid was added as indicated. Cells were harvested at 72 h after transfection and analyzed as described above.
**RESULTS**

**Tip60 Interacts with the Ligand Binding Domain of the AR—**

Yeast two-hybrid screening, which was originally described by Fields and Song (25), using the AR construct AR559–918 comprising the DNA and ligand binding domains (DBD and LBD, respectively) as bait identified Tip60 as an AR-interacting protein (see “Experimental Procedures”). In an attempt to define the specificity of the interaction with the AR, we examined the association of Tip60 with various GAL4DBD:AR constructs in the yeast two-hybrid system in the presence of 1 μM DHT. AR constructs spanning the first 300 residues (AR1–150 and AR1–300) and the DBD of the AR (AR559–624) failed to interact with the Tip60:GAL4 fusion protein (Fig. 1a), whereas both AR559–918 and AR624–918 interacted specifically with Tip60. Therefore, Tip60 appears to interact specifically with the LBD of the AR. The interaction appeared to be increased significantly with the attachment of the DBD to the LBD, although the DBD alone does not readily interact by itself. A potential explanation for this observation is that the DBD may be prevented from folding into the optimal conformation for interaction when positioned directly at the COOH terminus of the GAL4DBD. The presence of the DBD may serve to distance the LBD from the GAL4DBD in this scenario, or, alternatively, it may be that the AR DBD is essential for directing or influencing the conformational change upon ligand binding.

The interaction of AR and Tip60 is not ligand-dependent but is enhanced in the presence of 1 μM DHT; yeast two-hybrid analysis performed in the absence and presence of 1 μM DHT showed a significant increase in interaction in the presence of DHT. Data are expressed as the mean of at least three separate experiments performed in triplicate ± S.D.

(D. M. Livingston, Dana-Farber Cancer Institute, Boston, MA). The reporter plasmid pMTV-Luc (a gift from R. Vogel, Merck and Co., Inc.) was used for experiments with the AR in COS-1 cells and for experiments with the PR in LNCaP cells. For the ER in LNCaP cells, the reporter plasmid was pVITREEluc (a gift from B. Westley, Newcastle University). In addition, pPSAAluc, a reporter construct derived from the PSA promoter, was used for AR-based experiments in LNCaP cells. A reporter plasmid was pVITEREluc (a gift from B. Westley, Newcastle University). In addition, pPSAAluc, a reporter construct derived from the PSA promoter, was used for AR-based experiments in LNCaP cells.

**Tip60 Interacts with the AR in Vitro—**

To confirm the interaction data obtained from the two-hybrid system, we sought to determine whether Tip60 could interact with the AR in vitro. Using proteins transcribed and translated in vitro, we attempted to co-immunoprecipitate the AR with Tip60 using an anti-His antibody recognizing His-tagged Tip60. The transcription factor Sap-1a (Etk4) (30), an Ets family-related protein, was included as a control for this experiment. Before immunoprecipitation, labeled proteins were mixed after in vitro translation and before immunoprecipitation (Pre-IP) as indicated in lanes 1–4. Samples were incubated with anti-His antibody at 4 °C overnight, which recognized the His-tagged Tip60. Antibody complexes were recovered with PGS, washed, and subjected to SDS-polyacrylamide gel electrophoresis. Resultant gels were soaked in Amplify (Amersham Pharmacia Biotech) and exposed to x-ray film (lanes 5–8, Post-IP). Significant amounts of AR co-immunoprecipitated with Tip60 (lane 8) versus immunoprecipitation in the absence of Tip60 (lane 7). Incubation of Tip60 with Sap-1a (lane 6) did not alter the amount of Sap-1a recovered (lane 5), demonstrating that the Tip60:AR interaction is specific.
Tip60 Enhances AR-mediated Transactivation—

Having outlined the role of Tip60 in AR-regulated promoters, we wished to investigate the role of Tip60 in transcriptional coactivation with other nuclear receptors. pMTVluc was used to study the effect of Tip60 on PR-dependent transactivation. Co-transfection of LNCaP cells with pMTVluc, PR, and Tip60 in the presence of progesterone led to a 4-fold increase in PR-mediated transactivation (Fig. 4a) without any effects on basal levels of transcription. This Tip60-mediated increase was comparable to levels observed with the AR (Fig. 3a) and was also observed with the PR in COS-1 cells (data not shown). We also investigated the effect of Tip60 on ER-dependent transactivation (Fig. 4b). Using pVITEREluc, a reporter vector derived from the vitellogenin gene, a 3-fold increase in ER-dependent transactivation was noted. Levels of enhancement were not as high as those observed with the PR; however, this may reflect the promoter constructs studied.

Tip60 Enhances PR- and ER-dependent Transactivation—

In an attempt to define the mechanism by which Tip60 acts as a coactivator, we sought to determine the existence, if any, of a transcriptional activation function within Tip60. The presence of an activation function has been demonstrated for SRC-1, whereas PCAF was shown to possess no activation function (24). The determination of this property is essential for the characterization of a coactivator. Although Tip60 contains an atypical zinc finger region (26), no DNA binding ability has been demonstrated. Thus, we fused Tip60 to a GAL4DBD and

FIG. 3. Tip60 enhances AR-mediated transactivation in LNCaP and COS-1 cells. a, effect of increasing amounts of pCMV5Tip60, as indicated, upon LNCaP cells transfected with 0.5 μg of pPSAluc and 0.2 μg of pCMV-βgal per 35-mm well. pSK was added to a total of 1 μg of DNA per transfected well. After transfection, medium containing 10 nm mibolerone (Mib) or vehicle was added. Mibolerone is a specific androgen analogue. Cells were harvested after 72 h, assayed for luciferase activity, and corrected for βgal activity to give relative activity. b, effect of increasing amounts of pCMV5Tip60 on COS-1 cells transfected with 0.2 μg of PCDN3-AR, 0.5 μg of pMTVluc, and 0.2 μg of pCMV-βgal per 35-mm well. pCMV5 was added to 1.1 μg/transfection. After transfection, medium containing 10 nm mibolerone (Mib) or vehicle was added. Cells were harvested 48 h later, and activity was calculated as described above. Data are expressed as the mean of at least three separate experiments performed in triplicate ± S.D.

FIG. 4. Tip60 enhances ER- and PR-dependent transactivation. a, effect of increasing amounts of Tip60 on PR-dependent transactivation. pCMV5-Tip60 was added as indicated to LNCaP cells transfected with 0.5 μg of pPSAluc and 0.2 μg of pCMV-βgal per 35-mm well. pSK was added to a total of 1 μg of DNA per transfected well. After transfection, medium containing 10 nm progesterone (P) or vehicle was added. Cells were harvested 72 h later, and relative activity was determined as described earlier. b, effect of increasing amounts of Tip60 on ER-dependent transactivation. pCMV5-Tip60 was added as indicated to cells transfected as described in a, with the exception that medium contained 1 nm estradiol or vehicle after transfection. Cells were harvested 72 h later, and relative activity was determined as described earlier. Data are expressed as the mean of at least three separate experiments performed in triplicate ± S.D.
examined its effect upon a GAL4-responsive reporter plasmid (Fig. 6). The observed activity was compared with the activity of a p53 fragment containing an identified activation domain, p531–42, fused to a GAL4DBD, and the GAL4DBD alone. It can clearly be seen that Tip60 appears to contain no intrinsic activation function, producing no additional activity when compared with GAL4DBD alone, thus distinguishing it from SRC-1. This feature groups Tip60 with PCAF with respect to coactivator properties.

**DISCUSSION**

In this study, we have identified Tip60 as a nuclear receptor coactivator. Tip60 is a member of the MYST/SAS family of genes that is implicated in transcriptional control and conserved between species (32). This family includes the yeast SAS2 and SAS3 genes implicated in transcriptional silencing (32), yeast gene product ESA1 with HAT activity that is essential for growth (33), and the Drosophila MOF gene required for X-linked dosage compensation (27). A significant member of the family is the human MOZ protein, which exhibits strong homology to Tip60, originally identified via a common translocation found in acute myeloid leukemia. Other related human cDNA sequences contain the MYST domain but have no defined function at present (34). Thus, it is apparent that Tip60 is a member of a family of proteins that are likely to be important in the normal and abnormal control of cellular growth.

The MYST/SAS family genes contain HAT-like domains, which are conserved between members, including Tip60 (32). However, no importance can yet be attached to this domain in Tip60 with respect to its role in coactivation. Tip60 has been shown to acetylate free histones but failed to acetylate nucleosomal histones (35), thus raising concerns about the physiological substrates, if any, for this domain. If it is not required for histone acetylation, there may be other non-histone substrates, for example p53 is acetylated by p300, resulting in a 20-fold increase in affinity for a p53 binding site (36). Thus, an important future task is to determine the significance, if any, of the HAT-like domain within Tip60.

An interesting feature contained within the amino acid sequence of Tip60 is the presence of a LXXLL motif in the COOH region of the protein (amino acids 458–462, GenBank accession number u40989). This LXXLL region is present in other NR coactivators such as GRIP1, CBP, and SRC-1 and has been shown to mediate hormone-dependent binding to nuclear receptors in some detail, with the deletion of this region abolishing the interaction between a NR and coactivator in some instances (37–39). Hence, peptide regions containing single or multiple LXXLL signatures are often designated as NR boxes.

The presence of this NR box in Tip60 may be responsible for its ability to act as a coactivator for several NRs. Other unidentified motifs may account for the ligand-independent binding observed between Tip60 and the AR.

The lack of intrinsic transcriptional activity within Tip60 raises mechanistic questions. This feature is similar to PCAF (24), which is known to interact with several other coactivators and is therefore thought to recruit additional necessary factors once it is bound to a NR. PCAF has also recently been shown to enhance transcription when tethered to a promoter in the presence of an enhancer element and its cognate transcription factor (40), but not in its absence, suggesting that it may well recruit factors necessary for the action of a particular transcription factor. It is interesting to hypothesize that Tip60 can act in a similar mode, and we are currently investigating this possibility.

Tip60 and the recently identified nuclear receptor coactivator NCoA-62 (41) both display broad specificity, like most coactivators (5). CBP interacts with many other transcription factors (reviewed in Ref. 42), and it is becoming increasingly evident that SRC-1 is a signal integrator not unlike CBP and p300. For example, it has recently been shown that SRC-1 can mediate AP-1-dependent transcription by directly interacting with c-Jun and c-Fos (43). The combination of SRC-1 and p300 at the AP-1 sites studied resulted in a synergistic response, highlighting cooperation between coactivators. Also, SRC-1 has been demonstrated to act as a coactivator for nuclear factor kB and is able to bind specifically to the p50 subunit of nuclear factor kB (44). However, as these features become more evident, the lack of specificity demonstrated by coactivators provokes questions regarding the manner in which distinct responses are elicited by nuclear receptors. The phosphorylation status of the coactivators is not well studied, although TIF1α was recently shown to be hyperphosphorylated in the presence of the ER upon estradiol treatment (45). TIF1α was also shown to possess the ability to phosphorylate TIFIIIEα, TAF128, and TAF155. It would therefore seem that specific transcriptional control is unlikely to be achieved by coactivators exclusive to a particular NR. This is more likely to be achieved by post-translational modification of transcription factors by coactivators and of coactivators themselves by other cellular factors. This will serve to alter the dynamic state of flux between distinct activating complexes that share many cofactors in order to achieve specificity.

In conclusion, we have demonstrated that Tip60 is a ligand-dependent coactivator for the AR and that it interacts directly via the LBD of the AR. The demonstration of this function has been achieved using transiently transfected reporter constructs. It would perhaps be more pertinent to examine the
effects of Tip60 on AR-responsive genes, such as ornithine decarboxylase (46) and prostate specific antigen (47), in their normal chromosomal context to truly assess its significance. However, it is clear that Tip60, in our system, appears to be as important as SRC-1 and CBP in AR-dependent transactivation and is thus worthy of further investigation into its mechanism of action.

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