Modulation of Nuclear Receptor Function by Chromatin Modifying Factor TIP60

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Nuclear receptors (NRs) are transcription factors that bind to specific DNA sequences known as hormone response elements located upstream of their target genes. Transcriptional activity of NRs can be modulated by binding of the compatible ligand and transient interaction with cellular coregulators, functioning either as coactivators or as corepressors. Many coactivator proteins possess intrinsic histone acetyltransferase (HAT) activity that catalyzes the acetylation of specific lysine residues in histone tails and loosens the histone-DNA interaction, thereby facilitating access of transcriptional factors to the regulatory sequences of the DNA. Tat interactive protein 60 (TIP60), a member of the Mof-Ybf2-Sas2-TIP60 family of HAT protein, is a multifunctional coregulator that controls a number of physiological processes including apoptosis, DNA damage repair, and transcriptional regulation. Over the last two decades or so, TIP60 has been extensively studied for its role as NR coregulator, controlling various aspect of steroid receptor functions. The aim of this review is to summarize the findings on the role of TIP60 as a coregulator for different classes of NRs and its overall functional implications. We also discuss the latest studies linking TIP60 to NR-associated metabolic disorders and cancers for its potential use as a therapeutic drug target in future. (***Endocrinology*** **159: 2199–2215, 2018)**

Nuclear receptors (NRs) are ligand-modulated transcription factors that are involved in nearly all aspects of physiological processes such as growth, reproduction, metabolism, and immune function (1–7). Deregulated NR signaling may cause disturbances in overall metabolism of the body and may lead to development and progression of many diseases including metabolic disorders, reproductive dysfunctions, and cancers (8–14). Because NRs typically control many aspects of physiology, they have been regularly used as therapeutic targets (15–18). Indeed, many natural NR ligands, synthetic NR agonists, and antagonists have been widely used as drugs for treatment and management of various diseases (19–25). Of the 48 NRs that have been identified in humans, approximately half have known ligands; for the rest specific ligands are not known, and these are called orphan NRs (26–29).

NRs are typically modular in structure and consist of several domains with specific functions. They include a highly variable *N*-terminal domain (NTD), a well-conserved DNA-binding domain (DBD), a short hinge region, and a ligand-binding domain (LBD) located at the C-terminus (Fig. 1A). The DBD region contains conserved cysteine residues that target the receptors to their hormone response elements (HREs) (30). LBDs of different NRs are sufficiently unique in size and are characterized by hydrophobic pockets with diverse amino acid compositions that ensure binding specificities for

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Abbreviations: ADP, adenosine diphosphate; AF-1, ligand-independent activation function; AF-2, ligand-dependent activation function; AR, androgen receptor; ATM, ataxia-telangiectasia mutated; ATPase, adenosine triphosphatase; DBD, DNA-binding domain; ER, estrogen receptor; ERE, estrogen response element; GPR50, G protein–coupled receptor 50; GR, glucocorticoid receptor; GRIP1, glutamate receptor–interacting protein 1; HDAC, histone deacetylase; HAT, histone acetyltransferase; HRE, hormone response element; LBD, ligand-binding domain; MYST, Mof-Ybf2-Sas2-TIP60; NR, nuclear receptor; NTD, *N*-terminal domain; PPAR, peroxisome proliferator–activated receptor; PR, progesterone receptor; PTM, posttranslational modification; PXR, pregnane and xenobiotic receptor; RXR, retinoid X receptor; SRC-1, steroid receptor coactivator 1; TIP60, Tat interactive protein 60.

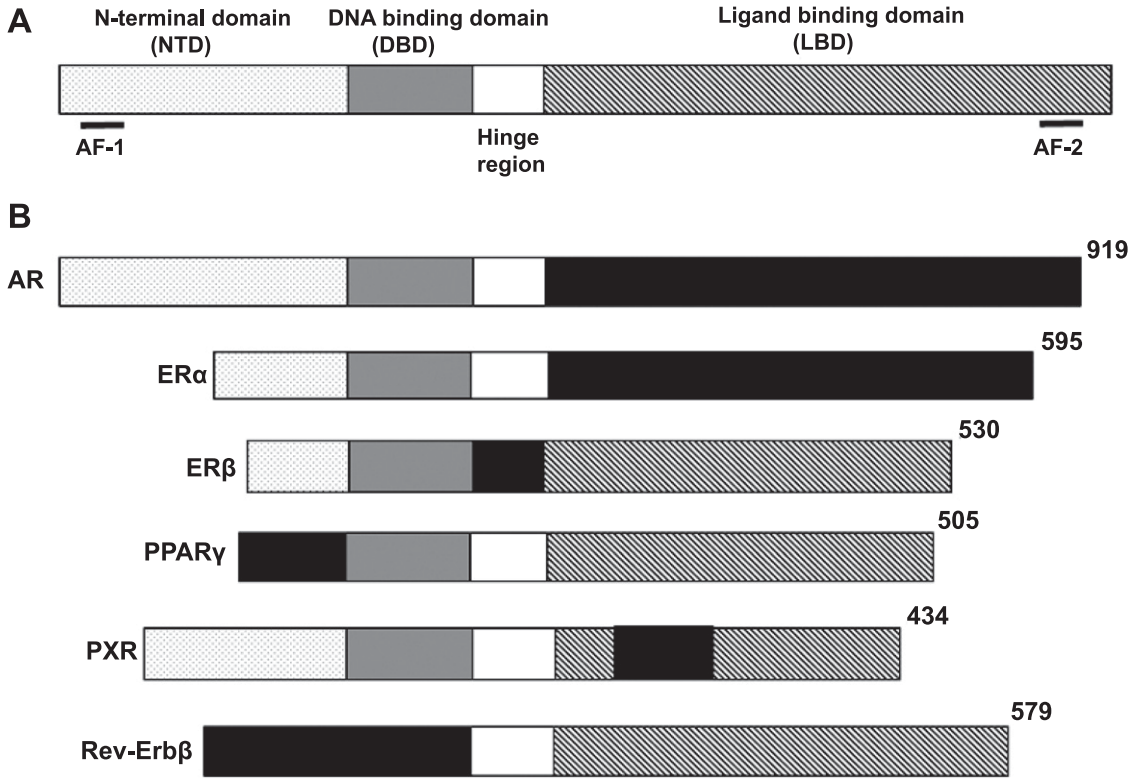

Figure 1. (A) Structural domains of an NR. Modular structure of a linearized NR protein represented by three main domains (NTD, DBD, and LBD). (B) Members of NR superfamily are similar in structural domain organization and are accordingly aligned domainwise in the figure. The amino acid length for each NR is indicated at the C-terminus. Area shaded with solid black signifies the region of each NR needed for its interaction with TIP60.

ligands. In addition, NRs may possess two distinct domains, ligand-independent activation function (AF-1) and ligand-dependent activation function (AF-2), present in the N and C-terminal regions, respectively. They facilitate the recruitment of transcriptional regulatory proteins to the DNA-bound receptor to regulate gene expression (31–33).

Members of the NR superfamily are expressed in a wide range of tissues and may show overlapping or distinct expression patterns depending on their function (34, 35). For instance, androgen receptor (ARs) and estrogen receptor (ERs) are localized predominantly to the reproductive organs because of their role in governing sex-specific traits and sexual reproduction. Alternatively spliced forms of NRs may also vary in their distribution profiles, suggesting they might have distinct cellular functions in different tissues (36, 37). Peroxisome proliferator–activated receptors (PPARs) exist as three subtypes (α, β, and γ) that vary in their expression, ligand recognition, and biological function (38). PPARα is expressed in tissues with high fatty acid oxidation activities that include liver, kidney, heart, and skeletal muscle, consistent with its prime role in regulating lipid catabolism (39). PPARβ is ubiquitously expressed, with higher levels found in brain, adipose tissue, and skin, whereas PPARγ regulates adipocyte differentiation promotes lipid and energy storage in mature adipocytes and thus is expressed at a high level in adipose tissue (40, 41). If different isoforms are expressed in the same cell, they can be independently regulated via distinct regulatory mechanisms involving protein-protein interactions and posttranslational modifications (PTMs), adding additional layers of complexity to the dynamics of NR-mediated signaling (42–45).

Mode of Action of NR

Despite the highly conserved structural organization of different members of the NR superfamily, their functions and modes of action are diverse (27, 46). Based on functional properties and modes of action, NRs are broadly grouped as type I NRs such as ARs, which bind to DNA as homodimers and recognize two consensus half-sites (5-AGAACA-3 and 5-AGGTCA-3), arranged as inverted repeats spaced by 3 bp in case of ERs (28, 47). Type II receptors form heterodimers with retinoid X receptor (RXR) and recognize HREs composed of two half-site motifs arranged as direct repeats, inverted repeats, or everted repeats (48, 49). Some examples of type II NRs are RXR and pregnane and xenobiotic receptor (PXR). The third category includes orphan NRs that mostly bind DNA as monomers to half-site HREs and

regulate gene transcription even in absence of ligands. Some examples of monomeric receptors are NURR77, Rev-Erbs, ROR, and SF-1 (50–53).

Our understanding of molecular events leading to NR-mediated transcription has been improved tremendously over the years through combinatorial use of molecular, genetics, biophysical, and pharmacological approaches (46). NRs can both activate and repress gene transcription via several mechanisms. To work as a transcription factor, NR binds directly to the HREs located within the genome near their cognate target genes. In general, unliganded type I NRs remain localized to cytoplasm in complex with chaperone proteins. Exposure to appropriate ligands releases the NR from the chaperone complex (*e.g.,* HSP90) and allows the receptor to enter the nucleus and form homodimer that binds to the HRE within the promoter of its target gene (54). In contrast, unliganded type II NRs reside predominantly in the nucleus, bound to their specific DNA response elements, often in complex with corepressor proteins such as NCoR and SMRT (55–58). Ligand binding activates the receptor and leads to dissociation of corepressors and recruitment of coactivator complexes (59–61).

LBD contains 12 α-helices (H1 to H12), and helix 12 (H12) is the crucial helical component necessary for ligand-activated AF-2 function. Ligand binding particularly induces dynamic repositioning of H12 that further stabilizes ligand-receptor interaction and provides the surface for coactivator interaction (62–64). Although not fully defined, AF-2 domains of NRs are known to mediate direct interactions with a number of coactivator proteins necessary for the full transcriptional activity of the receptor. Mutations within the AF-2 domain may alter the intermolecular interaction between receptor and coactivators and may result in significantly reduced ligand-dependent transcriptional activity (65, 66).

NR Coregulators

Tight wrapping of DNA around the core histones in a nucleosome makes it inaccessible to the general transcription machinery and prevents transcription of DNA. For efficient transcriptional regulation, transcription factors need access to specific recognition sequences and dynamic modification of chromatin architecture. Such changes to chromatin architecture can be achieved either by enzymatic modification of histones or through chromatin remodeling. A vast array of coregulatory proteins and chromatin modifiers have been identified that modulate promoter accessibility to transcription factors and to the basal transcriptional machinery. Coregulators that increase the rate of transcriptional activation are called coactivators, whereas corepressors suppress the rate of gene transcription (67, 68). NR coregulators generally do not bind to DNA; rather, they form multiple contacts with the DNA-bound NR and other accessory proteins in a complex to modulate NR-dependent gene transcription.

NRs interact with coactivators in the presence of an agonist or selective receptor modulators, whereas corepressors and their complexes associate with NRs when unliganded or bound to antagonists (69–71). Primary coactivators directly interact with the ligand-bound NR and promote sequential recruitment of additional intermediary coregulators or secondary coactivators, which dock onto the primary coactivators and work together in a multiprotein complexes at the target gene promoter to facilitate gene activation (42, 72–77). Every subunit serves a specific function and contributes to regulate different steps of transcriptional process via a variety of mechanisms, including histone modification and chromatin remodeling (74, 76, 78–80). Interestingly, some NR coactivators may function as both primary and secondary coactivators; for instance, steroid receptor coactivator 1 (SRC-1), a member of the p160 coactivator family, serves as a primary coactivator for many NRs, such as progesterone receptor (PR) and ER, and it is recruited as a secondary coactivator by PGC-1α, a transcriptional coactivator for the PPAR/RXR complex (78, 81, 82). Coactivators may have different binding specificities for NRs, whereas NRs may share overlapping preferences for a coactivator and may compete for the same (83–87). Furthermore, the overall composition of the coactivator complex, the availability of individual partners, variations in the expression levels of individual members, binding affinity, order of recruitment, and the type of PTMs carried by them may also regulate the actions of the whole complex and in turn influence the outcome of NR-mediated transcription (88, 89).

Acetylation is a prominent PTM that alters chromatin in a favorable conformation to increase the transcriptional activity of NRs (90). Addition of acetyl groups to the lysine residues within histones reduces the positive charge on them and thus disrupts electrostatic interactions between histones and DNA, resulting in an open chromatin structure. Based on these properties, histone acetyltransferases (HATs) are usually grouped in the category of coactivators. Conversely, deacetylation is mediated by an opposing class of enzymes called histone deacetylases (HDACs), and their recruitment onto the promoter is generally associated with transrepression. Coregulatory proteins are often characterized by the presence of specialized domains such as bromodomain, chromodomain, Really Interesting New Gene fingers, and SANT domains that contribute to the recognition of specific histone modifications.

Analyses of NR coactivators have revealed the existence of a highly conserved amphipathic "LXXLL"

motif (where *X* is any amino acid and *L* codes for leucine), also called NR boxes, which play an important role in mediating the interaction between coactivators and NRs. NR box copy number may vary between categories of coactivators; for instance, coactivator SRC-1 contains three or more NR boxes within a single polypeptide, whereas a single copy of the NR box is present in Tat interactive protein 60 (TIP60). Mutating these residues typically compromises the binding affinity of coactivators and disrupts their interaction with the general transcriptional machinery (91, 92).

TIP60, an Emerging NR Coregulator

TIP60 (HIV-Tat interactive protein, also known as KAT5) has emerged as an important transcriptional regulator known for its ability to interact with unrelated families of transcription factors and coordinate regulation of multiple genes in response to diverse cellular stimuli. TIP60 belongs to the Mof-Ybf2-Sas2-TIP60 (MYST) family of acetyltransferases and was initially characterized as an interacting partner of HIV-1 Tat protein (93). Subsequent studies revealed its involvement in variety of cellular processes, including DNA damage repair, apoptosis, chromatin remodeling, and transcriptional regulation (94–97). TIP60 is characterized by the presence of an *N*-terminal chromodomain and a highly conserved MYST domain (Fig. 2). TIP60 isoform 2 (TIP60 α) is one of the best characterized and frequently investigated splice variants (98, 99). Yamamoto and Horikoshi (100) provided the first biochemical evidence of HAT activity of TIP60 and showed its substrate specificity for histones. Although recombinant TIP60 readily acetylated free histones (H2A, H3, and H4), the effect greatly decreased when nucleosomes were used as substrates. This finding led researchers to speculate that TIP60 might function as a member of a multiprotein complex *in vivo* and requires additional factors to acetylate histones in nucleosomal context (100, 101). In agreement with this speculation, Ikura *et al.* (94) discovered that the majority of TIP60 existed as a multimeric protein complex of at least $\geq$14 protein subunits, and the complex displayed DNA helicase and structural DNA-binding activities in addition to adenosine triphosphatase (ATPase) activity. Later, additional subunits of TIP60 complex were identified, and at present human TIP60 is known to form a complex of 18 subunit proteins (102–104) (listed in Table 1). At present, our knowledge of the role of individual subunits of TIP60 complex in terms of NR function is limited, and of all known members of the TIP60 complex, at least seven are known to modulate NR function, as shown in Table 1. It would be interesting to investigate whether these subunits act alone or as TIP60 complex subunit to regulate NR-mediated function.

TIP60 possesses intrinsic HAT activity and exhibits limited sequence specificity for protein acetylation (121). TIP60 preferentially binds to methylated histones through its chromodomain (consists of hydrophobic amino acids, which interact with methylated lysine residues) (107, 122). Sun *et al.* (122) showed that binding of TIP60 chromodomain to histone H3K9me3 activates TIP60 acetyltransferase activity and facilitates DNA double-strand break repair. HAT activity of TIP60 affects gene transcription mainly by altering the interaction between DNA and histones (which results in loosening of chromatin structure and enhancement of chromatin access for transcription factors and the transcriptional machinery) and by recruiting other transcriptional regulators (123, 124). Kusch *et al.* (125) showed that in drosophila, TIP60-mediated acetylation of phospho-H2Av promotes its exchange with an unmodified H2Av in the nucleosome during DNA damage. In a recent study, Ikura *et al.* (104, 126) showed that in response to DNA damage, TIP60-mediated H2AX acetylation at Lys5 enhances adenosine diphosphate (ADP) ribosylation activity of PARP-1, which promotes dynamic binding of PARP-1 to damaged chromatin, which in turn facilitates dynamic exchange of H2AX at damaged sites.

In addition to acetylating histones, TIP60 acetylates many nonhistone proteins to modulate their functions by altering their stability, localization, and DNA-binding ability depending on the site of acetylation and physiological status (97). Some well-characterized nonhistone substrates of TIP60 are p53, MYC, and ataxia-telangiectasia mutated (ATM) kinase (127–129). Because of its ability to interact with a diverse range of

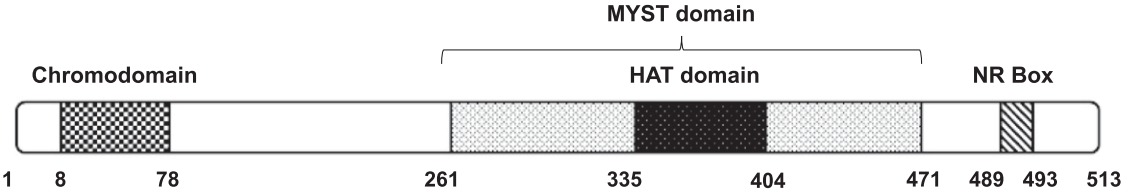

Figure 2. Schematic representation of TIP60. TIP60 contains a chromodomain and a MYST domain with catalytic activity. TIP60 possesses a single NR box at the C-terminus, necessary for its interaction with NRs.

Table 1. TIP60 Complex Subunits and Their Role in NR-Mediated Signaling

TIP60 Complex Subunit	Domains Present	Molecular Function	Role in NR-Mediated Signaling
TIP60 (Tat interactive protein 60)	Acetyltransferase domain, chromodomain, NR box	Possesses HAT activity TIP60 can acetylate both histone and nonhistone substrate	AR (105, 106) ER (106, 107, 108) PR (105) GR (106) PPARγ (109) Rev-Erbβ (110) PXR (111)
RUVBL1 (RuvB-like 1)	Walker A and Walker B motif	ATPase activity, DNA helicase activity	AR (112)
RUVBL2 (RuvB-like 2)	Walker A and Walker B motif	ATPase activity, DNA helicase activity	ER (113)
P400 (E1A binding protein p400)	RNA-dependent ATPase subunit, RING domain	Histone tail binding/adenosine triphosphate–dependent helicase	PPARγ (114)
TRRAP (Transformation/transcription domain-associated protein)	FATC domain Phosphatidylinositol 3-kinase-like domain FRAP, ATM, and TRRAP domain	Adapter protein, recruitment of HATs to chromatin	LXR (115) FXR (115) ERα (116)
BRD8 (Bromodomain containing 8)	Bromodomain	Binding to acetylated histones, transcriptional coactivator	PPARγ (114) TR (117) AR (118)
EPC1 (Enhancer of polycomb 1)		Protein interaction within complex, regulation of HAT activity	
DMAP1 [DNA methyltransferase (DNMT)-1 associated protein 1]	SANT domain	Histone tail binding	
MRG15 (Morf-related gene on chromosome 15)	Leucine zipper domain		
MRGBP (MRG binding protein)		MRG domain-binding protein	
ING3 (Inhibitor of growth protein 3)	Plant homeodomain finger	Chromatin acetylation	AR (119)
YL-1		H2A-variant binding, histone chaperone	
BAF53a (BRG1 associated factor 53a)	Actin-related protein	Phospho-H2A-variant-dependent DNA recruitment upon DNA damage	
GAS41 (Glioma Amplified Sequence 41)	YEATS domain and alpha acidic activation domain	Transcriptional activation, nuclear matrix interaction	
Eaf6 (ESA1-associated factor 6)		Unknown	
Actin	Actin	ATPase activity, actin related	
PARP-1 [Poly(ADP-ribose) polymerase 1]	DNA binding domain BRCT domain Catalytic domain	Possess ADP ribosylation activity, histone exchange	ERα (120)
MBDT1 (Malignant Brain Tumor domain)	Histone reader domain	Recognizes H4K20me1/2	

Abbreviations: BRG, Brahma-related gene; ESA, essential SAS2-related acetyltransferase; GR, glucocorticoid receptor; LXR, liver X receptor; MRG, MORF-related gene; RING, Really Interesting New Gene; TR, thyroid hormone receptor.

cellular proteins in a complex regulatory pathway in the cell, TIP60 is also considered an essential hub gene (130). Normal expression and functioning of TIP60 are essential for maintaining genomic integrity in eukaryotic cells. TIP60 regulates the repair of DNA damage at various levels in cooperation with several proteins. TIP60-dependent acetylation and activation of ATM kinase is a necessary step for the detection and repair of double-stranded DNA breaks (128, 131, 132). Interestingly, in the case of unrepairable DNA damage, TIP60 promotes apoptosis by acetylating p53, which in turn activates genes involved in apoptosis (129). Impaired TIP60 activity may lead to increased sensitivity to ionizing radiation and increased risk of developing cancer (133–135).

In addition to its well-established role in DNA damage repair and apoptosis, TIP60 is also recognized as an NR coregulator. In the course of searching interacting partners for AR, Brady *et al*. (105) first identified TIP60 as a ligand-dependent coactivator of AR. The magnitude of TIP60-dependent AR activation was comparable to those of other NR coactivators such as SRC-1, p300, and CBP. A similar level of enhancement was observed with ER-mediated transactivation when coexpressed with TIP60,

but TIP60 was unable to influence the transcriptional activity of class II NRs vitamin D receptor, thyroid hormone receptor, and RXR. Findings from these studies initially led to the view that TIP60 specifically coactivates class I NRs (105, 106). However, van Beekum *et al.* (109) first provided evidence that TIP60 positively regulates transcriptional activity of PPARγ, a class II NR. Most recently, our laboratory has shown that TIP60 interacts with PXR (a class II NR) in a ligand-independent manner (111). Additionally, Rev-Erbβ, an orphan NR, was shown to be negatively regulated by TIP60 (110). Interaction of TIP60 with different NRs is mediated by an NR interaction motif or NR box (LXXLL) located at its extreme C-terminus (Fig. 2). Point mutations introduced in NR boxes either inhibited or completely abolished the ability of TIP60 to bind and coactivate NR function. Figure 1B depicts the regions of different NRs involved in their interactions with TIP60 (see black boxes). In this review, we have described different classes of NRs coregulated by TIP60 and summarized the findings on TIP60-mediated regulation of NR activity and function (Table 2). We conclude the review by offering possible directions for future research in this area.

TIP60 and AR

AR, a member of the class I subgroup of the NR superfamily, was the first and the most well-characterized NR coregulated by TIP60 (105). AR activity is responsible for development of the reproductive system and secondary sexual characteristics in males, and normally its action depends on androgens (136, 137). A full-length AR is ~919 amino acids long and is organized into distinct structural and functional domains (138, 139). A putative bipartite nuclear localization signal sequence is located in the hinge region of AR and plays an important role in determining its intracellular dynamics. Unliganded AR resides in the cytosol but translocates into the nucleus upon binding to its ligand, which is crucial for its functions (140, 141).

The transcriptional activity of AR can be modulated via ligand-dependent and ligand-independent mechanisms (142–144). Several coactivator proteins with HAT activity are involved in increasing AR-mediated gene regulation, either by acetylating local chromatin or by altering the acetylation status of AR protein itself (145–148). Gaughan *et al.* (106, 146) showed that TIP60 interacts with the LBD of AR and acetylates the lysine residues positioned within the KLKK motif in the hinge region, which is crucial for TIP60-dependent enhancement of AR activity. Interestingly, in another study Shiota *et al.* (149) demonstrated that an acetylation-mimicking mutant of AR (K630/632/633Q) remained localized inside the nucleus despite androgen depletion, and TIP60 knockdown inhibited nuclear translocation of AR. Together, these studies suggest that TIP60 induce AR nuclear import in a ligand-independent manner but can augment its transactivation only in presence of its ligands.

The possible physiological and pathological importance of TIP60 and AR interaction has been studied mainly in context of prostate cancer (149, 150). Halkidou *et al.* (150) showed that TIP60 can occupy the promoter of AR-targeted gene *PSA* and may increase its expression levels in both an AR-dependent and AR-independent manner. Also, TIP60-dependent AR acetylation has been shown to promote androgen-independent prostate cancer cell proliferation, but the mechanism remains undefined (149). These studies have also shown increased expression levels of TIP60 messenger RNA and protein in castration-resistant prostate cancer cells that coincides with increased nuclear accumulation of both TIP60 and AR, even under serum-deprived conditions. However, factors regulating differential expression of TIP60 in normal and cancerous cells are not known, and further evaluation is needed to elucidate the complex behavior of TIP60 in relation to AR in different cellular contexts.

TIP60 and ER

The physiological actions of estrogens are mediated through two isoforms of ER, ERα and ERβ, encoded by distinct genes located on different chromosomes (151). Both ERα and ERβ consist of structural domains similar to those of other members of the NR family. ERα and ERβ show high sequence homology in the DBD region (>95% amino acid identity), whereas AF-1 is the least conserved region, showing 30% identity (152–154). The ligand-binding cavity of ER shows ~56% sequence homology, and many ligands have a similar affinity for both receptor subtypes. The ligand-activated ER binds as a homodimer to the estrogen response elements (EREs) located upstream of its target genes; however, in some cases they have also been shown to form heterodimers on EREs. ERα and ERβ have different downstream transcriptional activities, resulting in their tissue-specific biological actions (155–159).

Interestingly, TIP60 has been shown to interact with both isoforms of ER but with distinct transcriptional outcomes. TIP60-mediated enhancement of ERα and ERβ transcriptional activity was observed in transiently transfected reporter assay experiments by Brady *et al.* (105) and Gaughan *et al.* (106), but the mechanism by which TIP60 contributed to ER signaling remained unclear. Consistent with the previous findings, in 2011 Jeong *et al.* (107) showed that TIP60 increased E2-induced

Table 2. Different Classes of NRs Regulated by TIP60

	Coactivator/ Corepressor	TIP60 Interaction With NR (Ligand Dependent/ Independent)	Target Lysine Residues for Acetylation	Functional Implications	References
Class I NRs					
AR	Coactivator	Ligand independent but enhances in presence of dihydrotestosterone	K630, K632, K633 (KLKK motif located in the hinge region)	TIP60-mediated acetylation induces nuclear translocation of AR.	Brady *et al*. (105)
				TIP60 upregulates AR-mediated transcription in a ligand-dependent manner.	Gaughan *et al.* (146); Shiota *et al*. (149)
ERα	Coactivator	Ligand-dependent interaction	Not known	TIP60 selectively enhances E2-induced expression of a subset of ERα target genes in a ligand-dependent manner.	Gaughan *et al*. (106) Jeong *et al*. (107)
ERβ1	Dual function coregulator	TIP60 can interact in either the absence or the presence of estrogen	Unable to acetylate ERβ1	TIP60 differentially modulates the ERβ1 transactivation in a *cis*-acting element-dependent manner.	Lee *et al.* (108)
PR	Coactivator	N/A	Not known	TIP60 enhances PR-mediated transactivation in a ligand-dependent manner.	Brady *et al*. (105)
GR	Coactivator	N/A	Not known	Interaction of TIP60 with GPR50 enhances GR-mediated signaling.	Gaughan *et al.* (106)
Class II NRs					
PPARγ	Coactivator	Ligand-independent	Not known [catalytically dead mutant of TIP60 (G380E) displays reduced ability to potentiate the transcriptional activity of PPARγ]	TIP60 potentiates PPARγ2 activity and promotes adipogenesis.	van Beekum *et al*. (108)
PXR	Interacting partner	Ligand-independent	K170	TIP60-PXR complex promotes cell migration and adhesion.	Bakshi *et al*. (111)
Orphan NRs					
Rev-Erbβ	Coactivator	Ligand-independent	K161, K162 located within RXKK motif in DBD	TIP60 acetylates Rev-Erbβ and relieves the *apoCIII* repression mediated by Rev-Erbβ. This de-repression effect depends on acetylation of Rev-Erbβ at its RXKK motif by TIP60.	Wang *et al.* (110)

Abbreviation: GPR50, G protein–coupled receptor 50.

expression of endogenous ERα target genes but in a selective manner. This study showed that TIP60 acts as a coregulator of selective ERα targeted genes as knockdown of TIP60 compromised the expression of certain number of ERα targeted genes (*TFF1, GREB1, SGK3*, and *PKIB*) only, even though TIP60 occupied EREs in promoter regions of all the examined targeted genes along with ERα in presence of hormones. It was also shown that binding of other chromatin remodeling factors and alterations in the local chromatin environment of targeted genes facilitates the TIP60-dependent coactivator function of ERα targeted genes. Chromatin immunoprecipitation studies revealed that estrogen-induced recruitment of TIP60 onto the promoter of ERα target genes proceeds in a sequential manner and requires coordinated actions of adenosine triphosphate–dependent chromatin remodeling complex SWI/SNF, containing Brahma-related gene 1 and histone methyltransferase MLL1. Overall, this study shows that TIP60 works in sync with other chromatin remodeling/modifying factors on the targeted chromatin. In the presence of estrogen, TIP60 along with ERα binds to the enhancer elements of targeted genes that are methylated at histone H3K4me1 by histone methyltransferases. Once recruited, TIP60 then acetylates neighboring histones (H2AK5) and prepares the chromatin for active transcription.

The regulatory role of TIP60 in the case of ERβ and the resulting transcriptional outcome was extensively investigated by Lee *et al.* (108). The study revealed remarkable differences in TIP60-mediated regulation of ERβ transactivation in comparison with ERα. Unlike ERα, binding of TIP60 to ERβ does not require ligands. Even the interaction domain used by the two isoforms to interact with TIP60 is different. Whereas ERα LBD is responsible for interaction with TIP60, ERβ uses its hinge domain. Interestingly, TIP60 was demonstrated as a dual function coregulator of ERβ exerting its effect in a regulatory element-dependent manner. TIP60 acts as coactivator of ERβ at the AP-1 site but reduces its transactivation at ERE sites (108). This is in contrast to ERα, where TIP60 occupies the promoter of ERα targeted genes but acts as a coactivator of selected genes only. In the case of ERα, the local chromatin environment is crucial for TIP60-dependent action; however, in the case of ERβ it was found that glutamate receptor-interacting protein 1 (GRIP1) acts as a tethering mediator for unliganded ERβ at the AP-1 site, and coexpression of GRIP1 synergizes the action of TIP60.

Another salient feature in TIP60-dependent coregulation of ERβ is that unlike its action on other targeted NRs, HAT activity of TIP60 is not essential for the regulation of ERβ transactivation. It might be possible that in the case of ERβ, TIP60 acts as an interacting partner for associated proteins, or TIP60 chromodomain activity might be necessary in the case of ERβ. Moreover, transcriptional activity of the ERβ1 target gene–harboring ERE site responds differently to TIP60 depending on the type of ligands. For instance, estrogenic compounds such as E2 (estradiol) and diarylpropionitrile upregulated ERβ1 transactivation at ERE, whereas selective estrogen receptor modulators and antiestrogens failed to induce ERE activation. It was concluded that the potency of TIP60 recruitment at these sites is controlled through binding to different ligands that may either increase or reduce the transcriptional response.

TIP60 and Glucocorticoid Receptor

Glucocorticoid receptor (GR) is a ligand-dependent transcription factor that controls a variety of physiological processes in response to glucocorticoids (160). Alternative splicing of the GR primary transcript results in the two most abundant GR isoforms, GRα and GRβ. In addition, alternative translation initiation from the single GRα messenger RNA produces eight GRα subtypes that have progressively shorter NTDs and are subject to a variety of PTMs (161, 162). A range of cellular coregulators interact with ligand-bound GR and further contribute to the specificity of transcriptional response exerted by GR (163, 164).

TIP60 interaction with GR was first reported by Gaughan *et al.* (106), but the molecular basis of TIP60-mediated regulation of GR signaling remained undefined. G protein–coupled receptor 50 (GPR50) is a mammalian ortholog of avian/amphibian MelIc melatonin receptor (165), but it does not bind melatonin and remains an orphan receptor. Using $GPR^{-/-}$ mice, Li *et al.* (166) demonstrated that GPR50 is necessary for GR signaling. GPR50 interacts with TIP60 and synergistically increases GR-targeted gene expression in presence of its ligand. Knockdown of either GPR50 or TIP60 drastically reduces the expression of GR-targeted genes, but the mechanism by which the GPR50-TIP60 complex leads to transactivation of the GR function is not yet identified. Despite showing TIP60's effect on GR signaling by GPR50, this study does not explore TIP60's direct role in GR activity, if any.

TIP60 and PPARs

PPARs are group of ligand-activated transcription factors that play major roles in lipid homeostasis and energy metabolism. PPARs serve as molecular targets for a number of marketed pharmaceutical drugs such as rosiglitazone, clofibrate, and fenofibrate that are used primarily to treat metabolic disorders such as diabetes and dyslipidemia (167–169). Three isotypes of PPARs (PPARα, PPARβ, and PPARγ) encoded by separate genes have been identified. They all bind to PPAR response elements as a heterodimeric complex with RXR, but they differ in terms of their ligand preferences, tissue-specific expression patterns, and biological outcomes (170–173). PPARγ abundantly expresses in adipose tissue and primarily regulates lipid metabolism, adipose tissue differentiation, and maintenance of adipocyte-specific functions (41, 174).

Two isoforms of PPARγ, PPARγ1 and PPARγ2, are generated through alternative promoter usage (175). Unlike PPARγ1, PPARγ2 contains an additional 28 or 30 amino acid extensions at its extreme *N*-terminus, which confers a further increase in the transcription-inducing ability of the AF-1 domain and is more efficient in promoting adipogenesis (176). Functional differences can be explained by alternative usage of coregulators in a context-dependent manner (177, 178). Coactivator interaction can be established with the LBD of PPARγ in a ligand-dependent manner, but in some cases the AF-1 domain of PPARγ is also involved. Some coactivators such as p300 and CBP are capable of increasing the transcriptional activity of both AF-1 and AF-2 domains separately (179).

van Beekum *et al.* (109) identified TIP60 as a novel coactivator for PPARγ2 by using tandem mass spectrometry. TIP60 specifically potentiates PPARγ2 activity and needs the AF-1 region between amino acids 31 and 136 of PPARγ2 for its coactivation (109). PPARα and PPARβ isoforms that have poorly conserved AF-1 regions are not coactivated by TIP60. However, TIP60 can interact with PPARγ2 in the absence or presence of ligand but potentiates PPAR-mediated transcription in a ligand-dependent manner. Interestingly, the NR box motif (LXXLL) of TIP60 located at its C-terminal region does not participate in the TIP60-dependent transactivation function of PPARγ2. Furthermore, the acetyltransferase activity of TIP60 contributes to the ligand-activated PPARγ2 transactivation function, as catalytically dead mutants of TIP60 lead to reduced coactivation of PPARγ2. However, the substrates involved and the site of lysine residues modified by TIP60 in case of TIP60-mediated coactivation of PPARγ2 are not yet known. Endogenous TIP60 binds to the promoter of PPARγ-targeted gene *Fabp4* in mature adipocytes only, indicating that TIP60 needs PPARγ for its recruitment to the PPARγ target gene. Interestingly, TIP60 protein expression increases during the first stages of 3T3-L1 differentiation, and TIP60 knockdown results in impaired differentiation of 3T3-L1 cells into adipocytes, suggesting that TIP60 is an adipogenic factor. In subsequent studies from the same laboratory, it was reported that TIP60 protein is protected from proteasomal degradation and is stabilized by USP7-mediated deubiquitination of TIP60 in the early stage of adipogenesis (180). Knockdown of TIP60 or USP7 drastically impaired mitotic clonal expansion, a process necessary for the differentiation of 3T3-L1 preadipocytes into adipocytes (180, 181). It would be important to identify the upstream regulators and downstream effectors involved to unravel the precise relevance of TIP60 in adipogenesis.

TIP60 and PXR

PXR is a member of the NR superfamily and is well known for regulating genes encoding drug-metabolizing enzymes and transporters (182–184). Although multidrug resistance protein 1 and cytochrome P450 3A4 are the two most important PXR target genes, the list of genes regulated by PXR is growing rapidly. Liver and intestines exhibit high expression levels of PXR. Unlike other NRs, PXR is a highly promiscuous receptor and displays broad ligand-binding specificity toward a wide range of chemicals (183, 185). To execute its transcriptional function, ligand-activated PXR heterodimerizes with RXRα and binds to PXR response elements located in the 5′-flanking regions of its target genes. Human PXR remains constitutively localized into the nucleus regardless of its unliganded state.

Recently, our laboratory has shown that TIP60 can directly interact with unliganded PXR and induce its intranuclear reorganization (111). TIP60 forms colocalized foci with PXR inside the nucleus. TIP60 uses its NR box to interact with PXR as mutation in NR box abrogates TIP60-PXR nuclear foci formation. TIP60 is shown to acetylate PXR at lysine 170 located within its LBD, and this TIP60-dependent acetylation is important for both TIP60-PXR interaction and focus formation. Interestingly, TIP60-PXR complex does not involve RXR, the obligatory partner of PXR for xenobiotic pathway genes activation. This shows that different types of NR complexes can be formed inside the cell depending on the cellular microenvironment.

Generally, TIP60 acts as an NR coregulator in a ligand-dependent manner; however, in the case of PXR, TIP60 is sensitive to PXR agonists, and the TIP60-PXR colocalized foci are disrupted in presence of PXR ligands, indicating that this complex might be involved in regulating different pathways other than genes targeted by ligand-bound PXR. Consistent with this finding, we showed that TIP60-PXR complex promotes cell migration and adhesion, but the pathways regulated by this complex that promotes cell migration and adhesion remain to be identified. It would be interesting to know under what circumstances TIP60-PXR complex might participate in these cellular phenomena because cell migration and adhesion are necessary from embryogenesis, where extensive cellular rearrangement takes place, to adulthood, where these phenomena are necessary for tissue healing, immune response, and cancer.

TIP60 and Rev-Erbs

Rev-Erbs were initially identified as an orphan member of the NR superfamily for which no physiological ligand was known (186). Later on, heme was characterized as a physiological ligand for Rev-Erbα and Rev-Erbβ (187, 188). Several synthetic ligands (agonist and antagonist) have also been identified for Rev-Erbs, suggesting that Rev-Erbs can be targeted for therapeutic application (189–191).

Unlike class I and class II NRs, the LBD of Rev-Erbs lacks the C-terminal helix 12 that is linked with the receptor's ability to recruit coactivators in a ligand-dependent manner (192). Rev-Erbα and Rev-Erbβ exhibit strong sequence homologies and bind to a common response element called retinoid-related orphan receptor response elements (186). Rev-Erbs have been characterized as a potent repressor of transcription that recruits

NR corepressor NCoR to its target gene promoters, leading to their repression (193). A number of physiological processes including the circadian rhythm and lipid and glucose metabolism are regulated by coordinated action of Rev-Erbs (190, 194, 195). Rev-Erbβ regulates the expression of *apolipoprotein CIII* in hepatocytes and genes involved in lipid absorption in skeletal muscle cells (110, 194).

Wang *et al.* (110) identified TIP60 as Rev-Erbβ interacting protein by using yeast two-hybrid screening and then confirmed the interaction between the proteins with glutathione S-transferase pulldown and coimmunoprecipitation experiments. TIP60 and Rev-Erbβ colocalized inside the nucleus, and both the NTD and DBD regions of Rev-Erbβ were shown to be involved in the interaction with TIP60. TIP60 was shown to acetylate Rev-Erbβ at lysine 161/162, located in the RXKK motif present in DBD that relieved Rev-Erbβ-mediated repression of *apoCIII* expression. However, the exact mechanism by which Rev-Erbβ acetylation by TIP60 leads to activation of *apoCIII* transcription remains unclear. Rev-Erbβ recruits both TIP60 and a deacetylase HDAC1 onto the promoter of *apoCIII*. HDAC1 can negate the repressive effect of TIP60 on Rev-erbβ to inhibit *apoCIII* transcription, showing a dynamic interaction of Rev-Erbβ, TIP60, and HDAC1 in the modulation of *apoCIII* gene expression. This study provides evidence that Rev-Erbβ signaling can be modulated through recruitment of different transcription coregulators.

Conclusions

Dynamic assembly of TIP60 as a transcriptional coregulator in complex with different NRs and their binding to different genomic regions may bring out multiple and distinct physiological outcomes. TIP60 uses its NR box to interact with various NRs through their different domains and acetylate these receptors at different lysine residues (Fig. 1B, Table 2). However, the basis of substrate recognition and lysine site selection for acetylation in terms of different NRs is not completely understood. Besides, TIP60 undergoes autoacetylation at several lysine residues, which may act as a regulatory mechanism to facilitate and stabilize its interaction with different substrates. Acetylation of TIP60 at lysine residue K327 in the MYST domain affects both its catalytic activity and substrate-binding affinity (196, 197). In concert with this finding, Xiao *et al.* (198) demonstrated that TIP60 autoacetylation modulates its interaction with other proteins and allows TIP60 to switch binding partners. Both TIP60 and p300 have been individually known to

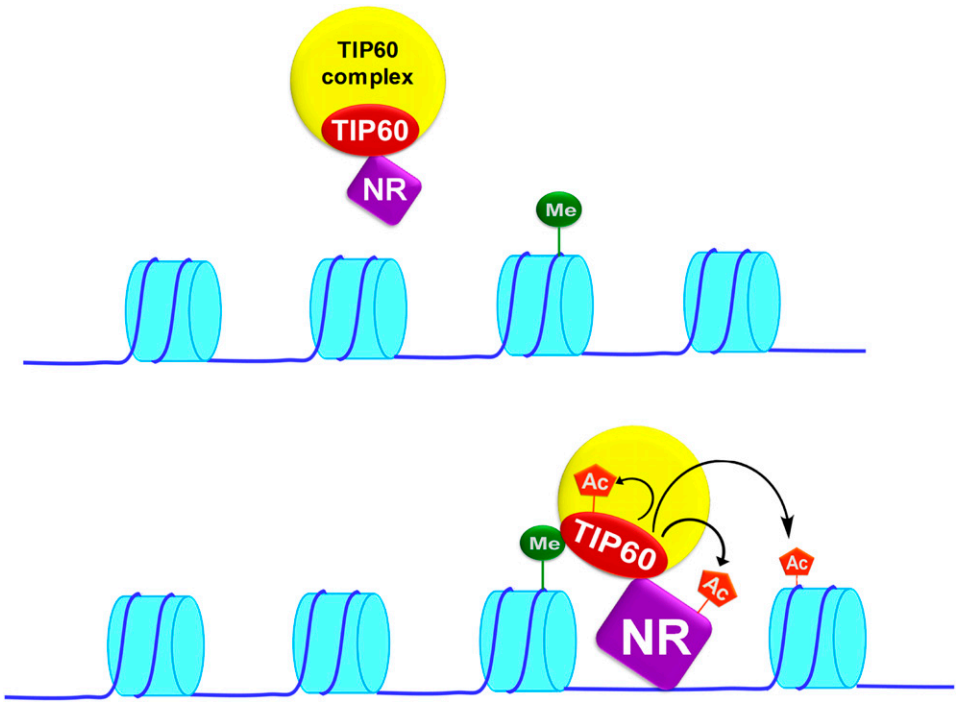

Figure 3. Hypothetical model showing TIP60-mediated regulation of NR function. TIP60 (probably as a part of TIP60 complex) can directly interact with NRs (usually in a ligand-dependent manner) through its NR box, located at C-terminus. TIP60 preferentially binds to methylated histone via its chromodomain, which stabilizes its interaction with nucleosome and leads to the docking of the TIP60-NR complex on targeted HREs. Once stabilized onto the chromatin, TIP60 acetylates nearby histones, leading to decompaction of local chromatin. Simultaneously, TIP60 may also acetylate itself or induce acetylation of the associated NR, which may induce successive recruitment of additional coregulators. Ac, acetylation; Me, methylation.

modulate the transcriptional activity of FOXP3, and autoacetylation of TIP60 at a single K327 residue plays a pivotal role in regulating the interactions of TIP60 with p300 and FOXP3. The same study showed that p300 interacted strongly with the acetylation-deficient mutant of TIP60 (K327R) while showing a weak interaction with the acetylation-mimicking form of TIP60 (K327Q). However, FOXP3 showed a much stronger interaction with TIP60 (K327Q) mutant as compared with the wild-type form. Based on these findings, it was suggested that the acetylation status of TIP60 may help TIP60 assume substrate-specific conformations needed for switching its interaction with other proteins.

Like various posttranslation modifications, acetylation is readily reversible. HDACs catalyze the removal of acetyl groups and counteract the activity of HATs. Finely tuned and balanced enzymatic activities of HATs and HDACs are essential for regulated gene expression, and deregulation of any of these sets of enzymes may result in a disease state. Atypical expression and activity of TIP60 may result in genomic instability and may influence cancer formation in multiple ways. Its role in the tumorigenesis of prostate cancer, lung cancer, and breast cancers is becoming more evident (135, 149, 199). For instance, aggressive cases of prostate cancer have been shown to overexpress TIP60. Functional upregulation of TIP60 in clinical prostate cancer specimens correlates with disease progression (150). TIP60 was shown to interplay with HDACs at the *PSA* gene promoter, suggesting that equilibrium between them can regulate the overall transcriptional outcome. Therefore, targeting TIP60 acetylase activity and its corresponding deacetylase could be a useful therapeutic strategy against many diseases. Considering the implication of TIP60 in promoting prostate cancer, in both an AR-dependent and independent manner, TIP60 has been targeted with its selective inhibitor (NU9056), leading to inhibition of cellular proliferation of prostate cancer cells (200). However, extensive research is needed to harness its clinical benefits for prostate cancer treatment. Similarly, TIP60 interaction with PPARγ affects the adipogenic pathways and can serve as a target for therapeutic intervention in the treatment of obesity. Likewise, TIP60 inhibitor can lead to Rev-Erbβ-dependent repression of *apoCIII* transcription and can be used to treat atherosclerosis. In view of these findings, it is also crucial to identify and characterize the role of different HDACs involved in reversing the effect of TIP60-mediated acetylation of different NRs.

Because TIP60 and other MYST HATs function in multisubunit protein complexes, it is not surprising that TIP60 may need additional partners of the complex to execute coregulatory activities (95). Availability of assisting partners may also govern TIP60 action in a cell type–specific manner. Recently, Li *et al.* (166) reported GPR50 as a signaling partner and modulator of the transcriptional coactivator TIP60. Interaction of TIP60 with GPR50 increased the GR signaling *in vitro* but attenuated the TIP60-mediated enhancement of PPARγ signaling. Li *et al.* suggested that binding of GPR50 may mask the site at which TIP60 binds PPARγ or block the binding of other associated proteins needed for TIP60/PPAR signaling. Divergent effects of GPR50 on TIP60/NR interactions may be caused by the physical interaction of the three proteins, suggesting that the regulation of NR activity by TIP60 could be much more complex than we expect.

We propose a hypothetical model depicting the ways in which TIP60 or TIP60 complex might regulate NR function (Fig. 3). TIP60 in complex with NR binds to methylated histones, stabilizing its interaction with chromatin. After stabilization, TIP60 modifies the local chromatin environment by acetylating the histones, leading to decompaction of the targeted chromatin and making it accessible for other coregulators to modulate NR-mediated transcription. Future research could give insight into the role of TIP60 in modulating NR signaling by various ways that have yet to be defined.

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