MINIREVIEW

Nuclear Hormone Receptor Coregulators In Action: Diversity For Shared Tasks

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INTRODUCTION

The nuclear hormone receptors are transcriptional regulators that activate gene expression upon binding of their respective ligands. A new class of protein, termed coregulators, has emerged during the last few years. These proteins have the faculty to repress (corepressors) or to enhance (coactivators) the activity of genes regulated by nuclear hormone receptors in a ligand-dependent fashion. In this review we describe most of these coregulators and discuss their mode of action. In particular, we comment on the link between coregulators and histone acetylation, which is a crucial event in the transcriptional response within chromatin. We describe novel alternative pathways, which elicit the recruitment of coregulators independently of the presence of any ligand and speculate on how the convergence of ligand-dependent and -independent mechanisms might enhance the transcriptional response of target genes.

DESCRIPTION OF THE NUCLEAR HORMONE RECEPTORS

Nuclear hormone receptors are ligand-inducible transcription factors that are involved in a number of physiological and cellular events (see Table 1 for nuclear receptor nomenclature). Together, they form a superfamily, which includes the classic steroid receptors (androgen, estrogen, glucocorticoid, mineralocorticoid, and progesterone receptors), the thyroid, vitamin D, and retinoid receptors, as well as many others that have been characterized more recently. All of them share common functional domains named A to F. The N-terminal A/B region is weakly conserved among the members of the superfamily, has a variable length, and contains an autonomous activation function (AF-1). The conserved C domain is the DNA-binding domain, which consists of two zinc-finger-like motifs. The D domain is a variable hinge. The multifunctional C-terminal half of the protein (domain E) encompasses the ligand-binding domain (LBD), a second activation function (AF-2), a dimerization domain, and a region involved in nuclear localization. The AF-2 autonomous activation domain (AF-2 AD) is composed of an amphipathic α-helix that is highly conserved among nuclear receptors and is critical for transcriptional activation (1–4). The most C-terminal region (domain F) is variable and has no known function. This domain is absent in some receptors such as the progesterone receptor (PR), peroxisome proliferator-activated receptors (PPAR), and retinoid receptors [retinoic acid receptor (RAR), retinoid X receptor (RXR)].

Transcriptional activation by both AF-1 and AF-2 of the estrogen receptor (ER) is cell type specific and relies on the promoter context of the hormone-response element (HRE) (5). This suggests the existence of different mediating or coactivating proteins, several of which have been identified to date (see below). These mediators interact with the LBD and some are capable of increasing the AF-2 response in a ligand-dependent fashion. On certain promoters, AF-1 and AF-2 must synergize to reach efficient transactivation.

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Table 1. Nomenclature According to the Nuclear Receptors Nomenclature Committee, 1999

Trivial Names of Receptors Mentioned in this Review	New Nomenclature
TRα, TRβ	NR1A1, NR1A2
RARα	NR1B1
PPARα, PPARγ	NR1C1, NR1C3
RevErbα	NR1D1
VDR	NR1I1
HNF4	NR2A1
RXRα	NR2B1
COUP-TF	NR2F3
ERα, ERβ	NR3A1, NR3A2
GR	NR3C1
MR	NR3C2
PR	NR3C3
AR	NR3C4
NGF1-B	NR4A1

NUCLEAR RECEPTOR COACTIVATORS

The observation of transcriptional interference or squelching between steroid hormone receptors provided evidence for the existence of limiting common transcriptional cofactors that mediate AF-2 function (6, 7). The subsequent biochemical identification of several nuclear receptor-interacting proteins in a ligand-dependent manner supported this hypothesis (8) (Table 2). These mediators or coactivators are required to achieve efficient transcription (reviewed in Refs. 9–11).

COACTIVATORS, A GROWING FAMILY

Numerous potential receptor-interacting proteins were identified and described in the past few years (Table 2), and many others will certainly be discovered in the near future. This rapid increase has led to some confusion in the nomenclature and raised questions about the definition of a coactivator. A real coactivator must fulfill certain requirements. First it must interact directly with the activation domain of a nuclear receptor in an agonist-dependent manner (but not in the presence of an antagonist), leading to enhancement of the receptor activation function. Most of the potential cofactors meet this definition. A coactivator should also interact with components of the basal transcription machinery. Finally, coactivators should not enhance the basal transcriptional activity by their own, although they contain an autonomous activation function (12, 13). Indeed, in the absence of a nuclear hormone receptor, coactivators cannot be recruited to promoters and therefore cannot coactivate transcription. Here, we will first discuss some well characterized coactivators and then we will comment on proteins whose coactivator status is not clearly established.

SRC-1/CBP/p300/pCAF: A COACTIVATION COMPLEX?

Among all the described coactivators to date, SRC-1 (steroid receptor coactivator 1) has attracted much attention. The human SRC-1 was first discovered as a ligand-dependent interacting protein for the progesterone receptor (14). It appeared, however, that the original cDNA clone was truncated at the N terminus (15, 16). In addition to the full-length SRC-1 (mSRC-1a, NCoA-1), several splice variants have been described, *e.g.* SRC-1b, -c, -d, and -e (15, 17).

The isoform SRC-1e is a more potent coactivator for ER than SRC-1a (13). For instance, the estrogen-regulated rat oxytocin promoter ($-363/+16$) is coactivated by SRC-1e but not by SRC-1a, as analyzed by transient transfection assay in Cos-1 cells. On the other hand, both SRC-1 isoforms stimulate ER-mediated transcription from an artificial ERE-containing promoter. Thus, coactivation by SRC-1a appears to rely on the promoter context of the receptor target gene. Both isoforms contain three nuclear receptor-interacting motifs (LXXLL) found in many co-factors (18). SRC-1a however possesses a fourth LXXLL motif at its C terminus (13). The function of this additional motif is unclear since its mutation does not affect transcription. The difference in activity results most likely from the presence of two distinct activation domains in SRC-1. The first domain interacts with the mediator CREB-binding protein (CBP)/p300, whereas the second domain activates transcription independently of CBP/p300. It seems that the extra C-terminal portion of SRC-1a, which is not present in SRC-1e, represses this CBP/p300-independent activation domain. The fact that the promoter context influences the ability of SRC-1a to coactivate ER suggests strongly that the recruitment of p300/CBP by SRC-1 is not always sufficient on some promoters. The target factor of the second activation domain is not known to date.

The interaction of SRC-1 with the estrogen receptors depends on ligand and the integrity of helix 12 within the LBD and requires the presence of two functional AF-2 domains in a receptor dimer (13). The ligand-dependent interaction between SRC-1 and TR was analyzed in detail (19). Five independent mutations within the LBD of TR abolished SRC-1a binding. These mutations include residues from helix 3, 5, and 12, which form a small interaction surface encircling a hydrophobic cleft. A similar mutation (K366 in helix 3) in the mouse ER was shown to interfere with SRC-1 recruitment (20). More recently, a complex containing the liganded PPAR-γ LBD (homodimer) and a portion of human SRC-1(623–710) was resolved at 2.3 Å (21). The crystal structure showed that each member of the receptor dimer interacts with a single and different LXXLL motif of the same SRC-1 molecule. The hydrophobic face of the LXXLL helix packs into a hydrophobic pocket formed by helices 3, 4, 5, and 13 (H12 in other receptors) of PPAR-γ. The nuclear hormone re-

Table 2. Nuclear Receptor Cofactors—Part I

Proteins	Interaction (*in Vitro*)	Coactivation (*in Vivo*)	Comments	References
SRC1	PR, RAR, RXR, TR, PPAR	ER, GR, PR, TR, RXR	Identified by yeast two-hybrid (bait: hPR LBD)	13, 14, 16, 24, 38
NCoA-1			Agonist-dependent interaction and coactivation Histone acetyltransferase (H3/H4) Interact with CBP Isoforms 1a and 1e differs in their ability to coactivate ER Autonomous activation domains Contains LXXLL motifs	
ERAP160/p160	ER, RAR, RXR	ER	Identified by GST pull-down with MCF-7 whole-cell extract (bait: hER LBD) Agonist-dependent interaction Interact with CBP p160 encoded by SRC-1 gene (variants 1b, 1c, 1d) Part of an estrogen receptor co-activator complex with ERAP140 and proteins of 300 (CBP), 100, 90 and 30 kDa?	8, 15, 25
GRIP1/TIF2	ER, AR, GR, TR, PR, RAR, RXR	ER, AR, GR, PR	Partial clone identified by yeast two-hybrid from 17-days old mouse embryo cDNA library (bait: mGR LBD) (GRIP1)	12, 118–121
SRC-2/NCoA-2	PPAR	But not TR, VDR, RAR, RXR	Ligand-dependent interaction Autonomous activation function Highly related to SRC-1/NCoA-1 GRIP1 stimulates ER AF-1 TIF2 contains LXXLL motifs and mediates transcription through CBP binding dependent and -independent pathways	
ACTR/AIB1/RAC3	ER, PR, TR, VDR, PPAR, RAR, RXR	ER, PR, TR, RAR, RXR, VDR	First identified by yeast two hybrid from a human brain cDNA library (bait: full length hRAR) (RAC3)	41, 122–125
SRC-3/TRAM-1	But not COUP-TFI		Related to SRC-1, GRIP1/TIF2 and p/CIP Agonist-dependent interaction and coactivation SRC-3 coactivates ERα AIB1 amplified in breast and ovarian cancers ACTR is an histone acetyltransferase ACTR and TRAM-1 recruit CBP and P/CAF	
p/CIP	ER, RAR	ER, PR, TR, RAR	Identified by screening of CBP interacting proteins (NCoA-1/SRC-1 and NCoA-2 were fished during the same procedure) Alternative splice form of the murine homologue of RAC3? Highly related to SRC-1/NCoA-1 and TIF2/NCoA-2 Interacts with a significant portion of CBP in the cell Ligand-dependent interaction and coactivation CBP and p/CIP are required together for nuclear receptor activation (functional complex)	32

Table 2. Continued

Proteins	Interaction (*in Vitro*)	Coactivation (*in Vivo*)	Comments	References
ERAP140/p140	ER	Not available	Identified by GST pull-down with MCF-7 whole cell extracts (bait: hER LBD) Estrogen-dependent interaction Part of an ER coactivator complex with ERAP160 and proteins of 300, 100, 90 and 30 kDa?	8, 25
RIP140	ER, PPARα, TR, RAR, RXR	ER	Identified by GST pull-down with COS-1 cell extracts (bait: mER LBD) Differs from ERAP140 Agonist-dependent interaction and coactivation (modest) Two distinct nuclear receptor interaction sites Antagonizes SRC-1 coactivation of PPAR (competition?) Mouse homolog is a co-repressor for nuclear orphan receptor TR2 (testis)	59–61, 126, 127
RIP160/p160	ER	Not available	Identified by GST pull-down with COS-1 cell extracts (bait: mER LBD) Differs from ERAP160	59
P/CAF	ER, AR, GR, RAR/RXR	RAR/RXR	Identified on the basis of an analogy with yGCN5 and various protein databases. Cloned from human cDNA libraries. hGCN5 was cloned during the same procedure Interacts with CBP/p300 (competes for CBP/p300 with E1A) Histone acetyltransferase (H3/H4) Part of a larger complex which contains TAFs	31, 33, 117
CBP/p300	ER, GR, TR, RAR, RXR	ER, TR, RAR, RXR	Identified by GST pull-down assay between fragments of CBP and hRAR Ligand-dependent interaction and coactivation Interacts with SRC-1/ERAP160 and P/CAF Interacts with numerous transcriptional activator Interaction with ER involves also SRC-1/ERAP160 Histone acetyltransferase (all core histones in nucleosomes)	15, 16, 25, 26, 33, 37, 40
ARA70	AR	AR	Identified by yeast two-hybrid from a human brain cDNA library (bait: hAR LBD)	128
	But not RXR, TR4	ER, GR, PR (weak)	99% homology with RET-fused gene (RFG) which is expressed in thyroid tumor Ligand-dependent interaction and coactivation	
Ada3	ER, TR, RXR	ER, RXR	Identified by yeast two-hybrid from a yeast genomic library (bait: mRXR LBD)	55, 129
	But not RAR		Component of yeast Ada coactivator complex Ada3, Ada2 and Gcn5 required for maximal AF-2 activity in yeast and Ada3 coactivates in mammalian cells	

Table 2. Continued

Proteins	Interaction (*in Vitro*)	Coactivation (*in Vivo*)	Comments	References
			Ligand-dependent interaction and coactivation (yeast) Human counterpart of yAda3 not yet identified	
Rap46	ER, AR, GR, PR, TR	Not available	Identification after screening of a human liver λgt11 expression library with baculovirus expressed mGR Ligand-independent interaction Interaction depends on prior receptor activation (*i.e.* no HSP) Residues 61–274 have 80% sequence identity to mBAG-1 which interact with the cell death repressor, Bcl-2	50
GRIP170	GR	GR (*in vitro* with purified GRIP170 containing fraction)	Identified by *in vitro* interaction of DNA bound hGR with HeLa nuclear proteins Proteins of 95 and 120 kDa identified at the same time as GRIP170 No data available on ligand requirement	130
TRIP1/SUG1	ER, TR, VDR, RAR, RXR But not GR	Not available See comments	Identified by yeast two-hybrid from HeLa cDNA library (bait: rTRβ D-E-F domains) (Trip1) Ligand-dependent interaction Similarity to ySUG1 (76%) which is a component of the yeast RNA pol II holoenzyme and of the PA700 proteasome regulatory complex Overexpression inhibits transactivation Interacts with TBP and TFIIB (SUG1)	54–57, 131
PGC-1	ERα, PPARγ, RARα TRβ	PPARγ/RXRα, TRβ/RXRα RXRα (very weak)	Identified by yeast two-hybrid from a murine brown fat cell cDNA library (bait: mPPARγ amino acids 183–505) Ligand-dependent interaction increased for ER, RAR, and TR but not for PPAR Involved in thermogenesis (PGC-1 mRNA expression is increased in brown fat and skeletal muscle upon cold exposure	132
PGC-2	PPARγ, ERα, TRβ	PPARγ, ERα	Identified by yeast two-hybrid from a adipocyte library (bait: PPARγ A/B domain) Ligand-independent interaction with PPARγ A/B domain Ligand-dependent increase of the transcriptional and adipogenic activities of PPARγ	133
SPT6	ER	ER	Identified by functional test of hER in the yeast *spt6* mutant strain Ligand-dependent interaction and coactivation (yeast and CV-1) Involved in nucleosome assembly and interacts with H3	134, 135
TIF1α	ER, PR, VDR, RAR, RXR	No coactivation described	Identified by a yeast genetic screen with a P19 embryonal carcinoma cell cDNA library and a chimeric receptor (hER DBD fused to mRXR LBD)	53, 55, 136

Table 2. Continued

Proteins	Interaction (*in Vitro*)	Coactivation (*in Vivo*)	Comments	References
	TR (weak)		Ligand-dependent interaction Interacts with two heterochromatin proteins (HP1, MOD1) Binding of TIF1 to liganded nuclear receptors may promote the conversion from an inactive heterochromatin-like structure to an active euchromatin-like structure (release of HP1 and MOD1)? Partial identity to T18 oncogene	
SW12/SNF2 Brahma	GR (SWI3)	ER, GR, RAR	Initially identified as required for HO (SWI2) and SUC2 (SNF2) genes transcription in yeast	62–66, 137–139
	ER		Homolog of *Drosophila* brahma (regulator of homeotic genes such as Src and Antp) Ligand-dependent interaction between ER and SNF2α (hbrahma) or SNF2β (BRG1) Subunit of the SWI/SNF chromatin remodeling complex SWI1, SWI2, SWI3 are required for GR and ER ectopic activation in yeast	
SNURF	With DBD of AR, ER, PR	AR	Identified by yeast two hybrid from a mouse embryo E10.5 cDNA library (bait: hAR DBD) Interacts with DBD as well as with TBP Enhances both steroid-dependent and basal transcription Does not contain a LXXLL motif Activates AP1 and SP1	140
RSP5/RPF1	No direct interactions (M. Imhof, personal communication)	GR, PR	Identified by genetic screening in yeast (hPR) Increases efficiency of weak agonists	35, 51, 141
		But not ER	Agonist-dependent coactivation Synergizes with *SPT3* ($TAF_{II}18$) Is a ubiquitin ligase Part of a coregulator complex with E6-AP?	
TRAP220	TR, VDR, RAR, RXR, PPARα, PPARγ	TR	cDNA isolated from a Jurkat library on the basis of amino acids sequences derived from polypeptides in the immunopurified TR-TRAP complex Contains two LXXLL motifs	48
	ER (weak)		Ligand-dependent interaction and coactivation Part of TRAP complex with TRAP100 (10 proteins)	
TRAP100	ER, RXR, PPARα, PPARγ	Not available	Isolated during the same procedure as TRIP220 Contains six LXXLL motifs Ligand-dependent interaction (marginal)	48
DRIP	TR, VDR PPARγ	VDR	Complex isolated from nuclear extracts from human Namalwa B cells with GST-VDR-LBD	46, 47, 49
	But not ER		Complex of at least 13 polypeptides ranging from 33 to 250 kDa 12 out of 13 subunits are shared with the activator-recruited cofactor (ARC) complex	

Table 2. Continued

Proteins	Interaction (*in Vitro*)	Coactivation (*in Vivo*)	Comments	References
	RAR and RXR associate with a different complex		Strict ligand-dependent interaction	
			Purified DRIP lacks histone acetyltransferase activity	
			DRIP100 which is part of the complex contains LXXLL motifs	
NSD1	ER, RXR	See comments	Identified by yeast two hybrid from a mouse embryo cDNA library (bait: hRAR DBD)	142
	TR, RAR	(Bifunctional factor-repression and activation)	Ligand-dependent reduction of interaction (TR, RAR)	
			Ligand-dependent interaction with RXR (domains D/E) and ER (domains D/E/F)	
	See comments		Contains a variant (FxxLL) of the LXXLL motif	
			Contains separate repression and activation domains	

ceptors contain similar LXXLL motifs within their own AF-2. Surprisingly, the crystal structure of the unliganded PPAR-γ homodimer indicates that the AF-2 helix of one receptor can interact with the LBD of a second receptor (21). This suggests that the ligand-dependent activation leads to the displacement of the AF-2 helix from the LBD of the other receptor in favor of the recruitment of an LXXLL motif of SRC-1. This model was also proposed for the RXR/RAR heterodimer (22).

SRC-1 is also capable of interacting with both the A/B and D/E regions of PR and ER through multiple receptor-interaction sites (23, 24). Furthermore, the binding of SRC-1 to steroid receptors is more efficient when both AF-1 and AF-2 are present. This could potentially explain the transcriptional synergy observed between AF-1 and AF-2 (5).

The ligand-dependent interaction between SRC-1 and nuclear receptors is established, but the way the transcriptional activation signal is transmitted to the transcriptional machinery remains obscure. One possibility is the direct binding of SRC-1 to the basal transcription machinery through TFIIB or TATA-binding protein (TBP) (17). Alternatively, SRC-1 may be part of a larger coactivator complex. Hence, upon estrogen binding, ER becomes associated with numerous proteins, including SRC-1 and p300 together with proteins of 140 (ERAP140), 100, 90, and 30 kDa (25). However, there is no clear evidence that these proteins are part of the same complex. Nevertheless, it was not surprising when SRC-1 was shown to interact directly with a conserved region in the C terminus of p300 and its homolog CBP (15, 16). Moreover, CBP/p300 is a coactivator that binds to nuclear hormone receptor in a ligand-dependent manner (26) and enhances steroid-dependent transcription in synergy with SRC-1 (27). However, there is increasing evidence indicating that the limiting CBP/p300 factor serves a broader function, *i.e*. as an integrator of many different activation pathways (28–30). Indeed, CBP/p300 has been shown to interact with an increasing number of other DNA-binding factors and with components of the basal transcription machinery. p300/CBP-associated factor (P/CAF) and p300/CBP cointegrator-associated protein (p/CIP) are two other nuclear hormone receptor coactivators that can associate with CBP/p300 (31–33). Both CBP/p300 and p/CIP, together with SRC-1 (NCoA-1), are required to allow full ligand-activated gene transcription in several cell lines (32). Finally, p/CIP and SRC-1 can bind P/CAF (34). Despite all the described potential interactions between all these cofactors, there is little biochemical evidence of the existence of such a complex *in vivo*. Some interactions may be mutually exclusive. Alternatively, various combinations of subsets of these coactivators may coexist in the cell, giving rise to a number of possibilities in term of specificity of regulation. In an attempt to isolate such complexes, cells were recently subjected to biochemical fractionation (35). This study indicates that the different cofactors cofractionate in various stable subcomplexes. These data also suggest that the liganded progesterone receptor recruits a preformed complex that contains SRC-1 and TIF2. Although many receptors can bind to a given coactivator, it is possible that they compete with each other and that each has a different cofactor affinity (36).

Interestingly, P/CAF, CBP/p300, and SRC-1 present histone acetyltransferase activity (HAT) (33, 37, 38). Since histone acetylation correlates with promoter activation (reviewed in Ref. 58), it may explain how these cofactors increase the transcriptional activation by nuclear receptors. But are all the different HATs required for the coactivation or do they have some specificity? It appears that inactivation of the HAT domains of CBP or SRC-1 has no influence on the coactivation of RAR (34). However, the HAT domain of P/CAF is indispens-

able for nuclear receptor activation. On the other hand, CREB (CRE-binding protein) function needs CBP-HAT activity and not P/CAF-HAT. This suggests that there is a selectivity in the specific HAT activity required for the action of different classes of transcription factors. In addition, P/CAF acetylates preferentially nucleosomal histone H3, whereas p300/CBP acetylates all nucleosomal core histones (SRC-1 and ACTR have a specificity for histones H3 and H4) (33, 37, 38, 40, 41). The presence of multi-HAT activities within a given complex may lead to various patterns of histone acetylation that are specific for a particular transactivator or for a promoter context. Interestingly, P/CAF and p300/CBP have the property to acetylate nonhistone proteins such as TFIIEβ, TFIIF (RAP74 and RAP30), EKLF, GATA-1, and p53 (42–45).

Recently, VDR-interacting protein (DRIP) was isolated and purified as a new coactivator complex (46, 47). Despite the lack of HAT activities, DRIP is a potent coactivator of the vitamin D receptor in a chromatin context. Any chromatin remodeling activity related to DRIP (directly or not) has not been identified to date. Interestingly, some DRIP subunits are homologous to components of mediator complex that are found associated with the RNA polymerase II complex as well. This finding gives us a clue as to how DRIP may target the RNA polymerase II to the promoter. Surprisingly, DRIP, and most probably its related TRAP (48) complex, shares most of the subunits with yet another complex, ARC (activator-recruited cofactor) (49). The latter, however, is a coactivator for transcription factors such as SREBP-1a, VP16, and NF-κB (p65 subunit) within chromatin. It appears likely that there is a convergence in the coactivation pathways of many transcriptional activators, the differences residing in the fine composition of coactivator complexes or subcomplexes.

OTHER POTENTIAL COACTIVATORS

According to the definition stated earlier in this review, a coactivator must interact directly with the activation domain of a nuclear receptor in an agonist-dependent manner but not in the presence of an antagonist. Rap46 was shown to interact *in vitro* with numerous receptors (ER, AR, GR, PR, TR) independently of the presence of any ligands, agonist or antagonist (50), but so far, no functional experiments have been performed. Another protein, RSP5/RPF1, potentiates hormone-dependent activation of transcription by GR and PR (51), although no direct interaction with either receptors was ever documented (M.O. Imhof, personal communication). Interestingly, in one case, there is ligand-dependent release of a coactivator. The constitutive androstane receptor β (CAR-β) is active in absence of its ligand. Surprisingly, the addition of androstenol or of androstanol promotes the dissociation of the steroid receptor coactivor 1 (SRC-1) and leads to transcriptional repression (52).

Another criterion for belonging to the coactivator family is the ability to enhance receptor function. This basic requirement is not observed with TIF1α, which down-regulates transactivation by ER, RAR, and RXR in Cos-1 cells (53). It is possible, however, that overexpression of TIF1 titrates out an essential limiting nuclear protein required for AF-2 activity. Proteins such as SUG1 (suppressor of a mutation in the transcriptional activation domain of the yeast activator Gal4) and Trip1 (TR-interacting protein 1) interact with several nuclear hormone receptors in a ligand-dependent fashion as well as with TBP (54, 55). The fact that SUG1 was proposed to be a component of the RNA polymerase II holoenzyme reinforced its classification as a coactivator (56). However, SUG1 is a subunit of the 26S proteasome (57, 58) and Trip1 inhibits transactivation (54). Therefore, it is likely that these proteins are not coactivators but rather are involved in receptor degradation.

A third criterion is the requirement for a direct contact between the cofactor itself and the basal transcription machinery in light of the bridging model. This aspect is difficult to assess and was not determined for all potential coactivators. One can also envision that individual cofactors are part of a larger complex, limiting the need for a direct interaction with basal transcription factors. Although RIP140 interacts with several nuclear receptors *in vitro* and enhances weakly ER function *in vivo*, it is not able to associate with either TFIIB or TBP (59–61). Does this disqualify it as a nuclear hormone receptor coactivator ? It is still possible that it interacts with other basal transcription factors. Moreover, the fact that RIP140 inhibits transcription upon overexpression argues in favor of the need for another intermediary factor (60).

Finally, coactivators should not enhance the basal transcriptional activity on their own, although they contain an autonomous activation function (12, 13). Indeed, in the absence of a nuclear hormone receptor, coactivators cannot be recruited to promoters and therefore cannot coactivate transcription.

The first described nuclear hormone-positive regulators are members of the SWI/SNF family of proteins. Ligand-dependent transcriptional enhancement of GR or ER in yeast requires several SWI gene products, such as SWI1, SWI2, and SWI3 (62), which are part of a large SWI/SNF chromatin remodeling complex (63, 64). The human homologs of SWI2, termed SNF2α, SNF2β, or brahma, were also shown to coactivate ER, GR, and RAR in mammalian cells (65, 66). It has not been established, however, whether or not the described interaction between SW3 and GR (which requires SWI1 and SW2) is direct (62). The finding that SWI1 contains nuclear hormone receptor-binding motifs (LXXLL), present in many cofactors (18), is puzzling and might suggest that it is potentially a coactivator (67). However, the importance of these LXXLL motifs was not tested for SW1.

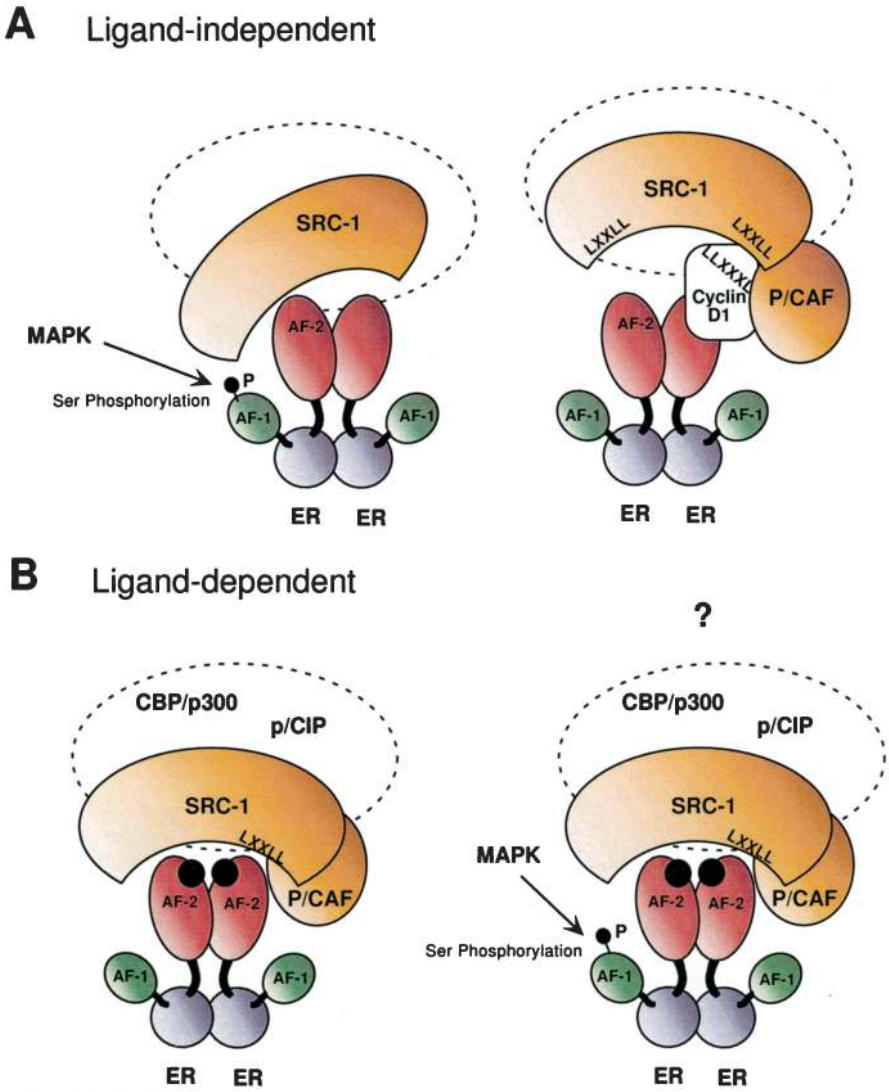

Fig. 1. The ER Can Activate Transcription Through Different Mechanisms.

A, Ligand-independent recruitment of coactivators by the ER. The MAPK-dependent phosphorylation of serine residues within the AF-1 domain allows the functional interaction with SRC-1 (*left panel*). Alternatively, the need for a ligand is abolished by the presence of cyclin D1, which acts as a bridging protein between the ER AF2 domain and SRC-1 and or P/CAF (*right panel*). In the latter situation, the described synergism between estradiol and cyclin D1 might result from their cooperation in the recruitment of SRC1. The presence of SRC-1 and/or P/CAF suggests that other components of a coactivation complex might be present as well (*dashed oval*). B, Ligand-dependent recruitment of coactivators by the ER. The presence of the ligand induces a conformational switch in the ER ligand binding domain that leads to the recruitment of a coactivation complex (*left panel*, see also Fig. 2) containing protein such as SRC-1, P/CAF, p300/CBP, p/CIP, and possibly many others (*dashed oval*). It is possible that ligand-dependent and -independent mechanisms cooperate to provide maximal transcriptional competency to the receptor (*right panel*).

COACTIVATOR AND LIGAND-INDEPENDENT TRANSACTIVATION

A list of nonsteroid compounds or extracellular signals can efficiently activate the ER including dopamine (68), EGF (epidermal growth factor) (69, 70), TGFα (tumor growth factor α) (70), cAMP (69, 71), insulin-like growth factor I (71), phorbol ester (tetradecanoylphorbol acetate) (69), and many others. Since all these molecules induce protein phosphorylation, it is likely that altered phosphorylation of the receptors (and/or associated proteins) is a key event in the ligand-independent activation. Moreover, okadaic acid, an inhibitor of protein phosphatases 1 and 2A, is also able to activate ER-dependent transcription (69).

Ligand-independent phosphorylation of the steroid hormone receptors has been known for a long time (reviewed in Refs. 63 and 64). The ER is mainly phosphorylated on serines residues in the A/B domain (74) although phosphorylation of a tyrosine residue in the

E/F domain was also reported (75, 76). The chain of events linking EGF to ER phosphorylation has been analyzed more extensively. EGF activates the Ras-Raf-MAPK cascade through its membrane receptor and leads to phosphorylation of hER on serine 118 and to enhancement of transcription (69, 77). However, the functional relationship between a particular phosphorylation site and transcriptional activation remained elusive until recently. Effectively, phosphorylation of two ERβ serines residues (Ser 102 and Ser 124 within the AF-1 domain), via the MAPK cascade, promotes the recruitment of SRC-1 in the absence of estrogen (Fig. 1) (78). Similar findings were made with the orphan nuclear receptor SF-1 (steroidogenic factor 1). Intriguingly, phosphorylation enhances the recruitment of both a coactivator [GR-interacting protein 1 (GRIP1)] and a corepressor [silencing mediator for retinoid and thyroid hormone receptor (SMRT)] to SF-1 (79). In this particular situation, the functional importance of phosphorylation in transcriptional activation appears unclear.

Phosphorylation is not the only event that directs ligand-independent transactivation. Cyclin D1 has the property to potentiate the activity of the ER in a cyclin-dependent kinase-independent mechanism (80, 81). Interestingly, cyclin D1 is able to interact with SRC-1 through a region that resembles the receptor leucine-rich coactivator binding motif (LLxxxL) in AF-2 (Fig. 1) (82). Cyclin D1 is essential for proper recruitment of coactivators to unliganded ER and functions as a bridging factor between the receptor and SRC-1. Similarly, recent experiments have shown that P/CAF associates functionally with cyclin D1 (83). Thus, cyclin D1 plays a crucial role in ER activation by recruiting HAT activities in the absence of any ligand. Altogether, these results indicate that the activity of a receptor can be modulated in multiple ways. The combination of various mechanisms could elicit widespread responses to different cellular stimuli (Fig. 1).

NUCLEAR RECEPTOR COREPRESSORS

Transcriptional activation is mediated by the recruitment of coactivators by the activated receptor. However, nuclear hormone receptors can repress transcription under various circumstances (reviewed in Refs. 9 and 74). Repression occurs mostly in the absence of a ligand or when an antagonist is bound to the receptor. In the latter situation, the antagonist competes away the natural ligand, preventing proper activation. Transcriptional repression involves several mechanisms (85). It may result from the binding of a repressor directly to DNA, leading either to a competition for the same DNA element (thus preventing the binding of the activator), to an interference with the activator function after binding to a nonoverlapping site (quenching), or to the direct silencing of the basal transcription machinery irrespective of the presence or absence of the activator. Alternatively, repression may be achieved after the recruitment of a limiting corepressor to the promoter by protein-protein interaction with the activator (Fig. 2). In this situation, the corepressor is not able to bind to DNA on its own. We will focus here on the repression mediated by the recruitment of a corepressor (Table 3).

A true corepressor must fulfill several criteria. First it has to interact directly with the unliganded receptor, leading to enhancement of basal transcription repression. A corepressor should also interact with components of the basal transcription machinery and possess an autonomous repression domain.

DISCOVERY OF COREPRESSORS

The active repression mediated by some members of the nuclear receptor superfamily in the absence of ligand has attracted a lot of interest. The unliganded TR, which is able to bind DNA, is not only transcriptionally incompetent but acts as a repressor (86–90). The finding that TR-mediated repression is reversed by cotransfection of either the unliganded RAR or the C terminus of the oncogene v-ErbA (viral TR homologue) revealed that TR corepressors might exist within the cell (86). Three such corepressors were then identified (Table 3): SMRT (91), N-CoR (nuclear receptor copressor) (92, 93), and SUN-CoR (small ubiquitous nuclear corepressor) (94). These proteins have the characteristic to interact with the unliganded TR or RAR associated with their RXR heterodimeric partner on DNA. The C terminus of N-CoR interacts with TR and RAR in a region encompassing the hinge domain (region D) and a portion of the ligand-binding domain (92). Interestingly, this interaction region (CoR box) is significantly conserved only between TR, v-ErbA, and RAR but not among the receptors that do not associate naturally with N-CoR such as ER (see below). Silencing is abolished upon ligand-dependent release of the repressor from the receptor. Protease resistance assays have suggested that the release of SMRT from TR is imposed by the conformational switch of the LBD (helix 12) upon hormone binding (95). Importantly, the constitutively inactive viral oncogene v-ErbA is associated with SMRT regardless of the presence or absence of a ligand. The behavior of v-ErbA argues that the release of SMRT is a prerequisite for proper transcriptional activation. Interestingly, the point mutant TR160 (Pro160->Arg), which is incapable of silencing but retains its ligand-dependent transactivation, cannot efficiently recruit SMRT, indicating that silencing is linked to the recruitment of SMRT (91). The necessity for a receptor to release a corepressor to activate transcription is well illustrated with the RAR/RXR heterodimer. It is

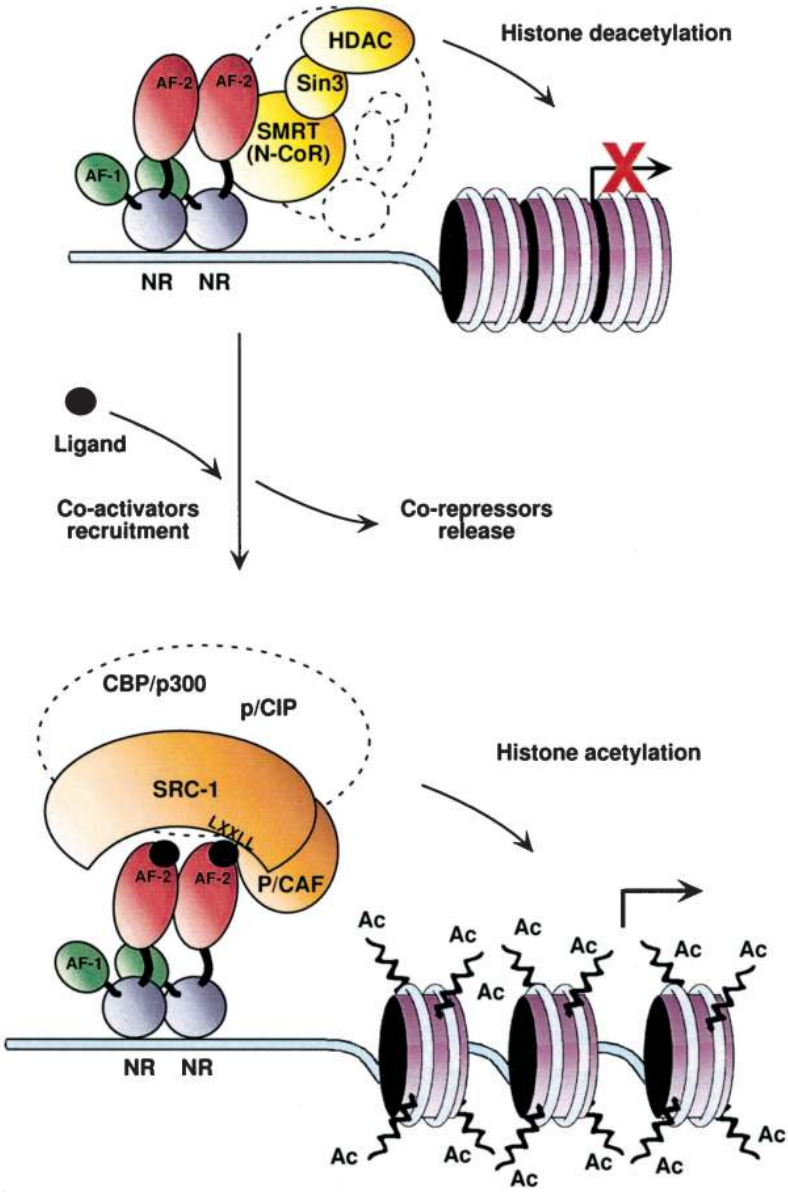

Fig. 2. Ligand-Dependent Switch between A Nuclear Hormone Receptor Associated Either with a Corepression or a Coactivation Complex

The nuclear hormone receptor (NR) is associated with a corepressor (N-CoR, SMRT), which in turn recruits a histone deacetylase (HDAC) through its interaction with Sin3. Deacetylation of histone tails leads to transcriptional repression. Addition of the ligand disrupts this repression complex in favor of the association of a coactivation complex (SRC-1, P/CAF, p300/CBP, pCIP, and others). These proteins possess a histone acetyltransferase activity that allows chromatin decompaction through histone modifications. The interaction between the nuclear hormone receptor AF-2 domain and the coactivation complex occurs through the LXXLL motif found in many coactivators. The coactivator and corepressor complexes are represented with *dashed lines* since their exact composition *in vivo* is not determined.

well documented that RXR and RAR activate transcription from direct repeats when spaced by five nucleotides (DR5), but not when spaced by only one nucleotide (DR1) (96, 97). This differential regulation stems from the incapacity of all-*trans*-retinoic acid to dissociate N-CoR from the RAR/RXR heterodimer on a DR1 DNA element and therefore to relieve repression (93). It appeared that RXR and RAR occupy the 5′- and 3′-half-sites of a DR5 element, respectively, whereas the polarity is inverted on a DR1 element (98). The latter polarity is likely to impose allosteric constraints on RAR, preventing the release of N-CoR. However, the occupancy of either a DR1 or DR5 response element by RAR/RXR has no impact on the ligand-dependent recruitment of coactivators (93).

It was first reported that ER and PR are unable to interact with either N-CoR or SMRT, in the absence

Table 3. Nuclear Receptor Corepressors

Proteins	Interaction (*in Vitro*)	Corepression (*in Vivo*)	Comments	References
SMRT/TRAC-2	RAR, TR, v-ErbA, PPARγ	RAR, TR	Identified by yeast two-hybrid (bait: hRXR) Ligand-dependent dissociation (but weak effect with RXR)	91, 115, 143, 144
	RXR (weak)	But not RevErb, PPARγ	Oncogene v-ErbA (TR mutant), which has strong silencing ability but no transactivation activity, interacts strongly with SMRT irrespective of the presence or not of the ligand SMRTe contains an N-terminal extension related to N-CoR	
N-CoR/RIP13	TR, RevErb, RAR, PPARγ	TR, RevErb, RAR	Identified from CV-1 whole cell extracts (bait: TR/RXR-DNA(TRE) ternary complex immobilized on a streptavidin-agarose matrix	92, 93, 99, 115, 145
	But not ER, PR, GR, VDR, RXR (in absence of any antagonist: see comments)	But not PPARγ	Cloned by yeast two-hybrid from a mouse pituitary cDNA library Ligand-dependent dissociation of full length N-CoR when TR/RXR or RAR/RXR heterodimers are bound to DNA The interaction between N-CoR and RXR/RAR on a DR5 DNA element is released upon ligand binding but not with RAR/RXR is on a DR1 DNA element) N-CoR contains two separate repression domains Partial sequence of N-CoR previously isolated as RIP13 Interacts with CoR box within TR hinge region CoR box not required for interaction with RevErb (encoded on the noncoding strand of the TRα gene (c-erbAα) ER and PR interact with N-CoR in the presence of the antagonist tamoxifen and RU486, respectively	
SUN-CoR	TR, RevErb	TR, RevErb	Identified by yeast two-hybrid from a 17-day old mouse embryo cDNA library (bait: RevErb amino acids 376-614) No homology with N-CoR or SMRT Small 16-kDa nuclear protein Contains an intrinsic repression domain Potentiates repression (2- to β-fold)	94

Table 3. Continued

Proteins	Interaction (*in Vitro*)	Corepression (*in Vivo*)	Comments	References
			Interacts with N-CoR and SMRT *in vitro* Associates with endogenous N-CoR *in vivo* Thyroid hormone does not dissociate TR/SUN-CoR interaction Expression induced during adipocyte and myogenic differentiation	
Ssn6/Tup1	Notavailable	ER, PR	Identified by genetic screening in yeast Ssn6 described previously as a mediator of glucose repression in yeast Represses AF-1 but not AF-2 Ssn6 is part of a yeast repressor complex which include Tup1 Tup1 interacts directly with histones H3 and H4	104–106, 146
TRUP	TR	TR, RAR	Identified by yeast two-hybrid from a human B-lymphocyte cDNA library (bait: hTR168-259 (hinge region + portion of LBD))	102
		But not ER, RXR	Identical to surf-3, PLA-X and L7a Represses transcription by interfering with the receptor binding on DNA (ligand has no effect on DNA binding)	
Calreticulin	GR, AR	GR, AR, RAR	Isolated by affinity chromatography from HOS cell nuclear extracts with a synthetic KLGFFKR peptide KLGFFKR is conserved among the nuclear hormone receptors DBDs (between the two zinc-fingers) Calreticulin also acts as a major Ca^{2+}-storage protein (lumen of the endoplasmic reticulum) Ca^{2+} has no effect on the interaction with GR Represses transcription by interfering with the receptor binding on DNA	101, 103
REA	ER	ER	Identified by yeast two-hybrid from a MCF-7 cDNA library (bait: dominant negative ER mutant) Specific for liganded receptor (estrogen or tamoxifen) Potentiates effectiveness of antiestrogens Competes for estradiol-occupied receptor with SRC-1 at high concentration 99% identical to BAP-37 (B cell receptor-associated protein)	116

of any ligand (92). It appeared, however, that their respective antagonists (tamoxifen and RU486) induce such an interaction. Interestingly, these antagonists switch into perfect agonists when the receptor ligand-independent activation function (AF-1) is activated by the MAPK pathway. This activation is concomitant to the release of the corepressors and to the recruitment of components of the coactivator complex (99). This phenomenon may explain why patients, treated for breast cancer, eventually acquire resistance to tamoxifen. Intriguingly, a small coactivator (L7 or SPA for switch protein for antagonist) has been recently identified and whose coexpression enhances transcription of antagonist-occupied ER and GR (100). Surprisingly, L7/SPA has no effect on agonist-dependent transcription by these receptors. In light of these data, it is possible that the cellular ratio between corepressors and coactivators such as L7/SPA might determine whether an antagonist-bound receptor would be active or not.

The above mentioned corepressors interfere directly with transcriptional activation. Transcriptional inhibition can also be efficiently achieved by preventing nuclear receptor from accessing DNA. TRUP and calreticulin are such proteins whose binding either to the hinge-domain of TR and RAR (TRUP) or to the DNA-binding domain of AR, GR, and RAR (calreticulin) interferes with their DNA binding (101–103). However, these proteins should not be considered as being real corepressors according to its definition mentioned earlier. Indeed, TRUP and calreticulin prevent transcriptional activation by interfering with receptor binding but not by enhancing basal transcription repression.

The yeast protein Ssn6 was isolated as a negative regulator of the estrogen and progesterone receptors (104). It appeared to repress the ligand-independent activity of ER-AF-1. It is not clear whether Ssn6 should qualify as a nuclear hormone corepressor especially because it affects AF-1 but not AF-2. In addition, there is no study available that could indicate whether Ssn6 fits all the criteria of the corepressor family, and since the steroid hormone receptors are not naturally expressed in yeast, it is unclear whether a similar mechanism would occur in mammals. Interestingly, Ssn6 is involved in glucose-mediated gene repression and requires a partner, Tup1, to achieve full repression (105). Tup1 has been shown to mediate repression by its ability to interact directly with histones H3 and H4 (106). This suggests that repression involves some chromatin components.

SMRT AND N-CoR MEDIATE TRANSCRIPTIONAL REPRESSION THROUGH THE RECRUITMENT OF A HISTONE DEACETYLASE COMPLEX

Immunoprecipitation experiments have revealed that N-CoR and SMRT are components of a cellular complex containing the proteins Sin3A/B and histone deacetylases (107–109). The N terminus repression domain (SD-1) of SMRT interacts with Sin3A, which in turn associates with the histone deacetylase HDAC-1 through one of its two silencing domains (110). No evidence of a direct interaction between HDAC-1 and SMRT was observed, suggesting that Sin3 acts as a bridging molecule between SMRT and the deacetylase complex. These findings argue that at least part of the silencing mediated by nuclear hormone repressors involves the deacetylation of histones through the recruitment of a histone deacetylase complex (Fig. 2).

The importance of histone deacetylation associated to corepression has been highlighted recently in human leukemia (111, 112). Two forms of acute promyelocytic leukemia (APL) are caused by chromosomal translocations that create oncogenic fusion proteins between RAR and either PML (promyelocytic leukemia) or PFLZ (promyelocytic leukemia zinc finger). Both PML-RAR and PFLZ-RAR recruit the corepressor-deacetylase complex through RAR in a ligand-independent fashion. These interactions are abolished with high-dose retinoic acid. However, PFLZ-RAR is also able to associate constitutively and stably with corepressors and deacetylases through the PFLZ moiety, irrespective of the presence of the ligand. This explains why PML-RAR APL patients usually recover after treatment with retinoic acid but not PFLZ-RAR patients. These data strongly suggest that leukemia induced by PML-RAR and PFLZ-RAR is derived from aberrant chromatin deacetylation.

Chromatin modification through acetylation cannot account solely for the repression of transcription mediated by unliganded receptors. Silencing is indeed observed in systems that are devoid of proper chromatin such as transient transfections and *in vitro* transcription (86, 87, 89). Therefore, alternative silencing pathways must exist and function independently of the recruitment of any histone deacetylase. Early results have suggested that TR silencing is mediated by its direct interaction with the general transcription factor TFIIB and that thyroid hormone is able to decrease this interaction (113). In agreement with these results, TFIIB was recently demonstrated to interact with the corepressors N-CoR and SMRT as well as with Sin3 (110). It appears that TFIIB binds *in vitro* to the same silencing domain (SD-1) of SMRT as does Sin3 (see above). It is not clear to date whether the binding of TFIIB and Sin3 to SMRT are mutually exclusive. Interestingly, overexpression of SMRT reduces the transcriptional activity of TFIIB tethered to a promoter indicating that their physical interaction is functional. In another study, N-CoR was shown to make simultaneous and noncompetitive contacts with the general transcription factors TFIIB, $TAF_{II}32$, and $TAF_{II}70$ (114). In this case the binding of TFIIB with N-CoR can occur in the presence of Sin3B and HDAC-1. The sequestration of TFIIB and $TAF_{II}32$ by N-CoR inhibits the functional interactions of the two former factors, which

is crucial for transcriptional initiation. SMRT contains two silencing domains within its amino-terminal region, namely SD-1 and SD-2, but only SD-1 reportedly interacts with Sin3A or TFIIB (110). Similarly, Sin3A possesses two silencing domains, one of which interacts only with the histone deacetylase HDAC-1. Moreover, the histone deacetylase inhibitor, trichostatin A, has no notable effect on the Sin3A ability to repress transcription. These results suggest that, in addition to the recruitment of either TFIIB or HDACs, other unidentified alternative silencing pathways may exist.

CONCLUDING REMARKS

The increasing number of described cofactors adds to the complexity of the transcriptional regulation mediated by nuclear hormone receptors. One of the future challenges will be to determine the specificities of the coregulator family. There is strong evidence that coregulators do not modulate the activity of all nuclear hormone receptors. For instance, it is known that neither SMRT nor N-CoR represses PPARγ activity although they interact in solution (115). In fact, the PPARγ/RXRα heterodimer fails to recruit these corepressors once bound to DNA, at least at the acyl CoA oxidase gene promoter. More interestingly, N-CoR but not SMRT potentiates RevErb repression indicating that these two corepressors do not possess redundant functions. Similarly, the recently described "repressor of estrogen receptor activity" (REA) appears to be selective for the liganded ER (116). Thus, the first level of specificity might be achieved by the selective recruitment of a given cofactor. We now know that some coregulators are part of multisubunit complexes such as DRIP and P/CAF (47, 49, 117). The presence of various accessory proteins within these complexes or alternative subcomplexes will likely influence the specificity of transcription. We have also seen that some coactivators possess a HAT activity. Finally, posttranslational modifications of coregulators or of other components within their complex may as well prove to be important for proper regulation. All these potential levels of regulation increase not only the complexity but also the number of possibilities available for a better tuning of transcriptional control. The active research in the nuclear hormone receptor during the last decade has dramatically changed the simple view of the mechanism of receptor action. More surprises are likely to come in the near future.

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