

## Coregulator Codes of Transcriptional Regulation by Nuclear Receptors\*

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Members of the nuclear receptor superfamily directly activate or repress target genes by binding to hormone response elements (HREs)<sup>1</sup> in promoter or enhancer regions, and by binding to other DNA sequence-specific activators and can inhibit the transcriptional activities of other classes of transcription factors by transrepression. Hormone response elements provide specificity to receptor homodimer heterodimer binding (reviewed in Ref. 2). Nuclear receptor functions are directed by specific activation domains, referred to as activation function 1 (AF-1), which resides in the N terminus, and activation function 2 (AF-2), which resides in the C-terminal ligand binding domain (LBD) (reviewed in Ref. 1). Regulation of gene transcription by nuclear receptors requires the recruitment of proteins characterized as coregulators, with ligand-dependent exchange of corepressors for coactivators serving as the basic mechanism for switching gene repression to activation. In this review, we discuss biochemical and genetic studies suggesting that coregulatory complexes are differentially utilized in both a cell- and promoter-specific fashion to activate or repress gene transcription. These coregulatory components, themselves targets of diverse intracellular signaling pathways, provide a combinatorial code for tissue- and gene-specific responses, utilizing both enzymatic and platform assembly functions to mediate the actions of nuclear receptor genetic programs critical for developmental and homeostatic processes in metazoan organisms.

### Nuclear Receptor Coactivators

A diverse group of proteins have emerged as potential coactivators for nuclear receptors. Ligand-dependent recruitment of coactivators is dependent on AF-2, which consists of a short conserved helical sequence within the C terminus of the LBD (2). Biochemical and expression cloning approaches have been used to identify a large number of factors that interact with nuclear receptors in either a ligand-independent or a ligand-dependent manner and are often components of large multiprotein complexes. Many of these factors are capable of potentiating nuclear receptor activity in transient cotransfection assays. In addition, a distinct set of coac-

tivators is associated with the AF-1 domain. As the number of potential coregulators clearly exceeds the capacity for direct interaction by a single receptor, the most plausible hypothesis is that transcriptional activation by nuclear receptors involves the actions of multiple factors. These factors act in a sequential and/or combinatorial manner to reorganize chromatin templates and to modify and recruit basal factors and RNA polymerase II (3, 4).

### ATP-dependent Chromatin Remodeling Complexes

As chromatinized transcription units are "repressed" compared with naked DNA, a critical aspect of gene activation involves nucleosomal remodeling (reviewed in Refs. 3–5). Two general classes of chromatin remodeling factors that appear to play critical roles in transcriptional activation by nuclear receptors have been identified. These are ATP-dependent nucleosome remodeling complexes and factors that contain histone acetyltransferase activity. The yeast SWI:SNF complex facilitates the binding of sequence-specific transcription factors to nucleosomal DNA and can cause local changes in chromatin structure in an ATP-dependent manner (3–12). Mammalian homologues of *Drosophila* SWI2/SNF2 such as BRG1/hBrm function as components of large multiprotein complexes. Transfection of ATPase-defective alleles of either *Brg1* or *hBrm* into several mammalian cell lines leads to a significant decrease in the ability of several nuclear receptors to activate transcription (3–6). Remodeling complexes containing ISWI (imitation SWI) may also be involved in nuclear receptor function (7–11).

### Acetyltransferases

Rates of gene transcription roughly correlate with the degree of histone acetylation, with hyperacetylated regions of the genome appearing to be more actively transcribed than hypoacetylated regions (reviewed in Ref. 7). The specific recruitment of a complex with histone acetyltransferase activity to a promoter may play a critical role in overcoming repressive effects of chromatin structure on transcription (4–7). This concept was further supported by the subsequent finding that the mammalian Gcn5 orthologues, including p/CAF, CREB-binding protein (CBP), adenovirus E1A-binding protein p300, and TAF<sub>II</sub>250, each possess intrinsic histone acetyltransferase (HAT) activity (7–11). Conversely, the discovery that a mammalian histone deacetylase (HDAC) was a homologue of the yeast corepressor, RPD3 (13), gave rise to the hypothesis that regulated activation events might involve the exchange of complexes containing histone deacetylase functions with those containing histone acetyltransferase activity (Fig. 1). It appears that in most cases the acetyltransferases are not directly recruited to nuclear receptors but associate with other coactivators that exhibit higher affinity for the liganded receptor. The acetyltransferase functions of factors such as CBP/p300 are directly required for enhanced transcription on chromatinized templates (14).

### Nuclear Receptor-interacting Coactivators

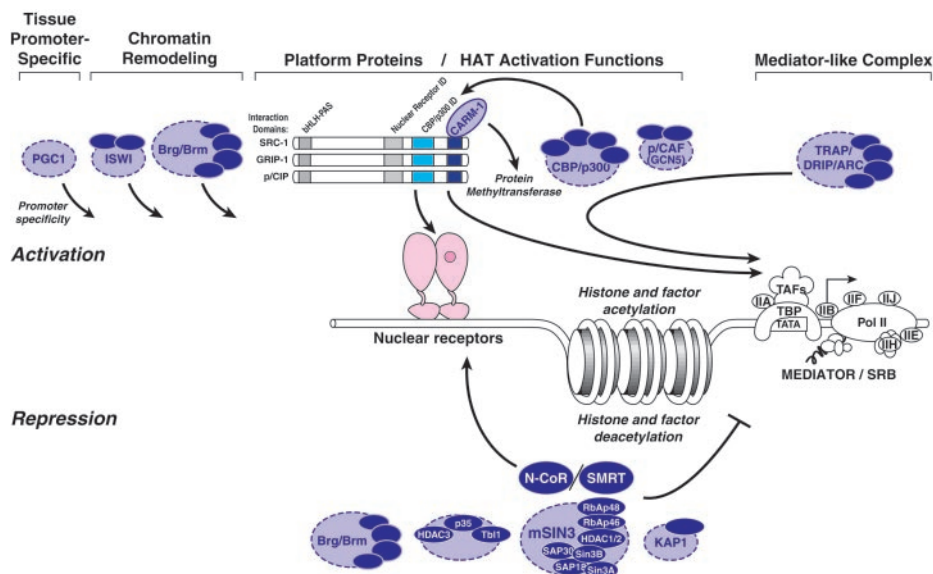
A large number of proteins that are recruited in a ligand-dependent fashion have the capacity to enhance transcriptional activation by transient transfection. Several insights into the mechanisms by which coactivator complexes are recruited to nuclear receptors in a ligand-dependent manner have been provided by the initial identification of the p160 family of nuclear receptor coactivators, referred to as SRC-1/NCOA1, TIF2/GRIP1, and p/CIP/A1B1/ACTR/RAC/TRAM-1 (reviewed in Ref. 15). The p160 factors consist of three members that exhibit a common domain structure, illustrated in Fig. 1. The central conserved domain mediates ligand-dependent interactions with the nuclear receptor LBD, whereas the conserved C-terminal transcriptional activation domains mediate interactions with either CBP/p300 or protein-arginine methyltransferase (16, 17). Based on the presence of three regulatory domains, members of the p160 family have been suggested to function as coactivators, at least in part, by serving as adapter molecules that recruit CBP and/or p300 complexes to promoter-

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<sup>1</sup> The abbreviations used are: HRE, hormone response element; PPAR<sub>γ</sub>, peroxisome proliferator-activated receptor; T<sub>3</sub>R, thyroid hormone receptor; ER, estrogen receptor; LBD, ligand binding domain; N-CoR, nuclear receptor corepressor; SMRT, silencing mediator of retinoic acid and thyroid hormone receptor; ISWI, imitation SWI; CREB, cAMP response element-binding protein; CBP, CREB-binding protein; HAT, histone acetyltransferase; MAP, mitogen-activated protein; HDAC, histone deacetylase; SRC, steroid receptor coactivator; RIP, RAR interacting protein; GRIP, glucocorticoid receptor interacting protein; TRAP, T<sub>3</sub>R receptor associated protein; DRIP, vitamin D receptor interacting protein.

**FIG. 1. Alternative activation and repression functions of nuclear receptors regulated by ligand (or signaling pathway) control of recruitment of either coactivators or corepressors.** These include complexes (Brg-1-Brm, CBP-p300, p/CAF-Gcn5L), TRAP-DRIP-ARC, and the p160 factors (SRC-1, GRIP1, p/CIP), which in turn can associate with an arginine methyltransferase, CARM1. The corepressors N-CoR and SMRT can recruit different complexes, some containing HDACs; components of the Brg-1-Brm complex appear to be involved in repression events.



bound nuclear receptors in a ligand-dependent manner (18, 19). Biochemical studies have also demonstrated strong ligand-dependent interactions between nuclear receptors and p140 factors, probably representing the coregulator RIP140, which results in a reproductive defect in female mice on gene deletion (20).

Analysis of the nuclear receptor interaction domain of the p160 family led to the identification of three repeated motifs with a consensus sequence LXXLL in which L represents leucine and X represents any amino acid. The LXXLL motif has been found to be necessary and sufficient for ligand-dependent interactions with the nuclear receptor ligand binding domain (19, 21–25). Structural studies of the PPAR $\gamma$ , ER, and T $_3$ R ligand binding domains complexed to fragments of the p160 nuclear receptor interaction domains revealed that these motifs form short  $\alpha$  helices (22–25), with multiple LXXLL motifs within a single coactivator mediating cooperative interactions with nuclear receptor dimers or heterodimers. The LXXLL helix is oriented and positioned at each end by a “charge-clamp” consisting of a conserved lysine in helix 3 of the ligand binding domain and a conserved glutamate in the AF-2 helix. These residues grip the LXXLL helix so that the internal leucine residues can pack into a hydrophobic pocket in the receptor C terminus. Most nuclear receptor coactivators have proved to contain functionally important LXXLL helices, with additional residues contributing to binding specificity (*e.g.* Refs. 26 and 27). Furthermore, these contacts are sensitive to conformational changes induced by structurally distinct ligands.

Many additional factors have been demonstrated to enhance nuclear receptor activity in functional assays, suggesting that they may serve as nuclear receptor coregulators (reviewed in Ref. 1). Biochemical studies and protein-protein interaction screens suggest that many of these proteins function as components of large multiprotein complexes and that additional enzymatic activities may be important for their function. For example, the p160 protein GRIP1 can associate with arginine methyltransferase 1 (CARM1), which potentiates ligand-dependent transcription by several nuclear receptors (16). PRMT1, a second arginine methyltransferase related to CARM1, also functions independently as a nuclear receptor coactivator (17). The CBP/p300 coactivators can recruit additional factors with HAT activity, such as the p/CAF-Gcn5L complexes (11, 18). The content and conformation of the recruited complexes may explain why distinct acetyltransferases are required by different DNA-bound transcription factors on specific gene targets (28).

#### The TRAP-DRIP-ARC Complex

In addition to coactivator complexes that harbor nucleosome remodeling or histone acetyltransferase activities, other coactivator complexes have been identified. The best characterized of these is the TRAP-DRIP-ARC complex, which enhances the transcriptional activities of nuclear receptors and other signal-dependent transcription factors *in vitro* (29–31). The TRAP-DRIP-ARC com-

plex is recruited to nuclear receptors in a ligand-dependent manner via a 220-kDa component referred to as PBP/TRAP220/DRIP205, which contains two alternatively utilized LXXLL nuclear receptor interaction motifs (32, 33). Disruption of the TRAP220/PRIP205/PBP gene in the mouse results in embryonic lethality at embryonic day 11.5, and initial studies in myocyte enhancer factors have suggested a defect in ligand-dependent thyroid hormone and PPAR $\gamma$  receptor function (31, 32). Intriguingly other classes of transcription factors remain competent to activate transcription in these cells. The TRAP-DRIP-ARC complex consists of more than a dozen polypeptides, a subset of which appears to constitute modules that are components of other activator complexes, including CRSP, NAT, SMCC, and mouse mediator, and have no known enzymatic functions (29, 31, 34). These factors may thus function to recruit RNA polymerase II holoenzyme to ligand-bound nuclear receptors. The TRAP-DRIP-ARC complex is not stably associated with RNA polymerase II but can be coimmunoprecipitated in the presence of ligand-activated vitamin D receptor (35), suggesting a conformational change or recruitment of additional components that allow stable interactions with RNA polymerase II complexes.

As more than 30 additional putative coactivators have been identified, including proteins with protease activity and an RNA that appears to function as a coactivator (reviewed in Ref. 15), it is likely that different protein complexes can act either sequentially, combinatorially, or in parallel, particularly in light of the evidence of rapid turnover of DNA-receptor interactions (36, 37). One potential scenario for a division of labor among coactivators would be for Brg-1-Brm-like complexes to carry out chromatin remodeling while ligand-dependent recruitment of the so called p160 factors, in concert with other factors such as CBP, p300, and p/CAF, bring required acetyltransferase activities. Finally, recruitment of complexes such as the TRAP-DRIP-ARC complex may function to enhance RNA polymerase II recruitment to the promoter.

#### Combinatorial Control of Receptor Function

In addition, a number of factors have been isolated that can act in a promoter-specific fashion, potentially adding important enzymatic activities or protein-protein interactions and acting synergistically or antagonistically with other complexes. For example, a coactivator ASC2/Rap250/NRC/PRIP/TRBP interacts both with nuclear receptors and CBP/p300 p160 factors or a TRAP component (DRIP130/CRSP130/Sur2) via a C-terminal domain and possibly also contacts factors in the basal transcription complex (38, 39).

Genetic evidence has revealed alternative promoter-specific redundancy in cofactor requirements or absolute dependence on specific coregulators. Both CBP and p300 are functionally limiting, exhibiting haploinsufficiency phenotypes (40, 41), and transfection studies in p300(–/–) embryonic fibroblasts suggest impairment in retinoic acid receptor signaling, supporting the idea from biochemical studies that correct regulation of transcription requires precise

levels of p300 and CBP (42). While mice lacking each of the p160 factors are viable, subtle defects are suggested in specific receptor functions (43–46); for example, p/CIP/SRC-3 exerts effects on somatic growth, modulating cell-autonomous cell cycle events (45, 46).

The alternative requirements for diverse coactivators reflect, in part, their tissue-specific distributions and covalent modifications of different coactivators, exemplified by the variations in CBP in specific cell types (47). However, a major conceptual problem is that the number of potential coregulators clearly exceeds the capacity for direct interaction by a single receptor. Using chromatin immunoprecipitation assays, CBP/p300-p160 complexes and TRAP-DRIP-ARC complexes are found to be “simultaneously” bound to estrogen receptor target genes in response to hormones (37). Whether these complexes indeed simultaneously contact each estrogen receptor cannot be established by this technique, especially in light of the evidence of rapid turnover of DNA-bound receptors (36). A very rapid turnover of receptors, on the glucocorticoid response elements of hormonally induced gene, was established by determining the turnover of fluorescent labeled glucocorticoid receptors in a cell line containing a multimerized contig of mouse mammary tumor virus promoter/transcription units (36). One might speculate that there is a correspondingly rapid exchange of receptors associated with different coactivator, which could then combinatorially mediate a series of essential and non-redundant steps required for transcriptional activation.

A striking example of a promoter-specific coactivator requirement has been provided by identification of the cold-inducible coactivator PGC-1 (48, 49). PGC-1 is induced in brown fat cells by thermal stimulation and acts as a coactivator, along with CBP and p160 factors, for PPAR $\gamma$ - and T $\beta$ R-mediated transcriptional activation. These observations raise the intriguing question of why specific combinations of coactivators are required for only some promoters regulated by the same nuclear receptor.

### Nuclear Receptor Corepressors

Several members of the nuclear receptor family appear to exert critical physiologic roles by actively repressing gene transcription, alternatively functioning as a ligand-independent repressor on some target genes or a ligand-dependent repressor on other transcription units (Fig. 1). A search for interacting proteins mediating these effects led to the cloning of the nuclear receptor corepressors N-CoR and SMRT (50–52). These factors harbor multi-independent repressor domains that can interact with mammalian homologues of proteins that have been defined genetically in yeast to mediate transcriptional repression, including Sin3 and histone deacetylases (53, 54). Thyroid hormone resistance syndromes can be correlated with mutations in the ligand binding domain of thyroid hormone receptor  $\beta$  that enhance ligand-independent interactions with N-CoR/SMRT (55). N-CoR also exerts repressive roles in the actions of other classes of transcription factors (reviewed in Ref. 1).

Genetic evidence has permitted linkage between N-CoR and repression, as deletion of the murine N-CoR locus relieves nuclear receptor-mediated repression of specific genes (56). Altered patterns of transcription in cells derived from N-CoR gene-deleted mice and the resulting block at specific points in erythrocyte, thymocyte, and neural development indicate that N-CoR is a required component of short term active repression by nuclear receptors and other factors. In addition, N-CoR also appears to be required for a subset of long term repression events. Thus, available data suggest that specific combinations of corepressor and histone deacetylases mediate the gene-specific actions of DNA-bound repressors on the development of multiple organ systems.

N-CoR and SMRT appear to be components of several distinct corepressor complexes. Although both proteins were initially suggested to interact with complexes containing Sin3 and specific HDACs based on coimmunoprecipitation experiments (53, 54), Sin3 complexes isolated under stringent biochemical conditions did not contain N-CoR or SMRT. However, purification of N-CoR from *Xenopus laevis* oocytes resulted in recovery of three distinct complexes (57). One complex contained Sin3, HDAC1, and RbAp48; the second contained a Sin3-independent histone deacetylase; and the third complex lacked HDAC activity. Purification of N-CoR complexes from HeLa cells has also resulted in the recovery of at least three complexes (58–61). One complex contains HDAC1, HDAC2,

and several other components found in the Sin3A-HDAC complex, consistent with the original immunoprecipitation studies (58). The second complex contains several additional components, including BRG-1, BAF170, BAF155, BAF47/INO1, and KAP-1, a corepressor that has been linked to heterochromatin silencing (53). What appears to be a third complex, identified through purification of either SMRT or N-CoR, contains transducin  $\beta$ -like protein 1 (TBL-1), a protein with structural and functional similarities to the WD40-containing Tup1 and Groucho corepressors (60). HDAC3 is also a component of the N-CoR/TBL-1 complex (60, 61), raising intriguing issues as to the specific functions of various HDACs in N-CoR action. A specific conserved corepressor domain of N-CoR and SMRT has also been shown to be capable of direct interaction with HDACs 4 and 5 (62, 63). In concert, these findings suggest that N-CoR associations with specific corepressor complexes are dynamically regulated and will exhibit promoter and cell-type specificity.

### Determination of N-CoR/SMRT, Receptor Interactors

Two sequences in the C-terminal regions of N-CoR and SMRT appear to function cooperatively to mediate interactions with DNA-bound thyroid hormone receptor/RXR heterodimers, each containing a conserved consensus sequence LXXXLXXX(I/L) that mediate interactions with unliganded thyroid and retinoic acid receptors (63–65). This motif is predicted to form an extended  $\alpha$  helix, one helical turn longer than the LXXLL recognition motif present in nuclear receptor coactivators. Biochemical findings indicate that the LXXXLXXX(I/L) motif in N-CoR and SMRT and the LXXLL motif in coactivators utilize overlapping surfaces for interactions, with inability of the corepressor helix to fit in the charge clamp. However, a clever phage display screen suggests that a second type of corepressor can be recruited to receptors, such as estrogen receptor in the presence of antagonist (66), although N-CoR also appears to be a required component (56, 67). Crystal structures of the estrogen receptor bound to tamoxifen or raloxifene indicate displacement of the AF-2 helix (*e.g.* Ref. 25), facilitating corepressor binding.

### Coactivators and Corepressors as Targets of Signal Transduction Pathways

Emerging evidence indicates that coactivators and corepressors are themselves targets of multiple signal transduction pathways, examples of which are illustrated in Fig. 2. Regulation of coactivator and corepressor function potentially provides a means for integration of responses to specific signals across families of sequence-specific transcription factors. For example, the histone acetyltransferase activity of CBP has been suggested to be regulated by cyclin-dependent kinases, which presumably alter its coactivator activities during the cell cycle (68). The ability of CBP to serve as a coactivator of CREB is enhanced in response to calcium signaling via a mechanism involving calmodulin kinase IV (69). The p160 nuclear receptors can be phosphorylated in response to different signaling events, causing redistribution of p/CIP from the cytoplasm to the nucleus (46). Further CBP-dependent acetylation of lysine residues adjacent to LXXLL motifs may facilitate the disassociation from DNA-bound receptors. Similarly, corepressors are apparent targets of signal transduction pathways, with activation of MAP kinase cascades correlating with a redistribution of SMRT from a predominantly nuclear location to a predominantly perinuclear or cytoplasmic compartment (69, 70). The N terminus of N-CoR has been shown to interact with mSiah2, the mammalian homologue of *Drosophila* Seven in absentia (71), implicated in regulating proteosomal degradation of proteins. Based on cotransfection assays mSiah2 can mediate a dramatic decrease of N-CoR protein levels, blocked by a proteasome inhibitor. The association of N-CoR/SMRT with nuclear receptors is modulated by cell signaling events that can regulate the association and activity of N-CoR/SMRT. Thus, activation of signaling pathways that stimulate the MAP kinase pathway decreased association of N-CoR with estrogen receptors in the presence of the antagonist tamoxifen, based on the phosphorylation of the ER N terminus (67). In addition, treatment with forskolin or epidermal growth factor resulting in serine phosphorylation of TR $\beta$ 1 and dissociation of SMRT with MAP kinase-extracellular signal-regulated kinase 1 directly inhibits interactions between SMRT and nuclear receptors or PLZF (72).

## Conclusions

Nuclear receptors can serve as repressors or activators, apparently dependent upon the regulated exchange of binding of factors and complexes, characterized by distinct enzymatic and platform functions. In addition to a ligand-dependent switch, various signal transduction pathways can modulate interactions of specific coregulators with nuclear receptors or mediate their activity or distribution between nuclear or cytoplasmic compartments. The potential for rapid exchange of nuclear receptors and cofactors has intriguing implications for the functional significance of ever expanding multiple receptors of coregulatory complexes.

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