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Strategies for Transcriptional Activation by Steroid/Nuclear Receptors

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Abstract Nuclear receptors regulate transcription in direct response to their cognate hormonal ligands. Ligand binding leads to the dissociation of corepressors and the recruitment of coactivators. Many of these factors, acting in large complexes, have emerged as chromatin remodelers through intrinsic histone-modifying activities or through other novel functions. In addition, other ligand-recruited complexes appear to act more directly on the transcriptional apparatus, suggesting that transcriptional regulation by nuclear receptors may involve a process of both chromatin alterations and direct recruitment of key initiation components at regulated promoters. J. Cell. Biochem. Suppls. 32/33:103–109, 1999. © 1999 Wiley-Liss, Inc.

Key words: ligand binding; transcription; chromatin

Nuclear receptors comprise a very large family of ligand-inducible transcription factors. Like other eukaryotic factors that regulate transcription, nuclear receptors bind selectively to DNA, primarily as dimers through two characteristic zinc-finger modules and a dimerization region that directs self-interaction or hetero-partnering. Moreover, they possess identifiable transactivation functions (AF) that can independently confer activation potential to heterologous DNA-binding domains. Transactivation is mediated by both constitutive and inducible AF (AF-1 and AF-2, respectively), the latter conferred by its integral location within the ligand-binding domain (LBD).

The ligands for nuclear receptors include steroids, retinoids, vitamin D, thyroid hormone, prostanoids, and cholesterol metabolites, such as oxysterols and bile acids. Their combined effects are vast, influencing virtually every fundamental biological process, from development and homeostasis, to proliferation and differentiation. For example, retinoids and vitamin D_3 are potent growth inhibitors and inducers of differentiation, particularly of cells of immune and hematopoietic lineages. In addition, PPARγ ligands have a remarkable effect on the induction of adipocyte differentiation. Elucidation of the mechanisms by which nuclear receptors regulate cellular processes will require both the identification of key target genes, as well as a detailed accounting of the molecular events that are initiated by the highly specific and tight interactions that occur between ligand and receptor, leading to transactivation. This review focuses on the latter question, emphasizing new insights into how ligand-binding facilitates the recruitment of receptor-associated protein complexes that in turn affect transcription initiation at regulated promoters.

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HISTONE MODIFYING COFACTORS

Cellular DNA is packaged into chromatin, a repeating array of a protein-DNA complex of which the minimal and recently crystallographically defined unit is the nucleosome, consisting of a histone octamer enveloped by 146 base pairs (bp) of DNA [Luger et al., 1997]. Yeast genetics correlated the acetylation state of the N-terminal tails of histones to gene expression and provided the first evidence for how chromatin might be regulated to control transcription [Kayne et al., 1988; Megee et al., 1990]. From these and other studies, it was postulated that hyperacetylation of histones promoted an "open" transcriptionally active state, and hypoacetylation a "closed" transcriptionally repressed state. A large number of nuclear receptor transcrip-

tional "coactivators" and "corepressors" have recently been isolated, identified genetically and biochemically in yeast and mammalian cells, and from extracts in vitro that harbor histone-acetylase (HAT) or -deacetylase (HDAC) activities. When deacetylase inhibitors such as Trichostatin-A or butyrate have been used in cells or in vitro, chromatin derepression and increased transcription have been observed [Sheridan et al., 1997; Côté et al., 1998; Nightingale et al., 1998]. One family of related proteins are collectively termed the p160 coactivators. They are represented by SRC-1/NCoA-1, TIF2/GRIP1/NCoA-2, and pCIP/ACTR/AIB1. Besides sequence homology, p160 proteins share an ability to stimulate ligand-dependent transactivation by a rather large number of nuclear receptors in transient overexpression experiments. A distinctive structural feature of the p160 coactivators is the presence of multiple LXXLL signature motifs (also called LXDs, NR boxes, or NIDs), which comprise determinants for direct interactions with the nuclear receptor AF-2.

Although the amino acid context surrounding the LXXLL motif appears to influence selectivity of interaction, it remains unclear what, if anything, influences the specificity of nuclear receptor/p160 binding. Several recent LBD crystal structures have established that, upon ligand binding, the α-helix containing the AF-2 core (helix 12) undergoes a major reorientation in the context of the overall LBD structure, forming part of a "charged clamp" that accommodates p160 coactivators within a hydrophobic cleft of the LBD; this occurs through direct contact with the LXXLL motif [reviewed in Xu et al., 1999, references therein]. Remarkably, estrogen antagonists such as tamoxifen and raloxifene appear to alter the position of the AF-2 core such that helix 12 itself occupies the hydrophobic cleft in the LBD, precluding coactivator binding [Brzozowski et al., 1997; Shiau et al., 1998]. In fact, several experiments preceding these crystal structure analyses indicated that a key mechanistic effect of hormonal antagonists is to inhibit p160 interaction with the LBD, lending further support to the biological relevance of coactivators in nuclear receptor function.

Insight into a potential mechanism of p160 coactivation came with the finding that SRC-1 is capable of interacting with the C-terminus of CBP/p300 and together they can coactivate synergistically [Yao et al., 1996]. In addition, CBP/p300 itself interacts directly with nuclear receptors in a ligand-dependent manner, again through the AF-2 domain [Chakravarti et al., 1996; Kamei et al., 1996]. Thus, one can imagine a growing HAT-containing, chromatin-remodeling complex composed of CBP, p160, and p/CAF recruited to nuclear receptors in response to hormone-binding (Fig. 1). Although some of these individual proteins have been observed to exert significant transcriptional effects when overexpressed or limited in cells, particularly CBP [Kamei et al., 1996] and SRC-1/NCoA-1 [Spencer et al., 1997; Onate et al., 1995; McInerney et al., 1998], or biochemically in vitro, [Kraus and Kadonaga [1998], it is becoming increasingly clear that they are associated with other polypeptides, many originally identified as direct nuclear receptor interacting proteins. For coactivators, these include pCAF/GCN5, p/CIP/AIB1/ACTR, and GRIP-1/TIF2. Moreover, pCAF, the mammalian homologue of the prototypical yeast HAT, GCN5, is part of a 20- or so subunit complex containing TAFs and TAF-like proteins [Ogryzko et al., 1998]. It interacts with both CBP and some p160 coactivators, as well as directly with nuclear receptors [Chen et al., 1997; Blanco et al., 1998]. Thus, these proteins may act in concert to modify histone tails and could thereby destabilize chromatin. Since CBP/p300 has also been found to modify several transactivators directly, including p53 [Gu and Roeder, 1997] and GATA-1 [Hung et al., 1997], as well as components of the general transcription machinery [Imhof et al., 1997], their direct role in chromatin remodeling remains uncertain and could be limited to modulation of enhancer binding affinity in a local chromatin context. Nevertheless, these complexes may be related to the yeast GCN5-containing SAGA, ADA, NuA3, and NuA4 HAT complexes, which have been demonstrated to direct chromatin-dependent transcription by select activators in vitro in response to acetyl-CoA [Utley et al., 1998].

LIGAND-INDEPENDENT RECRUITMENT OF COACTIVATORS

Other signal transduction pathways impinge on nuclear receptors independently of hor-

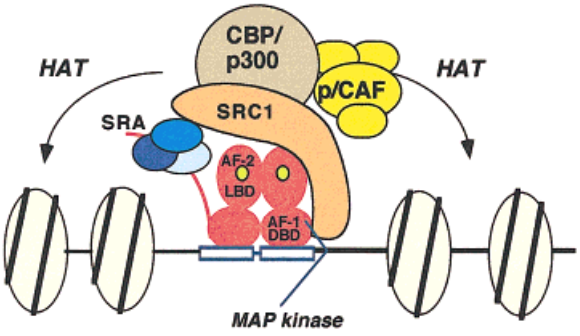

Fig. 1. p160 coactivators such as SRC-1 anchor a complex composed of CBP/p300 and p/CAF and other factors to nuclear receptors through ligand-dependent AF-2 interactions and, in some cases, MAP kinase-inducible phosphorylation sites in the AF-1. The net effect of these interactions would be to provide HAT activity, resulting in a remodeling of chromatin.

monal ligands. These appear to involve the activation of several kinases, including cyclin-dependent kinases (CDK) and MAP kinase (MAPK) by growth factors. MAPK-induced phosphorylation of specific serines within the N-terminal AF-1 of estrogen receptor-β (ERβ) or the orphan receptor steroidogenic factor 1 (SF-1), respectively, lead to an enhancement of coactivator recruitment and subsequent transactivation. For ERβ, serine phosphorylation in AF-1 (Ser 106 and Ser 124) stimulates the recruitment of SRC-1 to the AF-1 domain, independent of AF-2, and regardless of the presence of the mixed agonist/antagonist tamoxifen [Tremblay et al., 1999]. However, a "pure" antiestrogen abolished phosphorylation-dependent coactivator binding. As the authors point out, these results may have important clinical implications in the treatment of breast cancer, since mixed agonist/antagonists such as tamoxifen and raloxifene would likely be ineffective in estrogen receptor (ER)-positive but estrogen-independent tumors that are stimulated through a kinase-activated pathway, whereas the use of pure antiestrogens might be significantly more efficacious.

Orphan nuclear receptors also appear to respond to phosphorylation. SF-1 responds to MAPK-mediated phosphorylation of a single serine residue (Ser 203) within its AF-1 domain by recruiting GRIP1, but it does so through its putative LBD [Hammer et al., 1999]. This result and several others all point to an intramolecular communication between AF-1 and AF-2, whereby phosphorylation of the N-terminal AF-1 might propagate conformational changes in the LBD presumably conducive to coactivator recruitment. But the control of nuclear receptor function by phosphorylation remains somewhat of an enigma. Multiple kinases and phosphorylation sites on receptors appear to be involved, raising questions about selectivity. Phosphorylation can also have an inhibitory effect: MAPK-induced phosphorylation of N-terminal residues in PPAR-γ reduces its ability to transactivate [Hu et al., 1996] apparently by decreasing the intrinsic binding affinity of its LBD for PPAR ligands [Shao et al., 1998]. Clearly, the implications of receptor regulation by phosphorylation are manifold, but its biological role still needs to be more convincingly demonstrated within a physiological context.

A recent two-hybrid screen for potential N-terminal human progesterone receptor (PR) AF-1-interacting proteins led to the isolation of several related cDNAs with a strongly conserved core sequence but highly divergent 5′ and 3′ regions [Lanz et al., 1991]. All the isoforms had potent coactivation activity with steroid (type I), but not nuclear (type II) receptors, suggesting that the coactivator, termed SRA, works exclusively through the N-terminal AF-1 domain (which was used as the original bait). Interestingly, the original GAL/SRA fusion used in the two-hybrid screen contained an inframe stop codon that prematurely terminated translation of the fusion protein, and that attempts to in vitro translate SRA protein or detect it with an antipeptide antibody raised against SRA failed. Various mutants that lacked ATGs or changed reading frames leading to multiple stop codons all retained the capacity to coactivate PR transcription in transfection assays. These results led the authors to hypothesize that SRA acts as an RNA, which was subsequently supported by the demonstration of cycloheximide-resistant coactivation of reporter mRNA expression, and the fractionation of SRA RNA in a 600- to 700-kDa complex that co-eluted and co-immunoprecipitated with SRC-1 (but not with CBP/p300). The fact that SRA can be detected in a large protein complex suggests that it might serve as part of a ribonucleoprotein scaffold through which SRC-1 is recruited to steroid receptors. The evidence for multisubunit complexes containing coactivator function is rapidly accumulating (see below); what is

novel here is an RNA species anchoring such a complex.

CONTACTS WITH RNA POLYMERASE II: THE DRIP COACTIVATOR COMPLEX

A recently discovered multi-subunit complex that binds to vitamin D receptor (VDR) [Rachez et al., 1998, 1999] thyroid hormone receptor (TR) [Fondell et al., 1996] and, most likely, many other members of the steroid/nuclear receptor family, points to the ultimate generality of transactivation. This complex, alternatively called TRAP or DRIP, is recruited to the nuclear receptor LBD AF-2 in response to ligand-binding most likely through a single subunit (DRIP205/TRAP220). However, this single subunit anchors an additional 13–15 proteins comprising the DRIP/TRAP complex, thereby conferring hormone-dependent recruitment of what appears to be a preformed complex. The generality of this complex stems from the surprising observation that other activators unrelated to steroid/nuclear receptors, such as VP16, p65 subunit of NFκB, and SREBP-1a, recruit this complex, called ARC [Näär et al., 1999] and that many of the DRIP/TRAP/ARC subunits are present in three similar, if not identical, SRB-associated complexes, NAT, SMCC, and mammalian SRB/Mediator, targeted by adenovirus E1A [Sun et al., 1998; Ito et al., 1999; Boyer et al., 1999]. Most importantly, these related complexes are required for transcriptional activation by these same activators as demonstrated using purified components in in vitro transcription assays.

With one notable exception [Ito et al., 1999], DRIP/TRAP/ARC appears to enhance transcription selectively from chromatin-organized templates, whereas it appears to repress transcription from naked DNA templates, using highly purified transcription systems [Sun et al., 1998; Boyer et al., 1999] (A.M. Näär and B.D. Lemon, unpublished observations). The observations made by Ito et al. [1999] might reflect subtle differences in the experimental conditions used, since utilization of a partially purified transcription system appeared to produce similar results with hSRB/Mediator [Boyer et al., 1999], suggesting that other activites may enable DRIP/ARC/TRAP to function on naked templates. At least seven DRIP/ARC/TRAP subunits are homologous to proteins described as components of Mediator, a complex originally found both to be required for transcription in a yeast model system in vitro and, together with SRBs, able to associate with yeast RNA polymerase II (Pol II) through the C-terminal repeat domain (CTD) of its large subunit [Kim et al., 1994]. A similar complex was subsequently found to associate with a mammalian Pol II CTD [Jiang et al., 1998]. While yeast genetics of homologous subunits and preliminary biochemical observations allude to its potential role in recruitment of, or contact with, the Pol II machinery at the core promoter (Fig. 2), it is also plausible that DRIP/ARC/TRAP may intrinsically contain or interact with as yet undefined chromatin remodeling activities. The direct biochemical roles of this multi-protein coactivator complex, as well as those of the structurally related cofactor, CRSP [Ryu et al., 1999], recently identified as required for Sp1 transactivation from naked DNA templates, await further characterization.

CONCLUSIONS AND PERSPECTIVES

Steroid and nuclear receptors have evolved to regulate the transcription of many genes di-

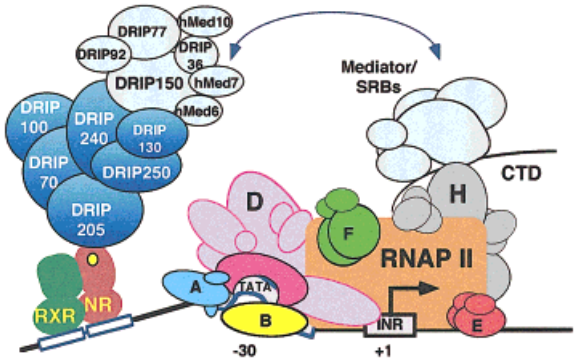

Fig. 2. Coactivator complex composed of DRIP/TRAP/ARC and Mediator/SRB subunits is recruited to nuclear receptors in a ligand-dependent manner through a single subunit, DRIP205 (TRAP220). A DNA-bound nuclear receptor/RXR heterodimer is shown. Mediator/SRB subunits that are shared between the nuclear receptor/DRIP/TRAP/ARC complex (silver) and RNA Pol II suggests that coactivation by the DRIP/TRAP/ARC complex can occur, at least in part, through recruitment or stabilization of RNA Pol II. Chromatin remodeling coactivators such as the p160/CBP/PCAF complex might bind directly to steroid/nuclear receptors or perhaps through ligand-recruited coactivators such as the DRIP/ARC/TRAP complex, opening up the chromatin to then allow the DRIP/ARC/TRAP complex to act directly on the preinitiation complex, potentially through shared SRB/Mediator subunits.

rectly in order to accommodate intricate metazoan developmental and differentiation programs in rapid response to environmental cues. In recent years, molecular genetics and biochemistry have identified many intermediary components, co-activators and co-repressors, involved in both ligand-dependent and ligand-independent signaling by these receptors as well as their direct target genes. How the DRIP/ARC/TRAP complex interfaces with the p160/CBP/pCAF system, for example, is an intriguing question but, given that DRIP/ARC/TRAP does not contain HAT activity [Rachez et al., 1999], one could envision a two-step process. In this model, chromatin remodeling coactivators either bound directly to steroid/nuclear receptors or through ligand-recruited coactivators such as the DRIP/ARC/TRAP complex could open up the chromatin to then allow the DRIP/ARC/TRAP complex to act directly on the preinitiation complex, potentially through shared SRB/Mediator subunits. Consistent with this two-step model, TR-RXR affects chromatin structure in response to thyroid hormone in *Xenopus* oocytes, but these changes exceed that necessary for derepression of transcription and subsequent activation, suggesting an additional, distinct function for transactivation to occur [Wong et al., 1998]. In addition, the N-terminal transactivation function of the glucocorticoid receptor (GR), AF1, interacts with a distinct DRIP subunit, DRIP150, whereas the C-terminal transactivation function, AF2, interacts with DRIP205 [Hittelman et al., 1999], suggesting that two separate activation functions might serve to bridge a multi-subunit complex like DRIP through multiple interactions (Fig. 3), and perhaps offers a possible explanation for the transcriptional synergism between these two transactivation domains of GR in response to hormone.

A further understanding of which intermediary factors are involved in the transcriptional control of particular target genes will require direct examination of endogenous loci and transgenes in a chromatin context within cells in concert with the continued development of highly integrated transcription systems that respond to multiple activators in a chromatin context in vitro. These types of experiments will allow for further identification of novel cofactors and the dissection and elucidation of the direct biochemical functions of particular chromatin modifying, remodeling, or general cofactors in coordinating the action of nuclear receptors and other classes of activators and repressors at complex promoters. In addition to potential enhancer-induced allostery and cooperativity, such experiments may also reveal novel activator specific [Armstrong et al., 1998] or gene-selective mechanisms of transcriptional control in response to multiple stimuli and, taken together, should increase our understanding of cellular proliferation and differentiation.

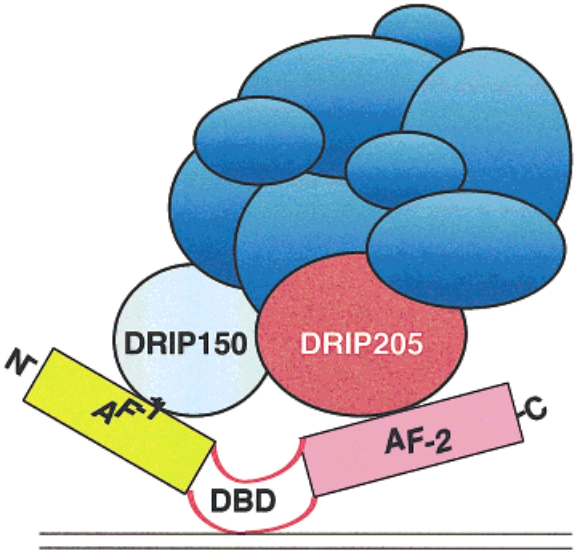

Fig. 3. Model for multiple DRIP interactions with glucocorticoid receptor. GR recruits DRIP150 through an association with its N-terminal AF-1 as well as through a steroid-dependent association of DRIP250 at its C-terminal AF-2. Other DRIP subunits that are part of this preformed complex are also depicted. The net effect is transactivation. These observations might account for the synergy seen between these two defined activation functions of GR.

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