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Nuclear receptor coactivators: multiple enzymes, multiple complexes, multiple functions☆

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Abstract

Nuclear receptors are ligand-inducible transcription factors which mediate the physiological effects of steroid, thyroid and retinoid hormones. By regulating the assembly of a transcriptional preinitiation complex at the promoter of target genes, they enhance the expression of these genes in response to hormone. Recent evidence suggests that nuclear receptors act in part by recruiting multiple coregulator proteins which may have specific functions during transcriptional initiation. Liganded receptors recruit members of the SRC family, a group of structurally and functionally related transcriptional coactivators. Receptors also interact with the transcriptional cointegrators p300 and CBP, which are proposed to integrate diverse afferent signals at hormone-regulated promoters. p300/CBP and members of the SRC coactivator family have intrinsic histone acetyltransferase activity which is believed to disrupt the nucleosomal structure at these promoters. Other nuclear receptor coactivators include a member of the SWI/SNF complex, BRG-1, which couples ATP hydrolysis to chromatin remodelling, and the E3 ubiquitin-protein ligases E6-AP and RPF-1. Finally, nuclear receptor coactivators appear to be organized into preformed subcomplexes, an arrangement that may facilitate their efficient assembly into diverse higher order configurations.

Keywords: Nuclear receptors; Coactivators; Enzymes; Proteins

1. Introduction

Steroid, thyroid and retinoid hormones control eukaryotic gene expression patterns by interaction with a group of intracellular ligand-inducible transcription factors which comprise the nuclear hormone receptor superfamily [1]. This superfamily is the single largest class of eukaryotic transcription factors and its members mediate signaling pathways in a wide variety of physiological systems. The superfamily is broadly divisible into three subclasses: the type I receptors for steroid hormones, including progestins (PR), estrogens (ER), androgens (AR), glucocorticoids (GR) and mineralocorticoids (MR); the type II receptors for thyroid hormone (TR), vitamin D (VDR), 9-*cis* (RXRs) and all-*trans* retinoic acid (RARs) and those for which cognate ligands have not yet been characterized, the orphan receptor subclass.

Recently, the cloning and functional characterization of coregulator proteins which interact with nuclear receptors to effect an efficient transcriptional response has gained increasing attention. Broadly speaking, these proteins fall into one of two classes: coactivators and their associated proteins, and corepressors and their associated proteins. This brief review, while summarizing some of the most significant advances in this area in recent years, will emphasize the role of coactivators in receptor action.

2. Overview of receptor action

Nuclear receptors undergo a series of functionally well defined steps which culminate in target gene activation (Fig. 1). Interaction between ligand and recep-

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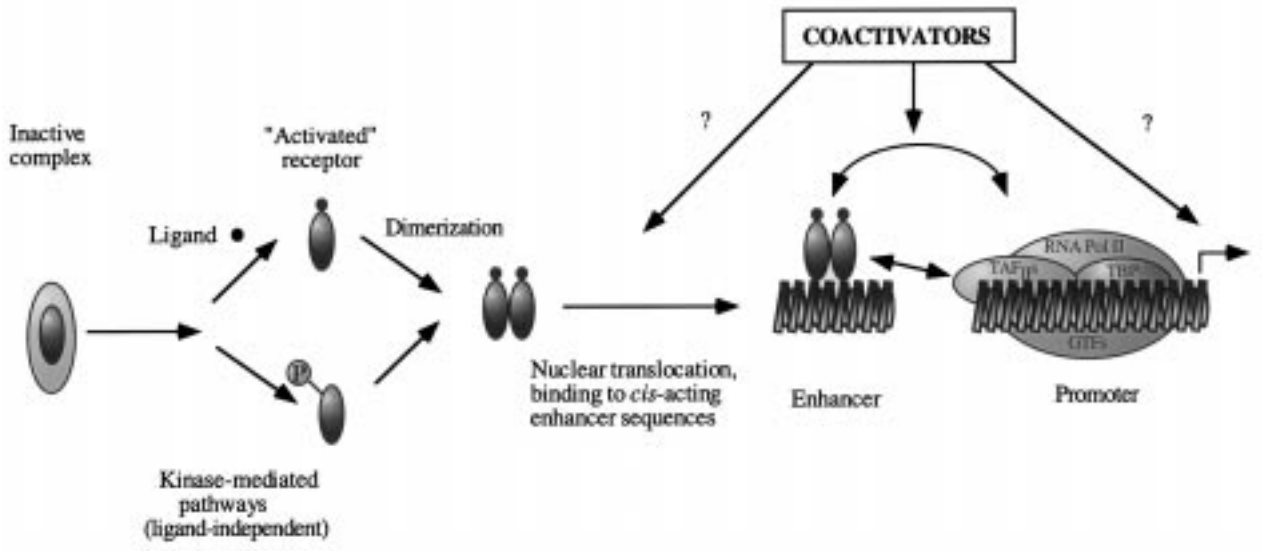

Fig. 1. Overview of events initiated by binding of ligand to nuclear receptor and culminating in transcriptional activation of a hormone-regulated gene. 'Activation' of receptor occurs either through hormone binding or by catalytic phosphorylation by kinases of specific residues on the receptor. Specific conformational alterations result in dimerization, nuclear translocation and apposition to a specific *cis*-acting hormone response element. The precise mechanism of assembly of a stable preinitiation complex composed of basal transcription factors and other promoter-specific factors is unknown. While receptor can directly contact general transcription factors, many coactivators are known to mediate these interactions. In addition, they are likely to play multiple roles in both processes which precede DNA binding and those which follow formation of the transcriptional preinitiation complex. Abbreviations: TBP, TATA box-binding protein; TAF_{II}s, TBP-associated factors; GTFs, general transcription factors; RNA pol II, RNA polymerase II.

tor occurs in two ways: (i) either in the cytoplasm or nucleus of target cells, inducing nuclear translocation of the ligand–receptor complex (for type I receptors) or (ii) always in the nucleus of target cells (for type II receptors). A second effect of ligand binding on several type I receptors, notably AR, GR and PR, is the dissociation of several chaperone proteins which maintain the receptor in a conformation optimal for hormone binding. Subsequent apposition of the hormone–receptor complex to target sequences in the promoters of target genes enhances their expression [1]. Such a functionally based model does not convey, however, the complexity of steps preceding initiation of transcription and recent research has begun to tease out the complexity of molecular events pursuant to ligand binding. It is now apparent that, by means of interaction with transcriptional coactivators, liganded receptor directs disruption of the nucleosomal structure around target genes by means of recruited chromatin-modifying enzyme activities. In addition, recruitment of basal transcription factors by coactivators is thought to lead to the establishment of a stable preinitiation complex at the hormone-regulated promoter. In this process, DNA-bound receptors and coregulators appear to function as large multiprotein complexes which, depending upon the cell/promoter context and stage of transcription, are thought to have multiple possible configurations.

3. Coactivators

3.1. Transcription-mediating proteins

In essence, the role of the activated nuclear receptor is to recruit and maintain a preinitiation complex at the promoter of the target gene. This is achieved by direct or indirect interaction of the liganded receptor with the basal transcription factors, a group of proteins comprised of RNA polymerase II, TATA-binding protein (TBP) and a host of TBP-associated proteins (TAF_{II}s), which are required for efficient regulated transcription of most eukaryotic genes [2]. In the 1980s, functional analysis of receptors had identified autonomous activation functions (AFs) within the amino-terminal and carboxy-terminal domains of the receptors which were thought to be key elements in transactivation. Studies on cell specificity and transcriptional interference of these AFs [3,4] gave rise to the suggestion that certain limiting receptor-specific factors, termed transcription intermediary factors [TIFs], mediated the transcriptional activity of the receptors [5].

Various independent lines of evidence have indicated that liganded receptors are capable of directly contacting basal transcription factors. In particular, TAF_{II}s, which appear to be cell-specific in their expression patterns, interact with liganded receptor [6, 7]. Three seminal studies suggested, however, that non-TAF_{II} proteins were important targets of liganded receptor. Isolation of a 160-kDa estrogen receptor (ER)-associated protein (ERAP-160) which co-purified with ER in the presence of ligand [8] suggested that ER underwent interactions with specific protein complexes prior to transcriptional initiation. Cavailles *et al.* (1994) published similar findings with respect to the receptor interacting proteins RIP-160, RIP-140 and RIP-80. The characterization of a 170 kDa GR-associated protein (GRIP-170), an enriched fraction of which stimulated GR transactivation *in vitro*, suggested that these endogenous cofactors were functionally limiting [9]. Notably, antihormones uncoupled the interaction of receptor with these proteins (collectively termed 'p160' proteins), suggesting that transcriptional activation was contingent upon the interaction of the receptor with these proteins. However, when cotransfected with receptor in a reporter assay, RIP-140 was not capable of significant coactivation of ER [10] and the function of the ERAPs and RIPs remains open to debate [11]. Several other receptor interacting proteins, such as the bromo domain-containing TIFs [12], Trip-1, the human homolog of the yeast transcriptional mediator Sug1 [13] and other Trips (thyroid receptor-interacting proteins), were identified and partially characterized, but their role in transcriptional regulation is, to date, largely undefined.

3.2. The SRC-1 subclass: cloning and functional domains

Using a genetic screen in a yeast-based human cDNA library to isolate PR ligand-binding domain-interacting proteins, our laboratory cloned and characterized a 160-kDa protein, steroid receptor-coactivator-1 (SRC-1), which bore no homology to RIP-140, TIF-1 or Trip-1. SRC-1 exhibits several properties which defined it as a prototypical coactivator for nuclear receptors [14]. Firstly, coexpression of SRC-1 with a variety of nuclear receptors in a reporter assay enhanced transactivation (5–10-fold) by the receptors, suggesting that it constituted a common limiting factor for the receptor superfamily. Secondly, coexpression of SRC-1 with two distinct receptors reversed the squelching, or transcriptional interference between the receptors, which had originally indicated the existence of limiting transcriptional intermediates [3, 4]. Thirdly, competitive coexpression of the receptor-interacting domain of SRC-1 (SRC-1 0.8) with SRC-1 in receptor cotransfection assays resulted in dominant-negative inhibition by SRC-1 0.8 of transactivation. Fourthly, SRC-1 contains two autonomous, transferable activation domains [15] which, when fused to heterologous DNA-binding domains, enhanced the expression of genes linked to heterologous *cis*-acting elements. Finally, addition of the antagonist RU486 abrogates the ability of SRC-1 to interact with and coactivate PR [14], suggesting a mechanistic basis for the antagonistic properties of RU486.

SRC-1, also designated NCoA-1 [16], given its molecular size, its widespread expression and functional interaction with a wide variety of nuclear receptors, was a plausible candidate for the biochemically-defined 'p160'. However, the subsequent cloning of GRIP1/TIF2/SRC-2[1] [17] and p/CIP [18] (also designated ACTR/RAC3/AIB-1/TRAM-1/SRC-3 herein) suggested that the term 'p160' encompassed a novel family of structurally-related nuclear receptor coactivators, the SRC-1 family. SRC-1, GRIP-1/TIF2/SRC-2 and p/CIP/SRC-3 exhibit common properties in the transcriptional activation of a wide variety of nuclear receptors [14, 16, 17, 19–25]. This family has a number of structural features in common, one of the most interesting being the presence of in their N-termini of domains present in the PAS (for Per-Arnt Sim homology)/bHLH (for basic helix–loop-helix) family of transcription factors. Members of the bHLH family are involved in regulation of cell type differentiation and proliferation and are characterized by the formation of homo- or heterodimeric complexes with bHLH partners for their function (for a review see Ref. [26]). Like other PAS-bHLH proteins [27], SRC-1 and TIF2 appear to be capable of forming multimeric complexes *in vivo* [28], but the role of the PAS domain in this interaction, if any, is unclear.

3.3. The LXXLL motif: interactions of coactivators with receptors

A second common structural feature of the SRC-1 family is the LXXLL sequence, a recurrent pentapeptide motif which appears to direct the interaction of SRC-1 family members (and other coregulators, see below) with their receptor partners [21, 29]. In order to encourage consensus, this review will adopt the proposed nomenclature [30] in discussion of these motifs. Heery *et al.* [29] defined the LXXLL motif as a crucial element in the interaction of RIP-140 and SRC-1 with nuclear receptors and showed that mutation of any of

[1] In the interests of brevity, we employ the unified nomenclature proposed by Li and Chen [92] who suggested the name 'SRC family' for this new family of coactivators. The name SRC-1 refers to SRC-1/NCoA-1, SRC-2 will refer to TIF2/GRIP-1/NCoA-2 and SRC-3 will refer to RAC3/AIB1/ACTR/TRAM-1/pCIP/NCoA-3.

the core LXXLL residues in these coactivators was sufficient to abrogate binding to nuclear receptors. Furthermore, they demonstrated the reciprocal importance for receptor–coregulator interaction of hydrophobic residues in the conserved helix 12 of the ER, a region corresponding to the functionally-defined AF-2 domain of nuclear receptors. Substantiating these results, Feng *et al*. [31] used scanning mutagenesis studies along with X-ray crystallography to depict the formation of a single site in AF-2 of the human TR which binds SRC-1 and GRIP-1/TIF2. Ligand binding induced the convergence of a small series of residues around the surface of a hydrophobic cleft in C-terminus of the TR by folding a C-terminal α-helix. These residues lie within portions of the TR that are conserved between nuclear receptors, suggesting that formation of such a groove might be a phenomenon which accompanies ligand binding by other members of the family [31]. Ding *et al*. [30] have gone some way towards explaining the existence of multiple SRC-1 family members by showing that receptors exhibited preferential binding to different SRC family members. AR, for example, binds preferentially to GRIP-1 over SRC-1. In addition, LXXLL motifs within a given coregulator exhibit binding specificity: the central domain of SRC-1 (NR boxes I–III) preferentially binds the LBDs of ER, PR, VDR and TR, while the more C-terminal NR-box IV strongly binds AR and GR.

3.4. Cointegrators: the CBP/p300 class of coactivators

CBP and p300 are ubiquitous, evolutionarily conserved proteins which have been shown to act as transcriptional coactivators for a host of diverse transcription factors, including CREB (cAMP-response element-binding protein) [32], STAT-2 [33] and p53 [34, 35]. Moreover, CBP has been shown to exist in a stable preformed complex with RNA Pol II [36], suggesting that interaction of transcription factors with CBP, either directly or indirectly, might result in a direct link to basal transcription factors. It has been proposed [16, 37] that nuclear receptors might also require the mediation of CBP/p300 for efficient transactivation. It was shown that CBP interacted weakly with nuclear receptors in a ligand-dependent manner, enhanced RAR-mediated transactivation, and was capable of binding SRC-1 directly. p300/CBP are proposed to be limiting, common cointegrators for distinct but convergent signalling pathways, functioning to integrate multiple afferent signals into an appropriate response at a common promoter [16]. Results from our laboratory substantiate the role of CBP in steroid receptor signalling, indicating that CBP and SRC-1 synergistically activate transcription from ER and PR-regulated promoters [38]. Biochemical analysis suggests however that CBP and SRC-1 exist in largely distinct preformed complexes [28], and it may be that they interact only transiently when recruited by liganded receptor at the promoter.

3.5. Nuclear receptors and chromatin

In order for efficient spatiotemporal patterns of gene expression to occur *in vivo*, eukaryotic genes are required to exist in conformations which maximize access to the *cis*-acting elements with which DNA-binding transcription factors specifically interact, while minimizing basal, unregulated expression of these genes. The consequence of this requirement is the organization of eukaryotic genes into structurally-repressed nucleosomes, the integrity of which is dependent upon periodic arrays of DNA-binding histones. Nucleosomes are the basic repeating unit of chromatin and it is their malleable and plastic nature which permits the strictly regulated access of transcriptional proteins to key regions of genes, allowing finely regulated control of transcription of these genes [39]. Reduction of their net positive charge and affinity for DNA by acetylation of core histones has long been known to be an important preface to transcriptional activity *in vivo*, and numerous studies have shown that histones in regions of transcriptionally active chromatin are hyperacetylated [40]. The link between chromatin disruption and transcriptional activity is now well established: for example, a critical transcriptional adaptor in yeast, GCN5, was identified as histone acetyltransferase, an enzyme which catalyzes the transfer of acetyl groups to nucleosomal histones [41].

The discovery that p300, CBP and a p300/CBP associated factor (PCAF) all contained histone acetyltransferase activity [42–44] indicated that nuclear receptors might function in part by recruiting these proteins and directing nucleosomal modification at their target promoters. This notion was further strengthened by the identification of similar activity in the SRC family members SRC-1 and ACTR/SRC-3 [23, 45]. Experimental evidence suggests that complexes containing these coregulators are recruited by receptor at hormone-regulated promoters [46], but the reason for the requirement of so many HATs is unclear. We are currently examining the possibility that different coregulator complexes may have different target histone specificities.

3.6. Chromatin modification: the SWI/SNF proteins

Studies in *S. cerevisiae* have provided convenient but far-reaching insights into the effect of transcriptional regulators on chromatin structure *in vivo*. Along with the ADA proteins, one of the first groups of yeast proteins to be identified and characterized as important transcriptional intermediaries were the SWI/SNF pro-

teins, which form a stable, preformed complex of approximately 2 MDa in size [47, 48]. Subsequent studies have demonstrated that purified SWI/SNF complexes have intrinsic ATPase activity and function, at least in part, by coupling ATP hydrolysis to nucleosomal remodelling at diverse promoters to facilitate the interaction of basal transcription factors with these promoters [49]. Unlike HATs, SWI/SNF complexes do not carry out covalent modification of histones, but rather catalyze the uncoupling of ionic interactions between histones and their substrate DNA. It is now clear that the SWI/SNF complex is highly conserved evolutionarily and SWI/SNF complexes have since been purified and characterized from mammalian sources [50]. Human SWI/SNF homologs have been found to enhance the activation functions of GR, ER and RAR [51–53], and it has been shown that GR directs ligand-dependent nucleosomal remodeling activity of the SWI/SNF complex in yeast [54]. The fact that SWI/SNF proteins and nuclear receptors interact functionally in yeast systems is strong evidence of their potential role in nuclear receptor signalling *in vivo*. One of the most highly conserved members of the SWI/SNF complex is SWI2/SNF2, which contains ATPase activity [55] and which is encoded by the *swi*2 and *snf*2 genes. Two closely-related mammalian homologs of the yeast *swi*2/*snf*2 genes are termed *brahma* and *brahma*-related gene-1 (*brg*-1). BRG-1 (hSNF2β), the product of the *brg*-1 gene, has been shown to interact with GR in a ligand-dependent manner [56]. Moreover, BRG-1 enhances transcriptional activation by ER in transient transfections in mammalian cells [57], further suggesting that mammalian SWI/SNF proteins may be key elements in nuclear receptor action. BRG-1 has been proposed to exist in a stable complex with SRC-1 [57] and our own data show that a minor pool of BRG-1 copurifies with SRC-1 [28].

3.7. E3 ubiquitin-protein ligases

Included in a fourth subclass of coactivators, which reiterates the role of enzymatic activities in transcriptional regulation by nuclear receptors, are the E3 ubiquitin-protein ligases RPF-1 [58] and E6-AP (Nawaz *et al.*, in press). This subclass of coregulators differs from the SRC-1 family, p300/CBP cointegrators and SWI/SNF homologs, in that they contain ubiquitin-protein ligase activity rather than HAT activity. These proteins were initially identified as factors required for defining substrate specificity in proteolytic degradation by the proteosome system. E6-AP does not require its ubiquitin protein-ligase function for coactivation of nuclear receptors, indicating that it has separable functions as a coactivator and a ubiquitin-protein ligase. Our laboratory and others are currently attempting to define the functional basis of coactivation by E6-AP and RPF-1. We have recently established that mammalian E6-AP and RPF-1 copurify precisely by gel filtration, suggesting their possible existence in a common complex, and that these ubiquitin-protein ligase coactivators synergistically enhance transcriptional activation by PR [28].

3.8. Coactivator interactions: modular complexes for a multistep process

Much of the discussion of coregulators has referred to the formation of transcriptional complexes, in which multiple receptor–coregulator and coregulator–coregulator interactions are envisaged to occur. Individual studies have documented many such interactions: liganded nuclear receptors interact with the SRC-1 family members SRC-1/NCoA-1 [14, 16, 28], GRIP-1/TIF2/SRC-2 [17, 19, 20, 28] and p/CIP/RAC3/AIB-1/ACTR/TRAM-1/SRC-3 [21–25], the cointegrators CBP and p300 [38], PCAF [46, 59], human homologs of the yeast SWI/SNF proteins [56] as well as the E3 ubiquitin-protein ligase family members RPF-1 [58] and E6-AP (Nawaz *et al.*, in press). In addition, multiple coregulator/coregulator interactions have been proposed, including p/CIP/CBP [21], CBP/PCAF [44], SRC-1/CBP [16], SRC-1/p300 [60], SRC-1/PCAF [45] and SRC-1/BRG-1 [57].

While these studies provide valuable information on potential interacting partners for coregulators, they yield little comparative data, such as the relative strength and importance of these interactions in the context of multiprotein complexes. Pertinent questions are raised concerning the functional organization of coactivators: do they exist in preformed complexes, or are transcriptional complexes assembled *de novo* by activated receptor? On the one hand, the free energy required to assemble large, transient complexes from individual components is intuitively prohibitive. On the other, the existence of large readily-primed complexes increases the potential for unregulated transcription. Our own comparative analysis of coregulator interactions indicates that they are governed by a hierarchy *in vivo*, resulting in largely distinct subcomplexes of different types of coregulators [28]. For example, minor pools of p300, BRG-1 and PCAF copurify with the elution peak of SRC-1 [28], supporting the contention that these proteins may exist in preformed complexes with SRC-1 [45, 57, 60]. In contrast, proposed complexes such as SRC-1/CBP [16] do not appear to exist in the steady state under our conditions. In agreement with our own data, Korzus *et al.* [61] have shown that promoters coupled to different enhancer elements (RARE, CREB and STAT) require different combinations of coactivators for maximal coactivation at each promoter. It may be that this is a functional consequence of the evidently modular character of

coactivator complexes, a character which we would predict contributes to cell and promoter-specificity of transcriptionally active complexes.

Transcriptional regulation is known to be comprised of multiple, functionally distinct steps, including chromatin remodelling and transcriptional activation. To illustrate this distinction, GR which failed to recruit BRG-1-containing complexes was capable of activating transcription from naked transiently transfected templates, but not from stably integrated templates [56]. Moreover, the elegant oocyte reconstitution system of Wong *et al*. [62] has shown that chromatin disruption is insufficient for activation of the TRβ-gene. In addition, Kraus and Kadonaga [63] have used an *in vitro* transcription system to draw a clear line between the role of p300 in 'preinitiation' and 'reinitiation' complexes assembled by liganded ER: from their data, it appears that the functional requirement for p300 is reduced for subsequent rounds of transcription after the first round.

The functional evidence for the multistep nature of transcription has been supported by biochemical studies in respect of TR [64, 65]. Constitutively liganded tagged TR copurified from HeLa cell nuclear extract with a series of proteins ranging in size from 80-220 kDa in size. When an *in vitro* TR transcription system was supplemented with purified fractions containing these proteins, coactivation was modestly enhanced over basal levels [65]. Interestingly, none of the TRAPs represented previously-identified coregulators. Further characterization of one of the members of this complex identified a protein, TRAP-220, which contained a consensus LXXLL motif and interacted with TR directly [64]. Similar complexes have been observed for VDR [66] and ER [67], the latter containing a protein with casein kinase 2-like activity. A model has been envisaged for the role of TRAPs in receptor transactivation, envisaging initial binding of complexes containing SRC-1 family members, CBP/p300, PCAF and other complexes. Displacement of these initial coactivator–coregulator complexes by TRAP-like complexes may then occur subsequently and these complexes may assume a more important role in repetitive initiation of transcription.

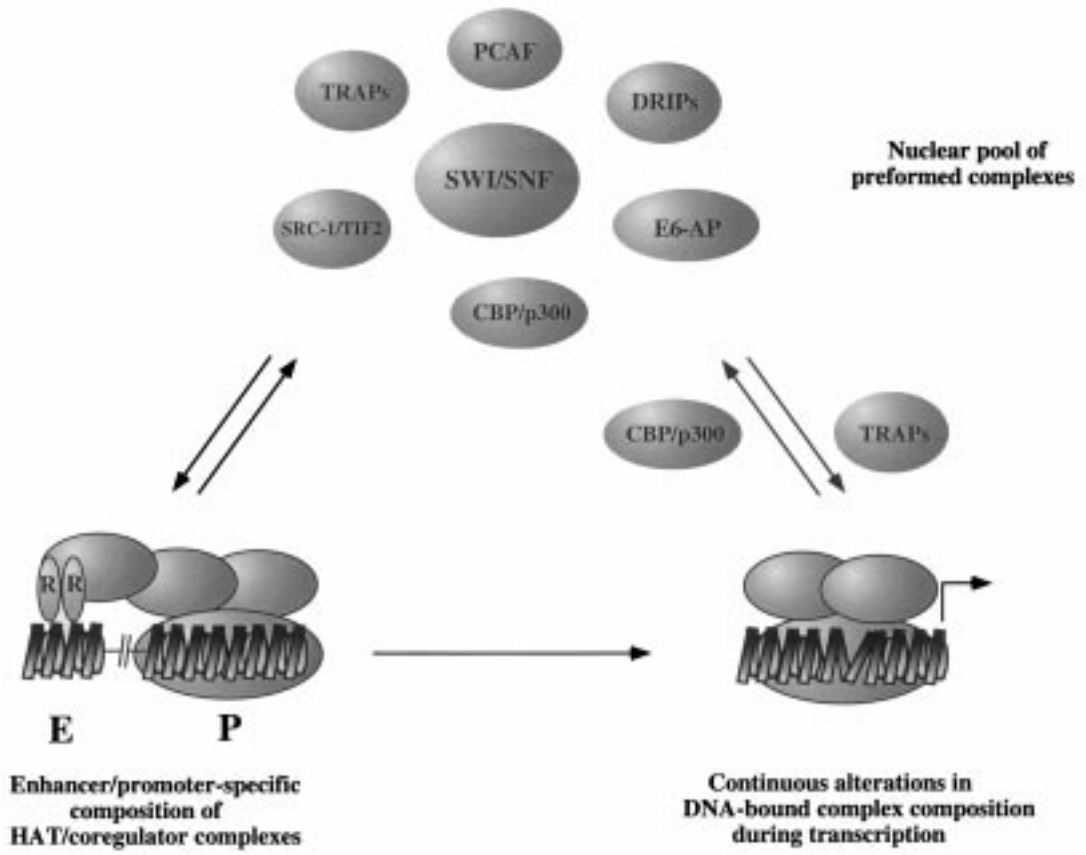

Fig. 2. Dynamic model of the potential role of preformed coregulator complexes in nuclear receptor (R) action. A nuclear pool of coregulators assembled into preformed complexes allows for enhancer (E) and promoter (P) specificity in transcriptional initiation and a rapid assembly of the preinitiation complex. In addition, the different functional stages of transcription are likely to require multiple complex configurations and there is likely to be continuous exchange between the nuclear pool and the transcriptional complex.

3.9. A model for coactivator action

These diverse lines of evidence may be incorporated into a model of coregulator action (Fig. 2) in which multiple preformed complexes, with specific functional characteristics, are recruited by liganded receptor at different stages during transcriptional activation. The functional diversity arising from such an arrangement facilitates the simultaneous assembly and disassembly of transcriptional complexes at diverse promoters, allowing the efficient and balanced integration of signals by different transcriptional activators. Mechanistically, the model concurs with data from our own and other laboratories and is in keeping with the notion of transcription as a modular process, requiring the mediation of functionally different subsets of complexes at different points. Biochemically, the complexes are largely distinct, but significant overlap exists between some of them, symptomatic of heterogeneity of their composition. Although the model conveys a static situation, we envisage a spectrum of interactions, resulting in fluid compositions of transcriptional complexes.

4. Corepressors

Along with punctual activation of target genes in response to hormones, an efficient spatiotemporal pattern of gene regulation by nuclear receptors requires timely silencing of these genes in the absence of ligand. While this review has concentrated on coactivators as transcriptional intermediaries for nuclear receptors, mechanistically symmetrical models are emerging for the role of corepressor proteins in transcriptional silencing by nuclear receptors. Similar to its role in gene activation, chromatin is an intrinsic part of the mechanism by which nuclear receptors silence their cognate promoters. Functional data suggests that, as in the case of transcriptional activation, multiple factors are recruited by unliganded receptors to participate in gene silencing. Moreover, evidence exists to suggest that these factors function as components of large multiprotein complexes which co-ordinate target promoter silencing by nuclear receptors.

The existence of repression domains in nuclear receptors was first suggested by experiments which indicated that transferable, autonomous silencing domains mediated transcriptional silencing by TR and PR [68, 69]. Soluble corepressor proteins were postulated to exist in cells and to interact with receptor repressor regions [70]. Since these initial studies, several proteins have been identified as potential mediators of repression by nuclear receptors corepressor complexes. RIP13/NCoR [71–73] and SMRT [74] were cloned as molecules which interacted in a ligand-dependent manner with RXR and TR and which contained transferable domains capable of silencing transcription at heterologous promoters. These corepressors are now known to have a broad range of specificity within the nuclear receptor superfamily and have been proposed to mediate repression not only by type II receptors, but also by type I [75, 76] and orphan [77–79] members of the family.

The transcriptional efficiency of certain genes in yeast is known to be regulated by several key proteins, including RPD-1/SIN3 and RPD-3. The discovery of homology between RPD-3 and a subunit of a yeast histone deacetylase complex [80] and the cloning of a mammalian homolog of RPD-3, histone deacetylase I [81], suggested that certain mechanisms of transcriptional repression might be conserved in eukaryotes. SIN3 was known as one of a family of proteins which contained transferable repression domains which mediated transcriptional repression in yeast [82–84]. The conservation of transcriptional mechanisms in yeast permits the reconstitution of steroid-receptor mediated transactivation in this system. Initial data from our laboratory identified SIN3 as a negative regulator of PR activity in yeast [85]. Numerous studies have since established functional interactions between NCoR/SMRT, histone deacetylases and the mammalian homologs of SIN3, mSin3a and mSin3b, in the context of transcriptional silencing by TR and RXR [86–89]. Moreover, biochemical characterization of histone deacetylase activity in *Xenopus* oocytes indicates that Sin3 proteins copurify with NcoR and HDAC-2 in multiprotein complexes [90, 91]. An integrative model of repression by nuclear receptors envisages recruitment by unliganded receptors of large, preformed complexes containing corepressors and associated histone deacetylase activities.

5. Conclusions

Steroid, retinoid and thyroid hormones direct finely-regulated patterns of gene expression which coordinate processes involved in development, differentiation and reproduction. While these events are relatively well characterized on a physiological level, the molecular events through which these hormones and their receptors regulate the transcription of their target genes are only partly understood. It is now emerging that transcriptional control is a multistep process, a fact reflected in the diversity of the coregulators, and their intrinsic enzyme activities, which liganded receptor recruits to the promoter. These coregulators are organized into stable, preformed multiprotein complexes, the modular character of which may facilitate the efficient assembly of functionally diverse complexes by a single receptor dimer. In addition, the modular charac-

ter of these complexes provides the potential for different activators to assemble diverse configurations of regulatory complexes at their cognate *cis*-acting elements. It is anticipated that further study of nuclear receptor coregulators and their complexes will yield significant insights into the basis of the complexity of signalling by steroid, thyroid and retinoid hormones.

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