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From ligand to response: generating diversity in nuclear receptor coregulator function

Neil J. McKenna, Bert W. O'Malley *

Department of Molecular and Cellular Biology, Baylor College of Medicine, One Baylor Plaza, Houston, TX 77030, USA

Abstract

Nuclear receptor ligands regulate diverse developmental and physiological processes by activating intracellular members of the nuclear receptor superfamily. Activated nuclear receptors mediate the expression of distinct gene networks in vivo by an as yet unspecified mechanism. Central to the process is the recruitment by these receptors of coactivators, a functionally diversified set of factors shown to be required for efficient transcriptional regulation by activated receptors. This article will highlight recent advances in selected mechanistic aspects of receptor function, as well as discussing the potential of coactivators to act as mediators of the intricate pharmacology of nuclear receptor ligands. © 2000 Published by Elsevier Science Ltd.

Keywords: Coregulators; Coactivators; Gene expression; Steroid receptors; Nuclear receptors; Steroid hormones; Ligands; Acetylation

1. Introduction

Steroid and thyroid/retinoid hormones are important signaling molecules in metazoans whose biological effects are manifest in processes as diverse as organogenesis during development, to governing cyclicity in reproductive tissues. Their myriad physiological functions occur as a result of specific interactions with target tissue intracellular receptors, which collectively constitute the nuclear receptor superfamily [1]. These receptors bind ligand in high affinity interactions, which generally speaking, are concomitant with their apposition to enhancer elements in the proximity of promoters of their target genes. Central to the efficient orchestration of events which lead to transcriptional activation at these promoters is the recruitment by receptors of coregulators–coactivators or corepressors — defined as factors, which interact with and affect transactivation by, nuclear receptors [2].

Recent research efforts have been directed towards establishing the basis of the discriminatory effects of nuclear receptor ligands, and have been aimed in particular at determining the potential of coactivators to mediate their distinct biological effects. This commentary will consider selected themes which enhance our current understanding of the pivotal role of coactivators in nuclear receptor function. It will be divided into two parts: the first will discuss current understanding of selected molecular events surrounding the interaction of liganded receptor with multiple coactivator complexes at hormone regulated promoters. The second will seek to place these events in a wider biological context by discussing the role of coregulators in mediating DNA element- and ligand specific functions of nuclear receptors. For a detailed discussion of the characterization of individual coactivators, the reader is referred to selected reviews [2,3].

2. Multiple coactivators and the dynamic promoter

To date, nearly thirty different coactivators or coactivator complexes have been implicated in transcriptional activation by nuclear receptors. The physiological relevance of what are predominantly in vitro observations can ultimately be answered only in knockout models of individual coactivators, such as that of SRC-1 [4]. While the abundance of coactivators is reflected in part by tissue-specific expression fingerprints for different coactivators, the coexpression of multiple coactivators

* Corresponding author. Tel.: +1-713-7986205; fax: +1-713-7985599.

E-mail address: berto@bcm.tmc.edu (B.W. O'Malley).

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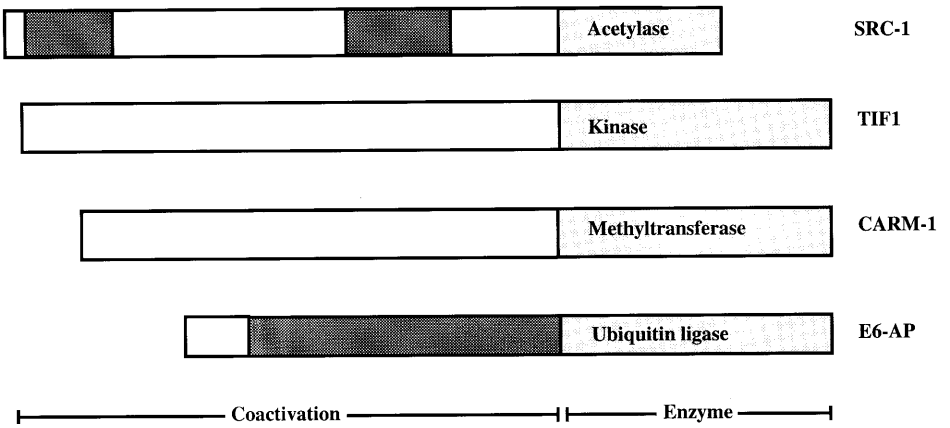

Fig. 1. Structural analogies among coactivators. An emerging theme in several coactivators is the juxtaposition of distinct coactivation functions and enzymatic activities. Some activation functions are better defined than others and are indicated by shading.

in a single tissue appears to be a general rule. Given the thermodynamic constraints upon the simultaneous interaction of these factors with a liganded receptor dimer, it can be presumed that, after binding of a specific ligand to a specific receptor, an ordered series of sequential receptor-coactivator interactions culminates in transcriptional initiation. Two important goals are: (i) to establish an order for such discrete interactions, which can account for the recruitment by nuclear receptors of functional domains as diverse as ATPases [5], acetyltransferases [6,7], methyltransferases [8], ubiquitin ligases [9], and an RNA coactivator [10]; and (ii) to discern the molecular signals which orchestrate this sequence of events.

A simplified sequence of events at hormone regulated promoters envisages initial targeting of chromatin modifying complexes such as SWI/SNF and the PCAF, p300 and SRC family[1] histone acetyltransferase (HAT) activities, resulting in nucleosome disruption. Subsequent recruitment of complexes thought to forge a direct link with general transcription complexes, such as DRIP/ARC and Mediator, results in transcriptional activation. While the exact mechanism behind this sequence of events is currently unclear, recent evidence has hinted that sequentiality and dynamism at the promoter may be driven at least in part by defined post-translational modifications of a variety of substrates, mediated by specific coactivator domains. These domains are enzymatic in nature and appear to be functionally autonomous with regard to their associated activation domains. In particular, HAT activity, initially identified as primarily directed towards histones, has more recently been proposed as a context and substrate-dependent mechanism for promoter dynamism.

Although p300 was initially characterized as a HAT [11], evidence for a role of p300 acetylase activity at a step subsequent to nucleosome disruption [12] suggests its function in this regard should be viewed in a broader context. It was shown that the acetyltransferase activity of p300 was required not for initial chromatin disruption but rather was required for transcriptional activation from a disrupted chromatin template. The study provided evidence that p300 targets the general transcription factors TFIIF/RAP74 and TFIIEβ for acetylation, casting acetylase activity in a more general role at an activated promoter. Indeed, p300-catalyzed acetylation has been shown to target lysine residues in the vicinity of the central LXXLL motifs of ACTR/hSRC-3, a modification which has been suggested to uncouple the intera ction between ACTR/hSRC-3 and estrogen receptor (ER) [13]. This event was placed in the context of sequential interactions between receptor and distinct nuclear receptor-recruited assemblies such as SRC-1 complexes, CBP complexes and other mediator-like complexes such as DRIP/ARC. Such results raise the possibility that targeted acetylation of the basal transcription machinery and other factors by p300 [12] may have a role in topological alterations at the promoter, but this is yet to be established.

Dissection of the functional domains of the coactivators characterized to date suggests that many coactivators are at least bifunctional, containing enzymatic activities in addition to coactivation domains, as classically defined in reporter gene assays (Fig. 1). The results alluded to above point to a possible rationale for the coupling of distinct activation and enzymatic domains in coactivators. Coactivation domains may mediate as yet undefined links between receptor and

[1] In the unifying SRC family nomenclature [2,29], the prefix 'h' is used for all human clones and the prefix 'm' identifies mouse clones, such that 'hSRC-1' represents SRC-1 and 'mSRC-1' corresponds to NCoA-1 [30]. The clone GRIP1 [31] is synonymous with mSRC-2 and hSRC-2 identifies TIF2 [32]. hSRC-3 is an umbrella term for the clones ACTR [7], RAC3 [33], AIB1 [34], TRAM-1[35] and SRC-3 [36]; p/CIP [37] is referred to as mSRC-3. Throughout this commentary, discussions of individual clones refer to original clone name/name under proposed nomenclature, e.g. GRIP1/mSRC-2.

downstream targets while their associated enzymatic activities serve as engines for promoter refurnishing. Domains harboring acetyltransferase, methyltransferase, kinase and ubiquitin ligase activities target histones, receptor, cofactor complexes and basal transcription factors, facilitating the entry of subsequent complexes and priming the promoter for initiation of transcription.

Recent studies have emphasized the fact that coactivators exist primarily in large molecular weight complexes, an important fact when considering the ability of coactivators to negotiate the local enhancer/promoter architecture. Such complexes may serve a structural role, to maneuver a single active subunit into the precise three-dimensional geometry of a specific promoter — much as a crane overcomes thermodynamic and physical constraints to maneuver a girder into its correct position in a building superstructure. To illustrate this idea, only half of the eight common subunits of human SWI/SNF are required to catalyze the bulk of its known enzymatic reactions [14]. An equally plausible scenario is that ancillary subunits may serve in a 'co-coregulatory' capacity to modulate the activity of the functional core of the complex.

These observations can be assembled into a general sequential model of receptor activation (Fig. 2). The model poses important questions concerning the order of recruitment of chromatin remodeling complexes, which are thought to create a transcriptionally permissive environment at hormone-regulated promoter. Recent data on the *S. cerevisiae HO* promoter suggest that binding of the SWI/SNF ATPase complex is required to observe increased acetylation of the promoter, which is concomitant with binding of SAGA [15], the yeast homolog of the PCAF complex [16]. Binding of both these complexes is required for transcriptional activation at the *HO* promoter. Nucleosome acetylation is increasingly being cast in the role of augmenting ATPase-dependent chromatin remodeling, helping to 'fix' the chromatin in an active state [17]. In Fig. 2, a liganded receptor initially recruits a member(s) of the SRC family and attendant protein/RNA coactivators, followed by targeting of a chromatin remodeling complex to the promoter. This in turn is required for binding of histone-targeting acetylase complexes, primarily the PCAF complex. Specific acetylation events directed towards non-histone targets then result in dissociation of SRC-1 family members and facilitate recruitment of complexes contacting the basal transcription machinery, such as Mediator and DRIP/ARC, which may also maintain contact with chromatin-remodeling activities to maintain the 'open' conformation of the promoter [18]. Components of the ubiquitination pathway would engage dissociating complexes for reprocessing by protein degradation pathways (Fig. 2). Within this model, cell context, enhancer and promoter-specific effects will influence both the composition of the recruited complexes and the sequence of events, which precede transcriptional activation (see below).

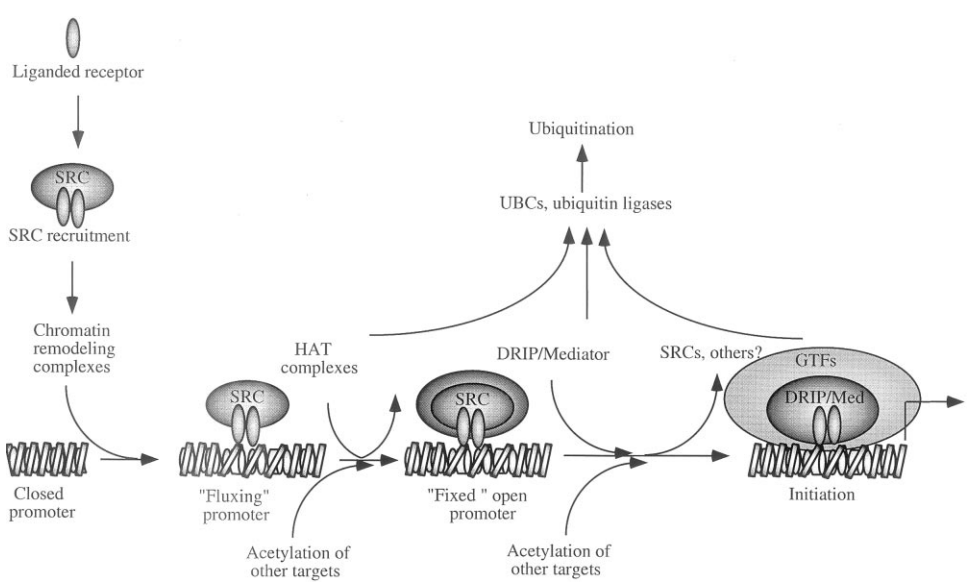

Fig. 2. General dynamic model of assembly and disassembly of distinct coactivator complexes at a hormone-regulated promoter. Acetylase activity and other targeted postranslational modifications may be act as catalysts for promoter fluidity and sequential recruitment of functional domains as required. Ubiquitination appears dominant in cessation of function of the transcriptional complex.

3. Coregulators as determinants of ligand specificity

3.1. Enhancer/promoter context

Promoter and enhancer context have emerged as important determinants of the nature of the nuclear receptor complexes which may be efficiently recruited by diverse transcription factors [19]. Such selectivity is starkly illustrated by transcriptional regulation of positive and negative thyroid response elements by thyroid hormone receptor (TR) and its coregulators [20]. While isolated DR4 (positive) elements permit binding of TR and CBP in the presence of ligand, negative TREs selectively recruit TR-HDAC2 (histone deacetylase) complexes in a ligand-dependent manner. Their results illustrate not only the ability of the promoter to discriminate between, and select for, the identity of coregulator complexes bound to ligand-bound TR, but suggest also that events other than binding of ligand by LBD are necessary to furnish the C-terminal activation function (AF-2) for interaction with coactivator complexes.

3.2. Ligand

Of particular interest currently is the possibility that multiple ligands for nuclear receptors may influence the biological activity of the receptor by influencing selective recruitment of coregulator complexes. It is becoming apparent that the type of agonist bound to a specific receptor is an important determinant of its affinity for a particular subset of coactivator complexes, thereby ultimately influencing the biological response to the ligand. The vitamin D_3 receptor (VDR) has been the focus of particular attention in this regard. Takeyama et al. [21] showed that the ability of vitamin D derivatives to elicit distinct biological responses might be a function of differential affinity of ligand-bound VDR for coactivator complexes in vivo. For example, whereas 1α,25-dihydroxyvitamin D_3 promoted interaction between VDR and all three SRC family members, 22-*oxa*-1α,25-dihydroxyvitamin D_3 (OCA) efficiently induced interaction of VDR only with TIF2/hSRC-2, and only TIF2/hSRC-2 was capable of potentiating VDR transactivation in the presence of OCA.

This concept has been extended to DRIP, a complex originally isolated using the VDR ligand-binding domain bound to 1,25 dihydroxyvitamin D_3 (D_3)[22]. While GRIP-1/mSRC-2 and DRIP-205 were recruited with comparable affinity by D_3-bound VDR, C-20 stereoisomers of D_3 (20-epi analogues) induced recruitment of DRIP205 by VDR at concentrations 100 fold lower than those at which D_3 or other derivatives, such as OCA, induced the VDR/DRIP 205 interaction. Interestingly, GRIP-1/mSRC-2 was not stably recruited by 20 epi-bound VDR until ligand concentrations were 100-fold in excess of those at which DRIPs were efficiently bound. Twenty epi-analogs of D_3 have for some time been known to modify proteolytic cleavage patterns of ligand-bound VDR, presumably by inducing specific conformational changes in the LBD. It was suggested that such specific alterations might result in structures which preferentially accommodate DRIP over SRC-1 or SRC-2-containing complexes [23]. Interestingly, DRIP205, a component of the DRIP complex, has been shown interact with glucocorticoid receptor (GR), suggesting that DRIP may have a more general role for both type I and type II receptors than was previously considered [24]. It remains to be established whether different GR agonists have a comparable effect upon recruitment of coactivator complexes by GR.

To place these observations in a physiological and clinical context, one can cite the biological activity of a burgeoning group of designer ER ligands, the selective ER modulators (SERMs). Through high affinity interactions with the ER, SERMs run the gamut of tissue-selective responses such that in certain tissues their effects are 'estrogenic' (estrogen-like) while in others they oppose the classic estrogen response-an 'antiestrogenic' effect. For example, while both raloxifene and tamoxifen oppose the action of estrogen in breast cells, only tamoxifen induces an estrogenic effect in the uterus, whereas raloxifene elicits an estrogenic response in bone which is more potent than that of tamoxifen [25]. Current models for SERM action postulate that tissue-specific coregulator fingerprints influence the net transcriptional flux in response to the ligand as a result of their selective interaction with different ER-SERM complexes. For example, L7/SPA enhances ER transactivation in response to certain partial ER agonists but does not influence transactivation by pure agonist-bound ER [26]. Furthermore, REA, (repressor of estrogen activity), is recruited by ER in an estrogen and antiestrogen-dependent manner to down-regulate the agonist effect of the respective ligand [27]. While the ability of L7-SPA and REA-like factors to mediate selective SERM effects in vivo remains to be established — for example, by a tissue specific expression profile-their potential to do so can be readily appreciated. Inherent in both these models is the notion that the changes in AF-2 similar to, but distinct from, those elicited by agonist binding can be effected by different SERMs [28]. Given its malleable structure, AF-2 might serve as a highly discriminate docking site for additional corepressors or coactivators, depending upon the cellular context.

A diagram summarizing the contribution of coactivators to the diversity of the biological response to ligand is shown in Fig. 3. In this scenario, binding of a specific ligand to a specific receptor in a given tissue commits the receptor to interaction with a particular subset of coactivators which activate a specific subset of genes in

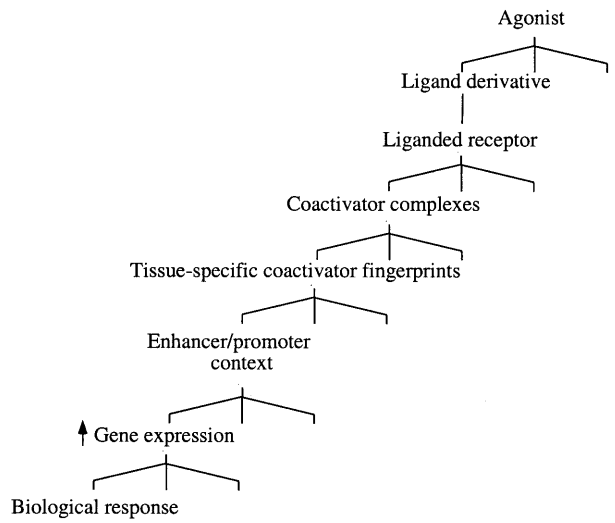

Fig. 3. Activation of specific gene networks in vivo by nuclear receptors resulting from multiple potential responses to ligand.

an enhancer and promoter-specific context. The potential for selective responses at each step ensures a flexible and adaptable response to physiological stimuli. Not included for the sake of clarity are the numerous post-translational modifications, some possibly instigated by parallel signal transduction pathways, which may further serve to modulate the amplitude and scope of the biological response to ligand.

4. Concluding remarks

Nuclear receptor ligands are exquisite pharmacological agents, eliciting a selective physiological response at a specific time, in a confined area for a specified period. This commentary has sought to highlight those lines of research which address the biological basis for their highly discriminate effects, focussing in particular on the profusion of coactivators known to be required by activated receptors for efficient transcriptional activation. To be sure, there is strength in numbers, and partial functional redundancy is known to exist between different coactivators, the phenotype of the SRC-1 mouse being the most obvious testament in this regard. The striking functional diversity of the coactivators characterized to date however argues for alternative explanations for their abundance. The discriminate in vivo effects of synthetic ligands has provided evidence at least for the existence of similar molecules in vivo, if not yet proving their physiological relevance. By influencing tissue-specific interpretation of ligand, diverse coregulator expression profiles can augment the pharmacological repertoire of individual ligands through successive developmental stages or during cyclic alterations in the composition of a specific organ, for example during pregnancy. Furthermore, in vitro evidence has established enhancer and promoter context as a significant factor in determining the nature and composition of receptor-coactivator complexes, which may be assembled at a given gene. Future work will place the relative contribution of these and other factors in a physiological context to more accurately assess their importance in the biological response to ligand.

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