Coregulator Interactions with the Thyroid Hormone Receptor

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The thyroid hormone receptor (TR) directly regulates the transcription of thyroid hormone-responsive genes in response to changes in levels of thyroid hormone. Mechanistically TR utilizes a complex set of binding interactions, with hormone, response elements, and coregulatory proteins, to provide specific local control of patterns of transcriptional response that are partially responsible for inducing the tissue-selective responses to the circulating hormone. One of the apparently dominant phenomena in the regulation of thyroid hormone responses is the protein interactions between TR and its coregulators. This review summarizes the current state of knowledge with respect to the identity of these coregulators, their interaction with TR, and the consequences of those interactions. Molecular & Cellular Proteomics 4:475–482, 2005.

Thyroid hormone controls essential functions in growth, development, and metabolism and is important for normal function of almost all tissues (1, 2). Most of the effects of thyroid hormone (TH) are relatively slow in onset and mediated by a family of high affinity receptor proteins known as the thyroid hormone receptors (TRs) that act directly as transcription factors (3). However, recent work has demonstrated that metabolites of thyroid hormone can also exert rapid biological effects through the G-protein-coupled receptors that act through secondary messenger pathways (4).

The TRs belong to the large superfamily of nuclear hormone receptors that regulate gene transcription (5–8). These proteins control a diverse set of target genes in response to specific physiological signals. Family members include the endocrine receptors, such as the estrogen (ER) and androgen (AR) receptors; the adopted orphan receptors, such as the retinoid X receptor (RXR) and peroxisome proliferator-activated receptor (PPAR); and the orphan receptors, receptors that do not require an endogenous ligand or for which a ligand has yet to be identified, such as steroidogenic factor 1 (SF-1) and liver receptor homolog 1 (LRH-1) (9, 10).

Like nearly all NRs, TRs contain three major domains (Fig. 1A): a ligand-independent amino-terminal transactivation domain, a central DNA binding domain, and a carboxyl-terminal ligand binding domain that adjusts transactivation in response to ligand. There are two different genes that express different TR subtypes, TRα1 and TRα2 (11). Each transcript can be alternatively spliced generating different isoforms (TRα1, TRα2, TRβ1, and TRβ2), which differ most in the composition of the amino-terminal transactivation domain and the far carboxy-terminal region of the ligand binding domain. While the isoforms are detectably expressed in almost all tissues they do have isoform-specific patterns of dominant expression. TRα1 is expressed most heavily in skeletal muscle and brown fat, while TRα2 is most highly expressed in the brain. TRβ1 is the most widely distributed subtype but is most highly expressed in the brain, liver, and kidney. TRβ2 is expressed almost exclusively in the pituitary and hypothalamus in adults. While TRα1, TRβ1, and TRβ2 bind TH with similar affinity, TRα2 does not bind to TH and is believed to inhibit the action other TRs.

A number of transgenic and knock-out mouse models have provided information on TR isoform-specific functions, and these have been reviewed (12, 13). In general, the studies show that the TRα and TRβ isoforms have distinct, non-redundant, and tissue-specific functions. Specifically it has been shown that TRα is an important regulator of heart function, influencing heart rate and contractility. On the other hand, TRβ appears to be a key regulator of hypothalamus-pituitary-thyroid feedback regulation and plasma cholesterol levels (3). One striking feature of the knock-out studies is that deletion of both TRα and TRβ induces only mild hypothyroidism and relatively viable animals, much more so than many of the single knock-outs (14–17). This points to the importance of repression of transcription by unliganded TR as a mecha-
TR-Coregulator Proteomics

**Fig. 1.** TR structure and regulation of gene transcription. A, diagram of the primary structure of the TR subtypes. The majority of the variation is in the A/B and F regions. Note that the one subtype with a highly variant E/F region (α2) does not bind triiodothyronine and is thought to act mostly through competitive inhibition of the action of the other subtypes. B, mechanism of TR transcriptional control. TR forms a heterodimer complex with RXR that recognizes specific TREs. In the absence of TH, this complex is associated with corepressors that repress transcription of the TRE-regulated gene. Upon binding of TH, TR undergoes a conformational change, releasing corepressors and allowing for the interaction of coactivators required for maximal gene activation. AF, activation function; LBD, ligand binding domain; NTD, amino-terminal transactivation domain; T3, triiodothyronine.

nism for thyroid hormone function. To take advantage of these clinical implications, isoform-specific ligands such as the TRβ-selective agonist GC-1 have been designed to reduce serum cholesterol levels without deleterious effects on the heart (18).

The TR DNA binding domain recognizes and interacts with short, repeated sequences of DNA found in thyroid hormone-responsive genes, termed the thyroid hormone response elements (TREs) (19). TR can bind to this half-site, AGGTCA, as a monomer, a homodimer, or a heterodimer with the RXR (20).

In the absence of thyroid hormone, the TR/RXR heterodimer is a monomer, a homodimer, or a heterodimer with the RXR (20). The regulation of gene expression by TR involves interaction with a complex network of coregulator proteins (Fig. 1B). These coregulators can either enhance (coactivators) or repress (corepressors) TR-driven gene transcription. Structural, biochemical, and genetic studies have provided a considerable amount of information about TR-coregulator interactions.

The best studied coactivators belong to the p160 protein family of steroid receptor coactivators (SRCs) (23–25). Members of this family include SRC1, (26) SRC2 (GRIP1/TIF2) (27, 28), and SRC3 (AIB1/TRAM1/RAC3/ACTR) (29–34). These proteins contain several functional domains including the nuclear receptor interaction domain, there are three repeated domains or protein-protein interaction surfaces for other coregulators required for maximal gene activation. AF, activation function; LBD, ligand binding domain; NTD, amino-terminal transactivation domain; T3, triiodothyronine.

**TR INTERACTION WITH COREGULATORS**

**Coactivators**

The regulation of gene expression by TR involves interaction with a complex network of coregulator proteins (Fig. 1B). These coregulators can either enhance (coactivators) or repress (corepressors) TR-driven gene transcription. Structural, biochemical, and genetic studies have provided a considerable amount of information about TR-coregulator interactions.

**Fig. 2.** Functional domains of the steroid receptor coactivator family. The primary structure of SRC1 is displayed with some of the important functional domains highlighted. The amino terminus contains highly conserved basic helix loop helix (bHLH) and PAS A/B domains. These domains are believed to function as DNA binding domains or protein-protein interaction surfaces for other transcription factors. The central nuclear interaction domain (NID) contains three nuclear receptor interaction motifs, LXXLL (NR boxes), that are known to interact with NR (the nomenclature for NR boxes is such that the most amino-terminal NR box has a -1 appended to the protein name, e.g. SRC1-1, and so on). In addition, SRC1 has two isoforms, SRC1a and SRC1e. SRC1a has an additional NR box at the carboxyl terminus designated SRC1-4 that has been shown to interact with some NRs. In addition there are two activation function domains (AD1 and AD2) that serve as protein-protein interaction surfaces for other coactivators (25).

**SRC1—SRC1 (also known as NcoA-1) was first identified**
binding affinities of individual NR boxes from SRC1 for TR were recently determined using a quantitative method with terminal of the LXXLL motif were critical for specificity. The action with TR and suggested amino acids residing carboxy-terminal (38, 39). These studies demonstrated that the second and third NR boxes from SRC1-2 and SRC1-3 were required for interaction with TR and suggested amino acids residing carboxy-terminal of the LXXLL motif were critical for specificity. The binding affinities of individual NR boxes from SRC1 for TRβ were recently determined using a quantitative method with SRC1-2 > SRC1-3 > SRC1-1 (40).

SRC1 null mice have provided further evidence that SRC1 is a critical coactivator required for TR regulation. Mice deficient in SRC1 exhibit partial resistance to sex steroid hormones and have features of resistance to thyroid hormone such as elevated free TH and thyroid-stimulating hormone (16). However, SRC1 does not globally affect all TH-responsive genes, and its effects appear to vary with TR isoforms. In the liver, SRC1 regulates the lipogenic enzyme Spot 14 but has no impact on malic enzyme or type 1 iodothyronine 5' -deiodinase levels. Similarly in the pituitary, SRC1 is linked to the regulation of thyroid-stimulating hormone but not growth hormone (41). In the heart, SRC1 modulates both TRα and TRβ effects on heart rate but does not appear to influence other inotropic and chronotropic cardiac genes (41, 42).

SRC2—SRC2, also known as GRIP-1 (mouse) (28) and TIF-2/NCoA-2 (human), (27) interacts with many NRs including AR, ER, GR, PR, RAR, SF-1, and TR. Yeast two-hybrid systems, mammalian transfection assays, and glutathione S-transferase pull-down assays have demonstrated that SRC2 strongly interacts with TR with relative NR box affinities of SRC2-2 > SRC2-3 > SRC2-1 (36, 43). More quantitatively determined binding affinities of NR box peptides of SRC2 to TR are consistent with these studies and revealed that NR boxes from SRC2 bind with comparatively higher affinities than all of the SRC1 NR box peptides (40).

It has been suggested that SRC1 and SRC2 are functionally redundant based on their high amino acid homology in their carboxy-terminal domains (50%) and increased expression levels of SRC2 observed in an SRC1 knock-out mouse (44–46). Although there is partial functional overlap between these two coactivators, it is clear that they also regulate different pathways. Mice deficient in either SRC1 or SRC2 have distinct phenotypes, and unlike SRC1 null mice SRC2 null mice display normal thyroid function (42, 46). In addition, these coactivators have differential tissue expression levels, potentially linking SRC2 to TR-regulated genes in the liver (47).

SRC3—The third member of the SRC family was simultaneously discovered by several groups, and hence there are several names associated with SRC3 (p/CIP (mouse homolog) and RAC3, ACTR, AIB-1, and TRAM-1 (human isoforms)) (29–34). A far-Western approach combined with glutathione S-transferase pull-down assays established SRC3 as a coactivator for TR (30). In vitro relative affinities of SRC3 NR boxes for TR were recently determined with SRC3-2 > SRC3-1 and SRC3-3. The binding affinities of SRC3 NR box peptides for TR are weaker or comparable to SRC1 NR box peptides (40).

The expression of SRC3 follows a more restricted tissue

### Table I

<table>
<thead>
<tr>
<th>Coregulator</th>
<th>Coregulatory role in thyroid hormone signaling</th>
<th>Other NRs bound</th>
<th>Relative affinities of NR boxes for TRs</th>
</tr>
</thead>
<tbody>
<tr>
<td>SRC1</td>
<td>SRC1-1/mice display RTH (16); linked to TSH down regulation (93); modulates TR effects on heart rate (42)</td>
<td>ER, PPAR, PR, RAR, RXR</td>
<td>TRβ: 2 &gt; 3 &gt; 1 (40)</td>
</tr>
<tr>
<td>SRC2</td>
<td>SRC2-2/mice have normal thyroid function; evidence of functional redundancy for TR regulation in pituitary (46); linked to TR effects in liver (47)</td>
<td>AR, ER, GR, PR, RAR, SF-1</td>
<td>TRβ: 2 &gt; 3 &gt; 1</td>
</tr>
<tr>
<td>SRC3</td>
<td>Linked to TR effects in liver (47)</td>
<td>AR, ER, LRH-1, PR, RAR, RXR, SF-1</td>
<td>TRβ: 2 &gt; 1, 3</td>
</tr>
<tr>
<td>TRAP220</td>
<td>Acts as a general coactivator</td>
<td>ER, PPAR, RAR, RXR, VDR, PPAR</td>
<td>TRβ: 1 &gt; 2; TRα: 2 &gt; 1 (50)</td>
</tr>
<tr>
<td>PGC-1</td>
<td>Linked to TR regulation of adaptive thermogenesis (52)</td>
<td>ER, PPAR</td>
<td>Ligand-dependent and ligand-independent (55)</td>
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<tr>
<td>TRBP</td>
<td>Ubiquitously expressed, acts as a general coactivator (56)</td>
<td>ER, PPAR</td>
<td>TRβ: 1 &gt; 2</td>
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<tr>
<td>p300</td>
<td>A general coactivator required for chromatin remodeling (94)</td>
<td>ER, AR, GR</td>
<td></td>
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<td>ARA70</td>
<td>Acts as corepressor (79); linked to down-regulation of CRABPI (86)</td>
<td>ER, LXR, PRAR, RXR, SF-1</td>
<td>TRβ: 5 &gt; 3 &gt; 8 &gt; 1, 4, 6, 7, 9</td>
</tr>
<tr>
<td>Rip140</td>
<td>Linked to TR regulation of steroidogenesis (89)</td>
<td>ER, LRH-1, SF-1</td>
<td>TRβ: 3 &gt; 2, 1</td>
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<tr>
<td>DAX-1</td>
<td>Linked to TR regulation of steroidogenesis (89)</td>
<td>ER, LRH-1, SF-1</td>
<td></td>
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<tr>
<td>SHP</td>
<td>Acts as a general corepressor (21)</td>
<td>DAX-1, ER, PR, RAR, RXR</td>
<td>TRβ: 1 &gt; 2; TRα: 1 &gt; 2 (75)</td>
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<td>NCoR</td>
<td>Acts as a general corepressor (21)</td>
<td>ER, PPAR, RAR, RXR</td>
<td></td>
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</table>

RTH, resistance to thyroid hormone; TSH, thyroid-stimulating hormone; CRABPI, cellular retinoic acid-binding protein I; VDR, vitamin D3 receptor.
pattern than the other SRC family members. High levels of SRC3 are found only in the oocytes, mammary gland, hippocampus, olfactory bulbs, smooth muscle, hepatocytes, and vaginal epithelium. Consequently mice deficient in SRC3 have a distinct phenotype of dwarfism, delayed puberty, and abnormal reproductive functions (48). Recent in vivo studies suggest that SRC3 may be involved in regulating TR genes in the liver (47).

**Thyroid Hormone Receptor-associated Protein (TRAP)**

The TRAP complex is a large multisubunit complex that has been shown to act as a general coactivator for many transcription factors (49). One of the proteins in this complex, TRAP220 (DRIP205/PBP) interacts with many NRs including ER, PPAR, RAR, RXR, TR, and vitamin D3 receptor through two distinct LXXLL motifs (50). The use of glutathione S-transferase pull-down assays demonstrated that NRs have different affinities for TRAP220 NR boxes. It was shown that RXR strongly interacts with the first NR box of TRAP220 (TRAP220-1), while TR prefers the second LXXLL motif (TRAP220-2). In addition, recent in vitro binding assays have revealed that TR isoforms also have unique NR box preferences with TRβ more strongly recruiting TRAP220-1 (40). Both homozygous disruption of TRAP220 and conditional hypomorphic expression of TRAP220 are embryonically lethal due to developmental defects in the liver and heart, perhaps indicating a role for this coactivator in thyroid function in these tissues (51).

**Peroxisome Proliferator-activated Receptor-γ Coactivator-1 (PGC-1)**

PGC-1 is a unique coactivator with tissue-specific expression that can be induced by external stimuli such as exposure to cold temperatures and exercise (52). This coactivator was originally identified as a PPAR-specific coactivator, but it has been subsequently shown to interact with a broader array of NRs and has been linked to important physiological pathways including adaptive thermogenesis and hepatic gluconeogenesis (52–54). Several groups have shown that TR can interact with PGC-1 in a ligand-dependent fashion via its one LXXLL motif (40, 55). In addition, it is believed that PGC-1 can also potentiate TR activity in a ligand-independent manner utilizing domains outside of the LXXLL motif in PGC-1 and ligand binding domain of TR (55).

**Thyroid Hormone Receptor-binding Protein (TRBP)**

TRBP, also known as PRIP, was identified as a TR coactivator in a yeast two-hybrid system. This coactivator contains one LXXLL motif that interacts fairly strongly with TRβ (40, 56). TRBP is believed to be a general coactivator capable of activating several transcriptional factors in addition to NR. Homologous disruption of TRBP leads to embryonic lethality due to failure to develop a normal placenta (57).

p300 — p300/CBP has been termed a coactivator because of its ability to form intranuclear complexes between nuclear receptors and transcriptional machinery (58). In addition, p300 has intrinsic histone acetyltransferase activity capable of modifying chromatin for gene transcription. Although in vitro binding studies have linked the interaction of p300 with NR, the precise physiological role of this interaction in thyroid signaling is not fully understood. There are some indications this cofactor may be required for myogenesis (59).

**Androgen Receptor Activator 70 (ARA70)**

ARA70 contains one LXXLL motif that has been shown to additionally interact with ER, PPAR, and TR (40, 60). Fusions of ARA70 have been associated with radiation-induced thyroid cancers (61). The precise role of ARA70 for TR function has not been elucidated.

**Other Coregulators**

There are several other coactivators known to interact with TR including Trip1/Sug1, RAP46/BAG-1, E6-AP, and translocated-in-liposarcoma (TLS). These coactivators do not contain LXXLL motifs, and in many cases the mechanism for activation of TR has not been worked out. Trip1/Sug1 was identified as thyroid-interacting protein 1 through a yeast two-hybrid system (62). It appears to interact with the ligand binding domain of TR in a ligand-dependent manner. Trip1 may be involved in the removal of ubiquitinated proteins from DNA by recruiting 26 S proteasome and therefore may be important for selectively targeting TR at a TRE for degradation or processing (63).

RAP46/BAG-1 belongs to a family of co-chaperones that contain a conserved carboxyl-terminal domain that can interact and inhibit the action of the molecular chaperone HSP70 (64). It appears that RAP46 uses multiple mechanisms to both enhance and repress transcriptional activity of NR.

E6-AP belongs to the E3 ubiquitin-protein ligase family and can enhance transcriptional activity of AR, ER, GR, PR, RAR, and TR (65). However, it has been shown that the ubiquitin-protein ligase function is not required for activation of NR. The mechanism for E6-AP coactivator function has yet to be defined. Homozygous disruption of E6-AP affects sex steroid signaling but has no readily apparent effects upon thyroid metabolism or signaling.

TLS was identified as a coactivator for RXR and TR using glutathione S-transferase pull-down assays (66). This coactivator belongs to the ribonucleoprotein family of RNA-binding proteins, and it is believed to be involved in RNA processing. Its precise function in TR signaling has not been investigated. Homozygous disruption of TLS has no readily apparent thyroid-related phenotype.

**Corepressors**

Repression of TR-regulated genes has been shown to be both ligand-independent and ligand-dependent (67–69). In the absence of ligand, TR is associated with corepressor proteins such as nuclear receptor corepressor (NCoR) and silencing mediator of retinoid and thyroid hormone receptors (SMRT) (70, 71). These proteins contain amino-terminal repression domains and carboxy-terminal nuclear receptor interaction domains. Within the nuclear receptor interaction domains are repeated motifs, (I/L)XX(I/V), termed CoRNR.
boxes, that are required for interaction with nuclear receptors (21). This motif is analogous to the coactivator motif, and structural studies have demonstrated that the binding site for coactivators and corepressors partially overlap (72).

The mechanism for thyroid hormone-dependent negative regulation of genes has yet to be fully elucidated. Several models have been postulated (73). One of these models suggests that liganded TR can associate with LXXLL-containing coregulators that are capable of repressing gene transcription by directly competing with other known coactivators. Some of these coregulators include receptor interacting protein 140 (RIP140), small heterodimer partner (SHP), and dosage-sensitive sex reversal-adrenal hypoplasia congenital critical region of the X chromosome (DAX) 1.

**NCoR and SMRT**—The interaction of NCoR and SMRT with TR has been extensively studied (21, 74–76). NCoR and SMRT both contain two nuclear hormone receptor interaction domains (CoRNR domains) that form an extended helical motif. Biochemical and cellular studies have shown that unliganded TR preferentially interacts with NCoR to repress basal transcription of target genes. Specifically it has been shown by several groups that TR interacts strongly with the first CoRNR motif in NCoR (21, 75). This preference is believed to derive from an additional NCoR interaction domain, termed N3, found upstream of CoRNR-1. This domain is not present in SMRT and appears to be specific for TR interaction.

To date there is very little information on repression of specific TR target genes by NCoR. The use of a dominant negative mutant NCoRi, however, has provided information of NCoR effects on TR hepatic target genes (77). This study demonstrated that NCoR represses basal transcription of Spot 14, Bcl-3, glucose 6-phosphate, and 5'-deiodinase. Additionally it appears that NCoR also prevents cellular proliferation of hepatocytes. An increased endogenous level of SMRT in the presence of NCoRi suggests a compensatory role for SMRT. These results provide the first evidence that NCoR represses basal transcription of TR target genes in vivo. Homozygous disruption of NCoR is embryonically lethal without obvious connection to thyroid signaling pathways (78).

**RIP140**—RIP140 was originally identified in breast cancer cell lines and isolated using the ligand binding domain of ER (79). It was subsequently shown to be ubiquitously expressed and able to interact with a number of different NRs. RIP140 contains nine LXXLL motifs and is recruited to NR through these domains in a ligand-dependent manner. However, unlike coactivators, RIP140 represses transcriptional activity (80–83). Quantitative in vitro binding assays determined that TR strongly interacts with NR box 5 in RIP140 and weakly interacts with the RIP140-3 and RIP140-8 (40). The remaining NR boxes in RIP140 do not interact with TR. Disruption of the RIP140 gene gives mice that are viable but undersized and infertile due to problems with ovulation (84). There was no demonstrated connection between the phenotype and thyroid hormone signaling.

Recently the interaction of TR and RIP140 was linked to the regulation of retinoic acid levels. Studies conducted in P19 embryonic carcinoma cells demonstrated that overexpression of RIP140 suppressed TH induction of cellular retinoic acid-binding protein 1, a protein thought to control intracellular retinoic acid levels (85).

**DAX-1**—DAX-1 is an orphan nuclear receptor lacking a traditional DNA binding domain. DAX-1 is recruited to nuclear receptors, such as ER, LRH-1, and SF-1, and represses gene transcription (86–88). There are four LXXLL-like motifs found in DAX-1. Recently it was shown that TR is also capable of interacting with some of the DAX-1 NR boxes in the presence of TH. Specifically TR strongly interacts with DAX-1-3, while only weak binding was observed with the remaining NR boxes (40).

Studies using mouse Leydig tumor cells explored TR regulation of steroidogenesis and demonstrated that TH can induce expression of steroidogenesis acute regulatory protein and SF-1. Overexpression of DAX-1, however, diminished the TH-mediated responses (89). It remains unclear whether DAX-1 directly interacts with TR to elicit this response or acts indirectly by inhibiting SF-1.

**SHP**—SHP is also an orphan nuclear receptor lacking the highly conserved DNA binding domain. It is believed that SHP can interact with a variety of NRs to repress transcriptional activity through an LXXLL motif found in the amino terminus (90, 91). SHP exerts its inhibitory effect through a two-step mechanism (92). The first step is direct interaction of SHP with the activation function-2 of NR where it has been shown to compete with coregulator proteins. The final step requires the autonomous repression function of SHP. A variety of in vivo and in vitro tests have shown that SHP interacts with and represses gene activation of ER, LRH-1, RAR, RXR, SF-1, and TR. The precise physiological response of TR-SHP interaction has not been documented.

**QUANTITATION OF THE INTERACTIONS OF TR AND COREGULATORS**

The majority of the work discussed in the preceding section has involved indirect or heterogeneous, non-quantitative methods for measuring the interaction of TR with cofactors in the presence or absence of ligands. In general these methods allow one to determine the likelihood of occupancy and the importance of interactions but not to determine relative affinities and thus predict the implications of potential competitions for limiting binding sites. Some work, including our own (40), as summarized above has dealt with the issue of relative affinities and with the change of affinity in response to variations in ligand structure.

To date, these data exist only for TRβ with two ligands (triiodothyronine and the TRβ-selective agonist GC-1) and for ERα with estradiol. Carrying out these studies with the full range of NR box structures has allowed the determination of consensus NR box sequences that drive the binding of coregulators by particular NR-ligand pairs. The consensus re-
sults of the studies with TR are presented in Fig. 3 along with the ER/estradiol results for comparison. TRβ itself requires three distinct residues outside the canonical LXXLL motif of the NR box for strong recruitment of a cofactor: a histidine-proline pair spaced one residue amino-terminal of the first leucine of the motif and a glutamine immediately carboxy-terminal of the last leucine of the motif. In addition to these defined amino acids, strongly recruited cofactors include within their NR box a hydrophobic amino acid immediately amino-terminal to the LXXLL motif and a series of hydrophilic amino acids after the requisite glutamine. One of the most interesting findings when one compares the results of examining the pattern of cofactor recruitment by TRβ when liganded with GC-1 with that just discussed is that the requirement for the histidine-proline pair no longer holds. That is to say that GC-1 still recruits NR box-containing cofactors to TRβ, but the molecular mechanism of the recruitment and the pattern of preferred cofactors have changed.

A major caveat to conclusions drawn from existing work is that all quantitative measurements to date have been garnered from the study of protein-peptide binding using NR box peptides, whereas the qualitative work has mostly been done with either the NR box-containing domain (typically holding one to three NR boxes) or intact protein. While the binding constants determined for peptide and full-length protein have always been in good agreement, some aspects of the interaction, particularly cooperativity, may not be faithfully modeled with the simpler peptide system. This may have particular significance with regard to the interaction of retinoid and thyroid signaling.

CONCLUSIONS

The work reviewed above shows that the field now has a fairly strong model relating the interaction of particular transcripational coactivators and corepressors with the liganded TR and explaining how these might affect transcription. The recent emergence of fairly comprehensive quantitative data has allowed one to begin to make predictions about the effects of perturbing these interactions in terms of affected physiology. Likewise a number of studies have monitored the global transcripational response to THs, particularly triiodothyronine, in a variety of settings. What is missing from the field right now is a comprehensive model relating the changes in cofactor interactions with the activation of particular genes. It is only in such a relational model that the proteomics of this pathway will be fully useful. Hopefully such a model will emerge from ongoing work in the not distant future.

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