

## Gene Regulation by Thyroid Hormone

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*Regulation of gene expression by thyroid hormones ( $T_3$ ,  $T_4$ ) is mediated via thyroid hormone receptors (TRs). TRs are DNA-binding transcription factors that function as molecular switches in response to ligand. TRs can activate or repress gene transcription depending on the promoter context and ligand-binding status. In most cases, in the absence of ligand, TRs interact with a corepressor complex containing histone deacetylase activity, which actively inhibits transcription. The binding of ligand triggers a conformational change in the TR that results in the replacement of the corepressor complex by a coactivator complex containing histone acetyltransferase activity, through which the chromatin structure is remodeled, thereby leading to activation of transcription. In addition, the finding that several TR-interacting coregulators act more directly on the basal transcriptional machinery suggests that mechanisms independent of histone acetylation and deacetylation also are involved in TR action.*

The roles of thyroid hormones (3,5,3'-triiodo-L-thyronine;  $T_3$  and thyroxine;  $T_4$ ) in development, homeostasis, cellular proliferation and differentiation have been widely documented. The biological functions of  $T_3$  are mediated largely through thyroid hormone receptors (TRs). TRs, along with the receptors for steroid hormones, retinoids and vitamin D, belong to the nuclear receptor (NR) superfamily<sup>1</sup>. Two distinct genes, *THRA* and *THRB* (encoding  $TR\alpha$  and  $TR\beta$ , respectively), produce various forms of TR proteins including the functional receptors  $TR\alpha 1$ ,  $TR\beta 1$  and  $TR\beta 2$ . Effects of TRs on gene regulation are initially achieved through binding to specific DNA se-

quences, known as thyroid hormone-response elements (TREs), in the regulatory regions of target genes. TRs bind to TREs even in the absence of  $T_3$ . TREs are usually composed of two or more receptor-binding 'half sites' arranged as direct repeats, inverted repeats or everted repeats. Although TRs are capable of binding to TREs as monomers or homodimers, TRs preferentially bind to many TREs as heterodimers with the retinoid X receptor (RXR), another member of the NR superfamily. TRs can enhance or inhibit gene expression depending on the nature of the TREs, the hormonal status and the cellular environment. Most of the characterized natural TREs are 'positive' TREs, in which gene transcription is repressed by unliganded TRs and activated by  $T_3$ -occupied TRs. Less well characterized are 'negative' TREs, from which transcription is stimulated by unliganded TRs and repressed by  $T_3$ -occupied TRs.

Structural and functional analyses have demonstrated that TRs and other

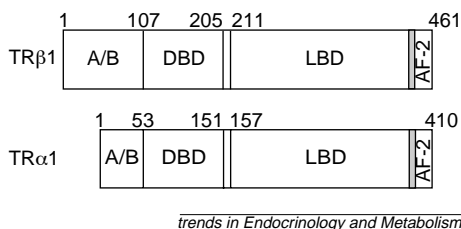
NRs exhibit a modular structure with distinct functional domains. These include an N-terminal A/B domain that often harbors a constitutive activation domain (AF-1), a centrally located DNA-binding domain (DBD) containing two zinc fingers, and a C-terminal ligand-binding domain (LBD) containing a ligand-dependent activation domain (AF-2). In general, TRs share a high degree of similarity in their DBDs and in their LBDs. However, the N-terminal domains of these proteins are unrelated (Fig. 1). Although  $TR\alpha 1$ ,  $TR\beta 1$  and  $TR\beta 2$  are structurally and functionally related, experimental evidence suggests that they have distinct functional roles. For example, the syndrome of resistance to thyroid hormone (RTH) is caused by mutations within the LBD of the  $TR\beta$ s (Ref. 2). No patients have been reported with mutations in  $TR\alpha$ . In addition, mice with a homozygous null mutation of  $TR\beta$  show an entirely different phenotype from  $TR\alpha 1$ -knockout mice. For example, mice with a homozygous null mutation of  $TR\beta$  show thyroid hormone resistance [raised serum  $T_4$ , non-suppressed thyroid-stimulating hormone (TSH)]<sup>3,4</sup>, whereas  $TR\alpha 1$ -knockout mice tend to have low circulating  $T_4$  and TSH levels<sup>5</sup>.

TR modulation of gene expression involves the coordination of an array of coregulatory proteins, including coactivators and corepressors. In general, the binding of unliganded TRs to positive TREs results in repression of transcription, and this is mediated by interaction of the TR with a corepressor complex. The binding of ligand induces conformational changes in the TR that result in release of the corepressor complex and recruitment of coactivators, thereby leading to gene activation.

### • Functional Roles of the Ligand-binding Domain in TR Action

The LBD is functionally complex, performing various activities, including

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**Figure 1.** Schematic representations of functional TRs  $\beta 1$  and  $\alpha 1$ . For simplicity, other splice variants are not shown. The N-terminal A/B domain is unrelated among various forms of TR proteins. TR $\beta 1$  and TR $\alpha 1$  are highly conserved in their DBDs and LBDs. The TR DBDs are approximately 100 amino acids in length and contain two zinc fingers. The LBD is approximately 250 amino acids in length and is primarily made up of 12  $\alpha$ -helices. A small hinge region separates the DBD from the LBD. The ninth heptad (shaded region) is part of the LBD helix 11, and is important for receptor dimerization. The core of the AF-2 domain is located in helix 12 near the C-termini of TR $\beta 1$  and TR $\alpha 1$ ; it is involved in interactions with coactivators. Abbreviations: AF-2, activation domain 2; DBD, DNA-binding domain; LBD, ligand-binding domain; TR, thyroid hormone receptor.

ligand binding, receptor dimerization and hormone-inducible transcriptional activation or repression. A conserved region known as the ninth heptad near the C-terminus (Fig. 1) appears to be important for mediating the formation of RXR–TR heterodimers or TR homodimers. The crucial role of the AF-2 domain in mediating ligand-dependent transcriptional activation was initially suggested by mutational analysis and subsequently confirmed by X-ray crystallography<sup>6,7</sup>. Crystal structures of several NR LBDs, including that of TR $\alpha 1$ , revealed that the LBDs exhibit a common structure containing 12  $\alpha$ -helices and several  $\beta$  turns folded into three layers to create a central hydrophobic binding pocket for the ligand<sup>7,8</sup>. The binding of ligand triggers significant conformational changes, including the repositioning of the amphipathic helix 12 containing the core of AF-2, which generates a coactivator-binding surface. The ligand- and AF-2-dependent recruitment of coactivators by NRs is important for transcriptional activation.

### • Gene Activation by T<sub>3</sub>

#### *Roles of Coactivators*

To date, the identified coactivators for TR action include at least: (1) three mem-

bers of the structurally and functionally related p160 family: steroid receptor coactivator 1 (SRC-1)/NCoA-1 (Ref. 9), transcriptional intermediary factor 2 (TIF2)/GRIP-1/NCoA-2 (Ref. 10) and p/CIP/ACTR/AIB1/RAC3/TRAM-1 (Ref. 11); (2) p300/CBP [cAMP-response element-binding protein (CREB)-binding protein]<sup>12</sup> and p300/CBP-associated factor (p/CAF)<sup>13</sup>; (3) TRAPs (TR-associated proteins)<sup>14</sup>; and (4) miscellaneous coactivators.

Mutational analyses have defined the helical LXXLL motif (where L is leucine and X is any amino acid) present in p160 family members and other coactivators as a crucial element in interacting with the AF-2 domain of ligand-bound NRs, including TRs (Ref. 15). p160 proteins contain three copies of the LXXLL motif in their central receptor interaction domains (NR boxes). Domain analysis has provided evidence that NRs can differentially interact with different combinations of these LXXLL motifs to form distinct coactivator complexes. For example, NCoA-1/SRC-1 employs the second LXXLL motif to mediate interaction with estrogen receptors (ERs)<sup>16</sup>, and it appears that each ER homodimer binds two molecules of SRC-1. By contrast, a single SRC-1 molecule uses two of its three LXXLL motifs to interact simultaneously with both receptors in RXR–RAR (retinoic acid receptor) heterodimers or peroxisome proliferator-activator receptor  $\gamma$  (PPAR $\gamma$ ) homodimers<sup>17,18</sup>. Mutational analysis has revealed that the sequences adjacent to the coactivator LXXLL motifs determine the preference of receptor binding<sup>16</sup>.

The existence of the multiple p160 proteins could reflect redundancy or could suggest that each protein subserves distinct functions. SRC-1-knockout mice exhibit partial steroid<sup>19</sup> and T<sub>3</sub> (Ref. 20) resistance. However, there is a compensatory increase in TIF2, suggesting partial redundancy among p160 proteins.

In addition to binding to nuclear receptors, p160 family proteins interact with CBP/p300. CBP and p300 are structurally conserved proteins that function as coactivators for a variety of transcription factors, including CREB, signal transducer and activator of transcription

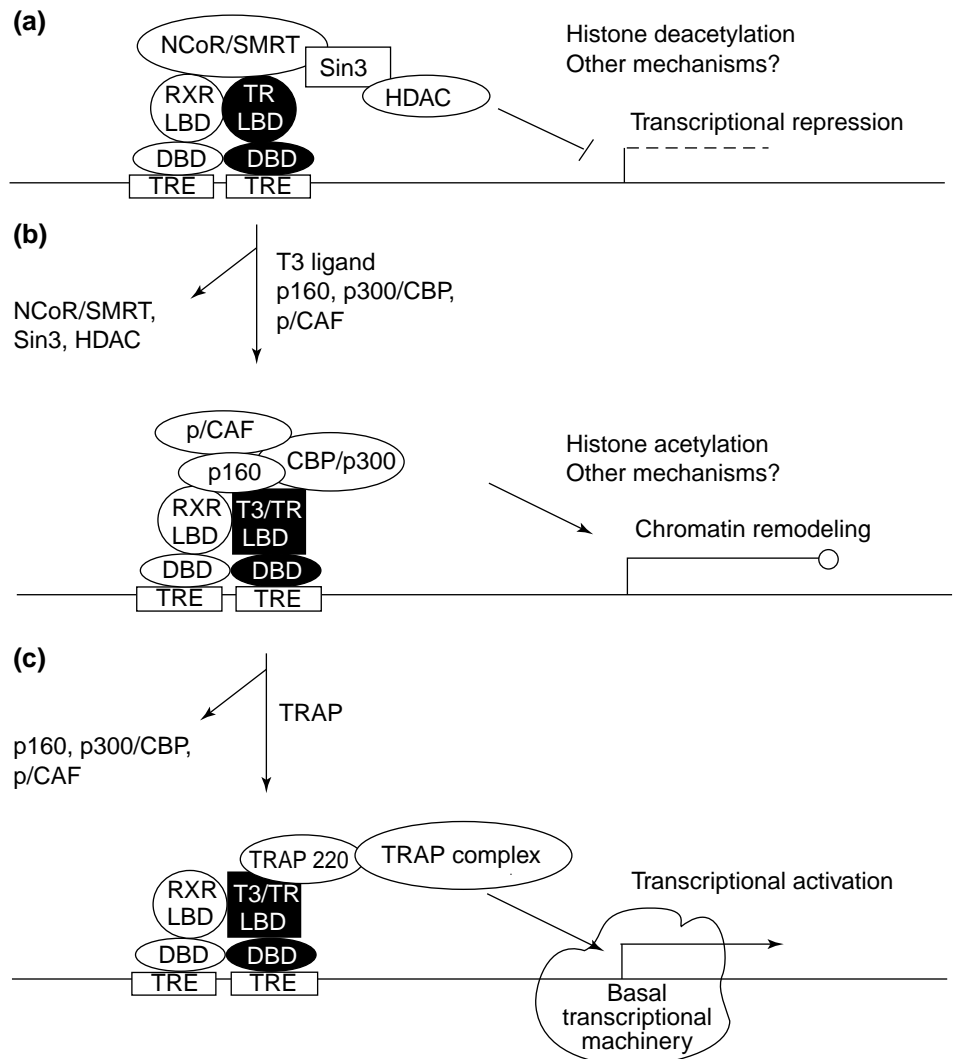
(STAT) proteins, nuclear factor kappa B (NF- $\kappa$ B), AP-1 and NRs. CBP enhances activation by TRs and other NRs in a ligand- and AF-2-dependent manner. P/CAF binds to CBP/p300 and to p160, and also plays a role in NR action<sup>13</sup>.

Numerous coactivators (including CBP/p300, p/CAF and p160 proteins) possess HAT (histone acetyltransferase) activity<sup>21,22</sup>. Histone hyperacetylation correlates with gene activation, presumably by facilitating access of key transcription factors to the promoter. Thus, it appears that TRs activate target gene expression in response to ligand at least in part by directing the assembly of a HAT-containing coactivator complex around promoters. However, studies using a *Xenopus* oocyte nuclei system have demonstrated that chromatin disruption by T<sub>3</sub> is necessary but not sufficient for transcription<sup>23</sup>. Furthermore, in this same system, p300 has no obvious effect on chromatin disruption, but can stimulate transcription from previously disrupted chromatin templates, and this requires HAT activity<sup>24</sup>. Notably, HATs are capable of acetylating non-histone substrates as well, including transcription factors such as p53 (Ref. 25) and basal transcription factors such as TFIIE and TFIIIF. In addition, liganded TRs enhance the recruitment of basal transcription factors to the promoter<sup>26</sup>. Taken together, these data indicate that although histone acetylation is likely to be crucial for gene activation by TRs, TRs might be involved in additional functional steps such as acetylation of non-histone proteins or formation of the preinitiation complex (PIC).

Rubinstein–Taybi syndrome (RTS) is a disease characterized by abnormal thumbs and facial features, short stature, mental retardation and other abnormalities. RTS is caused by mutations in one allele of the gene encoding CBP (*CREBBP*). Because CBP is important for TR action, one might expect RTS to be associated with thyroid hormone resistance. Surprisingly, patients with RTS have normal serum levels of thyrotropin and thyroid hormone<sup>27</sup>, suggesting that one normal *CREBBP* allele might be sufficient for T<sub>3</sub> signaling, or that CBP homologs, such as p300, can replace CBP for this function.

Biochemical purification schemes led to the identification of TRAP, a large multiprotein complex that associates with T<sub>3</sub>-bound TRs (Ref. 14). The TRAP complex is composed of at least nine proteins and is very similar to or identical with DRIP (Ref. 28) and ARC (Ref. 29), which are multiprotein complexes identified by their interactions with ligand-bound vitamin D receptors and transcription factors Sp1 and NF-κB, respectively. Thus, the TRAP/DRIP/ARC complex appears to play a broad role in gene activation. TRAP is targeted to the LBD of liganded TR through a single protein, TRAP220, of the complex, and this interaction is mediated by a TRAP220 LXXLL motif in an AF-2-dependent manner<sup>30</sup>. However, TRAP does not contain p160–CBP–p/CAF proteins and lacks HAT activity. *In vitro*, TRAP and p160 compete for binding to the TR AF-2 domain<sup>31</sup>. Two components of TRAP are closely related to the yeast Mediator complex proteins, Med 6 and Med 7, which are known to associate with RNA polymerase II. In addition, TRAP220 can interact directly with the basal transcription factor TATA box-binding protein (TBP), and can enhance gene activation in an *in vitro* transcription assay using naked DNA templates<sup>30,31</sup>. All these data indicate that, in contrast to the p160–CBP–p/CAF complex, TRAP probably does not function in chromatin remodeling. Instead, the TRAP complex might help form the PIC or convert the PIC from a repressive state to an active state. Perhaps the ligand-occupied NR first recruits a p160–CBP–p/CAF complex, which remodels chromatin. This coactivator complex might then be displaced by TRAP, which would interact with basal transcription factors to enhance gene expression (Fig. 2). However, this model is very speculative, and the details of how the TRAP complex enhances TR action must await further experimentation.

By contrast to the above coactivators, which are relatively nonspecific, a novel protein designated NRIF3 (nuclear receptor-interacting factor 3) was found to be a specific coactivator for TR and RXR, but not for other NRs (Ref. 32). NRIF3 has no homology with other identified coactivators. Other potential



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**Figure 2.** Model of gene repression by unliganded TR and activation by liganded TR. **(a)** In the absence of ligand, the DNA-bound RXR–TR heterodimer interacts with a corepressor complex composed of NCoR/SMRT, Sin3 and HDAC, and actively represses gene transcription. **(b)** In the presence of ligand, the TR undergoes a conformational change, which results in the replacement of the corepressor complex by a coactivator complex composed of p160 proteins, p300/CBP, p/CAF and perhaps other proteins. The histone acetyltransferase activity derived from coactivators results in an ‘open’ transcriptionally active chromatin configuration. **(c)** Ligand-occupied TR then associates with the multiprotein TRAP complex, which activates transcription, perhaps by interaction with general transcription factors. This model, including the displacement of the coactivator complex by TRAP, is speculative. Abbreviations: CBP, cAMP-response element-binding protein (CREB)-binding protein; DBD, DNA-binding domain; HDAC, histone deacetylase; LBD, ligand-binding domain; NCoR, nuclear corepressor; pCAF, p300/CBP-associated factor; RXR, retinoid X receptor; SMRT, silencing mediator for RXR and TR; TRAP, thyroid hormone-associated protein; T<sub>3</sub>, thyroid hormone; TR, thyroid hormone receptor; TRE, thyroid hormone-response element.

coactivators such as p120 have been described<sup>33</sup>, but the *in vivo* roles of each of these proteins remains poorly understood.

#### Role of Corepressors

On ‘positive’ TREs, unliganded TRs associate with corepressors to repress

transcription. Binding of ligand to TRs promotes dissociation of the corepressor complex and recruitment of the coactivator complex, which leads to transcription. NCoR (nuclear corepressor)<sup>34</sup> and SMRT (silencing mediator for RXR and TR)<sup>35</sup> are two functionally and structurally related corepressors. NCoR and

SMRT interact with the protein Sin3, which itself associates with histone deacetylases (HDACs) to form a corepressor complex<sup>36</sup>. Antibody blocking of each component of the NCoR–Sin3–HDAC complex causes relief of repression by TR and RAR, suggesting that each component of the complex is important for repression. In addition to the repressive role of NCoR–SMRT–Sin3–HDAC complexes in NR action, HDAC complexes have been linked to repression by various other transcription factors, including Mad-Max (Ref. 37) and antagonist-occupied steroid receptors<sup>38</sup>. Sin3A–HDAC also associates with methyl-CpG-binding proteins to mediate DNA methylation-dependent transcriptional repression<sup>39</sup>.

The finding of HDACs in the NCoR–SMRT–Sin3 repressor complex suggests that gene silencing is mediated by histone deacetylation, presumably by restricting the accessibility of key transcriptional factors to targeted promoters. However, it is possible that other mechanisms might also contribute to repression. For example, unliganded TR can directly interact with general transcription factors such as TFIIB and TFIID, which might interfere with the formation of a functional PIC on TREs (Ref. 40). Interactions between NCoR, SMRT and Sin3 and general transcription factors including TAF<sub>II</sub>32, TAF<sub>II</sub>70 and TFIIB have also been observed<sup>41</sup>.

Sequence alignments and mutational analyses identified a signature motif containing the sequence L/I-X-X-I/V-I (called CoRNR) within two NR interaction domains of NCoR or SMRT (Ref. 42). Structural predictions suggest that this motif forms an amphipathic  $\alpha$ -helix. Functional studies show that a short interaction domain containing this L/I-X-X-I/V-I motif is both necessary and sufficient for NR binding, a finding reminiscent of the LXXLL motifs within coactivators. Notably, replacement of the p160 (GRIP1) LXXLL motifs with CoRNRs converts GRIP1 from a ligand-dependent coactivator to a ligand-independent coactivator, demonstrating parallel mechanisms for the interaction of coactivators and corepressors with TRs. In addition, these data suggest that the CoRNRs are important for NR

recognition but have no effects on other separable functional domains. Thus, these findings provide a mechanistic link between repression and activation of gene expression by NRs.

#### • Gene Repression by T<sub>3</sub>

T<sub>3</sub>-dependent repression of negatively regulated genes is a very important property of TRs. For example, several negatively regulated genes such as those encoding the thyrotropin (TSH)  $\alpha$ - and  $\beta$ -subunits (*TSHA* and *TSHB*, respectively) and thyrotropin-releasing hormone (*TRH*) are crucial targets for physiological feedback by T<sub>3</sub>, through which plasma thyroid hormone levels are tightly controlled. In contrast to positive TREs, a consensus sequence for negative response elements (nTREs) has yet to be established. Several lines of evidence suggest that specific target genes might adopt distinct mechanisms for repression, and that, in fact, TR–DNA binding might not always be required for gene repression by T<sub>3</sub>.

In general, it appears that genes that are downregulated by T<sub>3</sub> are upregulated by unliganded TRs. Surprisingly, corepressors might be involved in the induction of the *TSHA*, *TSHB* and *TRH* genes by unliganded TRs (Ref. 43). For example, the ability of unliganded TRs to enhance transcription of the *TSH* and *TRH* genes is greatly reduced when mutations that impair the interaction with corepressors are introduced into the TR. Furthermore, overexpression of the genes encoding SMRT or NCoR enhances stimulation of these genes by unliganded TRs. Further study of the *TSHA* gene has led to the equally surprising finding that coactivators are involved in T<sub>3</sub>-dependent repression<sup>44</sup>. Consistent with this, SRC-1-knockout mice have central resistance to T<sub>3</sub>, manifested by an impaired ability of T<sub>3</sub> to suppress TSH synthesis and secretion<sup>20</sup>. In transfection experiments, TR mutations that abolish p160 binding abolish T<sub>3</sub>-mediated repression of the *TSHA* promoter, but do not impair gene activation by unliganded TRs (Ref. 44). These data suggest that the roles of corepressors and coactivators in negatively regulated genes are reversed compared with those in positively regulated genes. A mechanism for this is

suggested by experiments that showed that TR binding to the *TSHA* promoter appears not to be necessary for negative regulation of that gene. On the basis of the *TSHA* gene, a two-step model for a subset of negatively regulated genes has been suggested. In the absence of ligand, DNA-unbound TR interacts with the corepressor–HDAC complex and sequesters HDAC from the promoter, thereby activating gene expression. Binding of ligand to TR causes the replacement of the corepressor–HDAC complex by coactivators, so as to make HDAC available to the promoter and to withdraw coregulatory factors like CBP/p300 and p/CAF from the promoter, thereby leading to ligand-dependent repression.

In contrast to *TSHA*, the negative regulation of the *TSHB* gene might require TR binding to its nTRE. Studies of the *TSHB* gene show that HDAC2 and TR $\beta$  are directly recruited to the negative response element of the *TSHB* promoter in a ligand-dependent manner<sup>45</sup>. The inhibition of HDAC activity greatly reduces T<sub>3</sub>-induced repression. These data suggest that HDAC2 might play a traditional role in effecting repression of the *TSHB* gene by T<sub>3</sub>. The overall data suggest that the mechanisms of negative regulation of the *TSHA* gene might be distinct from that of *TSHB*.

## References

- 1 Mangelsdorf, D.J. *et al.* (1995) The nuclear receptor superfamily: the second decade. *Cell* 83, 835–839
- 2 Refetoff, S. *et al.* (1993) The syndromes of resistance to thyroid hormone. *Endocr. Rev.* 14, 348–399
- 3 Forrest, D. *et al.* (1996) Recessive resistance to thyroid hormone in mice lacking thyroid hormone receptor beta: evidence for tissue-specific modulation of receptor function. *EMBO J.* 15, 3006–3015
- 4 Gauthier, K. *et al.* (1999) Different functions for the thyroid hormone receptors TR $\alpha$  and TR $\beta$  in the control of thyroid hormone production and post-natal development. *EMBO J.* 18, 623–631
- 5 Wikström, L. *et al.* (1998) Abnormal heart rate and body temperature in mice lacking thyroid hormone receptor alpha1. *EMBO J.* 17, 455–461
- 6 Baretino, D. *et al.* (1994) Characterization of the ligand-dependent transactivation domain of thyroid hormone receptor. *EMBO J.* 13, 3039–3049
- 7 Wurtz, J.-M. *et al.* (1996) A canonical structure for the ligand-binding domain of nuclear receptors. *Nat. Struct. Biol.* 3, 87–94

- 8 Wagner, R.L. *et al.* (1995) A structural role for hormone in the thyroid hormone receptor. *Nature* 378, 690–697
- 9 Oñate, S.A. *et al.* (1995) Sequence and characterization of a coactivator for the steroid hormone receptor superfamily. *Science* 270, 1354–1357
- 10 Voegel, J.J. *et al.* (1996) TIF2, a 160 kDa transcriptional mediator for the ligand-dependent activation function AF-2 of nuclear receptors. *EMBO J.* 15, 3667–3675
- 11 Torchia, J. *et al.* (1997) The transcriptional co-activator p/CIP binds CBP and mediates nuclear-receptor function. *Nature* 387, 677–684
- 12 Chakravarti, D. *et al.* (1996) Role of CBP/P300 in nuclear receptor signalling. *Nature* 383, 99–103
- 13 Blanco, J.C.G. *et al.* (1998) PCAF is a nuclear receptor coactivator. *Genes Dev.* 12, 1638–1651
- 14 Fondell, J.D. *et al.* (1996) Ligand induction of a transcriptionally active thyroid hormone receptor coactivator complex. *Proc. Natl. Acad. Sci. U. S. A.* 93, 8329–8333
- 15 Heery, D.M. *et al.* (1997) A signature motif in transcriptional co-activators mediates binding to nuclear receptor. *Nature* 387, 733–736
- 16 McNerney, E.M. *et al.* (1998) Determinants of coactivator LXXLL motif specificity in nuclear receptor transcriptional activation. *Genes Dev.* 12, 3357–3368
- 17 Westin, S. *et al.* (1998) Interactions controlling the assembly of nuclear-receptor heterodimers and co-activators. *Nature* 395, 199–202
- 18 Nolte, R.T. *et al.* (1998) Ligand binding and co-activator assembly of the peroxisome proliferator-activated receptor-gamma. *Nature* 395, 137–143
- 19 Xu, J. *et al.* (1998) Partial hormone resistance in mice with disruption of the steroid receptor coactivator-1 (SRC-1) gene. *Science* 279, 1922–1925
- 20 Weiss, R.E. *et al.* (1999) Mice deficient in the steroid receptor co-activator 1 (SRC-1) are resistant to thyroid hormone. *EMBO J.* 18, 1900–1904
- 21 Ogryzko, V.V. *et al.* (1996) The transcriptional coactivators p300 and CBP are histone acetyltransferases. *Cell* 87, 953–959
- 22 Spencer, T.E. *et al.* (1997) Steroid receptor coactivator-1 is a histone acetyltransferase. *Nature* 389, 194–198
- 23 Wong, J.M. *et al.* (1998) Distinct requirements for chromatin assembly in transcriptional repression by thyroid hormone receptor and histone deacetylase. *EMBO J.* 17, 520–534
- 24 Li, Q. *et al.* (1999) p300 stimulates transcription instigated by ligand-bound thyroid hormone receptor at a step subsequent to chromatin disruption. *EMBO J.* 18, 5634–5652
- 25 Gu, W. and Roeder, R.G. (1997) Activation of p53 sequence-specific DNA binding by acetylation of the p53 C-terminal domain. *Cell* 90, 595–606
- 26 Kim, M.K. *et al.* (1999) *In vivo* transcription factor recruitment during thyroid hormone receptor-mediated activation. *Proc. Natl. Acad. Sci. U. S. A.* 96, 10092–10097
- 27 Olson, D.P. and Koenig, R.J. (1997) Thyroid function in Rubinstein-Taybi syndrome. *J. Clin. Endocrinol. Metab.* 82, 3264–3266
- 28 Rachez, C. *et al.* (1999) Ligand-dependent transcription activation by nuclear receptors requires the DRIP complex. *Nature* 398, 824–828
- 29 Näär, A.M. *et al.* (1999) Composite coactivator ARC mediates chromatin-directed transcriptional activation. *Nature* 398, 828–832
- 30 Yuan, C.X. *et al.* (1998) The TRAP220 component of a thyroid hormone receptor-associated protein (TRAP) coactivator complex interacts directly with nuclear receptors in a ligand-dependent fashion. *Proc. Natl. Acad. Sci. U. S. A.* 95, 7939–7944
- 31 Treuter, E. *et al.* (1999) Competition between thyroid hormone receptor-associated protein (TRAP) 220 and transcriptional intermediary factor (TIF) 2 for binding to nuclear receptors – implications for the recruitment of TRAP and P160 coactivator complexes. *J. Biol. Chem.* 274, 6667–6677
- 32 Li, D.S. *et al.* (1999) NRIF3 is a novel coactivator mediating functional specificity of nuclear hormone receptors. *Mol. Cell Biol.* 19, 7191–7202
- 33 Monden, T. *et al.* (1997) Isolation and characterization of a novel ligand-dependent thyroid hormone receptor-coactivating protein. *J. Biol. Chem.* 272, 29834–29841
- 34 Hörlein, A.J. *et al.* (1995) Ligand-independent repression by the thyroid hormone receptor mediated by a nuclear receptor co-repressor. *Nature* 377, 397–404
- 35 Chen, J.D. and Evans, R.M. (1995) A transcriptional co-repressor that interacts with nuclear hormone receptors. *Nature* 377, 454–457
- 36 Nagy, L. *et al.* (1997) Nuclear receptor repression mediated by a complex containing SMRT, mSin3A, and histone deacetylase. *Cell* 89, 373–380
- 37 Ayer, D.E. *et al.* (1995) Mad-Max transcriptional repression is mediated by ternary complex formation with mammalian homologs of yeast repressor Sin3. *Cell* 80, 767–776
- 38 Wagner, B.L. *et al.* (1998) The nuclear co-repressors NCoR and SMRT are key regulators of both ligand- and 8-bromo-cyclic AMP-dependent transcriptional activity of the human progesterone receptor. *Mol. Cell Biol.* 18, 1369–1378
- 39 Nan, X. *et al.* (1998) Transcriptional repression by the methyl-CpG-binding protein MeCP2 involves a histone deacetylase complex. *Nature* 393, 386–389
- 40 Fondell, J.D. *et al.* (1996) Unliganded thyroid hormone receptor alpha can target TATA-binding protein for transcriptional repression. *Mol. Cell Biol.* 16, 281–287
- 41 Muscat, G.E.O. *et al.* (1998) The corepressor N-CoR and its variants RIP13a and RIP13Delta1 directly interact with the basal transcription factors TFIIB, TAF<sub>II</sub>32 and TAF<sub>II</sub>70. *Nucleic Acids Res.* 26, 2899–2907
- 42 Xu, X. and Lazar, M.A. (1999) The CoRNR motif controls the recruitment of corepressors by nuclear hormone receptors. *Nature* 402, 93–96
- 43 Tagami, T. *et al.* (1997) Nuclear receptor corepressors activate rather than suppress basal transcription of genes that are negatively regulated by thyroid hormone. *Mol. Cell Biol.* 17, 2642–2648
- 44 Tagami, T. *et al.* (1999) Mechanisms that mediate negative regulation of the thyroid-stimulating hormone  $\alpha$  gene by the thyroid hormone receptor. *J. Biol. Chem.* 274, 22345–22353
- 45 Sasaki, S. *et al.* (1999) Ligand-induced recruitment of a histone deacetylase in the negative-feedback regulation of the thyrotropin beta gene. *EMBO J.* 18, 5389–5398

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