Ligand-dependent Heterodimerization of Thyroid Hormone Receptor and Retinoid X Receptor*

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The thyroid hormone receptors (TRs) bind to cis-acting DNA elements as heterodimers with the retinoid X receptors (RXRs). These heterodimers display distinct specificities in mediating the hormonal response to target gene transcription. We characterized the interaction between TRα1 and RXRa via their ligand binding domains (LBDs) and the effect of ligands on the interaction using a yeast two-hybrid system. The DNA binding domain (BD) of yeast Gal4 fusion to the LBD of TRα1 had no transcriptional activity on its own, but when it was coexpressed with the activation domain (AD) of yeast Gal4 fusion to LBD of RXRa conferred activation to a reporter gene harboring a Gal4 binding site, indicating that LBDs of TRα1 and RXRa interact with each other in solution. Furthermore, T₃ and 9-cis-RA increased the reporter activity, and an additive effect was observed when both ligands were added, indicating that the TRα1-RXRa heterodimerization is augmented by their respective ligands in vivo. Using an in vitro pull-down experiment, we confirmed the ligand-dependent interaction observed in the yeast system. Matrix-bound glutathione S-transferase-RXRa specifically coprecipitated the ³⁵S-labeled TRα1 above the control, and associated ³⁵S-labeled TRα1 was increased by the addition of T₃ and 9-cis-RA. These results imply a complex, sensitive cross-talk in vivo among nuclear receptors and their respective ligands through distinct hormonal signaling pathways.

Effects of thyroid hormone on a wide variety of tissues are mediated via specific nuclear thyroid hormone receptors (TRs) (1) which are the cellular homologs of v-erbA (2). Several isoforms of TRs and TR variants have been isolated (2–6) and shown to be members of a gene superfamily that includes steroid receptors, retinoic acid receptors (RARs), vitamin D receptors, peroxisome proliferator-activated receptors (PPARs), and numbers of proteins with high homology but as yet unidentified ligands.

Based on sequence homology and functional analysis, the nuclear receptors exhibit a modular structure with functionally separable domains. Members of the superfamily are characterized by a highly conserved cysteine-rich DNA binding domain containing two zinc finger structures necessary for sequence-specific DNA interaction (7). The complex carboxyl-terminal region of the receptors contains ligand binding, receptor dimerization, and putative transcriptional activation functions (8).

The TRs, as well as other members of the superfamily, regulate transcription by binding to response elements containing two or more copies (often degenerate) of the consensus motif AGGTCA (9, 10). Recently it was shown that RARs, TRs, vitamin D receptors, and PPARs form heterodimers with the RXRs on bipartite hormone response elements composed of nonsymmetrical head-to-tail tandem AGGTCA half-sites (11–13).

To date two distinct dimerization surfaces were proposed in the DNA binding domain (DBD) and ligand binding domain (LBD) of TR. The surface in the DNA binding domain conferred selective power in DNA-dependent dimer formation (14). In contrast to the interface within the DBDs, dimerization motifs in the LBDs permit the heterodimeric complex subsequently to interact with response elements. The carboxyl-terminal LBD is responsible for DNA-independent dimerization that in vitro allows performance of certain dimers in solution before DNA targeting. This dimerization function is believed to stabilize the complex and promote the recognition of DNA. Several heptad repeats in LBD are well conserved among the members of the erbA-related nuclear receptor family and have been proposed to form a hydrophobic surface that might act as a receptor dimerization interface (15, 16), which is structurally similar to the leucine zipper dimerization domain found in Jun-Fos (17). The heterodimerization influences the recognition of DNA targets and confers specificity for a defined spacing between two directly repeating hexameric sequences. Deletion of heptad repeats abolished the trans-activation function of the receptor (18, 19). Furthermore, the formation of heterodimers results in cross-talk among different ligands potentially to affect a range of physiological processes. The effect of ligand on the formation of TR/RXR heterodimers in solution has not been demonstrated clearly. To investigate the role of ligand in the process of receptor dimerization before binding to the target DNA, we have used the yeast two-hybrid system that allows the measurement of specific protein-protein interaction in solution. In the present study, we demonstrated that TR/RXR interaction occurred in solution before DNA targeting and was augmented by T₃ and 9-cis-RA additively both in vivo and in vitro.

MATERIALS AND METHODS

Yeast Strains and Methods—The genotype of the Saccharomyces cerevisiae reporter strain SPY526 is MATα, ura3–52, his3–200, ade2–101, lys2–801, trp1–901, leu2–3, 112, can1, gal4–542, gal80–538, URA3::GAL1-lacZ (obtained from CLONTECH). The genotype of HF7c...
strains is MATa, ura3–52, his3–200, lys2–801, ade2–101, trp1–901, leu2–3, 112, gal1–542, lys2S::GAL1-HIS3::URA3::GAL1 17-mers3-CYC1-laZ (obtained from CLONTECH). Both yeast host strains carry a lacZ reporter gene under the control of GAL1 binding site. HFC7 contains a second reporter gene (HIS3), also under the control of GAL4 response elements. Yeast strains were grown at 30 °C in YPD medium (1% yeast extract, 2% Bacto-Pepitone, 2% dextrose) or in synthetic selection medium with appropriate supplements.

**Gal4BD Fusion Plasmids**—Gal4BD fusion proteins were expressed by transfecting pGBT9 (CLONTECH) vector harboring the cDNA encompassed TR1 LBD (amino acids 120–410), or RXR LBD (amino acids 200–461) (Fig. 1). The pGBT9-TR1(LBD) (amino acids 120–410) and pGBT9-RXR(LBD) (amino acids 200–461) plasmids were constructed by inserting the cDNA sequence encompassing the hinge and the LBD of human TR1 or RXR (20) into BamHI-SalI sites or EcoRI-BgII sites of pGBT9, respectively. To introduce the EcoRI and BamHI sites into 5′- and 3′-ends of the LBD of TR1 or RXR, pME21 (4), which contains the entire coding region of hTR1 cDNA, was amplified by polymerase chain reaction (PCR) using following synthetic oligonucleotide primers: 5′-gaattcATGAGGCGGAAGCCGGTGCAG-3′ (salmon primer) and 5′-ggtagCGATCTCTCTAGAGGCGGCG-3′ (reverse primer). The forward primer contains the BamHI site (gaattc) and an additional 2 base pairs (gt) to adjust the reading frame followed by the coding strand sequence just after of TR1 LBD. The reverse primer included the SalI site (ggatcc) and the coding sequence at the carboxyl terminus of TR1. The hinge and LBD of hRXR were amplified by PCR using following forward and reverse oligonucleotide primers: 5′-gaattcATGAGGCGGAAGCCGGTGCAG-3′ and 5′-ggtagCGATCTCTCTAGAGGCGGCG-3′ (reverse primer). The forward primer contains the BamHI site (gaattc) and an additional 2 base pairs (gt) to adjust the reading frame followed by the coding strand sequence just after of RXR LBD. The reverse primer included the SalI site (ggatcc) and the coding sequence at the carboxyl terminus of RXR.

**RESULTS**

**GAL4BD-TR1(LBD) and GAL4BD-RXR1(LBD) Fusion Proteins Interact in Yeast**—To investigate the ability of TR1 and RXR to heterodimerize through their LBD, the interaction of GAL4BD-TR1(LBD) and GAL4BD-RXR1(LBD) fusion proteins in yeasts was examined using the yeast two-hybrid system. The yeast reporter strain HF7c was cotransformed with pGBT9-Tra1(LBD) or pGAD424-RXR1(LBD) or both plasmids and selected with tryptophan and leucine dropout medium. Transformed colonies were streaked onto tryptophan and leucine dropout medium with (1 mg/ml) or without histidine. In the assay, the formation of a complex between TR1(LBD) fused to GAL4BD and RXR(LBD) fused to GAL4AD confers histidine auxotrophy and β-galactosidase activity. As shown in Fig. 2, the yeast expressing GAL4BD-TR1(LBD) and GAL4AD-RXR1(LBD) are allowed to grow in the absence of histidine. The yeast cotransformed with pairs of GAL4BD-TR1(LBD) and GAL4AD, or
Gal4BD and Gal4AD-RXRα(LBD), did not permit growth in the absence of histidine, indicating that histidine auxotrophy is the result of the interaction between TRα1(LBD) and RXRα(LBD). Similar results were obtained in the reverse experiment using cotransfectants expressing Gal4BD-RXRα(LBD) and Gal4AD-TRα1(LBD) (data not shown).

**Effect of Ligands on the Interaction between Gal4BD-TRα1(LBD) and Gal4AD-RXRα(LBD) in Yeasts—**First, we examine the ligand-dependent transcriptional activity of Gal4BD-TRα1(LBD) or Gal4BD-RXRα(LBD) alone (Fig. 3). pGBT9-TRα1(LBD) or pGBT9-RXRα(LBD) was introduced into yeast strain SFY526 to express Gal4BD-TRα1(LBD) or Gal4BD-RXRα(LBD) protein. Yeast colonies were selected with tryptophan dropout medium. Five independent yeast colonies from each transformant were cultured overnight in the presence of various concentrations of T3 (10^{-6} M) or 9-cis-RA. β-Galactosidase activities of yeast cultures were determined using CPRG as substrate (see “Materials and Methods”).

The LBD of TRα1 or RXRα cannot function as a transcriptional activator even in the presence of ligands in the yeasts. Neither Gal4BD-TRα1(LBD) nor Gal4BD-RXRα(LBD) alone activates the transcription of GAL1 promoter.

Then we tested the ability of the heterodimers between LBDs of TR and RXR as a transcriptional activator for Gal4 DBD. pRXRα(LBD), just an expression vector for RXRα(LBD), was cointroduced into SFY526 with pGBT9-TRα1(LBD). No increase of β-galactosidase activity was observed in the yeasts transformed with Gal4BD-TRα1(LBD) and RXRα(LBD) expressing vector, and T3 or 9-cis-RA did not show a significant increase of β-galactosidase activity (Fig. 3). It is concluded, therefore, that the heterodimers of LBDs of TR and RXR cannot function as a transcriptional activator in the yeasts.

When a combination of Gal4BD-TRα1(LBD) and Gal4AD-RXRα(LBD), or Gal4BD-RXRα(LBD) and Gal4AD-TRα1(LBD), were introduced into yeast strain SFY526, a significant increase in β-galactosidase activities was observed. Both T3 and 9-cis-RA increased the β-galactosidase activity, and an additive effect was observed when both ligands were present. Dose dependence of ligands for activation of TR/RXR interaction was assessed. Yeast colonies were cultured overnight in the presence of various concentrations of T3 or 9-cis-RA. As shown in...
were performed to show the T3 dose-response curve in the lanes bound to glutathione-Sepharose beads, as indicated.35S-
second lane third lane or a GST-RXR fusion protein (panel B). β-Galactosidase activities were determined using CPRG ("Materials and Methods"). Values are the mean ± S.D. for at least three independent experiments performed in duplicate.

Fig. 4, T3 and 9-cis-RA increased the β-galactosidase activity in a dose-dependent manner. A half-maximal increase was observed at 10^{-8} M for T3 and 10^{-6} M for 9-cis-RA. We examined further the effect of 9-cis-RA (10^{-6} M) on the T3-dependent TR/RXR interaction. As shown in Fig. 5A, the presence of T3 further activated the β-galactosidase activity without changing the sensitivity to 9-cis-RA. In Fig. 5B, the reverse experiments were performed to show the T3 dose-response curve in the presence or absence of 10^{-6} M T3. Similarly, the presence of 9-cis-RA further activated the β-galactosidase activity without changing the sensitivity to T3. All fusion proteins were expressed at approximately the same level in the transformed yeasts, as determined by ligand binding assay (data not shown). The above results were also verified by cotransforming the yeast host strain HF7c with the two hybrid vectors. In HF7c, the lacl reporter gene is under the control of a promoter different from that used to control the lacZ gene in SFT526. These two promoter share only GAL4 response elements in common; the rest of the promoter sequences differ significantly.

We next tested the effect of T3 analogs on activating the BD-TRa1(LBD) interaction. As shown in Fig. 6, the order of potency of each analog to induce β-galactosidase activity is consistent with previously determined affinity constant of binding of the ligands to the TR (23). Half-maximal activation was obtained at 10^{-8} M for Triac, 10^{-7} M for L-T3, D-T3, and 10^{-6} M for L-T4 (Triac < L-T3 < D-T3 < L-T4). These compounds did not affect the growth property of the yeasts. Effect of Ligand on the Interaction between the LBDs of TRa1 and RXRa in Vitro—The GST-RXRa fusion protein was used to investigate the effects of ligands on the interaction between the LBD of RXRa and TRa in vitro. Complexes with GST-RXRa were retained on glutathione-Sepharose, the beads were washed and pulled down by centrifugation, and associated proteins were analyzed by SDS-polyacrylamide gel electrophoresis and autoradiography. TRa1 was labeled with [35S]methionine by in vitro translation and incubated with GST (Fig. 7, upper panel, second lane) or a GST-RXRa fusion protein (third through sixth lanes) bound to glutathione-Sepharose beads, as indicated. 35S-Labeled TRa1 was specifically retained in the presence of GST-RXRa but did not bind to the GST control protein (second lane). Approximately 7.5% of the total input of TRa1 was specifically bound to the GST-RXRa fusion protein. Addition of T3 or 9-cis-RA increased the amount of 35S-labeled TRa1 that associated with GST-RXRa, and further increase was observed when both ligands were present.

Interaction Properties of TRβ1 and Their Mutant Receptors with RXRa—We next investigated the ability of TRβ1(LBD) to interact with RXRa(LBD). Similar to the results with TRα1 and RXRa, both ligand-independent (constitutive) and ligand-induced interactions were observed with TRβ1 and RXRa (Fig. 8). In addition, we also examined the heterodimerizing properties of specific mutant receptors, TRβ1(G345R) and TRβ1(I345R), which was isolated from a patient with resistance to thyroid hormone (24), has no detectable T3 binding activity because of a glycine to arginine substitution at amino acid 345 in the hormone binding domain.
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TRβ1∧422 is an artificial mutant receptor with 4 amino acids insertion in the 9th heptad region, which is known to be essential for heterodimerization with RXR (18). The ligand binding-defective mutant TRβ1(G345R) revealed the constitutive and 9-cis-RA-induced interaction but did not show the T3-induced interaction. Heterodimerization-defective mutant TRβ1∧422 failed to support both constitutive- and ligand-induced interaction in the yeasts (Fig. 8).

DISCUSSION

The TRs are believed to function as heterodimers with RXR and exert their physiological activities through binding to the thyroid hormone response elements in DNA (16). Dimerization of receptors through the specific interfaces that exist in the LBD has been demonstrated for the glucocorticoid receptor, estrogen receptor, and progesterone receptor (26–28). Evidence for heterodimer formation between TR and RXR (20) and TR homodimer formation (19) has been suggested based on TR/RXR interaction in cotransfection studies and gel mobility shift assay or cross-linking studies (11–13). To examine in detail the interaction between TR and RXR in solution and the effect of their ligands in vitro, we have established the yeast two-hybrid system as an in vitro approach to analyze the heterodimerization between the LBD of TR and RXR. In this report, we provide evidence that the TRs are able to heterodimerize with RXR in the absence of DNA, and T3 and 9-cis-RA augment this interaction in vivo, supporting the physiological importance of the heterodimer formation in solution.

LBDs of TRα1 and RXRa act as transcriptional regulators in mammalian cells when fused to the heterologous DBD of the transcription factors (29). Therefore, it is important to know whether Gal4BD-TRα1(LBD) or Gal4BD-RXRa(LBD) alone can activate the reporter gene in a ligand-dependent manner in the yeast system. If the ligand-induced activity of the reporter gene could be caused by activation of Gal4BD-TRα1(LBD) or Gal4BD-RXRa(LBD) by the ligands, the activities of the reporter gene do not exactly reflect the interaction of the two proteins. In Fig. 3, we showed that neither of Gal4BD-TRα1(LBD) nor Gal4BD-RXRa(LBD) alone activates the reporter gene, irrespective of the presence of ligands. Moreover, using pRXRa(LBD), which lacks Gal4AD, we further analyzed the capability of the TRα1(LBD)/RXRa(LBD) heterodimer to function as a ligand-dependent transcriptional activator in the yeasts. As shown in Fig. 3, a combination of Gal4BD-TRα1 and RXRa(LBD) did not activate the reporter gene even in the presence of ligands. These results indicate that neither TRα1(LBD) nor a combination of TRα1(LBD) and RXRa(LBD) confers ligand-dependent activation to the reporter gene in the yeast system. Therefore, it is concluded that the activity of the reporter gene indicates the reconstitution of the Gal4 molecule, allowing the measurement of the strength of interaction between TRα1(LBD) and RXRa(LBD).

Because the yeast two-hybrid system is extremely sensitive and can detect very transient interactions, we utilized the in vitro pull-down experiment as a second more stringent assay to confirm the ligand-induced heterodimerization seen in the yeast system. As shown in Fig. 7, it is demonstrated that the dimerization can occur in solution and that it is augmented by ligands in a pull-down experiment using the bacterially expressed RXRa fused to GST.

It has been shown in mammalian systems that cotransfection of a Gal4-RXR expression vector and an expression vector

![Fig. 7. In vitro interaction of TRα1 with RXRa.](image-url)

![Fig. 8. Interaction properties of T3 binding-defective mutant and heterodimerization-defective mutant TRβ1.](image-url)
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for the LBD of the TR can confer T₃ responsiveness to a promoter containing a Gal4 binding site (29). This experiment indicates that TR/RXR can form functional heterodimers in vivo in the absence of DBDs. Our results in the yeast system are consistent with the reported data in mammalian systems. In addition, augmentation of the TR/RXR interaction by T₃ analogs correlated with the biological potency and ligand affinity of thyroid hormone analogs (Triac > T₃ > T₄), suggesting a physiological importance of ligand-induced heterodimerization in solution.

In mammalian cells, the enhancement of T₃-dependent reporter gene activation by TR-RXR heterodimers is well established, and the binding of TR to thyroid hormone response elements is much more efficient in the presence of RXR. Herein, we provide more direct evidence that TR and RXR form heterodimers before DNA targeting in vivo, and ligand binding clearly enhances receptor associations with each other. Previous studies have shown that ligand binding induced conformational change in TR in solution (30–33). The structures of the LBD of RARα (34) and TRα (33) crystalized in the presence of their respective ligands revealed that helix 12 was aligned over the ligand binding pocket, in contrast to its position in unliganded receptors, in which it protrudes away from the LBD. In liganded receptors, hydrophobic residues within helix 12 face toward the pocket, perhaps contacting the ligand, whereas the negatively charged residues are exposed on the protein surface. Thus, as suggested by Renaud et al. (34), realignment of helix 12 over the ligand binding pocket when the receptor binds ligand may generate a novel surface for interaction with the partner proteins or bridging proteins. Ligand binding seems to stabilize protein-protein interactions that lead to high affinity DNA binding and trans-activation. Although it is clear that ligand induces conformational change in the DNA-bound receptors, the precise molecular mechanism by which the TRs regulate transcription in response to the binding of ligands remain enigmatic. Ligand-dependent heterodimerization of TR and RXR is involved, at least in part, in the ligand-induced gene activation.

It has been suggested recently that the DBD of TR and RXR can bind to a thyroid hormone response element sequence as a heterodimer in vitro, and a dimer interface found in the DBD has selective power for recognition of specific DNA interaction (36). On the other hand, we demonstrated that DNA binding is not necessary for heterodimer formation via the surface of the LBD, suggesting that several domains cooperate for forming heterodimers on target DNA in vivo. These results are consistent with the two-step hypothesis for binding of heterodimers to DNA (37). In the first step, TR would form solution heterodimers with RXR through their LBDs. In the second step, the DBDs, by virtue of their proximity, would be able to bind a high affinity site in DNA. Once bound to DNA, the receptors are capable of modulating transcription.

Since RXR plays a central role in mediating many hormonal signals, including retinoids, thyroid hormone, vitamin D₃ and peroxisome proliferator activators, ligand (T₃)-induced heterodimerization leads to an influence on other nuclear receptor signaling by squelching out the common partner, RXR. Recently, Chu et al. (25) reported that TR inhibits PPAR signaling by squelching out RXR. They observed that T₃ enhances the inhibition of PPAR activity by TR. Our results explain this phenomenon well, because T₃ increases the number of TR/RXR heterodimers, resulting in a decrease in the number of active PPAR-RXR heterodimers.

Recently the apparent hormone dependence was observed in an estrogen receptor dimerization experiment (26). Wang et al. (35) studied extensively estrogen receptor homodimerization using a yeast two-hybrid system. A particularly useful feature of the yeast two-hybrid system is the ability to study the heterodimerization activity of the various receptor forms. It would be interesting to analyze solution interaction among nuclear receptors including orphan receptors. This approach may lead to an understanding of the role of ligand in transcriptional activation by nuclear receptors.

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