Thyroid hormone plays important roles in development, differentiation, and metabolic homeostasis by binding to nuclear thyroid hormone receptors, which regulate target gene expression by interacting with DNA response elements and coregulatory proteins. We show that thyroid hormone receptors also are single-stranded RNA binding proteins and that this binding is functionally significant. By using a series of deletion mutants, a novel RNA-binding domain was localized to a 41-amino acid segment of thyroid hormone receptor α1 between the second zinc finger and the ligand-binding domain. This RNA-binding domain was necessary and sufficient for thyroid hormone receptor binding to the steroid receptor RNA activator (SRA). Although SRA does not bind directly to steroid receptors, it has been identified as a steroid receptor coactivator, and was thought not to be a coactivator for thyroid hormone receptors. However, transfection studies revealed that SRA enhances thyroid hormone induction of appropriate reporter genes and that the thyroid hormone receptor RNA-binding domain is important for this enhancement. We conclude that thyroid hormone receptors bind RNA through a novel domain and that the interaction of this domain with SRA, and perhaps other RNAs, enhances thyroid hormone receptor function.

Thyroid hormone 3,5,3′-triiodo-l-thyronine (T3) plays important roles in development, differentiation, and metabolic homeostasis. T3 action is mediated by thyroid hormone receptors (TRs), which belong to the nuclear receptor superfamily that includes receptors for steroids, retinoids, vitamin D, and numerous other ligands (1). Based upon similarities in structure and function, nuclear receptors can be divided into functional domains designated as A-E/F, which include a divergent N-terminal A/B domain that often contains a transcriptional activation function, a well conserved DNA-binding domain (C domain), a hinge region (D domain), and the C-terminal E/F domain that binds the ligand and interacts with various corepressor or coactivator proteins. TRs are encoded by two genes, Thra and Thrb, that produce several proteins through the use of alternate promoters and/or alternative splicing. The major functional TRs are denoted TRα1 and TRβ1. These proteins are highly conserved in sequence but are expressed at different levels in various organs and have distinct biological functions (2).

The ability to bind specific T3 response elements (TREs) in target genes is crucial for TR function. TRs bind to DNA constitutively, even in the absence of ligand, as heterodimers with retinoid X receptors (RXRs) (3) or possibly as homodimers (4, 5) or monomers (5, 6). TRs regulate gene expression essentially by functioning as scaffolding proteins; they serve as a nidus for the formation of protein complexes at the target promoter, which then regulate transcription. In the absence of T3, the conformation of the TR is such that it generally attracts a corepressor complex that has histone deacetylase activity (7, 8). In the presence of T3, the corepressor complex is released, and various coactivator complexes can be recruited. It is unclear how many distinct coactivator complexes exist or how many are required for T3 induction of gene expression, but the number of coactivator proteins identified is large and growing. A major coactivator complex contains histone acetyltransferase (HAT) and protein methyltransferase activities (9). This complex includes the steroid receptor coactivator family of p160 proteins, SRC-1 (10), SRC-2/TIF2/GRIP1 (11), and SRC-3/pCIP/ACTR/AIB1/TRAM1/RAC3 (12). The p160 proteins bind to other coactivators and also possess HAT activity, which serves to loosen chromatin structure and facilitate protein-DNA interactions (13, 14). A second coactivator complex, known as DRIP/TRAP, probably binds to the ligand-occupied receptor after the HAT complex. Numerous other coactivators have been described, and exactly where and when they function in transcriptional regulation is unclear. Steroid receptor RNA activator (SRA) is a steroid receptor coactivator that does not bind directly to steroid receptors, but probably functions as part of a complex with p160 proteins (15). Although most nuclear receptor coactivators are quite promiscuous in their action, SRA has been considered to be a specific steroid receptor coactivator, not a TR coactivator. The most intriguing aspect of SRA is that it seems to function as an RNA.

Herein we demonstrate that TRs are RNA-binding proteins. A novel RNA-binding domain was identified distal to the TR zinc fingers and proximal to the ligand-binding domain. TRs bind SRA in vitro and in cells, and SRA functions as a TR coactivator by interaction with this novel TR RNA-binding domain.

**EXPERIMENTAL PROCEDURES**

**Plasmids and Proteins**—Full-length mouse TRα1 (16) and rat TRβ1 (17) were expressed in Escherichia coli as glutathione S-transferase (GST) fusion proteins using the vector pGEX-KG (18). To maximize the recovery of full-length proteins, the constructs were further tagged with six histidines at their C termini (GST-TRα1-His6 or GST-TRβ1-His6), which then regulate transcription. In the absence of T3, the conformation of the TR is such that it generally attracts a corepressor complex that has histone deacetylase activity (7, 8). In the presence of T3, the corepressor complex is released, and various coactivator complexes can be recruited. It is unclear how many distinct coactivator complexes exist or how many are required for T3 induction of gene expression, but the number of coactivator proteins identified is large and growing. A major coactivator complex contains histone acetyltransferase (HAT) and protein methyltransferase activities (9). This complex includes the steroid receptor coactivator family of p160 proteins, SRC-1 (10), SRC-2/TIF2/GRIP1 (11), and SRC-3/pCIP/ACTR/AIB1/TRAM1/RAC3 (12). The p160 proteins bind to other coactivators and also possess HAT activity, which serves to loosen chromatin structure and facilitate protein-DNA interactions (13, 14). A second coactivator complex, known as DRIP/TRAP, probably binds to the ligand-occupied receptor after the HAT complex. Numerous other coactivators have been described, and exactly where and when they function in transcriptional regulation is unclear. Steroid receptor RNA activator (SRA) is a steroid receptor coactivator that does not bind directly to steroid receptors, but probably functions as part of a complex with p160 proteins (15). Although most nuclear receptor coactivators are quite promiscuous in their action, SRA has been considered to be a specific steroid receptor coactivator, not a TR coactivator. The most intriguing aspect of SRA is that it seems to function as an RNA.

Herein we demonstrate that TRs are RNA-binding proteins. A novel RNA-binding domain was identified distal to the TR zinc fingers and proximal to the ligand-binding domain. TRs bind SRA in vitro and in cells, and SRA functions as a TR coactivator by interaction with this novel TR RNA-binding domain.
In Vitro RNA-binding Assay—Purified GST and the GST-TR proteins were adjusted to 1 μg of protein per 30 μl of beads with dilution empty glutathione agarse beads. For each assay, 6 μl of the diluted beads were incubated with 200,000 cpm of a [32P]RNA probe in binding buffer (10 mM Tris, pH 8.0, 2.5 mM MgCl2, 100 mM NaCl, 0.5% Triton X-100, 2.5 mM dithiothreitol, RNase inhibitor (Roche Applied Science), and 0.5 μg of bovine serum albumin/μl) for 40 min at 4 °C with gentle rocking. The [32P]RNA probe was made by in vitro transcription using T3 or T7 RNA polymerase and α-[32P]UTP either from pBluescript KS(+) or pSCT-SRA that had been linearized by digestion with PvuII. After incubation, the beads were washed 4× with 100 μl of binding buffer, resuspended in 50 μl of RNase-free water, and transferred to scintillation vials for determination of radioactivity in a Beckman LS2800 liquid scintillation analyzer.

Commmunoprecipitation Assay and RT-PCR Analysis—CV-1 cells in 60-mm Petri dishes were transfected with either 6 μg of empty FLAG vector, FLAG-TRα1, or FLAG-TRβ1 using Lipofectamine/Plus according to the vendor’s protocol (Invitrogen). Cells were harvested 48 h post-transfection, and nuclear extracts were isolated using the reagent NE-PER (Pierce). The nuclear extracts were incubated with anti-FLAG M2 agarse (Sigma) at 4 °C for 2 h. After extensive washing, the communoprecipitated RNA was analyzed for SRA by RT-PCR. The RT-PCRs were performed by using a Qiagen one-step RT-PCR kit and the following conditions: 30 min at 50 °C, 15 min at 95 °C; 45 cycles of 1 min at 95 °C, 1 min at 60 °C, and 1 min at 72 °C; and a final step of 10 min at 72 °C. Products were visualized on 1.4% agarose gels by ethidium bromide staining. The SRA-specific primers used for RT-PCR were SRA RT-F, 5’-CGC GCC TGG AAG AAC CCG CCG C3’- and SRA RT-R, 5’-TAG GAG ATG GTG TTC GGT GAG TCT G3’.

Cell Culture and Transfection Assay—CV-1 cells were maintained in minimum essential media supplemented with 10% fetal bovine serum and 2 μg/ml gentamycin at 37 °C and 5% CO2. For transfection experiments, cells were split in 24-well plates 16 h before transfection and were grown in media with 10% charcoal-stripped fetal bovine serum. All transfections were performed using Lipofectamine/Plus reagents. CV-1 cells were cotransfected with pCDM-TRα1, pCDM-TRβ1, or pCDM-TRα1C1C2; T3-Renilla luciferase vector (Promega); and psCT-SRA or empty psCT (doses are described subsequently). After transfection, cells were cultured with or without 100 nM T3. Cell lysates were harvested 48 h later for analysis of firefly and Renilla luciferases with the Promega dual luciferase reporter assay system. Renilla luciferase was used to normalize for transfection efficiency.

RESULTS

TRs Bind to RNA through a Novel RNA-binding Domain—Because RNA-binding proteins commonly bind RNA with relatively low specificity, screening assays for RNA binding often utilize probes of arbitrary sequence (23). Therefore, we developed an RNA-binding assay in which purified GST fusion proteins adsorbed to glutathione agarse beads were incubated with a 32P-labeled 240-nucleotide RNA probe transcribed from PvuII-linearized pBluescript KS(+) with T3 polymerase. By using this assay, ~35% of the input RNA probe bound to GST-TRα1 (Fig. 2, bar 2), which was 10- to 20-fold greater than the amount that bound to GST (bar 1).

To identify the protein domain responsible for RNA binding, we tested a series of TRα1 truncation or deletion mutants (illustrated schematically in Fig. 1). As shown in Fig. 2, we found that the TRα1 ligand-binding domain (amino acids 162–410) is not involved in RNA binding, because this domain by itself has almost no RNA-binding activity (bar 3), and deletion of this domain from TRα1 does not impair RNA binding (bar 4). We next found that a fragment of TRα1 extending from the amino terminus through to the end of the second zinc finger (amino acids 1–110, denoted ABDN) also does not bind RNA (Fig. 2, bar 5). By a process of elimination, this suggested that the RNA-binding domain lies between the second zinc finger and the ligand-binding domain. This was confirmed, as this domain (amino acids 111–161, denoted DNA-binding domain C (DBDC)) possessed full RNA-binding activity (Fig. 2, bar 6).

In contrast to steroid receptors, the DNA-binding domain of TRs contains an extension carboxyl terminal to the zinc fingers.

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**Fig. 1. Schematic presentation of TR proteins.** TRβ1, full-length TRβ1. Functional domains are indicated as N-terminal domain (AB), DNA-binding domain (DBD), hinge region (unlabeled region immediately following the DBD), and ligand-binding domain (LBD). The protein contains 461 amino acids. TRα1, full-length TRα1. The DBD is subdivided into the zinc fingers (amino acids 50–110), a region containing the T region (111–127), and a region containing the A helix (128–151). The protein contains 410 amino acids. TRα1 DBD, TRα1 ligand-binding domain (amino acids 162–410); TRα1 LBD, TRα1 without the ligand-binding domain; TRα1ABDN, TRα1 N-terminal fragment terminating immediately after the second zinc finger; TRα1DBDC, the 51 amino acids immediately carboxyl terminal to the zinc fingers (the first 41 residues include the T region and A helix of the DBD, and the last 10 residues are the hinge region); TRα1C1, the 17 amino acids immediately after the zinc fingers that include the T region; TRα1C2, the 24 amino acids immediately following TRα1C1 that include the A helix; TRα1C3, hinge region (10 amino acids) of TRα1C1C2, regions C1 and C2 combined; TRα1C2C3, regions C2 and C3 combined; TRα1C1C2, TRα1 ligand-binding domain. This was confirmed, as this domain by itself has almost no RNA-binding activity (bar 3), and deletion of this domain from TRα1 does not impair RNA binding (bar 4). We next found that a fragment of TRα1 extending from the amino terminus through to the end of the second zinc finger (amino acids 1–110, denoted ABDN) also does not bind RNA (Fig. 2, bar 5). By a process of elimination, this suggested that the RNA-binding domain lies between the second zinc finger and the ligand-binding domain. This was confirmed, as this domain (amino acids 111–161, denoted DNA-binding domain C (DBDC)) possessed full RNA-binding activity (Fig. 2, bar 6).
To confirm the assignment of C1C2 as the RNA-binding domain, we tested the ability of poly(A) to compete well. We took advantage of these data to test the bound counts/min were determined. The proteins are defined in Fig. 1. The assay was performed in duplicate, and the results are representative of at least three experiments. Bars indicate standard deviations.

This extension includes previously described regions known as the T region and A helix (24, 25), and these lie within the DBDC fragment (Fig. 3). Therefore, we subdivided DBDC into three smaller fragments, denoted C1 (amino acids 111–127), C2 (amino acids 128–151) or C3 (amino acids 152–161). C1 contains the T region, C2 contains the A helix, and C3 contains the hinge region that separates the DBD from the ligand-binding domain. None of these fragments was capable of binding RNA (Fig. 2, bars 7–9). This led us to test the somewhat larger fragments C1C2 (amino acids 111–151) and C2C3 (amino acids 128–161), which revealed that C1C2 has full RNA-binding activity (Fig. 2, bar 10), but C2C3 does not bind RNA (bar 11). To confirm the assignment of C1C2 as the RNA-binding domain, we removed C1, C2, or C1C2 from intact TR1 and tested these deletion mutants for RNA binding. The results indicate that TR1ΔC1 has 75% of wild-type RNA binding (Fig. 2, bar 12), TR1ΔC2 has 25% (bar 13), and TR1ΔC1C2 does not bind RNA (bar 14). These data confirm that C1C2 (amino acids 111–151) accounts for the RNA-binding activity of TR1.

Because sequence analysis indicates that the RNA-binding domain C1C2 of TR1 is highly conserved in TRβ1 (80% identity), we also tested TRβ1 for RNA binding. As expected, TRβ1 bound RNA with activity comparable with TR1 (Fig. 2, bar 15).

RNA-binding specificity of TRα1—RNA-binding proteins commonly bind different RNA homopolymers with different binding specificities (26). Therefore, we tested the ability of non-radiolabeled poly(U), poly(C), poly(G), or poly(A) to compete with the radiolabeled RNA probe for binding to TRα1 (Fig. 4). The data indicate that all of the homopolymers except poly(A) compete well. We took advantage of these data to test whether TRα1 prefers to bind single- versus double-stranded RNA. We found that annealing poly(A) to poly(U) destroyed the ability of poly(U) to compete with the [32P]RNA probe, but mixing poly(A) with poly(G) had no effect upon competition by poly(G) (data not shown). These results suggest that TRα1 prefers to bind single-stranded RNA.

TRα1 binds to Steroid Receptor RNA Activator in Vitro and in Intact Cells—Steroid receptor RNA activator potentiates steroid hormone receptor transcriptional activity as an RNA transcript by an indirect mechanism that does not involve SRA-steroid receptor binding (15). Because TRs bind RNA, we tested whether TRs bind SRA. The interaction of TRα1 and SRA was first examined by using [32P]SRA as a probe in the in vitro RNA-binding assay. As shown in Fig. 5A, full-length TRα1 (bar 2), TRβ1 (bar 3), and the TRα1 RNA-binding domain C1C2 (bar 6) bound the SRA probe comparably well, whereas the TRα1 deletion mutants TRα1LBD, ABDN, and TRα1ΔC2, and TRα1ΔC1C2 had a very low affinity for SRA (bars 4, 5, 8, 9). These data confirm that TRs bind SRA through their RNA-binding domain, C1C2. To examine whether TRs bind SRA in cells, CV-1 cells were transfected with FLAG-TRα1, FLAG-TRβ1, or empty FLAG vector. Nuclear extracts were immunoprecipitated with anti-FLAG-conjugated agarose beads, and the RNA that coprecipitated was applied to an RT-PCR using SRA-specific primers. SRA was detected in the samples from cells expressing FLAG-TRα1 or FLAG-TRβ1, but not in the immunoprecipitate from cells transfected with empty FLAG vector (Fig. 5B). These data indicate that TRs also bind SRA in cells. It should be noted also that the RT-PCRs produced, in addition to the expected 680-bp product, a band of ~490 bp. Apparently, identical products were detected in cells by RT-PCR using the same primers in the original characterization of SRA (15). Whether this smaller band represents an
alternative splice product or the product of a closely related gene is not known.

SRA Functions as a Thyroid Hormone Receptor Coactivator—SRA has previously been cloned and characterized as a steroid receptor RNA coactivator that functions through an indirect mechanism possibly involving p160-SRA interaction (15). Because we found that TRs bind SRA, we examined whether SRA functions as a TR coactivator. Indeed, by cotransfection we found that SRA enhanced T3 induction of 8DR4-Luc (Fig. 6A). Coactivation was observed for the modest T3 induction because of endogenous TRs (Fig. 6, bars 1–4), as well as for cotransfected TRα1 (bars 5–8) or TRβ1 (bars 9–12). Similar results were obtained by using a second TRE reporter construct, 2×Pal-Luc, except that endogenous TRs did not support T3 induction from this TRE (Fig. 6B).

To determine whether the TR RNA-binding domain is required for SRA coactivation, we performed cotransfection experiments comparing wild-type TRα1 with TRα1ΔC2 (Fig. 7). With wild-type TRα1, SRA stimulated the T3 induction of luciferase from −40 units to −140 units (Fig. 7, bar 6 versus 8). However, with TRα1ΔC2, SRA stimulation only reached −80 units (Fig. 7, bar 12), even though TRα1 and TRα1ΔC2 had identical activities in the absence of exogenous SRA (bar 6 versus 10). These data suggest that the TR RNA-binding domain is important for coactivation by SRA.
DISCUSSION

Our in vitro RNA-binding assay revealed a novel RNA-binding domain in TRα1, which we denoted C1C2, consisting of a 41-amino acid segment located between the second zinc finger and the ligand-binding domain. The crystal structure of an RXR DBD-TRβ DBD dimer complexed with DNA has been solved, and this revealed that C1C2 includes the previously described T region and A helix (24, 25), as shown in Fig. 3. The T region is a connector between the zinc fingers and the A helix, which is an α-helix composed of 24 mostly charged residues. The A helix binds to the minor groove of DNA and, hence, can strengthen the major protein-DNA interactions formed through the zinc fingers. In fact, the A helix was first described in the orphan nuclear receptor nerve growth factor inducible gene B, where it was shown to be required for receptor monomer binding to DNA (24). TR monomers also can bind DNA (6), and in general, nuclear receptors that can bind DNA as monomers contain an A helix. In contrast, steroid receptors do not bind DNA as monomers and do not contain an A helix.

The A helix, which corresponds to our region C2, may be the most critical component of the C1C2 RNA-binding domain. Although C2 by itself is not capable of binding RNA, deletion of C2 resulted in the loss of ~75% of RNA binding in TRα1 (Figs. 2 and 5A). In contrast, deletion of C1 resulted in the loss of only ~25% of RNA binding. Interestingly, all-helical structures have also been found in various other RNA-binding domains (27). Therefore, we speculate that the α-helical nature of the A helix and possibly its charged character are critical for RNA binding of TR. In addition, we speculate that other nuclear receptors that contain A helix sequences also might be RNA-binding proteins. It is interesting to compare the sequence of the TR RNA-binding domain with the RNA-binding motifs of other RNA-binding proteins, such as SR, DEAD box, and ribonucleoproteins. There is no obvious strong sequence homology between C1C2 and these other proteins. However, C1C2 does appear to share some homology with DEAD box proteins, especially the DEAD box subfamily p72 and p68 (Fig. 8; Ref. 28). DEAD box proteins comprise a large family of RNA-binding proteins, some of which have helicase activity. They participate in many cellular events, including transcription, RNA splicing, nuclear export of RNA, translation, and RNA degradation (29). DEAD box proteins contain six short conserved motifs, but otherwise share very little sequence conservation. The limited homology between C1C2 and p68/p72 is most apparent around motif II, which classically participates in ATP binding but not substrate RNA binding. The significance of this homology is unclear. However, it is interesting to note that the p68/p72 proteins participate in transcriptional regulation; more specifically, they interact with estrogen receptor α, p160 coactivators, and SRA to enhance gene activation by estrogen (28). Thus, there is a functional similarity between these DEAD box proteins and the TR C1C2 domain.

Our transfection data strongly suggest that SRA is an RNA coactivator for TRs as well as steroid receptors. However, the mechanism of coactivation seems to differ, in that steroid receptors do not interact directly with SRA (15). We found that deletion of the C2 portion of the TR RNA-binding domain severely impaired but did not abolish the ability of SRA to function as a TR coactivator. This might simply reflect the fact that TRα1ΔC2 retains ~25% of wild-type RNA binding by in vitro assay, or it could suggest that SRA has an additional mechanism of action with TRs, such as the indirect effect through SRA-p160 protein interactions that seems to apply to steroid receptors. We were unable to interpret cotransfection data with the full RNA-binding domain deletion TRα1ΔC1C2, as this protein was completely non-functional (data not shown), suggesting that it is deficient as a TR for reasons unrelated to SRA. In any case, the mechanism(s) by which TR-SRA interactions enhance the transcriptional activity of T3 are not known. Because SRA interacts with the RNA-binding DEAD box proteins p72/p68 as well as SRC-2/TIF2/GRIP1 to enhance estrogen receptor α transactivation, SRA coactivation of TRs also might involve the formation of a complex with additional RNA-binding proteins.

As is typical of many RNA-binding proteins (23, 29), in vitro binding studies indicate that TRs bind RNA in a relatively promiscuous manner. Thus, homopolymers of poly(C), (U), or (G) all compete with the 32P–RNA probe, although poly(A) does not. An important question is how to resolve these data with the presumed need for TRs (or other RNA-binding proteins) to bind specific RNA molecules. Perhaps the RNA-binding specificity of TRs is controlled primarily by their location within the cell and the overall protein context of the TR ribonucleoprotein complex. However, it is possible that subtle preferences for binding to specific RNA sequences become important in vivo. The selection and characterization of RNAs that bind TRs with high affinity from a random sequence RNA pool could shed light on this question. In addition, it is plausible that TRs have important functional interactions...
with RNAs other than SRA. For example, although TRs are almost entirely nuclear, they do shuttle between the cytoplasms and nucleus (30), and nucleocytoplasmic shuttling proteins include hnRNPs and other RNA-binding proteins (31). In addition, the TRo primary transcript is subject to alternative splicing, and it is interesting to consider that TR proteins might regulate TR RNA splicing as part of a ribonucleoprotein spliceosome complex.

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An RNA-binding Domain in the Thyroid Hormone Receptor Enhances Transcriptional Activation
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