Functional Interaction between Oct-1 and Retinoid X Receptor*

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The retinoid X receptor (RXR) is a member of the nuclear hormone receptor superfamily and heterodimerizes with a variety of other family members such as the thyroid hormone receptor (TR),1 retinoic acid receptor, vitamin D receptor, and peroxisome proliferator-activated receptor. Therefore, RXR is supposed to play a key role in a ligand-dependent regulation of gene transcription by nuclear receptors. In this study, we have identified the octamer-binding transcription factor-1 (Oct-1) as a novel interaction factor of RXR. In vitro pull-down assays using RXR deletion mutants showed that the interaction surfaces were located in the region encompassing the DNA binding domain (C domain) and the hinge domain (D domain) of RXR. We also showed that RXR interacted with the POU homeodomain but not with the POU-specific domain of Oct-1. Gel shift analysis revealed that Oct-1 reduced the binding of TR/RXR heterodimers to the thyroid hormone response element (TRE). In transient transfection assays using COS1 cells, Oct-1 repressed the T3-dependent transcriptional activity of TR/RXR heterodimers, consistent with in vitro DNA binding data; however, transcriptional activation by Gal4-TR(LBD) (LBD, ligand binding domain), which lacks its own DNA binding domain but retains responsiveness to T3, was not influenced by Oct-1. These results suggest that Oct-1 functionally interacts with RXR and negatively regulates the nuclear receptor signaling pathway by altering the DNA binding ability of the receptors.

The steroid/thyroid hormone receptor superfamily is a large group of related transcriptional factors that control cellular differentiation, development, and homeostasis by direct interaction with distinct cis-elements in target genes (1, 2). This superfamily includes receptors for steroids, thyroid, vitamin D3, retinoids, and a large number of orphan receptors whose cognate ligands are still unknown (3). 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 (4). The complex carboxyl-terminal region of the receptors contains ligand binding, receptor dimerization, and putative transcriptional activation function (5). Members of the superfamily regulate transcription by binding to response elements containing two or more copies (often degenerate) of the consensus motif AGGTCA (6, 7). Recently it was shown that retinoic acid receptor, TR, VDR, and peroxisome proliferator-activated receptor form heterodimers with the RXR on bipartite hormone response elements composed of non-symmetrical head-to-tail tandem AGGTCA “half-sites” (8–10). More than half of the orphan receptors have been shown to heterodimerize with RXR (3). Thus, RXRs are supposed to play a key role in ligand-dependent transcriptional activity of nuclear receptors.

The mechanisms by which nuclear hormone receptors regulate target gene transcription are currently under intensive investigation. The ligand-activated nuclear receptors may promote formation of preinitiation complex of the basal transcriptional apparatus and facilitate transcription by RNA polymerase II. Recently, a number of nuclear receptor-associated proteins have been identified that interact with receptors and regulate their transcriptional activities. A nuclear receptor corepressor, N-CoR or a related factor SMRT, binds to unliganded receptors and acts as a transcriptional silencer of nuclear receptors (11–13). It has been shown that N-CoR and SMRT recruit mSin3 and mRPD3 that possess histone deacetylase activity and make the chromatin transcriptionally inactive (14). When ligands bind to receptors, the co-repressor complex dissociates, and a co-activator complex containing N-CoA1/SRC-1, CBP/p300, and p/CAF associates with the receptors (15–21). Interestingly, these complexes have histone acetyltransferase activity and make the chromatin unwind, resulting in the transcriptionally active state (22–24).

Although recent extensive studies have depicted a model of nuclear receptor action, it is still not enough to explain the divergent biological effect of nuclear hormone receptors in development, differentiation, and cell cycle regulation. Therefore, it is reasonable to speculate that a large number of novel factors may associate with nuclear receptors. By using a biochemical technique, we have identified the octamer-binding transcription factor-1 (Oct-1) as a novel interaction factor of RXR. Oct-1 is ubiquitously expressed and activates the octamer motif containing promoters which has been shown to be related to cell cycle regulation of the human histone H2B gene and the constitutive expression of small nuclear RNA genes (25–27). Oct-1 is a member of a family of transcription factors characterized by the presence of a bipartite DNA binding domain, the POU domain (28, 29). This POU domain consists of two conserved regions, a POU-specific domain and a POU homeodomain. Both subdomains have a helix-turn-helix motif and act
as the DNA binding domain but are also involved in protein-protein interactions. A number of transcription factors have been identified to interact with the POU domains of Oct-1 and/or Oct-2, e.g. TBP, TFIIIB, HMG2, and the lymphoid-spe-
sific transcriptional co-activator OBF-1 (30–34). Oct-2 has a highly similar POU domain to Oct-1 and is expressed in a B
cell-specific pattern and has a distinct transcriptional regul-
tory potential (35–37). In this study we have demonstrated a
novel interaction of RXR with Oct-1/2 through their DNA bind-
ing domains. The POU domain of Oct-1/2 has influenced the
RXR/TR heterodimers binding to thyroid hormone response
element (TRE). Furthermore, these interactions negatively
regulated the transcriptional activity of the TRE-containing
promoter.

EXPERIMENTAL PROCEDURES

Isolation of Interacting Proteins—Rat GH3 cDNA library was con-
structed using T7 expression phage and screened by a full-length hu-
man RXRs as a probe. Isolated clones were subcloned into pGEM 3 and
sequenced by Applied Biosystems 3300 autosequencer. [35S]Methi-
done-labeled proteins were produced using the T7 TNT-coupled system
(Promega), and their interactions with RXRs were confirmed by pul-
down experiment using matrix-bound glutathione S-transferase (GST)–
RXR. About 1 × 10⁶ clones were screened, and one clone that corre-
sponds to human Oct-1 cDNA containing amino acid residues 371–438
was confirmed as an interacting partner with RXR.

Plasmid Constructions—The Oct-1/2 expression vectors pcDNA3HA
Oct-1/2 were gifts from Dr. H. Singh (see Ref. 38). The in vitro tran-
scription and translation vector for Oct-1 p6His Oct-1 was from Dr.
R. G. Roeder (see Ref. 39), and pBS Oct-1 was from Dr. W. Herr (see
Ref. 26). The eukaryotic GST expression plasmid for Oct-1 POU do-
main, POU-homeodomain, and POU-specific domain were gifts from
Dr. van der Vliet (see Ref. 40).

The RXR and VDR cDNA were gifts from Dr. R. M. Evans (see Ref.
41) and Dr. D. O’Malley (see Ref. 42), respectively. To construct the full-length RXRs, TRα1 (43), and VDR cDNA were inserted in frame into
BamHI and EcoRI cloning sites of the pGEX-2T vector (Amersham
Pharmacia Biotech). The following oligonucleotides were used to am-
plify the full-length human RXR: forward primer, 5'-agatgctatAGT-
GGACCAACACGATTGCCG-3' and reverse primer, 5'-ggatcctACAC-
GTCCACTCAGGCA-3'; TRα1, forward primer, 5'-atggatccGACGAG-
GAAGACCAAGGAC-3', and reverse primer, 5'-atggatccTTAAGAT-
TCTGTATGCTCTC-3'; and VDR, forward primer, 5'-atggatccTTAAGG-
AGACATGGGCCC-3', and reverse primer, 5'-atggatccCTCAGGAGA-
CTATCCATGC-3'. AP-2 cDNA was a gift from Dr. R. Tjian (see Ref.
44). To construct the bacterial expression vector for GST fusion protein of
AP-2 cDNA, full-length AP-2 cDNA was inserted in frame into
EcoRI- and SalI-cloning sites of the pGEX-6P1 vector (Amersham
Pharmacia Biotech). The following oligonucleotides were used to am-
plify the full-length AP-2: forward primer, 5'-atggatccATGGCT-
GGAAAATGGAC-3', and reverse primer, 5'-atggatccTACTCTTCTGT-
GCTCAGC-3', TRα1 expression vector, pcDM TRα1 was described
previously (45).

The Pax2/TK luciferase gene contains two copies of a palindromic
TRE upstream of the thymidine kinase (TK) promoter in the PA3
luciferase vector (46). The rGH chloramphenicol acetyltransferase re-
porter plasmid that contains rat growth hormone promoter region span-
ing from -257 to +8 from the transcription start site was a gift from
D. D. Moore (see Ref. 47). To construct the mammalian expression
vector for Gal4 DBD fusion protein, PCR-amplified ligand binding do-
main of TRα1 was inserted in frame into BamHI- and SalI-cloning sites
of the pM vector (CLONTECH). The following oligonucleotides were
used to amplify the TRα1 LBD: forward primer, 5'-atggatccATGGC-
CATGGACTTGGTCTC-3', and reverse primer, 5'-atggatccTATCA-
CTTCTCAGC-3'. UAS4x TK luc reporter plasmid was gift
from Dr. R. M. Evans (see Ref. 48).

Transient Transfection and Reporter Assays—Cos1 cells were grown in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal calf serum, 100 units/ml penicillin G, and 0.25 mg/ml
streptomycin at 37 °C in 5% CO₂. Transfection was done in Cos1 cells
using the standard calcium phosphate procedure. Typically, 0.25 µg of
Pax2-driven luciferase reporter was co-transfected with 100 ng of the
indicated expression vectors. Cells were incubated for 12 h, and the
medium on the cells was replaced with fresh medium and 10⁻¹⁻° M T3 was
added. Cells were harvested after 12 h. β-Galactosidase activity was
measured by the method previously described using chlorophenol red-
β-naphthyl acetate as a substrate (49). Luciferase assays were per-
formed using the PicaGene Luciferase Assay System (Toyo Inki, Tokyo,
Japan). Luciferase activity was determined using Lumat LB9501
(Berthold, Bad Wildbad, Japan) and was expressed as relative
light units normalized to the β-galactosidase activity. Chloramphen-
ocoly transferase activities were measured as described previously (50)
and quantitated by PhosphorImager. Each transfection was conducted
in triplicate, and data represent the mean ± S.D. of more than three
individual experiments.

In vitro Transcription and Translation—Coupled transcription and
translation of Oct-1/2 RXR were carried out using a T7 TNT in vitro
transcription/translation kit (Promega) according to the manufacturer’s
instructions.

Overnight cultures of Escherichia coli BL21 carrying the recombi-
nant GST-RXRα and GST control plasmids were diluted 100-fold, cul-
tured for 5–6 h, and then induced with 0.1 mM isopropyl β-thiogalact-
opyranoside. After another 3 h, bacteria were collected and then
washed with PBS. Pellets were suspended in PBS containing 1% (v/v)
Triton X-100 and were then sonicated. Debris was removed by centri-
figulation. The fusion protein or the GST control protein was bound to
glutathione-Sepharose (Amersham Pharmacia Biotech) and extensively
washed with PBS containing 1% (v/v) Triton X-100. Matrix-bound pro-
teins were used for interaction experiments.

GST Pull-down Assay—Ten µl of GST-Sepharose beads containing 2–
5 µg of GST recombinant proteins were incubated with [35S]Mel-
nithionine-labeled proteins for 1 h at 4 °C. Complexes were then centrifuged,
three times in gel shift buffer, and separated by SDS-polyacryl-
amide gel electrophoresis. Radiolabeled signals were visualized and quantified using a PhosphorImager (Fuji BAS 1500). DNase 1 (5 units/µl) was added to the reaction in experiments shown in Fig. 1B.

Gel Retardation Assay—Synthetic oligonucleotides representing each
of the strands of the sequences were purified by polyacrylamide gel elec-
trophoresis, eluted, and annealed. Double-stranded oligonucleotides
were radiolabeled with dCTP (>3300 Ci/mmol; ICN, Costa Mesa, CA)
by fill in reactions using Klenow large fragment DNA polymerase.
Radiolabeled probes (10 fmol, 20,000–30,000 cpm) were then incubated
with binding proteins in 30 µl of reaction mixture containing 10 mM
KPO₄, pH 8.0 buffer, 1 mM EDTA, 80 mM KCl, 1 µg of poly(dI-dC), 1 mM
dithiothreitol, 0.5 mM MgCl₂, 5 µg of bovine serum albumin, 10 mM
glycerol, 1 mM phenylmethylsulfonyl fluoride, 2 mg/ml apotinin, 1 mM
leupeptin, 1 mM pepstatin. These reactions were incubated for 30 min
at room temperature and analyzed on a 5% non-denaturing polyacryl-
amide gel in TAE buffer. Electrophoresis was performed at a constant
voltage of 200 V at 4 °C in the same buffer.

Expression of Recombinant Proteins—To express the fusion proteins
with GST, PCR-amplified full-length RXRs cDNA or truncated frag-
ments were inserted in frame into BamHI- and EcoRI-cloning sites of
the pGEX-2TK vector (Amersham Pharmacia Biotech). Overnight
cultures of E. coli BL21 carrying the recombinant GST fusions or GST
control plasmid were diluted 100-fold, cultured for 5–6 h, and then
induced with 0.1 mM isopropyl β-thiogalactopyranoside. After another
3 h, bacteria were collected and washed with PBS. Pellets were sus-
pended in PBS containing 1% (v/v) Triton X-100 and sonicated. Debris
was removed by centrifugation. The fusion protein or the GST control
protein was bound to glutathione-Sepharose (Amersham Pharmacia
Biotech) and extensively washed with PBS containing 1% (v/v) Triton
X-100. Matrix-bound proteins were used for interaction experiments.

Interaction Experiments—In vitro translated 35S-labeled proteins
(1–2 µl) were incubated for 20 min at room temperature with glutathi-
one-Sepharose (10 µl) preloaded with GST fusion or GST control
protein in 250 µl of binding buffer (20 mM Tris-Cl, pH 7.8, 100 mM NaCl, 10%
glycerol, 1 mM dithiothreitol, 1 mM EDTA, 1 mM phenylmethylsulfonyl
fluoride, 1 mM leupeptin, 1 mM pepstatin, 2 mg/ml aprotinin) in the
presence or absence of 10⁻⁶ M of T3. After extensive washing with
binding buffer, bound proteins were eluted in 25 µl of Laemmli sample
buffer, boiled for 10 min, and resolved by sodium dodecyl sulfate-
polyacrylamide gel electrophoresis (10%) followed by autoradiography.
The results of the in vitro reactions and the amount of 35S-labeled
protein bound by GST fusions were visualized and quantified using a
PhosphorImager (Fuji BAS 1500).

RESULTS

Isolation of Oct-1 as a Interacting Protein with RXR—In order to iden-
tify the interacting protein with RXR, we used biochemical methods. Rat GH3 cell cDNA library was screened

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Oct-1 interacts with CD Domain of the RXR—To examine the interaction between Oct-1 and RXR, we used the matrix-bound fusion protein of glutathione S-transferase with RXR (GST-RXR) for in vitro pull-down assay. As shown in Fig. 1A, 

![Fig. 1](image)

Oct-1 Inhibits the Binding of TR/RXR Heterodimer to Hormone Response Element—The above results were of interest because the DNA binding domain of RXR has been reported to be involved in the formation of TR/RXR heterodimers on direct repeat DNA element. To characterize further interaction between Oct-1 and receptor heterodimers, we performed gel mobility shift assays using bacterially expressed and purified TR and RXR. The results shown in Fig. 3 indicated that addition of increasing amounts of bacterially expressed and purified GST-Oct-1 POU domain attenuated the binding of RXR/TR heterodimers to TRE (lanes 4 and 5), whereas addition of GST alone did not alter the binding (lane 3). The DNA binding activity of TR/RXR heterodimers was decreased by addition of GST-Oct-1 POU domain. These results showed that association of Oct-1 to RXR inhibited the RXR/TR heterodimers from binding to DNA elements.

Oct-1/2 Repress the Hormone-dependent Transcriptional Activity—To test the possible role of Oct-1 and Oct-2 in T3-dependent transcriptional activation, we performed transient transfection experiments in COS1 cells. Full length Oct-1 or Oct-2 expression vectors or empty expression vectors were co-transfected with a luciferase reporter plasmid containing two copies of the TR response element into COS1 cells. After 12 h, cells were harvested, and luciferase activities were determined. As shown in Fig. 4, both Oct-1 and Oct-2 repressed the T3-dependent transcriptional activity. In the presence of T3, co-expression of Oct-1 decreased the TR activity by approximately 40% and Oct-2 by approximately 30%. Co-expression of Oct-1/2 did not influence the amount of expression of TR when determined by T3 binding assay. Furthermore, Oct-1/2 had little effect on cytomegalovirus promoter (data not shown). These data suggest that Oct-1 can function as a co-repressor for the T3-dependent transcriptional activity of the TR/RXR heterodimers. We next examined the effect of Oct-1 expression on naturally occurring T3-responsive promoter. As shown in Fig. 4B, rat growth hormone promoter, which was one of a well characterized T3-responsive promoter, was inhibited in a similar manner, suggesting the physiological relevance of the inhibitory role of Oct-1 in T3-dependent transcription.

Oct-1/2 Also Interact with TR and VDR—Because highly

with GST fusion containing full-length human RXRs as a probe. Positive clones were transcribed by T7 RNA polymerase, translated into 

![Fig. 2](image)
conserved DNA binding domain of RXR was involved in the interaction, it is likely that other nuclear receptors could also interact with Oct-1. We next examined the interaction of other nuclear receptor family members with Oct-1 and Oct-2. As we expected, both 35S-labeled Oct-1 and Oct-2 associated to matrix-bound TR and VDR as well as RXR (Fig. 5A). In order to confirm the heterodimerization ability of GST fusion proteins with RXR, 35S-labeled RXR was incubated with matrix-bound GST fusions (lanes 11–15). Significant associations were detected with GST-TR and GST-VDR, whereas only weak association was detected with GST-RXR, consistent with previous data showing preference of heterodimerization of RXR. We next tested whether Oct-1 can interact with irrelevant DNA-binding transcription factor AP-2. As shown in Fig. 5B, 35S-labeled Oct-1 did not bind to the GST-AP-2, whereas significant amounts of 35S-labeled Oct-1 associated with GST-RXR, suggesting the specific interaction of Oct-1 with nuclear receptors.

Oct-1 Did Not Influence the Transcriptional Activation by Gal4-TR(LBD) Fusion Protein—We further investigated the effect of Oct-1 on transcriptional activation by Gal4-TR(LBD) which lacks its own DNA binding domain but retains responsiveness to T3. As shown in Fig. 6, Oct-1 did not influence the transcriptional activation by Gal4-TRα(LBD) fusion protein on upstream activating sequence luciferase reporter. These data are consistent with in vitro results showing that Oct-1 interacted with nuclear receptors via their DNA binding domain and inhibited their DNA binding activity. The DNA binding domain of nuclear receptor was required for the inhibitory effect of Oct-1.

![Fig. 3](image1)

**Fig. 3.** Oct-1 POU domain reduced the TR/RXR heterodimer binding to DR4 element. Bacterially expressed and purified RXR and TR were incubated with radiolabeled DR4 probe in the presence of 1 (lane 4) and 5 mg (lane 5) of GST-Oct-1 POU domain or 5 μg of GST alone (lane 3). DR4 element comprises AGGTCA direct repeat spaced by four nucleotides in a gel retardation assay. Positions of RXR/TR heterodimer, TR/TR homodimer, and TR monomer binding were indicated by arrows.

![Fig. 4](image2)

**Fig. 4.** Role of interaction in ligand-dependent activation by nuclear receptor. 0.1 μg of control vector, Oct-1, or Oct-2 expression vector were co-transfected into COS1 cells with 0.25 μg of Palz2TK luciferase (Luc) reporter (A) or rGHTRE TK chloramphenicol acetyltransferase (CAT) reporter (B) and 0.1 μg of TRα1 expression vector. Relative luciferase activities and chloramphenicol acetyltransferase activity in the absence (solid bar) or presence (hatched bar) of T3 (10−7 M) are presented after being normalized by the internal control β-galactosidase activities. Each transfection was conducted in triplicate, and data represent the mean ± S.D. of more than three individual experiments. HA, hemagglutinin.

![Fig. 5](image3)

**Fig. 5.** Both Oct-1 and Oct-2 interact with TR and VDR as well as RXR. A. 35S-labeled Oct-1, Oct-2, and RXRs were synthesized by in vitro translation and incubated separately with GST (lanes 2, 7, and 12), GST-RXR (lanes 3, 8, and 13), GST-TR (lane 4, 9, and 14), or GST-VDR (lanes 5, 10, and 15) bound to glutathione-Sepharose beads. 10% input from the 35S-labeled proteins is indicated (lanes 1, 6, and 11). B. 35S-labeled Oct-1 was separately incubated with GST (lane 2), GST-RXR (lane 3), and GST-AP-2 (lane 4) affinity matrices. 10% of 35S-labeled proteins added to the incubations is indicated (lane 1).

**DISCUSSION**

In this study, we have examined the interaction between RXR and POU domain of Oct-1. Our results indicated that Oct-1 interacted with nuclear receptors by direct protein-protein interaction and influenced the ligand-dependent transcriptional activity of nuclear receptors.

Recent data show that nuclear receptor co-activators such as SRC-1 and CBP/p300 recruit histone acetyltransferase, p/CAF, and pCIP to DNA-bound nuclear receptors and lead to the unfolding of the DNA-core histone complex (22–24, 51). In addition to co-activators, nuclear receptor co-repressor N-CoR and related factor SMRT, which were initially discovered through their ability to bind to unliganded nuclear receptors, recruit histone deacetylase (mSin3 and mRPD3) and result in the condensation of the chromatin structure to repress the basal transcription (14, 12, 52). Co-activator and co-repressor interact with the ligand binding domain and hinge domain of nuclear receptors, respectively. So far, little is known about potential role of the DNA binding region of nuclear receptors on transcriptional regulation. We report here the identification of the transcription factor Oct-1/2 as a binding protein for the DNA binding domain (LBD) of RXR and influence of ligand-dependent transcriptional activity of nuclear receptors. The highly conserved DBD of nuclear receptors could also serve as a site of interaction for co-regulator proteins, suggesting that Oct-1/2 function is analogous among the members of the nuclear receptors. Our results demonstrated that the POU homeodomain of Oct-1, which is known to form a complex with the herpes simplex virus transactivator VP16 (53), was involved in the interaction with RXR. POU homeodomains have been
promiscuous cross-talk between POU transcription factors and nuclear receptors can be expected. It would also be of interest to examine the role of nuclear receptors in the transcriptional activity of Oct-1 on the octamer-binding site.

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