Differential Interaction of Nuclear Receptors with the Putative Human Transcriptional Coactivator hTIF1*

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Hormonal regulation of gene activity is mediated by nuclear receptors acting as ligand-activated transcription factors. Intermediary factors interacting with their activation functions are required to mediate transcriptional stimulation. In search of such receptor interacting proteins, we have screened a human cDNA expression library and isolated a human protein that interacts \textit{in vitro} with transcriptionally active estrogen receptors (ER). Sequence analysis reveals that this protein is the human homolog of mouse TIF1 (transcription intermediary factor 1) shown to enhance nuclear receptor ligand-dependent activation function 2 (AF2) in yeast. We have characterized the nuclear receptor binding site on hTIF1 and shown that a region of 26 residues is sufficient for hormone-dependent binding to the estrogen receptor. As shown by point mutagenesis, the AF2 activation domain of ER is required for the binding of hTIF1 but not sufficient, since a short region encompassing the conserved amphipathic α-helix corresponding to this domain fails to precipitate hTIF1. We also demonstrate that hTIF1 association with DNA-bound ER requires the presence of estradiol. Finally, we show that the interaction of hTIF1 with receptors is selective since strong \textit{in vitro} hormone-dependent binding is only observed with some members of the nuclear receptor superfamily.

The estrogen receptor (ER) has been shown to recruit intermediary and associated factors, hTAFII30, also interacts selectively with the hormone binding domain of the estrogen receptor and appears to contribute to transcriptional activity \textit{in vitro}. However, the interaction was unaffected by the binding of either 17β-estradiol or antiestrogens such as 4-hydroxytamoxifen and was mapped to a region that is inactive in mammalian cells.

Other factors acting as bridging proteins are probably involved in transcriptional activation by nuclear receptors. Using \textit{in vitro} protein interaction assays or yeast two-hybrid systems with different nuclear receptor hormone-binding domains as bait, several factors that associate with activated receptors have been characterized. These include hRIP140 (23–26), mTIF1 (27), hTRIP1/mSUG1 (28, 29), several isoforms of SRC-1 (30–33), and CBP/p300 (34–37). Two other factors, namely N-CoR and SMRT, that interact with unliganded thyroid hormone and retinoic acid receptors, have been isolated and shown to act as transcriptional corepressors, which are released upon ligand binding (38, 39). In fact, it seems likely that these intermediary factors (activators or repressors) form a large family of molecules with differential binding sites or affinities for various nuclear receptors.

We report here the cloning of a human factor, which interacts \textit{in vitro} with transcriptionally active estrogen receptors and appears to be the homolog of mouse TIF1 (27). We have characterized the interaction of hTIF1 with nuclear receptors and shown that a short region is sufficient for hormone-dependent binding to various members of the superfamily. However, it appears that this interaction is selective, since \textit{in vitro} hormone-dependent interaction with hTIF1 is not observed with receptors belonging to the glucocorticoid receptor subclass.
**EXPERIMENTAL PROCEDURES**

Isolation of hTIF1 cDNA—A random-primed human fetal liver Agt11 expression library (CLONTECH) was screened using the *in vitro* ³²P-labeled GST-AF2 probe, as described previously (24). A single positive clone (clone 8) containing a 675-base pair insert was isolated, screened again and purified. This insert was then randomly labeled with ⁴¹PdCTP (Megaprime DNA labeling system, Amersham) and used to screen a sub-library constructed from NIH 3T3-human breast cancer cell cDNA library in zAP11 (24). Several positive clones were isolated and plBluescript phagemids containing the inserts of interest were excised in *E. coli* with coinfection with the R408 helper phage. Inserts were then sequenced by the dyeoxy chain termination method using a Sequenase version 2.0 DNA sequencing kit (U. S. Biochemical Corp.). The 5′-end of the cDNA was obtained by reverse transcription-PCR using total RNA from ZR75–1 cells and specific primers generated from the mTIF1 cDNA sequence (27).

*Recombinant Vectors*—The recombinant vectors allowing expression in *E. coli* of GST-TF1B, GST-AF2 (wild-type and mutants), or the plasmid used for *in vitro* labeling of hRIP140 (pBRIP140) were described previously (24), GST-AF2-AD was constructed by inserting a PCR-generated 96-nucleotide fragment encoding residues 545–558 of mouse ER into the EcoRI site of pGEX-2TK (Pharmacia Biotech Inc.). The nine GST-hTIF1 constructs (wild-type and mut1–mut8) encoding different domains of hTIF1 receptor binding site fused to glutathione S-transferase were constructed by inserting the corresponding DNA fragments produced by PCR from the original clone 8 into the EcoRI site of pGEX-2TK. GST-hRIP140, which encoded a fusion between GST and residues 752–1158 of hRIP140, was generated by inserting a BamHI/BglII fragment from pBRIP3 (24) into the BamHI site of pGEX2TK. Human receptor cDNAs and their cognate ligands used in this study correspond to ER (estradiol), RARα (retinoic acid; RA), RXRa (9-cis-RA), VDR (vitamin D₃), TRα1 (T₃), GR (dexamethasone), PR-A and B (R5020), AR (DHT), MR (aldosterone), COUP-TFI, COUP-TFI, and HNF4 (EMBL data bank). All of them were in pSG5 vector (except MR, which is in pGEM4) under the control of the bacterial T7 polymerase promoter.

**GST Pull-down Assay**—*In vitro* binding assays were essentially as described (24). Briefly, ⁴¹P-labeled proteins (receptors or interacting proteins) were cell-free-synthesized using the TNT lysate system (Promega) and incubated overnight at 4 °C with bacterially expressed and purified GST, GST-AF2, GST-AF2-AD, GST-hRIP140, or GST-hTIF1 fusion proteins in the presence of the cognate ligands at micromolar concentrations. Protein interactions were analyzed by SDS-PAGE followed by fluorography (Amplify; Amersham) and quantified using a PhosphoImager (Fuji BAS1000). In some cases, the gel was stained with Coomassie Brilliant Blue (Bio-Rad) prior to fluorography, to visualize the GST fusion proteins present in each track.

**Gel Shift Assay**—The double-stranded oligonucleotide corresponding to the vitellogenin A₂ estrogen response element (ERE) (40) was ³²P-labeled using Klenow enzyme. Binding reactions (20 μl) were performed in the presence or absence of ligands (1 μM) on ice for 1 h using 4 μl of ER-primed reticulocyte lysate and 30 μg of purified GST or GST fusion proteins in 10 mM Tris, pH 7.5, 75 mM KCl, 5% glycerol, 0.5 mM EDTA, 0.5 mM dithiothreitol, 0.1 μg/μl poly(dI-dC), plus protease inhibitors. The labeled ERE (50 fmol) was then added, incubated for 20 min at room temperature, and analyzed on a 5% polyacrylamide gel.

**RESULTS**

Cloning of hTIF1 and Interaction with GST-AF2 Probes—To isolate cDNAs encoding putative mediators of the ligand-dependent activation function of nuclear receptors, we have applied the strategy previously used to clone hRIP140 cDNA (24). We have screened a human fetal liver random-primed cDNA expression library with the ³²P-labeled probe containing the mouse ER hormone binding domain fused to glutathione S-transferase (GST-AF2 probe). We have isolated a single positive clone clone containing a 251-base pair acid peptide, which interacted directly with the wild-type GST-AF2 probe in an estrogendependent manner (Fig. 1A). The binding characteristics of the protein encoded by this clone were similar to those previously observed for hRIP140 and hRIP160 (23), i.e. lack of interaction (i) in the absence of ligand (ii) in the presence of the antiestrogen 4-hydroxytamoxifen (iii) with transcriptionally defective mutants in the conserved amphipathic α-helix (Fig. 1A).

![FIG. 1. In vitro interaction of hTIF1 with GST-AF2 probes. A, far Western blot analysis of hTIF1 protein encoded by the positive clone (clone 8). After the first round of screening, the single positive colony corresponding to clone 8 was purified and plated again. After transfer onto nitrocellulose, the lift was cut into four pieces and hybridized as described previously (24), with ³²P-labeled GST-AF2 probes. We used either wild-type probe in the presence of 1 μM estradiol, 1 μM 4-OH-tamoxifen, or solvent alone (Control) or mutant probe in the presence of estradiol. B, in vitro expressed ³²S-hTIF1 was incubated in a batch assay with GST (lane 2) or wild-type GST-AF2 (lanes 3–6) bound to glutathione-Sepharose beads. Incubations were done overnight at 4 °C in the presence of 1 μM estradiol (E), 4-hydroxytamoxifen (O), or ICI 164384 (I) or in the absence of ligand (C). Lane 1 corresponds to 25% of labeled hTIF1 input. Bound proteins were analyzed by SDS-PAGE and fluorography. The positions of molecular size markers are indicated at the right. C, effect of mutations in the conserved amphipathic α-helix on the binding of hTIF1 to GST-AF2. Cell-free-synthesized hTIF1 was incubated with GST or GST-AF2 either wild-type (Wild-type), M547A/L548A mutant (547/548), L543A/L544A mutant (543/544), or E546A mutant (546) in the presence of estradiol (E), 4-hydroxytamoxifen (O), or in the absence of ligands (C).](http://www.jbc.org/content/12063/7/12063/F1.large.jpg)
library a clone coding for an hTIF1 isofrm with the same insertion of 34 amino acids already described for the mouse protein (27) suggesting that this variant form, perfectly conserved between the two species, could be of physiological importance.

Using GST pull-down experiments with a 90-kDa peptide in vitro expressed from clone 16, we confirmed that hTIF1 interaction with wild-type GST-AF2 was strongly increased (−14-fold) by estradiol (Fig. 1, panel B, lanes 3 and 4, and panel C) but not by the antiestrogens 4-hydroxytamoxifen or ICI164,384 (lanes 5 and 6). This association was also dramatically reduced by various mutations in the conserved amphipathic α-helix that abolish AF2 transcriptional activity (7). When either of two pairs of hydrophobic residues (547/548 or 543/544) or the negatively charged glutamic acid residue at position 546 were mutated, the effect of estradiol on hTIF1 binding was reduced to less than 2-fold (Fig. 1C). In these GST pull-down assays, hTIF1 binding to wild-type GST-AF2 in the presence of estradiol (57% of input; 14-fold increase versus control; Fig. 1C) was very similar to that of hRIP140 (56% of input; 12-fold increase versus control; data not shown).

Binding Sites Characterization—The initial hTIF1 cDNA clone 8 isolated from the library encoded a 225-amino acid peptide (Fig. 2B). This fragment overlapped the region between residues 539 and 750 in the mouse protein, which was shown to be the minimal domain sufficient to interact with RXRα in the yeast two-hybrid system (27). To define more accurately the border of the nuclear receptor binding site (NRBS) on the hTIF1 molecule, we generated by PCR a GST-hTIF1 vector and several deletion mutants (mut1–mut8; Fig. 2C). We then tested their ability to interact with 35S-labeled in vitro translated ER in GST pull-down experiments. As shown in Fig. 2C, strong estradiol-dependent interaction (19-fold increase over control) was observed with GST-hTIF1. Deletion of 102 residues from the COOH terminus (mut1) affected only moderately this interaction (10-fold induction in the presence of estradiol). By contrast, when the hTIF1 fragment was reduced to 96 (mut2) or 73 amino acids (mut3), hormone-dependent binding was totally abolished, indicating that an important motif was localized in the last 27 residues of mut1. Starting from mut1, we then generated five other mutants (mut4–mut8). In GST pull-down assays, hormone-inducible binding of ER was retained with mut4–mut7 but not with mut8. Together, these results indicate that the minimal NRBS on hTIF1 is localized between residues 716 and 741 that the 11 amino acids at the NH2 terminus of mut7 are necessary for ER binding. As shown in Fig. 2D, this sequence exhibits some homologies (conservation of Ser and Leu residues) with sequences in the two NRBS of RIP140 (25).

Since the integrity of the AF2 activation domain core plays a crucial role in the binding of hTIF1 to ER (Fig. 1, A and C), we have examined whether the region of the receptor encompassing this domain was sufficient to support in vitro interaction with hTIF1. The region from amino acid 525 to 556 was fused to GST and used to precipitate labeled hTIF1. As shown in Fig. 3 (lane 5), no specific binding was obtained, even though the level of GST-AF2-AD was slightly higher than those of GST-AF2 wild-type or mut. This suggests that other regions of the

**Fig. 2. Characterization of the receptor binding site.** A, schematic representation of hTIF1 with the different domains identified in the molecule. The position of the NRBS is represented by the solid box. The percent conservation in these domains between mouse and human is indicated between parentheses. The regions of more than 50 residues that are perfectly conserved between the two species are represented by solid boxes. The arrowhead indicates the position of the internal insertion. B, predicted amino acid sequence of hTIF1 clone 8 isolated by protein-protein interaction with GST-AF2 probe. Residues that are different in the mouse protein are shown above the sequence. The minimal receptor binding site is underlined. C, schematic representation of the GST-hTIF1 fusion proteins. The dotted lines represent the position of the deduced minimal NRBS. The length and coordinates of the hTIF1 moiety are indicated. The presence (+) or absence (−) of hormone-dependent interaction of ER with the corresponding GST-hTIF1 is also indicated. The autoradiogram of pull-down experiments performed with the longest GST-hTIF1 fusion protein using in vitro labeled ER in the presence of 1 μM estradiol (E), 4-hydroxytamoxifen (O), or ICI164,384 (I), or in the absence of ligands (C) is also shown. Similar amounts of the different hTIF1 fusion protein were used as judged by Coomassie Blue staining of the gel prior to fluorography. D, sequence alignment between hTIF1 NRBS and sequences from RIP140 sites 1 and 2 (25). Positions in the corresponding sequences are indicated, and conserved residues are underlined.
Interaction of hTIF1 with Nuclear Receptors

FIG. 3. The AF2-AD core is necessary but not sufficient to interact with hTIF1. A, schematic representation of the four proteins used in the experiment shown in B. B, pull-down experiment using GST, GST-AF2 or GST-AF2-AD fusion proteins to precipitate 35S-labeled hTIF1 as described under “Experimental Procedures.” The experiment was done either in the absence of ligand (C) or in the presence of 1 μM estradiol (E) or 4-hydroxytamoxifen (O). However, since similar results were obtained in all conditions for GST, GST-AF2mut, or GST-AF2-AD, we only show the track in the presence of estradiol (lanes 2, 5, and 6). The lower part of the figure corresponds to the Coomassie Blue staining of the gel prior to fluorography. The positions of both precipitated labeled hTIF1 and that of the different fusion proteins are indicated on the right. The positions of molecular size markers are indicated at the left.

ER ligand binding domain are probably required to generate the complete binding site.

Since in vitro binding characteristics of hTIF1 (i.e. the requirement for hormone and for an intact AF2 activating domain) were similar to those obtained for hRIP140 (23–25), it was possible that these two potential transcriptional coactivators contact the same region of the hormone binding domain. To investigate this possibility, we performed pull-down experiments to test the ability of ER to contact simultaneously hTIF1 and hRIP140. We used GST-hTIF1 or GST-hRIP140 to precipitate, respectively, labeled hRIP140 or hTIF1 bound to ER. As shown in Fig. 4A, labeled ER efficiently bound (almost 50% of input) to GST-hTIF1 in an hormone dependent manner (compare lanes 3 and 4). We then preincubated increasing amounts of labeled hRIP140 with ER before precipitation with GST-hTIF1 (lanes 5–9) and looked for the formation of a ternary complex GST-hTIF1-ER-hRIP140. Whereas binding of ER was still clearly observable, specific precipitation of hRIP140 in these conditions was almost undetectable since for the highest amount of hRIP140 used (lane 9), less than 2% of input material was bound. Moreover, most of this binding was not ER-mediated since a similar amount of hRIP140 was precipitated by GST-hTIF1 in the absence of ER (lane 10). Identical results were obtained when we used GST-hRIP140 fusion protein in the presence of estradiol, the ER-ERE complexes migrated faster than in the absence of ligand or in the presence of 4-hydroxytamoxifen (lanes 1–3), probably reflecting a different conformation of the receptor. Addition of purified GST-hTIF1 did not modify the position or intensity of the retarded bands in the absence of ligand or in the presence of 4-hydroxytamoxifen (compare lanes 1 and 3 to lanes 4 and 6). By contrast, in the presence of estradiol, we observed a shift in the position of the ER-ERE complex and a slight decrease in the intensity of the band (compare lanes 2 and 5). This shift was reproducibly obtained even when ER was produced in COS-1 cells or in baculovirus-infected insect cells (data not shown), and it probably corresponds to the formation of an heteromeric complex of GST-hTIF1 and ER on DNA. We have checked that this altered migration was not due to a modification in the estradiol binding capacity of ER or in the dissociation kinetics of hormone after binding of GST-hTIF1 (data not shown). Moreover, similar results were obtained when we used GST-hRIP140 fusion protein (Fig. 5, lane 8), thus confirming previous results showing
that, in DNA-dependent assays for protein-protein interaction, the binding of hRIP140 to ER (25) or to RAR/RXR heterodimers (43) was also ligand-dependent. By contrast, no retardation was observed with GST-TFIIB (Fig. 5, lane 10), emphasizing the specificity of this effect.

**Interaction of hTIF1 with Other Nuclear Receptors**—To study the specificity of hTIF1 interaction with nuclear receptors, we have tested whether other members of the superfamily were able to interact with GST-hTIF1 in the presence of their cognate ligands. As shown in Table I, vitamin D3 (VDR), thyroid hormone (TR), retinoid X (RXR), and retinoic acid (RARα) receptors bound to GST-hTIF1 in the presence of their cognate ligand (more than 12% of input). Specific binding (which represents less than 2.5% of input in the absence of ligand) is increased by more than 8-fold in the presence of hormone. In addition, as observed for ER in the presence of antiestrogens, the interaction of RARα was not significantly increased in the presence of the antagonist Ro 41–5253 (44). Moreover, we have checked that chimeric proteins found in acute promyelocytic leukemia and resulting from the fusion of RARα to promyelocytic leukemia protein (PML) in t(15;17) or promyelocytic leukemia zinc finger protein (PLZF) in t(11;17) (45) also retained a strong retinoic acid-dependent interaction with GST-hTIF1 (data not shown).

By contrast, when we evaluated the interaction of the other steroid receptors, namely glucocorticoid (GR), progesterone (PR form A and B), androgen (AR), and mineralocorticoid (MR) receptors, we observed a weak interaction (less than 5% of input) with GST-hTIF1 even in the presence of the cognate hormone. A slight increase in binding to GST-hTIF1 was, however, detectable with MR in the presence of aldosterone. In addition, we analyzed the association of GST-hTIF1 with two orphan receptors that bind DNA as homodimers and behave as transcriptional repressor (COUP-TFII) or activator (hepatocyte nuclear factor 4; HNF4) and observed very low specific interaction representing less than 3% of input (data not shown). Other transcription factors such as c-Fos, c-Jun, CREB, E1A, or MyoD, shown to bind CBP (46), also failed to interact specifically with hTIF1 in vitro (data not shown). Together these results indicate that, in our experimental conditions, hTIF1 selectively interacts in a ligand-dependent fashion only with specific members of the nuclear receptor superfamily.

**DISCUSSION**

Using a protein-protein interaction assay, we have searched for human transcription intermediary factors able to bind the hormone-dependent activation domain of the estrogen receptor. We have isolated a single cDNA clone, which appears to be the human counterpart of mTIF1, a murine factor isolated using a yeast genetic screen based on the capacity to stimulate RXRγ activity (27). This factor, initially characterized as a fusion protein with the equivalent of the human proto-oncogene B-RAF (41), exhibits interesting structural features. Several domains (a RING finger, B box fingers, a coiled-coil domain, a plant homeodomain finger, and a bromodomain) potentially involved in protein-DNA or protein-protein interactions (47–49) have been identified. Most of the consensus residues in these domains are conserved between mouse and human, and the overall conservation between the two species is around 93% (for comparison, another potential coactivator for nuclear receptors, hTRIP1/mSUG1 is 99.3% conserved) (29). The region of hTIF1 located in the middle of the molecule is one of the most divergent from mTIF1, and it also contains the potential alternative splicing site generating an isoform with a 34-amino acid insertion perfectly conserved between the two species.

We have shown that a short sequence of 26 residues is sufficient for the *in vitro* binding of hTIF1 to the estrogen receptor in the presence of estradiol. This domain presents significant homologies with the two receptor binding sites characterized on hRIP140 (25), suggesting that they could contact the same interface on nuclear receptors. On the other hand, our results also indicate that the α-helix of ER, which contains the AF2 activation domain, is required but not sufficient for the interaction between the receptor and hTIF1. This suggests that other parts of the hormone binding domain participate in the formation of the binding interface and is apparently not in accord with several reports, which have shown that the amphipathic α-helix from mouse RXXα or β (10, 50) and chicken TRα (9) can autonomously transactivate when fused to a DNA-binding domain. However, it should be noted that, in all three cases, transcriptional activation was lower than that obtained with the full-length hormone binding domain, suggesting that only suboptimal configurations of the activation domain are generated in such chimeric proteins and thus possibly explaining the undetectable *in vitro* association with hTIF1. Moreover, it has been shown in the case of mSUG1 that the AF2-AD, while essential, was also not sufficient for an efficient interaction in yeast two hybrid experiments (29).

Recent studies based on the determination of the crystal structure of different nuclear receptor hormone binding domains (11–13) have demonstrated that in the unliganded
RXRa, the amphipathic helix that contains the AF2 activation domain points away from the core of the molecule. In the liganded RARγ, this helix (H12) is folded back and residues in the core of AF2-AD establish contacts both with the ligand and other part of the HBD such as helix 4. It seems therefore likely that helix 12 alone, while necessary, is insufficient for binding proteins such as hTIF1 and that the interface is rather a tridimensional structure generated upon conformational change of the HBD (involving the swing of H12). In agreement with this hypothesis, it has been shown that a point mutation in H4 of RARγ (K264A) or RXRa (R307A) decreases the in vitro interaction of mTIF1 (51).

The hypothesis that different parts of the HBD participate in the formation of an active binding site for putative transcriptional coactivators could explain our observation showing that only a subgroup of nuclear receptors (ER, TR, RAR, RXR, and VDR) exhibit hormone-dependent interaction with hTIF1. The structure of the AF2-AD core is so well conserved among all members of the superfamily that the binding specificity probably involves other regions of the HBD. It is striking to note for instance that the important position corresponding to the above-mentioned Lys-264 in RARα (K264A) or RXRα in vitro. However, it is obvious that, in the nucleus, additional factors could allow simultaneous binding of these two proteins. It is also possible that the recruitment of these receptor interacting proteins is sequential, one acting after the other. Depending on the cell type and/or the promoter context, specific binding of only one type of intermediary factor could take place on the receptor, and such a mechanism could be involved, at least partly, in tissue-specific regulation of gene expression. Further studies such as gene inactivation will be necessary to define the exact role of these factors in transcriptional control by nuclear hormone receptors.

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**Note Added in Proof**—While this manuscript was under review, Le Douarin et al. reported the mapping of the minimal NRBS of mTIF1 to the same region and demonstrated that mTIF1 exerts a transcriptional repressing activity in mammalian cells (Le Douarin, B., Nielsen, A. D., Garnier, J. M., Ichinose, H., Jeanmougin, F., Losson, R., and Chambon, P. (1996) EMBO J. 15, 6701–6715).

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