Tuberous Sclerosis Gene 2 Product Modulates Transcription Mediated by Steroid Hormone Receptor Family Members*

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Tuberous sclerosis (TSC) is a genetic disorder that results in the development of hamartomatous lesions in a variety of organ systems. Both the prevalence of the disease and the often devastating consequences of these tumors pose a serious health and medical care problem. The disease has been mapped to two distinct genetic loci in humans, and although the genes (TSC1 and TSC2) for both loci have recently been cloned, their function remains an enigma. Data presented here demonstrates that TSC2 protein can bind and selectively modulate transcription mediated by members of the steroid receptor superfamily of genes. These data place TSC2 into a growing list of nuclear receptor coregulators and strengthen the expanding body of evidence that these coregulators may play critical roles in cellular differentiation.

Tuberous sclerosis (TSC) is an autosomal dominant neurocutaneous disorder associated with the development of hamartomatous lesions in a wide variety of tissues, including skin, kidney, brain, eye, lungs, and heart (1). The birth frequency has been estimated at approximately 1 in 6000 (2). Pathologically, TSC is classified as a disorder of cellular migration, proliferation, and differentiation. The tumors associated with TSC are diagnostically distinct, very seldom progress to malignancy, but often have very devastating consequences. The most classical are those that occur in the brain, where they frequently cause epilepsy, mental retardation, autism, and/or attention deficit disorders (1, 3). The relatively high prevalence and serious consequences of TSC make it an important health concern both here in the United States and throughout the world.

TSC has been genetically linked to two loci in humans (4). About 60% of TSC cases are sporadic, but in families it has autodominant inheritance with high penetrance. TSC was first linked to chromosome 9q34 in 1987 (5), and this locus was autodominant inheritance with high penetrance. TSC was first linked to chromosome 9q34 in 1987 (5), and this locus was termed TSC1. Later studies identified a second locus on chromosome 16p13 (6) that was called TSC2. The focal nature of TSC tumors suggests that TSC1 and TSC2 may function as tumor suppressor genes, and this is further supported by evidence for inactivating TSC2 germ line mutations and loss of heterozygosity at the TSC2 locus in TSC-associated tumors.

The genes for both TSC1 and TSC2 have recently been cloned. Both were cloned by consortiums of investigators sequencing the specific regions of chromosome 9 (7) and chromosome 16 (8) to which TSC1 and TSC2 had been mapped, respectively. TSC1, or hemartin as it was named by the authors, encodes a cDNA of 8599 base pairs containing a 1164-amino acid open reading frame. TSC2, or tuberin, also encodes a rather large protein of 198 kilodaltons as specified by a cDNA of 5474 base pairs containing a 1784-amino acid open reading frame. The lack of any obvious structural similarities between TSC1 and TSC2 would suggest their relationship to tuberous sclerosis is either through some functional homology or through some converging function.

Very little is known about the function of TSC1. The large TSC2 protein appears fairly inert, with a small leucine zipper domain at the amino end of the protein and a region of homology to Rap1 GTPase-activating protein (GAP) domain at the carboxyl end. Two groups have recently used regions containing the GAP domain as bait in yeast two-hybrid screens in an effort to establish a functional relevance for it. Xiao et al. (9) identified a protein, rabaptin-5, that could bind TSC2 and stimulate hydrolysis of Rab5. Their conclusion was that TSC2 functions as a Rab5GAP, which could negatively regulate Rab5-GTP activity in endocytosis. In a second yeast two-hybrid study, Tsuchiya et al. (10), using a similar region of the carboxyl terminus of TSC2, found this region to contain transcriptional activation domains within it. These authors went on to characterize two transcriptional activation domains in the carboxyl terminus of TSC2 but are unable to clearly demonstrate an association of TSC2 with DNA or even a strong association with the nucleus of transfected cells. Together these studies suggested TSC2 may be an integral component of some signal transduction pathway, and defining that pathway might be critical to understanding TSC2’s role in TSC.

In the present study, a cDNA for TSC2 was serendipitously cloned as a modulator of transcription events mediated by the retinoid X receptor (RXR). Evidence is further presented for TSC2 interaction with and modulation of several steroid receptor family members. These data suggest a possible avenue for TSC regulation of cellular differentiation and perhaps a mechanism for tuberous sclerosis.

**EXPERIMENTAL PROCEDURES**

**Yeast Transcription Assays—**The yeasts expression vectors (YEpRXR, YEppPPAR, YEppRAR) and yeast reporter vectors (YEpRXRE, YEpPPRE) were generated as described previously (11). Yeast transcription assays were also performed essentially as described previously (11). Briefly, prototrophic yeast transformants were grown under selection to an *Aₖ₆₃₃* of 0.5–1.0, cells were plated (100 μl) into 96-well plates, ligand was added (±10 mM CuSO₄), and plates were incubated...
at 30 °C. After 22 h, chloroform readings were taken, the cells were lysed, o-nitrophenyl-β-D-galactopyranoside substrate was added, the plates were incubated at 37 °C for 30 min, stop buffer (1 M Na₂CO₃, 0.5% Antifoam A) was added, and the plates were read at 420 nm. Normalized β-galactosidase values were determined from triplicate samples as a measure of transfection efficiency with a rat brain cDNA library (a generous gift of Dr. Robert Dickson, University of Kentucky) inserted upstream of the alcohol dehydrogenase promoter in the pYAD-ley yeast expression plasmid. Transfected yeast were plated onto yeast nitrogen base plates supplemented with 2% glucose, 20 μg/ml adenine sulfate, 20 μg/ml histidine, 10 μM CuSO₄, 0.5 μM all-trans-retinoic acid and 0.06 mg/ml 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside. Blue colonies were picked, grown in liquid culture, and assayed for β-galactosidase activity using a standard o-nitrophenyl-β-D-galactopyranoside-based in vitro transcription assay (11). CDNAAs from clones expressing >1.5-fold activity (with respect to the parental RXR/Reporter yeast strain) were rescued and examined by restriction analysis for insert size and by dideoxy sequencing for DNA sequence identity.

**Gel Mobility Shift Assays—**Receptor expression plasmids used in the mammalian assay were constructed by directionally cloning the specific receptor cDNA gene downstream from the constitutive RSV-long terminal repeat promoter in the pRSV eukaryotic expression plasmid (13). Response element reporter plasmid constructions were generated by inserting synthetic oligonucleotides into the polylinker located 5’ of the inducible thymidine kinase promoter in the previously described pBlu promoter vector (14). The integrity of all constructs was verified by DNA sequencing.

Mammalian cotransfections were performed essentially as described (11, 14). Briefly, HepG2 cells, grown as a monolayer in Dulbecco’s modified Eagle’s medium containing 10% (v/v) fetal calf serum, were plated at 70% confluence 24 h prior to transfection. The recombinant DNA constructs were transiently transfected into HepG2 cells by calcium-phosphate coprecipitation. After 6 h, medium was removed from transfected cells, cells were washed, and each receptor tested in triplicate and at seven incremental ligand concentrations (10⁻⁹ to 10⁻³ M). After 38 h, the cells were washed with phosphate-buffered saline, lysed and luciferase activities in cell extracts were assayed on a Dynatech luminometer. To determine the efficiency of transfection and to standardize expression of activity, a pRSV-β-galactosidase activity plasmid was included in all cotransfections and analyzed as described previously (11, 14). Each transfection was run in triplicate, and the average luciferase activity for the three independent transfections was normalized to the average β-galactosidase activity (average luciferase activity/average β-galactosidase activity/min).

**Gel Mobility Shift Assays—**Gel mobility shift assays were performed essentially as described previously (15). Briefly, a double-stranded synthetic oligonucleotide (5’-TAAGGGTTACCGAAAGTTCACTCGCAT-3’) coding for the DR5 response element motif found in the promoter region of the βRAR gene (16) and containing 5’-overhang SalI restriction endonuclease sites was radioactively labeled with [α-³²P]dCTP using a standard Klenow fill in protocol (17). Labeled response element was incubated with yeast extracts lacking or expressing the proteins indicated in the figure legend, and the response element/protein complexes were distinguished by electrophoretic separation on nondenaturating polyacrylamide gels and autoradiography.

**TSC2 Pull-down Assays—**A TSC2-GST fusion construct, spanning nucleotides 3452–5525 of the published TSC2 sequence, was created by subcloning a blunt-ended XbaI/XbaI fragment into the Smal/XbaI sites in the poly-linking site of the pGEX-4T bacterial expression vector (Amersham Pharmacia Biotech). TSC2-GST fusion proteins were isolated essentially as described previously (18, 19). Briefly, BL21 cells transfected with the TSC2-GST fusion construct were grown to log phase (0.5 OD at 600 nm) at room temperature, induced for 3 h with isopropyl-β-D-thiogalactopyranoside, and harvested. Cell pellets were incubated in TES buffer (50 mM Tris, pH 7.5, 40 mM EDTA, 25% sucrose, 100 μg/ml leupeptin and aprotinin) to which 0.1 mg/ml lysozyme was added, followed by SDS-polyacrylamide gel electrophoresis. The presence of unique selection markers on each plasmid was confirmed through appropriate selection in yeast, and plating of the library onto yeast minimal medium plates containing 5-bromo-4-chloro-3-indolyl-β-D-galactopyranoside, a chromogenic substrate for β-galactosidase, permitted selection of those cDNAs capable of turning on the transcription of the β-galactosidase gene. Plates were analyzed for the presence of β-galactosidase activity, and an initial screening of 150,000 trans-
formsants yielded 10 positive colonies from which plasmid DNA was rescued and partial cDNA sequence information was obtained. Sequence data were analyzed for homology to known genes using standard National Center for Biotechnology Information Entrez BLAST search programs, and several of the sequences revealed matches to previously described genes. To our surprise, DNA sequence analysis and homology search data suggested that none of these proteins were members of the steroid receptor superfamily. The most interesting of these were three genes that showed greater than 95% homology to portions of previously described genes, all of which have been implicated in some way or another in differentiation or carcinogenesis events. The closest any came to a transcription factor was clone pADcRB-1, which demonstrated 98% homology to the recently published sequence for rat TSC2 (Fig. 1). The pADcRB-1 clone expressed complete identity with the last 44 amino acids of the carboxyl end of the rat TSC2 protein. This region was homologous to one previously reported as containing transcriptional activation potential (10), although the exact mechanism or significance of this observation was unclear.

These data suggest TSC2 may directly interact with RXR in mediating transcription. To examine this possibility, a full-length TSC2 clone was used to determine the influence of TSC2 protein on transcription mediated by several steroid receptor family members. Glucocorticoid receptor, a ligand-dependent homodimerizing receptor, as well as the RXR heterodimerizing family members. To explore the logical possibility that TSC2 is mediating its effects through direct associations with receptors, TSC2 was initially examined for its effects on receptor-DNA complex formation in gel mobility shift assays. The results from these studies were somewhat inconclusive. Although TSC2 did not bind DNA directly and did not appear to directly change the mobility of the shift complexes, it often distinguishably changed the amount of shift complex, a process that is illustrated for the ligand-dependent homodimeric RXR complex and the ligand-independent heterodimeric RXR-RXRα complex (Fig. 3A). Both complexes, generated by mixing yeast-expressed receptor proteins with a 32P-labeled DR5 response element motif derived from the promoter of the RARα gene, are substantially enhanced by the presence of yeast-expressed pADcRB-1 protein, but lack any significant change in mobility.

One reasonable explanation for these data would be that TSC2 was binding receptors and, in effect, recruiting them to the response element, but the TSC2-receptor interactions were not strong enough to withstand the electrophoresis process. In an attempt to address this possibility the somewhat milder receptor pull-down assay was tried. A 660-amino acid encoding cDNA fragment from the carboxyl terminus of the human TSC2 gene was subcloned into a pGEX bacterial expression vector. A GST-TSC2 fusion protein was generated in *Escherichia coli* and purified using glutathione-agarose (GA). GA-bound GST-TSC2 and GA-bound GST were mixed with baculovirus extract expressing either a recombinant RXRα protein, a recombinant VDR protein, or native extract. Unbound material was washed away, and bound material was electrophoresed and analyzed in Western blots by probing with antisera to the respective receptors (Fig. 3B). In this assay, TSC2 appears to definitively pull down receptor protein, demonstrating that these receptors are capable of directly interacting with TSC2 protein.

These data, coupled with the transcription data, suggest TSC2 might be directly bridging receptors with basal transcription machinery, serving as some type of scaffold for receptors and other basal machinery transcription factors. Over the past 4 years a variety of putative steroid receptor coregulators have...
baculovirus expressing recombinant hRXR
rose and glutathione-agarose-bound GST-TSC2 (expression vector. GST-TSC2 protein was purified on glutathione-nondenaturing electrophoresis and analyzed by autoradiography. B, TSC2 pull-down assays with baculovirus expressed recombinant hRXRα and hVDR protein. A cDNA sequence encoding the carboxyl 680 amino acids of the TSC2 protein was fused to GST in a pEX bacterial expression vector. GST-TSC2 protein was purified on glutathione-agarose and glutathione-agarose-bound GST-TSC2 (lanes 1, 3, 4, and 6) or glutathione-agarose-bound GST (lanes 2 and 5) were incubated with extracts of S9 cell infected with wild type baculovirus (lanes 1 and 4), baculovirus expressing recombinant hRXRα (lanes 2 and 3), or baculovirus expressing recombinant hVDR (lanes 5 and 6). Bound proteins were analyzed in a Western blot using antisera specific for RXRα (lanes 1–3) or VDR (lanes 4–6). Control lanes 7 and 8, identifying the baculovirus expressed receptor proteins, include the baculovirus extracts Western blotted from the same gel and probed with their respective antisera. Specific locations for RXRα and VDR proteins are as indicated.

been cloned and characterized (28–39). The majority of these were cloned using steroid receptor ligand binding domains as bait in a yeast two-hybrid assay and, unlike TSC2, are generally found to be universally repressors or activators of steroid receptor-mediated transcription. The functional significance of these proteins has recently been demonstrated in a series of articles ascribing a chromatin remodeling function through interactions with acetylases and deacetylases, enzymes responsible for attaching and removing acetyl groups from histones. Furthermore, several of these proteins have also been shown to complex with other transcriptional repressors as well as the transcription scaffolding protein Sin3 (40–42). Of possible relevance here is the observation that these interactions directly affect a mammalian histone deacetylase (HDAC1), which has been implicated in cell cycle and differentiation events (43–46). Even more recently, Anzick et al. (47) reported the direct correlation of breast and ovarian cancer with the overexpression of AIB1, a member of the SRC-1 family of steroid receptor coregulators. These coregulators, similar to what was seen here for TSC2 with PPAR and VDR, enhance ligand-dependent transcription. It is attractive to hypothesize that TSC2, and perhaps TSC1, function in a similar manner and therefore serve as important regulators of cellular differentiation in a variety of steroid receptor-sensitive tissues. This would be especially relevant for the RXR and RAR members, whose expression has been directly correlated with cellular differentiation events and whose tissue distribution closely resembles that of TSC2 and TSC1 (7, 8, 24). Ongoing studies are currently directed at establishing the associations between TSC2, basal transcription machinery, and histone acetylation.

Alternatively, the available data do not completely eliminate a role for TSC2 in nuclear transport or cytoplasmic signaling events. Circumstantial data supporting a role for TSC2 in nuclear transport include: 1) cytological staining evidence that demonstrates a localization of TSC2 to the perinuclear spaces (10) and 2) the presence of a Rap1GAP- and/or Rab5GAP-like domain in the carboxyl end of the TSC2 protein (8, 9). Although these specific G-proteins are not thought to be involved with nuclear transport, the strength of the activity studies for these proteins is not overly convincing. What the data do support is the presence of a GAP activity associated with TSC2, and it has been clearly demonstrated that at least one small GTPase (Ran) is associated with nuclear transport (48, 49). Finally, nuclear receptor activity has also been correlated with a variety of intracellular signaling events (50–55). The majority of these incorporate specific phosphorylation events, which ultimately facilitate either the activation or repression of nuclear receptor-mediated transcription. A more discriminating and thorough examination of TSC2 associations with cytosolic and nuclear structures may be highly informative with respect to what exactly TSC2 is doing in the cell.

In summary, the above data for the first time assign a functional correlation between TSC2 and steroid receptor coactivator. These data offer a hypothetical mechanism for TSC2 effects on differentiation and a pathway for hemartoma development during critical cellular differentiation events. It is known that disruption of RXR-mediated signaling pathways critically affect embryonic survival and development (25, 26), and the data presented here suggest that TSC2 could be involved in modulation of these pathways. This modulation event could conceptually result in tissue-specific ligand-dependent growth abnormalities that would not be expressed as a transformed phenotype but rather as benign outgrowths whose growth and development are constrained by natural hormone and gene expression events dictated by development. Future evaluations of TSC1’s association with cell signaling events, and particularly RXR-mediated transcription, may help to clarify the accuracy of the hypothesis.

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