Silencing Mediator of Retinoid and Thyroid Hormone Receptors and Activating Signal Cointegrator-2 as Transcriptional Coregulators of the Orphan Nuclear Rector Nur77*

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For the orphan nuclear receptor subfamily that includes Nur77 (NGFI-B), Nurr1, and NOR-1, no transcriptional coregulators have been identified thus far. In this report, we found that Ca2+/calmodulin-dependent protein kinase IV enhances Nur77 transactivation in co-transfections either alone or in synergy with AF2-dependent coactivator ASC-2, whereas corepressor silencing mediator for retinoid and thyroid hormone receptors (SMRT) is repressive. Interestingly, Nur77 interacted with SMRT but did not directly bind ASC-2, and accordingly, the putative AF2 core domain of Nur77 did not affect the Nur77 transactivation. SMRT harbors transferable repression domains that associate with various histone deacetylases. Surprisingly, histone deacetylase inhibitor trichostatin A was unable to block the repressive effect of SMRT while dramatically stimulating the Nur77 transactivation. These results suggest that SMRT and ASC-2 are specific coregulators of Nur77 and that SMRT may dynamically compete with a putative adaptor molecule, which links ASC-2 to Nur77, for the identical binding sites within Nur77 in vivo.

The nuclear receptor superfamily is a group of ligand-dependent transcriptional regulatory proteins that function by binding to specific DNA sequences named hormone response elements in the promoters of target genes (for a review, see Ref. 1). The superfamily includes receptors for a variety of small hydrophobic ligands, such as steroids, T3, and retinoids, as well as a large number of related proteins that do not have known ligands referred to as orphan nuclear receptors. Functional analysis of nuclear receptors has shown that the ligand-binding domain (LBD)† exhibits ligand-dependent transcriptional activation function referred to as activation function-2 (AF2). Notably, this region has been shown to play a critical role in mediating transactivation by serving as a ligand-dependent interaction interface with many different coactivators (for reviews, see Refs. 2 and 3). Transcriptional coactivators either bridge transcription factors and the components of the basal transcriptional apparatus and/or remodel the chromatin structures. In particular, cAMP-response element-binding protein (CREB)-binding protein (CBP) and its functional homologue p300, steroid receptor coactivator-1 (SRC-1) and its family members, and activating signal cointegrator-2 (ASC-2) were shown to be essential for the activation of transcription by a large number of regulated transcription factors, including many members of the nuclear receptor superfamily (2, 3). Interestingly, SRC-1 and its family member activator of thyroid and retinoic acid receptors (ACTR) along with CBP and p300 were recently shown to contain histone acetyltransferase activities and associate with another histone acetyltransferase protein p300/CBP-associated factor (PCAF) (2, 3). In contrast, nuclear receptor corepressor (N-CoR) and its homologue silencing mediator of retinoid and thyroid hormone receptors (SMRT) harbor transferable repression domains that can associate with various histone deacetylases (HDACs) (2, 3). These results are consistent with the notion that acetylation of histones destabilizes nucleosomes and relieves transcriptional repression by allowing transcription factors access to recognition elements, whereas deacetylation of the histones stabilizes the repressed state.

A distinctive structural feature of the AF2-dependent coactivators is the presence of LXXLL signature motifs (i.e. NR box) (4, 5). The AF2 core region (helix 12) was recently shown to undergo a major restructuring upon ligand binding, forming part of a “charged clamp” that accommodates coactivators within a hydrophobic cleft of the receptor LBD through direct contacts with these NR boxes (2). Interestingly, the N-CoR/SMRT nuclear receptor interaction motifs exhibited a consensus sequence of [(ILx)xxI/H/I] (i.e. CoLNR box, in which H indicates hydrophobic residues) (6, 7), which was able to interact with specific residues in the same receptor pocket required for coactivator binding. Thus, discrimination of the subtle differences between the coactivator and corepressor interaction helices by the nuclear receptor AF2 core may provide the molecular basis for the exchange of coactivators for corepressors with ligand-dependent formation of the charged clamp that stabilizes NR box binding and interacts with the CoRNR box helix.

SHARP, SMRT/HDAC1 associated repressor protein; ROR, retinoid-related orphan receptor; COUP-TF, chicken ovalbumin upstream transcription factor.
The orphan nuclear receptors Nur77 (NGFI-B), Nur1, and NOR-1 constitute the NGFI-B subfamily within the nuclear receptor superfamily (for a review, see Ref. 8). Nur77 was originally isolated as an immediate early gene rapidly expressed in response to serum or phorbol ester stimulation of quiescent fibroblasts. Other diverse signals, such as membrane depolarization and nerve growth factor, also increase Nur77 expression. Inactivation of a Nur77-related protein results in agenesis of mesencephalic dopamine neurons (9). Nur77 is also involved in the regulation of apoptosis in different cell types. It is rapidly induced during apoptosis of immature thymocytes and T cell hybridoma (10, 11), lung cancer cells treated with synthetic retinoid (12), and prostate cancer cells treated with different apoptosis inducers (13, 14).

Calmodulin (CaM), the most ubiquitous and abundant Ca2+-binding protein in cells, is an essential protein that serves as a receptor to sense changes in calcium concentrations and, in this fashion, mediates the second messenger role of this ion (for a review, see Ref. 15). Calcium binds to CaM by means of a structural motif called an EF-hand, and a pair of these structures is located in both globular ends of the protein. CaM binds to and activates target enzymes. These Ca2+/CaM-dependent protein kinases (CaMKs) include CaM kinase kinase, CaMKI, and CaMKIV, which are phosphorylated and activated by CaM kinase kinase, and CaMKII. In particular, CaMKIV is a monomeric multifunctional enzyme that is expressed only in sub-anatomical portions of the brain, T lymphocytes, and postmeiotic male germ cells. CaMKIV is present in the nucleus of the cells in which it is expressed and has been implicated in the regulation of transcription of a number of genes including those encoding interleukin-2, members of the immediate early gene family such as c-fos; tumor necrosis factor receptors; the neurotrophin brain-derived neurotrophic factor (BDNF); an Epstein-Barr virus gene involved in the switch to the lytic cycle called BZLF1; and orphan members of the steroid receptor superfamily such as retinoic-acid-related orphan receptor (ROIR) and chicken ovalbumin upstream transcription factor (COUP-TF) (15). However, the only direct substrates for CaMKIV involved in transcription that have been defined to date are CREB, cAMP response element modulator (CREM), and the NFκB component p65 (16–18), although CBP has also been indirectly implicated as a possible substrate (19).

In this work, we show that SMRT and ASC-2 are transcriptional coregulatory proteins of Nur77. We further present experimental evidence that CaMKIV stimulates the Nur77 transactivation, likely through modulation of various functional aspects of SMRT and ASC-2. Coupling of these two distinct signaling pathways (i.e. CaMKIV and Nur77) may play an important role in a subset of tissues that express both Nur77 and CaMKIV, such as brain and T lymphocytes.

EXPERIMENTAL PROCEDURES

Plasmids—The polymerase chain reaction-amplified fragments for Nur77AF2, Nur77-TRAP2, the SMRT residues 1074–1291 and 1299–1495 (i.e. SMRT-D/N and SMRT-D/C, respectively), the SMRT residues 1660–1478 (i.e. SMRT-DJs), and SMRT-Dm and SMRT-DmJs, which are identical to SMRT-D (the SMRT residues 1660–1495) and SMRT-DJs, respectively, except for mutations in the CoRNR motifs, were subcloned into EcoRI and XhoI restriction sites of the B42 fusion vector pJG4-5, the in vitro translation and mammalian expression vector pcDNA3, the LexA fusion vector pEG20PL, and the glutathione S-transferase (GST) fusion vector pGEX4T1 (Amsersham Pharmacia Biotech). Expression vectors for Nur77, ASC-2; constitutively active forms of CaMKI, CaMKII, and CaMKIV; E1A and E1A(AΔ2–36); Gal4 fusions to Nur77, ASC-2, ASC-2AD2/3, and SMRT-D; VP16 fusions to SMRT-D and Nur77; B42 fusion to SMRT-D; LexA fusion to the LBD of Nur77 and Nur77 to SMRT-D; LexA fusion to SMRT-D, were cotransfected into CV-1 cells, and the resulting nuclear extracts were subjected to gel shift analysis in the presence of Dr. Dean Edwards at University of Colorado Health Sciences Center); and blotted with polyclonal antibody against Nur77 (Santa Cruz Biotechnology, Santa Cruz, CA) as described previously (24).

The Yeast β-Galactosidase Assay—The cotransformation and β-galactosidase assay in yeast were done as described previously (24). For each experiment, at least three to six independently derived colonies expressing chimeric proteins were tested.

GST Pull-down Assays—Equal amounts of GST alone or GST fusions to SMRT-D, SMRT-D/N, SMRT-D/C, and ASC2-2C, expressed in E. coli, were purified, were bound to glutathione-Sepharose 4B beads and incubated in reaction buffer (20 mM NaCl, 25 mM Hepes [pH 7.9], 20% glycerol, 0.2 mM EDTA, 1 mM dithiothreitol, and 1.5% bovine serum albumin) with labeled Nur77 expressed by in vitro translation by using the TNT-coupled transcription-translation system with conditions as described by the manufacturer (Promega, Madison, WI). Specifically bound proteins were eluted from beads with 40 mM reduced glutathione in 50 mM Tris (pH 8.0) and were analyzed by sodium dodecyl sulfate-polyacrylamide gel electrophoresis and autoradiography as described previously (24).

RESULTS

Stimulation of the Nur77 Transactivation by CaMKIV—CaMKIV has recently been found to stimulate transactivation by a subset of orphan nuclear receptors such as ROR and COUP-TF (15). These results led us to examine whether CaMKIV similarly modulates the Nur77 transactivation. In CV-1 cells, coexpressed CaMKIV stimulated the Nur77 transactivation with two different reporter constructs driven by upstream Nur77 binding sites (23) (Fig. 1A). NBRE was iden-
Coregulators of Nur77 Transactivation

SMRT as a Transcriptional Co-repressor of Nur77—While examining other known coregulatory proteins of nuclear receptors, we found that SMRT directly interacts with Nur77. SMRT-D encodes the C-terminal subregion of SMRT (i.e. the SMRT residues 1060–1495) that contains two CoRNR boxes (6, 7) as summarized in Fig. 3A. SMRT-Dm is identical to SMRT-D except for mutations in both CoRNR motifs ((L/I)XXH/I), where H represents hydrophobic residues, to AXXA that abolished interactions with thyroid hormone receptor β and retinoic acid receptor α in the GST pull-down assays as expected (results not shown). SMRT-D, but not SMRT-Dm, fused to transcriptional activation domain B42 further stimulated the constitutive transcriptional activities directed by the LexA fusion to the LBD of Nur77 in yeast (Fig. 3B). The Nur77-interacting region was further localized to SMRT-D/C (i.e. the SMRT residues 1292–1495) that contains the second CoRNR motif. The B42 fusion to the LBD of Nur77 also stimulated transcriptional activity by the LexA fusion to SMRT-D. Similar results were also obtained with the mammalian two-hybrid-based assays (Fig. 4A). In addition, the full-length Nur77 and its LBD alone, produced and radiolabeled by in vitro translation, specifically bound the GST fusion to SMRT-D, SMRT-Dm, and SMRT-D/C (Fig. 4B and results not shown). Consistent with the yeast results (Fig. 3B), however, SMRT-D/C, but not SMRT-D/m, showed specific interactions with Nur77 under more stringent conditions (i.e. 100–150 mM NaCl instead of 20 mM) (results not shown). Notably, Nur77 did not show any interaction with GST fusions to ASC2-2C and other ASC-2 fragments (Fig. 4B and results not shown). Confirming the functional significance of these interactions, cotransfected SMRT repressed the Nur77 transactivation, either in the absence or presence of CaMKIVc, in a dose-dependent manner (Fig. 4C and results not shown). Interestingly, SMRT-D, but not SMRT-Dm, was also sufficient to repress the Nur77 transactivation. Notably, SMRT-Dm still exhibited significant repression, suggesting that SMRT-D may contain other cryptic receptor or Nur77 binding sites. In addition, the deletion of 17
Dynamic Interplay between Coregulators of Nur77—We have recently demonstrated that CaMKIV results in a novel translocation of SMRT from the nucleus to the cytoplasm (18). Accordingly, αSMRT-mediated immunoprecipitates of cells cotransfected with expression vectors encoding Nur77 and SMRT retained Nur77 less efficiently in the presence of coexpressed CaMKIV (Fig. 2A). In addition, the Nur77 transactivation was tremendously increased in the presence of 100 nM TSA, an inhibitor of HDAC (Fig. 2B), as expected from the previously suggested role of SMRT as an adaptor molecule (2, 3) between HDAC and target transcription factors such as Nur77. Interestingly, the TSA-stimulated level of the Nur77 transactivation was impaired by cotransfected SMRT in a dose-dependent manner. Under this condition, it was noted that SMRT-D was a much stronger inhibitor (Fig. 2B) than was SMRT-Dm (Fig. 2A). These results suggest that SMRT may function as a CaMKIV-responsive, indirect coactivator of Nur77—mediated transactivation of Nur77 (22, 25–28) (Fig. 2A). It is noted that CaMKIV also potentiates the autonomous transactivation function of ASC-2 (22), the autonomous transactivation function of ASC-2 is expected to be essential for the action of ASC-2 (22, 28). Based on the results with CBP-neutralizing viral oncoprotein E1A and a mutant protein E1AΔΔ–36) that fails to bind CBP (22), the autonomous transactivation function of ASC-2 is expected to be essential for the Nur77 transactivation both in the absence and presence of CaMKIV (Fig. 2B). Consistent with the inability of ASC-2 to directly interact with Nur77, mutations of the AF2 core region of Nur77 did not affect the Nur77 transactivation (Fig. 2C). Overall, these results suggest that ASC-2 may function as a CaMKIV-responsive, indirect coactivator molecule of Nur77 via a putative adaptor molecule that recognizes a non-AF2 subregion of Nur77. We recently found that ASC-2, a protein of 250 kDa, exists as a steady-state complex of ~2 MDa in vivo,2 which consists of multiple polypeptides. One

2 Y. C. Lee and J. W. Lee, unpublished results.
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**Fig. 5.** Dynamic interplay between coregulators of Nur77. A, expression vectors for Nur77, SMRT, and CaMKIVc were transfected into 293T cells as indicated, and the resulting nuclear extracts were subjected to immunoprecipitation against SMRT monoclonal antibody and blotted with polyclonal antibody against Nur77. Control experiments with preimmune serum as well as the expression levels for Nur77 and SMRT are as indicated. B, HeLa cells were transfected with LacZ expression vector and NurRE-Luc reporter gene and various expression vectors as indicated. Cells were grown for 24 h before harvest either in the absence or presence of 100 nM TSA. The results were expressed as -fold activation (-fold) over the value obtained with a reporter alone, and the error bars are as indicated. C, the action of CaMKIV to regulate the Nur77 transactivation is as schematically shown where ASC-2 is indirectly recruited to Nur77 via an unknown factor, whereas SMRT is directly recruited to Nur77. The "active complex" appears to be in a dynamic equilibrium with the "repressive complex" via a shared interaction interface that binds both SMRT and the putative adaptor molecule. CaMKIV stimulates the autonomous transactivation function of ASC-2 and facilitates translocation of SMRT to the cytoplasm.

The polypeptides of these peptides can be an excellent candidate adaptor molecule that links ASC-2 to Nur77, although another unrelated protein may also accomplish this mission.

In contrast to ASC-2, SMRT directly binds Nur77, likely through the second CoRNR motif of SMRT (6, 7), and repressed its transactivation potential in a dose-dependent manner (Figs. 3 and 4). The C-terminal fragment of SMRT (i.e. SMRT-D) that contains the CoRNR motifs and a recently described novel repression domain (29) was sufficient to transmit the repressive effect of the SMRT to Nur77. This C-terminal repression domain associates with SHARP (29), a potent transcriptional repressor whose repression domain interacts directly with SMRT and at least five members of the nucleosome remodeling and histone deacetylase complex (for a review, see Ref. 30), including HDAC1 and HDAC2. As expected from the functional association of SMRT with various HDACs, the repressive effect of SMRT-HDACs on the Nur77 transactivation was relieved in the presence of HDAC inhibitor TSA, resulting in dramatically enhanced transcriptional activities of Nur77 (Fig. 5B). Surprisingly, however, cotransfected SMRT and SMRT-D were still repressive of the Nur77 transactivation in the presence of TSA. These results strongly suggest that SMRT may bind identical or overlapping binding sites within Nur77 that are also utilized by the putative coactivator/adaptor molecule. Thus, this adaptor molecule may contain a CoRNR-type interaction interface to interact with Nur77. Alternatively, it is also possible that SMRT binding may force Nur77 to adopt a distinct conformation that is incapable of interacting with the putative Nur77 coactivator/adaptor. However, the limited proteolysis experiments indicated that Nur77 conformation is not affected by the presence of SMRT-D (results not shown).

From the results presented in this work, we propose a working model (Fig. 5C) in which ASC-2 is indirectly recruited to Nur77 via unknown adaptor factor(s), in contrast to the direct recruitment of SMRT (Fig. 4B), and the "transcriptionally active ASC-2 complex" could be in a dynamic equilibrium with the "repressive SMRT complex." In this model, CaMKIV stimulates both the autonomous transactivation function of ASC-2 and translocation of SMRT to the cytoplasm, leading to a switch in equilibrium toward the active complex and the maximum stimulation of the Nur77 transactivation. Likewise, the model also predicts that the level of SMRT in a given cell type is an important determinant for the maximum level of the Nur77 transactivation that can be achieved. In this regard, it is noted that transcriptional repression by retinoic acid receptor can be either positively or negatively regulated by changes in the levels of N-CoR expression (31).

Recently CaMK signaling was shown to promote myogenesis by disrupting MEF2-HDAC complexes and stimulating HDAC nuclear export (32, 33). Similarly, phosphorylation of SMRT by MEKK-1 was shown to inhibit the ability of SMRT to physically tether to its transcription factor partners and led to a redistribution of the SMRT protein from a nuclear compartment to a more perinuclear or cytoplasmic compartment (34). We have also shown that CaMKI and CaMKIV, but not CaMKII, led to the cytoplasmic translocation of SMRT (18), consistent with their activity profile for the Nur77 transactivation (Fig. 1B). Consistent with these results, the amount of SMRT associated with Nur77 in vivo decreased upon cotransfection of cells with the CaMKIVc expression vector (Fig. 5A). Close examinations of the SMRT, Nur77, and ASC-2 sequences revealed that these proteins contain the known consensus phosphorylation sequences for CaMKIV, RXRS(T)/Y (15). Currently we are examining if these proteins (particularly ASC-2) are a direct phosphorylation substrate for CaMKIV.

In T lymphocytes, where both Nur77 and CaMKIV are expressed, the Ca\(^{2+}\)-dependent activation of MEF2 appears to lead to programmed cell death by activating the Nur77 transcription factor (35). Thus, our studies suggest that CaMKIV may synergize with Nur77 to induce apoptosis in T lymphocytes, providing a positive feed-in mechanism to stimulate the Nur77 transactivation potential along with this calcium-responsive MEF2-dependent up-regulation of Nur77 expression (35). However, the calcium-dependent control of programmed cell death is complicated and often cell type-dependent. Greenberg and colleagues (36) recently found that Ca\(^{2+}\) stimuli that protected neurons from cell death activated MEF2-dependent transcription in a calcineurin-dependent fashion. Presumably the genes that are activated by MEF2 in neurons protect them from cell death. Several reports have also demonstrated that inhibition of CaMK activity is associated with apoptosis and proliferation. Inhibition of CaMK activity with specific inhibitors induces apoptosis in NIH 3T3 cells (37) and sensitizes etoposide-resistant cells to apoptotic challenge (38). Nonetheless, we suspect that coupling of these two distinct signaling pathways (i.e. CaMKIV and Nur77) may play a pivotal role in tissues that express both Nur77 and CaMKIV.

In summary, we have shown that SMRT and ASC-2 mediate transcriptional repression and activation by Nur77, respectively. It is important to note that SMRT appears to be in a dynamic equilibrium in vivo with a putative adaptor molecule that may enable Nur77 to indirectly recruit the CaMKIV-repressive transactivation function of ASC-2. Molecular cloning of this putative adaptor molecule will facilitate complete un...
understanding of the Nur77 regulatory circuit, particularly with regard to CaMKIV signaling.

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