Steroid and nuclear receptor coactivators (NCoAs) have been implicated in the regulation of nuclear receptor function by enhancing ligand-dependent transcriptional activation of target gene expression. We have previously isolated receptor-associated coactivator 3 (RAC3), which belongs to the steroid receptor coactivator family. In this study, we investigated the differential mechanisms by which RAC3 interacts with and modulates the transcriptional activity of different nuclear receptors. We found that the vitamin D receptor (VDR) and estrogen receptor β interact with different α-helical LXXLL motifs of RAC3. Peptides corresponding to these motifs have diverse affinities for the VDR and estrogen receptor β, and mutation of specific motifs differentially impairs the ability of RAC3 to interact with these receptors in vitro. Consequently, these mutations inhibit the enhancement of transcriptional activation by these receptors in vivo. Furthermore, we found that the activation function-2 (AF-2) domain of the retinoid X receptor interferes with RAC3 binding to a DNA-bound VDR/retinoid X receptor (RXR) heterodimer, whereas the VDR AF-2 domain is required for this interaction. These results suggest a receptor-specific binding preference for the different LXXLL motifs of RAC3, which may provide flexibility for RAC3 to differentially regulate the function of different nuclear receptors.

The vitamin D receptor (VDR) and estrogen receptor β (ERβ) belong to the steroid/thyroid hormone receptor superfamily, which is a large class of ligand-dependent transcription factors that plays critical roles in regulating genes involved in a wide array of biological processes, including development and homeostasis (1). This superfamily can be divided into three subgroups. The ERβ is a Type I receptor, which also includes receptors for steroids such as progestins, androgens, glucocorticoids, and mineralcorticoids. These receptors are coupled to heat shock proteins and sequestered to the cytoplasm in the absence of ligand. Upon hormone binding, they dissociate from the heat shock proteins, homodimerize, and translocate to the nucleus where they bind to cognate response elements consisting of palindromic repeats. The VDR is a Type II receptor like those for thyroid hormone (TR) and all-trans retinoic acid (RAR). These receptors are strictly nuclear and form heterodimers with the receptor for 9-cis retinoic acid (RXR). They also bind constitutively to response elements consisting of direct repeats (DRs). A third class of nuclear receptors is the orphan receptors, so-called because endogenous ligands for these proteins are currently unknown.

Most members of the nuclear receptor superfamily share a common domain structure. The N terminus contains the variable A/B region, which also includes the ligand-independent AF-1 activation domain. The highly conserved DNA binding domain and the C-terminal ligand binding domain (LBD) follow this region. The LBD contains the ligand-dependent AF-2 activation domain and also mediates dimerization of nuclear receptors. In the absence of ligand, nuclear receptors are able to repress basal transcription via functional interactions with the nuclear receptor corepressors SMRT and NCoR (2, 3). SMRT and NCoR are found in complexes with the coressor mSin3 and the histone deacetylase HDAC1, suggesting that transcriptional repression by nuclear receptors may involve histone deacetylation (4–6). Ligand binding triggers the release of these corepressors and subsequent recruitment of coactivators through a drastic conformational change in the AF-2 domain of the receptor. Structural studies have demonstrated that helix 12, which contains the AF-2 domain, projects away from the LBD in the unbound RXR structure, but rotates nearly 180° to pack tightly against the LBD upon hormone binding in the RAR, TR, and ER (7–10). This conformational change, together with induced changes in helices 3–5, is believed to facilitate interactions of the receptor with coactivators (11–16).

Coactivators recruited by ligand-bound nuclear receptors include members of the SRC family of coactivators such as SRC1 (also known as NCoA-1), TIF2/GRIP1 (also known as SRC2 or NCoA-2), and RAC3/ACTR/pCIP/AB1 (also known as SRC3 or NCoA-3) (reviewed in Refs. 17 and 18). SRC family members share an N-terminal basic helix-loop-helix/PER-Arnt-Sim (BHLH/PER-Arnt-Sim) domain of unknown function, centrally located receptor interaction domain, and C-terminal transcriptional activation domain. These cofactors interact with receptors in a hormone- and AF-2-dependent manner and enhance transcriptional activation by nuclear receptors. Both coactivators and receptors also have been demonstrated to interact with the general transcriptional activators CBP/p300 and PCAF (19–26), suggesting that a large multi-protein complex is assembled at the target gene promoter to activate transcription. Furthermore, several coactivators, including SRC1, ACTR, PCAF, and CBP/p300, possess

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intrinsinc histone acetylation activity, which disrupts nucleosomes (21, 27–30). Therefore, the mechanism by which nuclear receptors activate transcription may entail the recruitment of a coactivator complex via the AF-2 domain that may chormatin structure, thereby facilitating access to the promoter by the general transcription machinery.

Intriguingly, members of the SRC family of coactivators have been found to contain several conserved motifs, termed NR boxes, with the consensus sequence LXXLL, where X is any amino acid (31). Motifs within the receptor-interacting domain and transcriptional activation domains of SRC1 and TIF2 have been demonstrated to mediate interactions with liganded nuclear receptors and CBP/p300, respectively (23, 32). Crystallographic and protein structure prediction analyses have indicated that these motifs form amphipathic α-helices with the leucine residues comprising a hydrophobic surface on one face of the helix (11, 12, 14, 24). The helical motif is able to interact with the AF-2 domain of the liganded receptor via a hydrophobic groove made up of residues from receptor helices 3, 4, 5, and 12 that is the result of the conformational change induced by hormone binding (11, 14, 16). Mutational analyses of the NR boxes of SRC1 and TIF2/GRIP1 have also uncovered a receptor-specific mode of interaction, where different nuclear receptors require different NR boxes to interact with the coactivator (32–34). These studies indicate that flanking residues outside the NR box may also be important to nuclear receptor-coactivator interactions.

In this study, we investigate the mechanisms by which RAC3 regulates the function of the VDR and ERβ, for little is known concerning the regulation of these receptors by SRC coactivators, particularly RAC3. These analyses reveal receptor-specific interactions in which the VDR and ERβ interact with different surfaces of RAC3. We demonstrate different preferences of these receptors for specific NR boxes of RAC3 and that single mutations in these LXXLL motifs are able to severely impair the ability of RAC3 to interact with and, thus, coactivate the VDR and ERβ. In analyzing the requirement of nuclear receptor AF-2 domains, we observe that the AF-2 domain of RXR can inhibit RAC3-RID binding to the DNA-bound VDR/ RHR heterodimer, whereas the AF-2 domain of VDR is required for this interaction. These data add a new level of complexity to the regulation of nuclear receptor activity by SRC coactivators and suggest that different classes of nuclear receptors may be regulated by RAC3 via different mechanisms.

**EXPERIMENTAL PROCEDURES**

**Far Western Analysis**—Far Western assays were carried out as described (20). Briefly, GST fusion proteins were expressed in DH5α cells and purified with glutathione-agarose beads (Amerham Pharmacia Biotech). Purified proteins were then separated by SDS-polyacrylamide gel electrophoresis and electroblotted onto a nitrocellulose membrane. Proteins were denatured with 6 M guanidine hydrochloride and renatured by the stepwise dilution of guanidine hydrochloride. Membranes were then blocked and hybridized overnight with 35S-labeled protein.

Proteins were denatured with 6 M guanidine hydrochloride and renatured by the stepwise dilution of guanidine hydrochloride. Membranes were then blocked and hybridized overnight with 35S-labeled protein. The membrane was washed, and bound probe was detected by autoradiography using ImageQuant software (Molecular Dynamics).

**Site-directed Mutagenesis**—NR box mutants were generated with the Quick-change site-directed mutagenesis system (Stratagene). The sequences of all mutant constructs were confirmed by dideoxynucleotide chain termination reactions using the T7 Sequenase protocol (U. S. Biochemical Corp.).

**Gel Electrophoresis Mobility Shift Assay**—The sequence of the DR3 element used for VDR/ERXR gel-shift assays is AGCTTAAGAGTTCA-GAAAGGTCACTGCACT. The double-stranded DR3 was end-labeled with [32P]dCTP by standard Klenow fill-in reaction. The purified probe was incubated with 35S-labeled receptors in binding buffer containing 7.5% glycerol, 20 mM HEPES, pH 7.5, 2 mM dithiothreitol, 0.1% Nonidet P-40, 1 mM of poly(dI-dC) and 100 mM KCl. Wild-type or mutant GST-RAC3-RID was eluted from glutathione-agarose beads with 10 mM glutathione and subjected to binding assay.

**RESULTS**

**VDR and ERβ Interact with Multiple Surfaces of RAC3**—We have previously defined the minimal receptor interacting domain (RID) of RAC3 to be amino acids 613–752, which contains the first three LXXLL motifs (Fig. 1A) (20). We wished to further determine if different receptors were capable of binding to the same regions of RAC3. To accomplish this, we purified a panel of GST-RAC3 fusion proteins, in total comprising the full-length RAC3 (Fig. 1A), and probed these fusions with bound protein was eluted in SDS sample buffer, subjected to SDS-polyacrylamide gel electrophoresis, and detected by autoradiography.

Cell Culture and Transient Transfection—HEK293 and CV-1 cells were maintained in Dulbecco’s modified Eagle’s medium supplemented with 10% fetal bovine serum and 5 μg/ml gentamycin at 37 °C, 5% CO2. Cells were plated for transfection in Dulbecco’s modified Eagle’s medium supplemented with 10% charcoal-stripped fetal bovine serum in 12- or 6-well plates 1 day before transfection. HEK293 cells were transfected using the standard calcium phosphate method, whereas CV-1 cells were transfected using LipofectAMINE according to the manufacturer’s protocol (Life Technologies, Inc.) Twelve hours after transfection, cells were washed with phosphate-buffered saline and refed fresh medium containing the indicated concentration of ligand. After 24 h, cells were harvested for β-galactosidase and luciferase activities as described (35). Luciferase activity was determined with a MLX plate luminometer (Dynex) and normalized relative to β-galactosidase activity.

**VDR and ERβ Interact with Different Fragments of RAC3**—A schematic illustration of RAC3 and its functional domains as well as the purified GST-RAC3 fragments used for Far Western assays. AD, activation domain; i–vi, RAC3 LXXLL NR boxes. hHLH, basic helix-loop-helix. B, Far Western assay using 35S-VDR to probe GST-RAC3 fusion proteins in the presence (top) or absence (bottom) of 1 μM 1,25-dihydroxy-vitamin D3. C, Far Western assay using 35S-ERβ to probe GST-RAC3 fusion proteins in the presence (top) or absence (bottom) of 1 μM 17β-estradiol.

**Far Western assay using 35S-VDR to probe GST-RAC3 fusion proteins in the presence (top) or absence (bottom) of 1 μM 1,25-dihydroxy-vitamin D3. Far Western assay using 35S-ERβ to probe GST-RAC3 fusion proteins in the presence (top) or absence (bottom) of 1 μM 17β-estradiol.**

Fig. 1.
with the Far Western assay (Fig. 1B). Equal protein concentrations of each GST fusion confirmed the specificity of these findings. Thus, these data support the above observations implicating NR box iii as being most critical to RAC3 interaction with the VDR.

The wild-type RID was also able to pull down significant amounts of 35S-ERβ in the GST pull-down assay (Fig. 3C). In contrast to the VDR, an alanine substitution for leucine in any of the three NR boxes weakened the interaction of the RAC3-RID with ERβ, with the mutation of NR box ii being the most deleterious, again supporting the results of LXXLL peptide competition experiments (Fig. 2B). However, with each mutation, significant binding above background between the RAC3-RID and 35S-ERβ was still observed. Furthermore, the GST-RAC3 342–646 fragment, with only NR box i, was able to interact efficiently with ERβ (Fig. 3C) as in the Far Western assay (Fig. 1C). These data suggest that although all three motifs are capable of interacting with ERβ separately, none of them is absolutely required for the interaction. In contrast, NR box iii of RAC3 appears to be essential for the interaction with the VDR.

**RAC3-RID Interactions with DNA-bound Nuclear Receptors**—The above data provide compelling evidence that the VDR interacts specifically with RAC3 in solution via the LXXLL motif of the RAC3 RID, particularly NR box iii. To gain further insight into the function of NR boxes in coactivator-VDR interactions on a heterodimeric complex bound to DNA, we performed gel-shift assays with VDR/RXR heterodimers on a DR3 element in the presence of wild-type or mutant RAC3-RID (Fig. 4). The VDR/RXR heterodimer bound strongly to the 32P-labeled DR3 probe and was unaffected by the addition of GST alone (Fig. 4A, lanes 1 and 2). The addition of the RAC3-RID resulted in a ligand-dependent shift of the

![Fig. 2. Peptides corresponding to the NR boxes of the RAC3-RID can compete for VDR and ERβ binding with the RAC3-RID.](http://www.jbc.org/)

A, Far Western assay using 35S-VDR to probe GST-RAC3-RID in the presence of 1 μM vitamin D and given concentration of each peptide. B, the data from A was quantified by PhosphorImager and plotted as percent GST-RAC3-RID binding to 35S-VDR versus peptide concentration. 100% RID binding represents the density of the band in the absence of peptide. •, peptide i; □, peptide ii; △, peptide iii. C, Far Western assay demonstrating that inhibition of 35S-VDR interaction with GST-RAC3-RID by peptide iii is specific. Peptide iii abolishes nearly all the interaction, whereas a control, random peptide has no effect. D, Far Western assay using 35S-ERβ to probe GST-RAC3-RID in the presence of 1 μM estradiol and given concentration of each peptide. E, the data from D was quantified by PhosphorImager and plotted as the percent GST-RAC3-RID binding to 35S-ERβ versus peptide concentration. •, peptide i; □, peptide ii; △, peptide iii.
motif preferences for VDR binding versus ERβ binding, further supporting a requirement of RXR. The strong interaction was abolished upon deletion of the domain can inhibit the interaction between RAC3 and VDR/RXR. 1.5 μl of each 35S-labeled nuclear receptor was added to a binding reaction (see “Experimental Procedures”) containing 1 μM vitamin D, equal amounts of the indicated GST fusion protein, and the [32P]dCTP-labeled DR3 probe. The arrow indicates the RID-receptor complex. wt, wild type. B, the RXR AF-2 domain can interfere with RID binding to VDR/RXR, whereas the VDR AF-2 domain is required for the interaction. The gel-shift assay was performed as in A, except the AF-2-truncated RXXR443 or VDR402 was used where indicated. *, nonspecific band from lysate. C, the VDR/RXR443 heterodimer has different NR box preferences than the wild-type receptor heterodimer. The gel-shift assay was performed as in A. *, nonspecific band from lysate. D, autoradiograph confirming the equal expression of the 35S-labeled receptors used in B and C.

Finally, we compared the RAC3 NR box preferences of VDR/RXR versus VDR/RXR443 (Fig. 4C). Intriguingly, the VDR/RXR443 heterodimer displayed different NR box preferences. Mutation of NR box i or iii greatly reduced the shift by the RXR-RID (Fig. 4C, lanes 3 and 5), whereas mutation of NR box ii only slightly weakened the binding (lane 4). Thus deletion of the RXR AF-2 domain resulted in a switch in the NR box requirements, with NR boxes i and iii being most important for VDR/RXR443 compared with NR boxes ii and iii for VDR/RXR. An autoradiograph confirmed equal expression levels of each 35S-labeled receptor (Fig. 4D). This finding supports the hypothesis that multiple LXXLL motifs provide RAC3 with the flexibility to adapt to different configurations of a nuclear receptor dimer.

Effects of NR Box Mutations on RAC3 Coactivation Function in Vivo—RAC3 has previously been shown to enhance the transcriptional activity of the RAR and progesterone receptor (37). However, its effect on VDR and ERβ function in vivo has not been demonstrated. To address this, we performed transient transfection assays in HEK293 and CV-1 cells using luciferase reporters harboring either two copies of the vitamin D response element of the osteopontin gene for VDR studies or a consensus ERE element for ERβ studies (Fig. 5). Transfection of the VDR into CV-1 cells minimally activated the vitamin D response element driven reporter (Fig. 5A). However, treating
these cells with vitamin D strongly stimulated its activity. Cotransfection of RAC3 further enhanced VDR transcriptional activation by approximately 50%, consistent with the coactivation function of RAC3 (37).

We then analyzed the role of the NR boxes in mediating the ability of RAC3 to potentiate VDR activity. Mutations of each NR box of the RAC3-RID were made in the context of the full-length RAC3 protein and tested for their ability to coactivate the VDR in transient transfection assays (Fig. 5A). Mutation of NR box i did not inhibit RAC3 enhancement of VDR activity; however, when NR box ii or iii mutations reduced the function of RAC3 in enhancing VDR activity (Fig. 5A), consistent with their requirement for interaction with DNA-bound VDR/RXR heterodimer (38, 39). As expected, the VDR402 mutant was transcriptionally inactive, and RAC3 could not modulate its activity (Fig. 5C, right). Thus, these data are consistent with the gel-shift data in demonstrating that the RXR AF-2 domain can inhibit RAC3 modulation of the VDR/RXR heterodimer, whereas the VDR AF-2 domain is absolutely required for this regulation.

**DISCUSSION**

In this study, we have investigated the role of the NR boxes of RAC3 in mediating the ability of this coactivator to bind and coactivate the VDR and ERβ. We found that NR box iii is most critical to VDR binding, whereas NR boxes i, ii, and iii are involved in ERβ interaction. Peptides corresponding to these motifs were able to compete with the RAC3-RID for binding to VDR and ERβ binding. The integrity of the two motifs was also important, for mutations in specific NR boxes inhibited RAC3 interaction with these receptors in solution and when bound to DNA. The AF-2 domain of VDR is required for binding of the RAC3-RID to DNA-bound VDR/RXR, whereas the AF-2 domain of RXR was able to antagonize this interaction. Removal of this inhibitory AF-2 helix of RXR enhances ligand-dependent binding of RAC3 to the VDR/RXR heterodimer and alters the NR box requirements. Furthermore, the mutation of NR box ii or iii blocked the ability of RAC3 to enhance transcriptional activation by the VDR in *in vivo*. In contrast, mutation of NR boxes i, ii, or iii reduced RAC3 coactivation of ERβ. Together, these *in vitro* and *in vivo* studies suggest a mechanistic difference in the manner by which RAC3 regulates VDR and ERβ activities.

The NR boxes are highly conserved among the SRC family of coactivators (18). Our data and that of others clearly reveal that multiple motifs are necessary for high affinity interactions with nuclear receptors (23, 32, 33). With the DNA-bound VDR/RXR heterodimer, we found that mutation of NR boxes i or iii of RAC3 weakens the interaction with the RAC3-RID. In contrast, NR box iii of RAC3 is the only critical motif for interaction with VDR in solution. Therefore, it is likely that each motif binds to each monomer of the receptor heterodimer, consistent with the structure of a peroxisome proliferator-activated receptor C-terminal nuclear receptor domain (38). As expected, the VDR402 mutant was transcriptionally inactive, and RAC3 could not modulate its activity (Fig. 5C, right). Thus, these data are consistent with the gel-shift data in demonstrating that the RXR AF-2 domain can inhibit RAC3 modulation of the VDR/RXR heterodimer, whereas the VDR AF-2 domain is absolutely required for this regulation.
ibility to interact with a broad range of nuclear receptors, resulting in the different preferences that are observed between nuclear receptors and distinct motifs, depending on the precise structural nuances of each receptor-coactivator interface. This is evident upon comparing the NR box requirements of the VDR/RXR heterodimer versus those of VDR/RXR443. Deletion of the AF-2 helix of RXR not only enhances RAC3-RID binding to the heterodimer but also switches the NR box preferences from motifs ii/iii to motifs i/ii. Finally, amino acids flanking the NR boxes also likely contribute to the specificity of interaction (15, 32), for, despite the high homology between the RAC3 NR boxes, peptides comprising each motif and surrounding residues displayed different affinities for VDR or ERβ binding. Thus, it is clear that the multiple NR boxes do not serve merely redundant functions.

Our finding that the AF-2 domain of RXR can interfere with RAC3-RID binding to a DNA-bound VDR/RXR heterodimer is consistent with studies suggesting allosteric inhibition of coactivator binding to RAR/RXR by the RXR AF-2 domain (36). This inhibition may be the result of competition between the AF-2 domain of RXR and the LXXL motif for the coactivator binding site on the other receptor (11, 12, 36). In the antagonist-bound ERα-LBD crystal structure, the AF-2 domain occupies the coactivator binding groove, mimicking the hydrophobic interactions of the NR box peptide with this domain in the agonist-NR box peptide-receptor complex (11). Biochemical studies with RAR/RXR and SRC1 support these observations, for binding of RAR- and RXR-specific ligands enhance SRC1 interaction with the receptor dimer relative to the interaction in the presence of either ligand alone (36). Presumably, one ligand binding recruits a single NR box to the receptor dimer, which displaces the AF-2 domain from the coactivator binding site and relieves allosteric inhibition, allowing the second ligand to bind to the other receptor monomer. This, in turn, enhances the interaction with coactivator by recruiting a second NR box (36). In the case of wild-type receptors, hormone does stimulate RAC3-RID binding to the heterodimer, but only weakly compared with the VDR/RXR443 dimer, where a very strong, vitamin D receptor activity. Hormone binding and RID recruitment must not be able to activate both AF-2 domains of the dimer, thus, fewer RID molecules are able to bind in the presence of the RXR AF-2 domain. This suggests that the AF-2 domain of RXR plays a critical role in regulating RAC3 modulation of receptor function. However, other possibilities may explain this finding, foremost being the hypothesis that deletion of the AF-2 domain of RXR results in a conformational change of the VDR/RXR443 dimer that enhances its affinity for the RAC3-RID.

Our data demonstrate for the first time that RAC3 can enhance the transcriptional activation function of the VDR and ERβ and that this coactivator activity depends on different NR box requirements. Several other coactivators have been found to stimulate VDR activity, including SRC1, GRIP1/TIF2, NCoA-62, and the DRIP (VDR-interacting proteins) complex (13, 40–42), whereas SRC1 can activate the ERβ (43). The role of multiple coactivators in the function of the VDR in vivo is unknown, but several possibilities exist that suggest that the function of these coactivators is not completely redundant. First, the relative contribution of each coactivator may depend on cell or tissue type and/or coactivator levels in these cells. RAC3 is expressed at a high level in placenta, heart, and HeLa cells relative to TIF2 and SRC1 (20); thus, it may serve a more prominent role in receptor function in these cells. Second, different coactivators may serve different functions that in total result in maximal transcriptional activation by the VDR. For example, RAC3 can interact with CBP; thus, RAC3 may recruit CBP to the VDR. SRC1 has intrinsic histone acetyltransfer activity, and the DRIP VDR-interacting proteins complex may remodel nucleosomes (21, 44), which also may contribute to the overall function of the VDR in stimulating target gene expression. Finally, we cannot rule out the existence of a complex containing multiple coactivators, which synergize to potentiate VDR activity.

In our study, we establish RAC3 as a potentiator of the vitamin D receptor and estrogen receptor β. Interestingly, RAC3 modulates the function of these receptors differently via interactions that depend on specific LXXL motifs in the RAC3 receptor-interacting domain. Although the biological role of RAC3 in nuclear receptor function remains to be explored, this study sheds light on the molecular mechanisms of RAC3 regulation of receptors that will hopefully lead to a better understanding of SRC coactivator function in vivo.

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