Interaction of the Corepressor Alien with DAX-1 Is Abrogated by Mutations of DAX-1 Involved in Adrenal Hypoplasia Congenita*

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The gene superfamily of nuclear hormone receptors (NHRs)† represents a large class of transcription factors including receptors for steroids, nonsteroids, and members for which no ligand has yet been identified, the so-called orphan receptors (for reviews, see Refs. 1 and 2). Gene silencing is mediated by a few members such as receptors for thyroid hormone (TR (NR1A)) (3) and retinoic acid (RAR (NR1B)) (4–10). Thereby, the receptor is associated with corepressors, and the complex of receptor and corepressors mediates target gene repression (2, 9–12). Among corepressors, N-CoR and SMRT represent one class, and Alien represents another class, which interacts in a hormone-sensitive manner with NHR (10–13). The silencing domain of NHRs is localized in the C terminus and overlaps with the hormone-binding domain to a great extent. In the case of TR and RAR, the silencing domain encompasses 230 amino acids (5, 14). Hormone binding by NHRs leads to a conformational change, dissociation of corepressors, subsequent binding of coactivators, and gene activation (for review, see Ref. 15). The transcriptional properties of nuclear receptors can be transferred to heterologous proteins and therefore represent functional domains (for review, see Refs. 2, 16, and 17).

DAX-1 is an unusual member of the nuclear hormone receptor (NHR) superfamily. Lack of DAX-1-mediated silencing leads to adrenal hypoplasia congenita and hypogonadotropic hypogonadism. Gene silencing through NHRs such as the thyroid hormone receptor (TR) is mediated by corepressors. We have previously characterized a novel corepressor, termed Alien, which interacts with TR and the edysone receptor but not with the retinoic acid receptors RAR or RXR. Here, we show that DAX-1 interacts with the corepressor Alien but not with the corepressor SMRT. This interaction is mediated by the DAX-1-silencing domain. Naturally occurring mutants of the DAX-1 gene fail to interact with Alien and have lost silencing function. Because the silencing domain of DAX-1 is unusual for NHRs, we mapped the interaction of Alien with DAX-1 and with TR. We show that Alien exhibits different binding characteristics to DAX-1 and TR. Furthermore, Northern experiments demonstrate that Alien is expressed in the adrenal gland and testis in tissues where DAX-1 is specifically expressed. Interestingly, a novel adrenal gland-specific mRNA of Alien was discovered. Thus, the impairment of Alien binding seems to play an important role in the pathogenesis mediated by DAX-1 mutants.

The abbreviations used are: NHR, nuclear hormone receptor; TR, thyroid hormone receptor; RAR, retinoic acid receptor; N-CoR, nuclear receptor corepressor; SMRT, silencing mediator for retinoic acid and thyroid hormone receptors; HA, hemagglutinin; GST, glutathione S-transferase; kb, kilobase(s); hAlien, human Alien.
mediate silencing. Here, we show that Alien interacts with DAX-1. The interaction of Alien with DAX-1 differs from the interaction of Alien with TR, suggesting that the corepressor Alien uses distinct protein domains to interact with different silencing domains. Furthermore, we identified a novel alien mRNA species that is specific for adrenal gland. In addition, naturally occurring DAX-1 mutants, involved in adrenal hypoplasia congenita and the associated symptoms of hypogonadotropic hypogonadism, fail to interact with Alien and lack silencing function. These findings suggest that the DAX-Alien complex is important in mediating the developmental function of DAX-1.

**EXPERIMENTAL PROCEDURES**

**Plasmids**—Mammalian expression vectors for Gal-DAX, Gal-DAX283, Gal-DAX346, and Gal-DAX423 were generated by excision of DAX-1 coding sequences from pSG-DAX (a generous gift from Dr. P. Sassone-Corsi) using EcoRI, Eco255I, NaeI, and Bsp I, respectively, and the in-frame insertion into pABgal94 linker (9). pABgal-DAXRK267P was generated by a three-fragment ligation using the Eco255I DAX-1 fragment from pABgal-DAX, a synthetic oligonucleotide bearing the mutation R267P (SalI/Eco255I ends) inserted into pABgal94 linker SalI/Eco255I sites. pABgal-DAXLR44–352 was created by deletion of the internal BonI fragment and religation. pABgal-TR265–461 was described earlier (29).

**Yeast Expression Plasmids**—The activator fusions of DAX-1 and deletions were cloned by excision of EcoRI from the corresponding pABgal-DAX vectors into the EcoRI site of pG4–5 (30). plex-hAlien fusion proteins were generated using restriction enzymes and by in-frame insertions of the hAlien cDNA from pABgal-hAlien (13) into pEG202 (30). Full-length plex-SMRT (10) was generated by insertion of the EcoRI fragment from pCMX-gal-SMRT (a generous gift from Dr. R. Evans) into the EcoRI site of pEG202.

Cell culture, yeast two-hybrid assay, and GST pull-down experiments were performed as described previously (13, 31). For yeast two-hybrid experiments the C terminus of TRβ (amino acids 175–461) was used as the activator fusion to the B42 activation domain (Ref. 30). Similarly, the DAX-1 C terminus was used as the activator, and hAlien was used as the bait (lexA fusion). For DNA transfection experiments 1 pmol of pABgal94 linker (9) or pABgal-DAX fusion expression plasmids and 1.5 pmol of 17mer6x-tkCAT/H reporter (5) were used for CaPO4 transfection experiments (31). In Fig. 3 the basal promoter activity resulted in 20% chloramphenicol acetyltransferase conversion, which was found to be 2.75% with DAX-1. For in vitro translation of full-length DAX-1 the vector pSG-DAX was used with the T7 coupled retilucocyte lysate system (Promega) according to the manufacturer’s protocol. Co-immune precipitations were performed using polyclonal anti-hemagglutinin (HA) antibody (Santa Cruz Biotechnology) bound to protein A-Sepharose beads (Amersham Pharmacia Biotech) with extracts derived from 293 cells transfected with expression vectors encoding HA alone or HA-hAlien together with AU5-tagged DAX-1 C terminus (amino acids 245–470). 293 cells were lysed with 0.1% Nonidet P-40, 50 mm Tris, pH 7.5, 450 mm NaCl, 1 mM dithiothreitol, and 0.2 mM phenylmethylsulfonyl fluoride. After centrifugation at 4 °C extracts were diluted with water 1:1 and incubated for 4 h with anti-HA antibody. After several washing steps the precipitates were analyzed by SDS-polyacrylamide gel electrophoresis. Western blotting was performed with the ECL kit (Amersham Pharmacia Biotech) using mouse anti-AU5 antibody (Berkeley Antibody) and peroxidase-coupled anti-mouse antibodies (Amersham Pharmacia Biotech).

**RNA Extraction and Northern Analysis**—Total RNA from tissues of adult Wistar rats was isolated via the guanidinium isothiocyanate phenol/chloroform procedure. 60 μg of total RNA obtained from each tissue was used. Radiolabeled hAlien cDNA (KpnI/BamHI fragment of pAB-hAlien) (13) was used as a probe with the random priming procedure. As controls, blots were stained with 0.3M sodium acetate plus 0.02% methylene blue to check RNA integrity and rehybridized for normalization (NIH image program) with a radiolabeled cyclophilin mRNA species that is specific for adrenal gland. In addition, naturally occurring DAX-1 mutants, involved in adrenal hypoplasia congenita and the associated symptoms of hypogonadotropic hypogonadism, fail to interact with Alien and lack silencing function. These findings suggest that the DAX-Alien complex is important in mediating the developmental function of DAX-1.

**RESULTS**

**DAX-1 Interacts with the Corepressor Alien**—We have recently characterized a novel corepressor for specific members of the NHR superfamily (13). Because DAX-1 is able to mediate silencing (24, 27, 28), we wanted to know whether Alien interacts with the silencing domain of DAX-1. For this purpose we used the yeast two-hybrid system (30). As bait, human Alien (lex-Alien) was used, and as activator, DAX-1 (amino acids 245–470) as a DAX-B42 fusion protein was used as the activator reveal that Alien binds to both DAX-1 and TR, whereas full-length SMRT lacks interaction with DAX-1. Miller units represent the β-galactosidase units obtained from the reporter. B, GST pull-down experiments were performed with bacterially expressed GST-hAlien and in vitro translated and [35S]-labeled full-length DAX-1. As controls [35S]-labeled luciferase was mixed with the DAX-1 in vitro translate. C, co-immunoprecipitation experiments were performed using polyclonal anti-hemagglutinin antibody and extracts of 293 cells cotransfected with expression vectors coding for AU5-tagged DAX and either HA tag alone (HA) or hemagglutinin-tagged Alien (HA-Alien). Western blotting was performed with the AU5 antibody. WCE, whole cell extract.

**Fig. 1. The corepressor Alien but not SMRT interacts with DAX-1. A, yeast two-hybrid experiments with either full-length Alien or SMRT (10) as bait and DAX-1 or thyroid hormone receptor (TR) as the activator reveal that Alien binds to both DAX-1 and TR, whereas full-length SMRT lacks interaction with DAX-1. Miller units represent the β-galactosidase units obtained from the reporter. B, GST pull-down experiments were performed with bacterially expressed GST-hAlien and in vitro translated and [35S]-labeled full-length DAX-1. As controls [35S]-labeled luciferase was mixed with the DAX-1 in vitro translate. C, co-immunoprecipitation experiments were performed using polyclonal anti-hemagglutinin antibody and extracts of 293 cells cotransfected with expression vectors coding for AU5-tagged DAX and either HA tag alone (HA) or hemagglutinin-tagged Alien (HA-Alien). Western blotting was performed with the AU5 antibody. WCE, whole cell extract.

**DAX-1 Has an Unusual Silencing Domain within the NHR**
Family—The silencing domain of TR and that of the closely related v-ErbA oncogene product are localized in the receptor C terminus and have been well characterized (5, 14, 29, 33). This domain encompasses 230 amino acids that include helices 1–11 of the receptor C terminus. Deletion of either helix 1 or 11 abrogates silencing function.

We aligned the amino acid sequence of the silencing domains of DAX-1, TR/v-ErbA, and RAR (Fig. 2). In addition, we indicated the amino acid borders of the TR/v-ErbA silencing domain and deletion end points that have lost silencing function (5, 14, 29).

Interestingly, the C terminus of DAX-1, which harbors the silencing domain, is unusual compared with TR and RAR (Fig. 2). Sequence alignment of TR, RAR, and DAX-1 shows that the striking characteristic of DAX-1 is an unusual insertion C-terminal to the Ti region. Furthermore, the N-terminal border of the DAX-1 silencing domain correlates with a region of TR that is not sufficient either to mediate gene silencing (Fig. 2) or to interact with hAlien (13). This raises the question of how Alien is able to interact with DAX-1.

Loss of the Silencing Function of DAX-1 Correlates with Loss of Interaction with Alien—To investigate whether the Alien-DAX-1 interaction correlates with the silencing function of DAX-1, we tested DAX-1 mutants in reporter and interaction assays. Expression plasmids coding for Gal-DAX fusion proteins were cotransfected along with the reporter 17mer6x tk-CAT into mouse L-cells. The C terminus of DAX-1 (amino acids 245–470) silences gene transcription in these cells (Fig. 3). In contrast, the homologous region of TR/v-ErbA does not mediate silencing (Fig. 3). Deletion of only 38 amino acids (DAX 283–470), which deletes part of the Ti region and the entire putative helix 3, abrogates this silencing function. Similarly, premature stop codons found in patients with hypogonadism and adrenal hyperplasia (19, 34–37), represented here by a C-terminal deletion (245–423), also result in loss of silencing. A patient-derived DAX-1 mutant having a one-amino acid exchange, R267P (19), in the Ti region lacks silencing function as seen previously (27).

One reason DAX-1 is able to mediate silencing whereas the homologous part of TR is not may be the insertion of additional amino acids C-terminal of the Ti region of DAX-1. Therefore, we generated an internal deletion mutant (ΔDAX344–352). However, this deletion does not affect the silencing activity (Fig. 3), indicating that these amino acids within the insertion are not critical for gene silencing.

Next, we wanted to analyze the interaction of Alien with DAX-1 mutants lacking silencing. Whereas the wild-type DAX-1 interacts with Alien, the DAX-1 mutants R267P or DAX 245–470 do not exhibit a detectable interaction (Fig. 4). Thus, the interaction of Alien with DAX-1 correlates with the silencing function of DAX-1, and mutants of DAX-1 fail to interact with Alien.
Interaction of the Corepressor Alien with DAX-1

Alien Interacts Differentially with DAX-1 and TR—Because the TR part that is homologous to the DAX-1 silencing domain does not mediate silencing and does not bind to Alien, we wanted to investigate which regions of Alien are required for binding of Alien to either TR or DAX-1. We generated deletions of human Alien and tested them for interaction with DAX-1 and TR in yeast two-hybrid assays (Fig. 5). The N-terminal deletion of Alien (amino acids 1–275) is able to bind to TR, whereas the interaction with DAX-1 is almost undetectable. Conversely, only a 30-amino acid C-terminal deletion of Alien (amino acids 128–305) is able to bind to DAX-1, but it shows strong binding to TR. This suggests that the C terminus of Alien is essential for binding to TR, although not sufficient, as shown by using other Alien deletion mutants (Fig. 5). Conversely, the N-terminal part of Alien is essential but not sufficient for binding to DAX-1. Thus, DAX-1 and TR interact with different regions of Alien.

Alien and DAX-1 Are Coexpressed in Adrenal Gland—DAX-1 is expressed specifically in the adrenals and testes, and mutations in the DAX-1 gene affect the development and differentiation of these tissues. Therefore, we tested whether Alien is also expressed in these tissues. Northern experiments were performed with total RNA from rat testis and adrenals using alien cDNA as a probe. Northern blot analysis (Fig. 6) revealed one major Alien-specific band at about 2 kb in testis, a result that is in agreement with Schaefer et al. (38), whereas various other tissues show two bands migrating at 2 and 4 kb. However, in adrenals, two Alien-specific bands are observed migrating at 2 and 4 kb, and a third Alien-specific band, which is novel yet undescribed, migrates at 6 kb (Fig. 6). Thus, Alien and DAX-1 are coexpressed in the adrenals.

DISCUSSION

Here, we show that the corepressor Alien interacts with the orphan receptor DAX-1. The interaction occurs in the DAX-1 C terminus. Importantly, all DAX-1 mutations found in patients with adrenal hypoplasia congenita have the common feature of an altered C terminus (27).

Mutations of thyroid hormone receptor β are involved in the disease of thyroid hormone resistance. Patients manifest various degrees of delay of bone development, hearing defects, and mental retardation. In these cases, receptor mutants have reduced or completely lost the hormone-dependent activation but...
have retained silencing function (17, 39). Accordingly, corepressors remain bound to the receptor’s silencing domain even in the presence of ligand (40). However, mutations of the DAX-1 gene result in mutants lacking silencing function and interaction with the corepressor Alien. Thus, unlike thyroid hormone resistance, the disease of adrenal hypoplasia congenita and the associated hypogonadism result from a lack of corepressor interaction and transcriptional silencing (27).

Our failure and the failure of others to observe a significant interaction of SMRT with DAX-1 indicate that DAX-1 binds to a subset of corepressors. Also, Alien interacts with a subset of nuclear receptors that is distinct from the subset bound by the corepressor SMRT. Furthermore, Alien does not bind to the C terminus of RARα (13), whereas SMRT/N-CoR does. Thereby, the small activation domain AF2-AD/r4/αc of RAR prevents the binding of Alien, providing a new role for AF2-AD/r4/αc of regulating the binding of corepressors in the absence of ligand. Thus, Alien interacts differentially with the silencing domains of different nuclear receptors. Alien’s lack of interaction with RAR may also explain the inability of RAR to relieve silencing mediated by DAX-1 in squelching experiments (27).

It is noteworthy that the extension of the DAX-1 silencing domain is different from that of other nuclear receptors such as TR or RAR. Interestingly, homologies in the amino acid sequence between the DAX-1 silencing domain and TR or RAR are found to be in a region of TR or RAR that is unable either to mediate gene silencing or to interact with corepressors (5, 10, 12–14, 29, 33). Thereby, the silencing domain of DAX-1 is homologous to the region of TR that excludes a major part of the hinge region required for interaction of TR with the corepressors SMRT/N-CoR and Alien. This is in agreement with our observation that the interactions of DAX-1 and TR with Alien are mediated through different domains.

Squelching of cofactors is efficiently performed when both the silencer factor and the overexpressed squelcher bind the same site on the cofactor. Alien interacts in a different manner with DAX-1 than it does with TR (Fig. 7), a difference that may explain the lack of significant squelching of DAX-1-mediated silencing by TR/αv-ErbA (not shown). It is also noteworthy that overexpression of the silencing domain of DAX-1 does not completely relieve its own silencing function (Ref. 27 and data not shown), which may indicate that DAX-1 also uses other non-corepressor-mediated pathways for gene silencing.

Alien is expressed very early in development and in a large number of tissues, albeit at different levels (38). Strong expression is observed in heart, brain, liver, skeletal muscle, kidney, and testis. Interestingly, multiple RNA species have been identified. In heart and skeletal muscle, two Alien mRNA species at 2 and 4 kb are seen, whereas in liver an additional 1.8-kb form is expressed. In testis only the 2-kb form is found (38). We show here that in adrenal glands, in addition to the 2- and 4-kb bands, a novel 6-kb RNA is expressed. The role of the tissue-specific RNA messages is unclear. However, there are several Alien protein forms. Whereas the Alien corepressor is composed of 305 amino acids, there are also other forms encoding a longer variant of Alien (Ref. 38 and data not shown). It is possible that different forms of the Alien protein may exhibit distinct interaction patterns with nuclear receptors.

When these results are taken together, they suggest that the presence of the corepressor Alien may be important in the developmental role of DAX-1 in testis and adrenals. Mutations in the DAX-1 gene that lead to adrenal hypoplasia congenita and hypogonadism inhibit the formation of the DAX-Alien complex and lack silencing function. Therefore, we suggest that the transcriptional repression mediated by DAX-1 through binding to Alien plays an important role in the natural development of the adrenal gland and testis.

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Interaction of the Corepressor Alien with DAX-1

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