Differential Transactivation by Two Isoforms of the Orphan Nuclear Hormone Receptor CAR*

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We have identified a new murine orphan member of the nuclear hormone receptor superfamily, termed mCAR, that is closely related to the previously described human orphan MB67, referred to here as hCAR. Like hCAR, mCAR expression is highest in liver. In addition to the most abundant mCAR1 isoform, the mCAR gene expresses a truncated mCAR2 variant that is missing the C-terminal portion of the ligand binding/dimerization domain. The mCAR gene has 8 introns, and this mCAR2 variant is generated by a splicing event that skips the 8th exon. mCAR1, like hCAR, binds as a heterodimer with the retinoid X receptor to the retinoic acid response element from the promoter of the retinoic acid receptor β2 isoform. Consistent with its lack of a critical heterodimerization interface, the mCAR2 variant does not bind this site. Both mCAR1 and hCAR are apparently constitutive transcriptional activators. This activity is dependent on the presence of the conserved C-terminal AF-2 transcriptional activation motif. As expected from its inability to bind DNA, the mCAR2 variant neither transactivates by itself nor inhibits transactivation by hCAR or mCAR1.

The nuclear hormone receptor superfamily includes the receptors for a number of potent biological regulators, such as steroids, retinoids, and thyroid hormone. With the recent addition of nuclear prostaglandin receptors (1, 2), and an oxy-sterol receptor (3), there are now more than 15 genes in mammalian genomes that encode such conventional receptors. An even larger set of genes encodes the orphan receptors, which are related to the conventional receptors but do not have known ligands. Particularly since individual genes for superfAMILY members frequently encode more than one isoform as a consequence of either alternative promoter utilization or alternative mRNA splicing, the total number of proteins that belong to the nuclear receptor superfamily is large.

The functions of the conventional receptors have been extensively characterized (4–7). The functions of the orphans are less well understood, although it is thought that they have crucial roles in a variety of processes. Thus, the profound effects of the knock out of the SF-1/PTZ-F1 (8, 9) or HNF-4 (10) genes demonstrate that both have essential developmental functions. The remarkable conservation of the Coup-TFs and genes demonstrate that both have essential developmental functions. The remarkable conservation of the Coup-TFs and genes demonstrate that both have essential developmental functions.

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EXPERIMENTAL PROCEDURES

mCAR Clones—A number of mouse CAR cDNA clones were isolated from a liver cDNA library using an hCAR (MB67) probe. Of 9 independ-
ent clones examined in detail, had an intact ligand-binding domain, as judged by comparisons to hCAR and other superfamily members. Three had an internal deletion of 107 amino acids. Representative sequences of these clones have been submitted to GenBank. One additional clone included 188 bp of intron derived sequences; it is unclear whether this cloning event causes a frame shift or a contaminating genomic precursor. The mCAR2 sequence used for further experiments corresponds to the cDNA clone that had the most extensive 5′-untranslated sequences, and the internal deletion. To generate the mCAR1 sequence used, the deleted region in this mCAR2 clone was replaced with the corresponding fragment from a clone that did not carry the deletion. An mCAR probe was used to screen a mouse genomic library, and a single clone was obtained. A NotI fragment containing the entire mCAR gene and 5′- and 3′-flanking regions was subcloned and sequenced in its entirety. This sequence has been submitted to GenBank.

**RNA Analysis**—A Northern blot containing 2 μg of poly(A)+ mRNA from a variety of tissues was obtained from CLONTECH, Inc. and hybridized sequentially with either a full-length mCAR probe or smaller probes generated by PCR. The N-terminal probe, consisting of 167 bp from the 5′-untranslated region, and the C-terminal probe, consisting of the last 200 bp of the mCAR coding region, were generated by PCR using the mCAR1 cDNA as a template, (5′-TTCTCTACTAGATGAGCC-3′) and 5′-GACCCTGCCTTCCCTGAG-3′. C-terminal primers: 5′-AGTGCTAATCTCCTGAGC-3′ and 5′-AGTGCTAGCTACTTCTCCTGAGC-3′. A 210-bp 3′-flanking probe extending from a position 130 bp downstream of the poly(A) addition site was generated by PCR using the genomic mCAR probe as template (primers: 5′-TAGAGGTTGAAGCTTCTCCTAGATGTTC-3′ and 5′-GATTGAGGTRGACTAGAGTTC-3′). Prior to each rehybridization, the membrane was exposed for at least 2 days to confirm the removal of the previous probe.

Standard conditions (28) were used for mRNA based PCR with mouse liver mRNA as a template and primers from exons 7 and 9. For Southern analysis of the PCR products, probes corresponded to a restriction fragment containing the mCAR1 ligand-binding domain, or an internal deletion. To generate the mCAR2 sequence used for further experiments, the deleted region in this mCAR2 clone was replaced with the corresponding fragment from a clone that did not carry the deletion. An mCAR probe was used to screen a mouse genomic library, and a single clone was obtained. A NotI fragment containing the entire mCAR gene and 5′- and 3′-flanking regions was subcloned and sequenced in its entirety. This sequence has been submitted to GenBank.

**DNA Binding**—For DNA binding studies, mCAR1, mCAR2, RAR, and RXR proteins were expressed using coupled *in vitro* transcription and translation (Promega, Inc.). Standard conditions were used for electrophoretic mobility shift assays with the DR-5 response element from the RARβ2 promoter (the βRAR) as the probe, as described for hCAR (24). Transfections—HepG2 cells were maintained and transfected using calcium phosphate or DEAE dextran (28). mCAR1 and mCAR2 expression vectors were generated by inserting appropriate fragments into the vector pCMV (28), as described previously for hCAR (24). The luciferase reporter plasmid (28) contained three copies of the βRAR upstream of the TK promoter. The reporter plasmids with wild type and mutant versions of the RARβ2 promoter were obtained from Drs. Nadeem Moghal and Ben Neel, and were as described (30). Transfections also included the pTKGH control plasmid which directs expression of human growth hormone (31).

For the TK reporter, pairs of 30-mm dishes were each transfected with 2 μg of reporter and pTKGH, and a total of 2 μg of mammalian expression vector. For the RARβ2 reporters, pairs of 30-mm dishes were each transfected with 1.5 μg of the reporter and the mammalian expression vector, and 2 μg of the pTKGH control. Transfections were carried out in media containing 10% charcoal-stripped serum, and luciferase activity was determined using the Promega luciferase assay system as described by the manufacturer. Luciferase values were normalized using the growth hormone expression directed by the TKGH internal control.

To confirm expression of mutant derivatives of mCAR1, whole cell extracts were prepared from appropriately transfected COSM6 cells as described (32). COSM6 cells do not express endogenous CAR proteins. These extracts were supplemented with similarly prepared COSM6 expressed RXR and used for electrophoretic mobility shift analysis using standard conditions.

**RESULTS**

**Isolation of mCAR1 and mCAR2 cDNAs**—Murine cDNA clones related to the previously described human orphan receptor MB67 (24) were isolated from a mouse liver cDNA library. Based on the ability of these murine and human orphan proteins to constitutively transactivate at least a subset of RAREs (see below), we refer to them as mCAR and hCAR. Two classes of cDNAs were obtained encoding proteins called mCAR1 and mCAR2. mCAR1 and hCAR share a high degree of sequence identity throughout the DNA and ligand binding/dimerization domains (Fig. 1, A and B). Both proteins have very short N-terminal regions. mCAR2 is identical to mCAR1 except for an out-of-frame 107-bp deletion in the ligand binding/dimerization domain. As a consequence of this deletion, only 6 new amino acids in mCAR2 substitute for the last 78 residues of mCAR1. This C-terminal region of mCAR1 includes both the heterodimerization interface referred to as the 9th heptad (25, 33) or the I box (26), and the AF-2 transactivation domain (34). hCAR and mCAR belong to a small, rather divergent subgroup within the nuclear hormone receptor superfamily that also includes an orphan receptor from Xenopus laevis (35) and the mammalian vitamin D receptor. hCAR and mCAR also show relatively strong similarity with the insect edysone receptor in the DNA-binding domain, but not other domains (Fig. 1B).

Two lines of evidence demonstrate that mCAR2 is not a cloning artifact. The first is simply that this 107-bp segment is...
missing in more than 5 independently isolated cDNAs. The second is a more direct demonstration of the existence of bands of the expected size using PCR with primers from the E domain and poly(A)+ mRNA from mouse liver as template. As shown in Fig. 2, the identity of these bands was confirmed by Southern blotting with probes containing either ligand/dimerization domain sequences present in both, or only sequences from exon 8. This analysis indicates that the mCAR2 variant is a relatively minor fraction of the total mRNA. In addition to these two species, an even lesser amount of an additional species larger than the mCAR1 product was also observed. Its size indicates that it corresponds to a nuclear precursor that includes intron 7, which interrupts the coding region at the start of the mCAR2 deletion (see below). A cDNA clone including only this intron was isolated, but it is unclear whether it represents an additional variant mRNA or a partially spliced nuclear precursor.

The similarity between the human hCAR and murine mCAR sequences is significantly less than the 90% or greater identity usually shared by true receptor homologs in different mammalian species. It is comparable to that shared by the various isoforms of the RARs, for example, suggesting that hCAR and mCAR are derived from distinct genes that encode two CAR isoforms.

Structure and Expression of the mCAR Gene—A single clone containing the mCAR gene was obtained from a screen of a mouse genomic library. As diagrammed in Fig. 3A, the murine mCAR gene is interrupted by eight introns. Exon 8 is absent in mCAR2, demonstrating that this variant is generated by alternative mRNA splicing. The 5' end of the mCAR transcript was mapped by primer extension (Fig. 3B). The sequences of the mCAR cDNAs, gene, and flanking regions have been submitted to GenBank.

In northern blots of poly(A)+ RNA from various mouse tissues hybridized at high stringency with CAR probes, mCAR expression is by far the highest in liver, as described previously for hCAR (24). In both mouse and human, the most prominent product is a rather broad band of approximately 1.3 to 1.7 kilobases. At least in mouse, this band presumably includes both mCAR1 and mCAR2 transcripts. Additional species of approximately 3.0, 4.0, and 5.7 kilobases are observed in mouse. Larger transcripts of somewhat different sizes are also present in human liver mRNA (24). All of these larger mouse transcripts were also identified by much smaller probes containing only 5'-untranslated or ligand/dimerization domain sequences (Fig. 4). The hybridization of the 5' probe indicates that these various species do not correspond to variants with distinct N-terminal sequences, as observed with TRβ1 and TRβ2, for example (36). Similarly, the identical pattern of hybridization with the ligand/dimerization probe indicates that the various transcripts do not include major substitutions of sequences in that region. Finally, a probe from the 3'-flanking
region of the gene hybridized only to the three larger species. Thus, these larger species are presumably generated as a consequence of a lack of addition of a poly(A) tract at the position used for the shorter transcripts. These longer, read-through transcripts must include extensive additional 3' untranslated regions, but it is not known whether the different larger species are generated by additional cases of alternative poly(A) addition, or by alternative mRNA splicing.

**FIG. 4.** Expression of mCAR transcripts. A Northern blot containing mouse poly(A)^+ mRNA from various tissues (CLONTECH) was sequentially hybridized with either a full-length mCAR probe (A) or a series of shorter probes as indicated. Probes B and C were generated by PCR using the mCAR cDNA as a template, and probe D was generated by PCR using the genomic clone as a template. Only the results with liver mRNA are shown for the smaller probes. In much longer exposures of hybridizations with either the full-length probe or the two probes from the 3' end, an additional transcript of approximately 2.8 kilobases is observed in heart, brain, skeletal muscle, and kidney. *UTR*, untranslated region.

**FIG. 5.** DNA binding by mCAR1 and mCAR2. mCAR1, mCAR2, RXR, and RAR proteins were expressed by in vitro translation and used for electrophoretic mobility shift assays with a βRARE probe as indicated. S indicates competition with the βRARE oligonucleotide; NS, competition with a nonspecific oligonucleotide. Equivalent amounts of mCAR1, mCAR2, and RAR were used in the binding reactions, as determined by [35S]methionine labeling.

**FIG. 6.** Transactivation by mCAR1 and mCAR2. A, a luciferase reporter containing three copies of the βRARE upstream of the TK promoter was cotransfected into HepG2 cells with the indicated receptor expression vectors and a TKGH control plasmid. Normalized luciferase activity is expressed by comparison to the activity observed with the CDM8 vector alone. B, two reporter constructs containing 336 bp of the RARβ2 promoter driving expression of luciferase (30) were cotransfected into HepG2 cells with control, mCAR1, or mCAR2 expression vectors, as indicated, along with the TKGH internal control. In the -336 mut reporter, the βRARE is inactivated by a cluster of point mutants (30). Normalized luciferase expression is presented.
In much longer exposures of hybridizations with either the full-length probe or the two probes from the 3′ end, an additional transcript of approximately 2.8 kilobases is observed in heart, brain, skeletal muscle, and kidney. This does not correspond to any of the liver transcripts in size, and could be either a transcript of the true murine homolog of hCAR, or another variant product of the mCAR gene.

**DNA Binding and Transactivation by mCAR1 and mCAR2**—To determine whether the mCAR proteins bind DR-5 response elements as heterodimers with RXR, like hCAR (24), mCAR1 and mCAR2 were expressed by in vitro translation. As expected, mCAR1/RXR heterodimers bound with high affinity to the RARE from the RARβ2 isomorph promoter (37, 38) (Fig. 5). As with hCAR (24), the apparent affinity of mCAR1/RXR heterodimers for this βRARE element was indistinguishable from that of RAR/RXR heterodimers. mCAR2 did not bind the βRARE or any other element tested either alone or with RXR. This lack of mCAR2 binding is consistent with the absence of the C-terminal portion of the ligand/dimerization domain, which is essential for heterodimerization (17, 27, 33, 39, 40).

Previous results demonstrated that hCAR specifically transactivates the βRARE in the absence of retinoids or any other exogenously added ligands (24). To determine whether mCAR1 shows similar effects, it was cotransfected with a luciferase reporter plasmid in which 3 copies of the βRARE were inserted upstream of the TK promoter. In various cell types and under a variety of conditions, hCAR transactivated this reporter approximately 20–100-fold, while mCAR1 was somewhat more effective, conferring a 50–300-fold activation (Fig. 6A). In the presence of all-trans-retinoic acid, RAR was an even more potent transactivator of this reporter (data not shown). As with hCAR, the apparently constitutive transactivation by mCAR1 was observed in the presence of serum treated with charcoal to remove retinoids or other potential ligands, and in several different cell types. As shown in Fig. 6A, mCAR2 did not transactivate this element, and also did not affect transactivation by hCAR or mCAR1. Similar results were obtained with higher ratios of mCAR2. As expected from these results, mCAR1, but not mCAR2 was able to transactivate a reporter containing the intact RARβ2 promoter, but not a mutant version in which the βRARE element was inactivated by point mutations (Fig. 6B).

To confirm that the transactivation observed is a direct effect of mCAR1, mutations were introduced into the mCAR1 AF-2 region. These mutations included both simple deletions and point mutants that were chosen based on comparisons of this region of mCAR to the analogous region in other receptors. As indicated in Fig. 7A, the Δ8 mutation and the point mutants L352A and E355A specifically affect the AF-2 motif. The larger Δ27 mutation extends into the region homologous to helix 10 of RAR (41), and the analogous helices in the TR (42) and RAR (43) structures, but stops short of the 9th heptad motif (25) within this helix. All of these mutations completely abrogated transactivation by mCAR1 (Fig. 7B). A Western blot with an antibody directed against an epitope tag present at the N terminus of the wild type and mutant proteins confirmed that all were expressed at similar levels (data not shown). As demonstrated in Fig. 7C, all the mutants except Δ27 were able to bind DNA. Although this mutant retains the 9th heptad motif, it is missing most of the helix that contains this motif. At least in the case of RXR homodimers, the C terminus of this helix is involved in an important dimer contact (41).

**DISCUSSION**

Many of the genes that encode the members of the nuclear hormone receptor superfamily express more than one protein product as a consequence of either alternative promoter utili-
zation or alternative mRNA processing. The independent isolation of a number of cDNA clones corresponding to the deleted mCAR2 product initially suggested that the mCAR gene belongs to this group, and the existence of distinct mCAR isoforms was confirmed by a PCR based approach. The mCAR gene also expresses additional transcripts with larger 3′-untranslated sequences as a consequence of a lack of poly(A) addition at the primary site. However, these larger transcripts do not encode variant mCAR proteins.

The mCAR1 and hCAR sequences contain a good match to the AF-2 transcriptional activation domain at their extreme C termini. This conserved motif is present in many conventional receptors and orphans (34), and has been directly associated with ligand dependent transcriptional activation in several conventional receptors (e.g. Refs. 44–47). Mutation of this conserved motif in mCAR also blocks transactivation. This demonstrates that the CAR component of the CAR/RXR heterodimer is actively involved in transactivation. It also confirms a prediction, derived from both sequence conservation and recent results with HNF-4 (48), that the conserved AF-2 motif is involved not only in ligand dependent transactivation, but also in the apparently ligand independent transactivation observed with several other orphans.

The mCAR2 variant is missing an additional conserved motif near the C terminus of the ligand binding/dimerization domain, which has been called the 9th heptad (25, 33) or the I-box (26). This region is required for heterodimerization with RXR (e.g. Ref. 27). Since heterodimerization is required for high affinity DNA binding, it is not surprising that the mCAR2 variant does not bind the βRAR or other elements. Particularly, mCAR2 is also missing the conserved AF-2 transactivation motif, it should not compete for coactivator binding, and should not inhibit transactivation by mCAR1, a prediction borne out in appropriate transfections. This leaves the function of the mCAR2 variant undefined, although it is possible that it could compete with the mCAR1 form for interaction with other, as yet undefined proteins.

Previous results have demonstrated a positive feedback loop in which the RARβ2 transcript is strongly induced by retinoids (37, 38). Although the levels of the RARβ2 transcript are very low in the absence of retinoids in some cultured cell lines, this transcript is present at significant levels in the livers of vitamin A-deficient animals (49). The combination of the expression of a number of cDNA clones corresponding to the deleted mCAR also blocks transactivation. This demonstrates that the CAR component of the CAR/RXR heterodimer is actively involved in transactivation. It also confirms a prediction, derived from both sequence conservation and recent results with HNF-4 (48), that the conserved AF-2 motif is involved not only in ligand dependent transactivation, but also in the apparently ligand independent transactivation observed with several other orphans.

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