Role of the Coiled-coil Coactivator (CoCoA) in Aryl Hydrocarbon Receptor-mediated Transcription*

The aryl hydrocarbon receptor (AHR) and AHR nuclear translocator (ARNT) are DNA binding transcription factors with basic helix-loop-helix/Per-Arnt-Sim (bHLH-PAS) domains. These two proteins form a heterodimer that mediates the toxic and biological effects of the environmental contaminant and AHR ligand 2,3,7,8-tetrachlorodibenzo-p-dioxin. The coiled-coil protein coiled-coil coactivator (CoCoA) is a secondary coactivator for nuclear receptors and enhances nuclear receptor function by interacting with the bHLH-PAS domain of p160 coactivators. We report here that CoCoA also binds the bHLH-PAS domains of AHR and ARNT and functions as a potent primary coactivator for them; i.e. CoCoA does not require p160 coactivators for binding to and serving as a coactivator for AHR and ARNT. Endogenous CoCoA was recruited to a natural AHR target gene promoter in a 2,3,7,8-tetrachlorodibenzo-p-dioxin-dependent manner. Moreover, reduction of CoCoA mRNA levels by small interfering RNA inhibited the transcriptional activation by AHR and ARNT. Our data support a physiological role for CoCoA as a transcriptional coactivator in AHR/ARNT-mediated transcription.

Polycyclic or halogenated aromatic hydrocarbons and other related planar organochlorinated compounds elicit many adverse biological effects, including immunosuppression, teratogenesis, tumor promotion, hormonal disregulation, and cardiovascular disease. All of these biological effects are believed to be mediated by the sustained activation of the aryl hydrocarbon receptor (AHR) (1, 2). AHR is a ligand-dependent transcription factor belonging to the basic helix-loop-helix/Per-Arnt-Sim/bHLH-PAS gene family (3). bHLH-PAS proteins share a conserved N-terminal structural motif. The bHLH domain of most (but not all) bHLH-PAS proteins is used for specific DNA binding and/or heterodimerization with other bHLH-PAS proteins. The PAS domain located immediately after the bHLH domain harbors two conserved hydrophobic repeats termed A and B and functions as a sensor of specific environmental signals, a ligand binding surface, and a protein-protein interaction surface in various bHLH-PAS transcription factors, such as AHR and hypoxia-inducible factors. Another member of this family, AHR nuclear translocator (ARNT) is an indispensable heterodimer partner for AHR and hypoxia-inducible factors. In addition to the heterodimerization with AHR or hypoxia-inducible factor 1α, ARNT homodimers are likely to play physiological roles by binding to the E-box core sequence found in some types of enhancer elements (4).

AHR is found in the cytosol in a heterotetrameric complex with two Hsp90 molecules and one X-associated protein 2 (XAP2) molecule (5, 6). Upon binding of xenobiotic compounds such as TCDD, the complexes translocate to the nucleus, where the AHR heterodimerizes with ARNT after Hsp90 dissociation (2, 6). Heterodimeric AHR/ARNT complexes bind to specific enhancer elements called xenobiotic response elements (XREs) found in the regulatory domains of numerous genes (7). Genes transcriptionally activated by AHR/ARNT encode several enzymes that metabolize xenobiotic compounds (e.g. cytochrome P-450 enzymes such as CYP1A1) and proto-oncogenes c-jun and c-fos (8, 9). AHR is also apparently involved in hepatic growth and development of the immune system, based on the phenotype of AHR knock-out mice, and may play a role in the cell cycle (10, 11).

Despite the structural and functional differences between AHR/ARNT and nuclear receptors (NRs), both are ligand-regulated transcription factors and share common coregulators to mediate their transcription-enhancing activities. For example, the NR corepressor SMRT binds to AHR/ARNT and inhibits AHR/ARNT activity (12). The AHR/ARNT heterodimer also interacts with NR coactivators such as the p160 coactivators SRC-1, GRIP-1, and p/CIP (13, 14), which enhance AHR/ARNT-mediated transcription in transient reporter gene assays. Although they have not been shown to bind DNA, the p160 coactivators also contain N-terminal bHLH-PAS domains (3, 15). Furthermore, p160 coactivators are recruited to the CYP1A1 enhancer region in a TCDD-dependent fashion (13).

We previously isolated a novel NR coactivator, CoCoA, using the bHLH-PAS domain of GRIP1 as bait in a yeast two-hybrid screen (16, 17). CoCoA is a new type of NR coactivator with a potent C-terminal activation domain and a central coiled-coil domain that binds the bHLH-PAS motif of p160 coactivators. Thus, CoCoA acts as a secondary coactivator for NRs, interacting with them indirectly through the primary p160 coactivators. Given the shared bHLH-PAS domains among p160 coactivators and bHLH-PAS transcription factors, we tested whether CoCoA could physically and functionally interact with AHR and ARNT as a coactivator in TCDD-dependent gene activation.

Received for publication, July 28, 2004, and in revised form, September 20, 2004 Published, JBC Papers in Press, September 20, 2004 DOI 10.1074/jbc.M408535200

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* This work was supported in part by National Institutes of Health Grant DK43093 (to M. R. S.). The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked “advertisement” in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

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§ The abbreviations used are: AHR, aryl hydrocarbon receptor; ARNT, AHR nuclear translocator; CoCoA, coiled-coil coactivator; NR, nuclear receptor; bHLH/PAS, basic helix-loop-helix/Per-Arnt-Sim; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; XRE, xenobiotic response element; ChIP, chromatin immunoprecipitation; CBP, cAMP-response element-binding protein (CREB)-binding protein; H4, histone H4; GST, glutathione S-transferase; HFK cells, human embryonic kidney cells; siRNA, small interfering RNA; ER, estrogen receptor; DBD, DNA-binding domain.
Chromatin Immunoprecipitation (ChIP)—HeLa-1 cells were treated with 10 nM TCDD for 60 min. ChIP assays were performed largely as described previously (17). The cross-linked, sheared chromatin solution was used for immunoprecipitation with 5 μl of anti-AHR antibody MA1–513 (Affinity BioReagents), 2 μg of anti-GRIP1 antibody A300–025A (Bethyl Laboratories), or 10 μl of an equal mixture of the two rabbit antisera against CoCoA (17). The immunoprecipitated DNAs were purified by phenol-chloroform extraction, precipitated by ethanol, and amplified by PCR using primers flanking the murine CYP1A1 enhancer region (−1141 to −784 from the transcription initiation site) or β-actin promoter region (−527 to −205): CYP1A1 (−1141–−784), 5′-CTAATTCGTATTTAACAAAAACCAACCCCAA-3′ (forward) and 5′-CTAAGTATGTTGAGAAGGGTG-3′ (reverse); β-actin (−527 to −205), 5′-ATTGTCAGACATTGTGACAGGGGAGT-3′ (forward) and 5′-GAGAAGCGAGATTGGAGAGGAGGAG-3′ (reverse).

**RNA Interference and Reverse Transcription-PCR—**COS-7 transfection with siRNAs, reverse transcription-PCR, and luciferase assays were performed as described previously (17). Hepa-1 cells were plated into 12-well plates, grown until 70–80% confluence, and transfected with 40 or 80 pmol of scrambled sequence or CoCoA-specific siRNA duplex using Lipofectamine 2000 after the manufacturer's instructions. Total RNA was extracted with TriZol reagent (Invitrogen). The reverse transcription-PCR analysis was performed with 1–50 ng of total RNA using the Access reverse transcription-PCR system (Promega). The primers used in reverse transcriptase-PCR reactions were as follows: CoCoA, 5′-CACCTCATATATCCCAAGCAACCTAAG-3′ (forward) and 5′-CTTCACTGACTTTGACT-3′ (reverse); CYP1A1, 5′-CCAGATCTTGAGTGTTGGTAG-3′ (forward) and 5′-CTCAGAAAATTTGAGGAGGG-3′ (reverse); β-actin, 5′-CTGGAATGTTGAGATGGTGAGATGG-3′ (forward) and 5′-TGGTGGGGCATCAGCACTTTTG-3′ (reverse).

**RESULTS**

**CoCoA Interacts with AHR and ARNT**—Because the bHLH-PAS domain of the p160 coactivators is also present in AHR, ARNT, and other bHLH-PAS transcription factors, we tested whether CoCoA has the ability to interact with AHR and ARNT. In an *in vitro* GST pull-down assay GST-CoCoA efficiently bound full-length AHR and ARNT synthesized in *vitro* (Fig. 1, A and B). The interaction with AHR was TCDD-independent. To study *in vivo* interactions by co-immunoprecipitation, COS-7 cells were transfected with expression plasmids for V5-tagged CoCoA and HA-tagged AHR or ARNT. Anti-V5 antibodies efficiently and specifically precipitated AHR and ARNT (Fig. 1, A and B). Again, the interaction between CoCoA and AHR was TCDD-independent (data not shown). Other AHR coactivators can also bind efficiently to AHR without its...
CoCoA Potentiates Dioxin-dependent AHR/ARNT-mediated Transcription—CoCoA functions as a secondary coactivator to enhance transcription by NRs; i.e., CoCoA binds to NRs indirectly through p160 coactivators, and the ability of CoCoA to enhance NR function depends on the presence of p160 coactivators (17). In contrast, CoCoA appears to interact directly with AHR and ARNT (Figs. 1 and 2). To investigate whether CoCoA can function as a primary coactivator for AHR-ARNT, we transfected AHR-ARNT-positive Hepa-1 cells with a luciferase reporter plasmid controlled by the XRE-containing CYP1A1 promoter together with expression vectors for GRIP1, CoCoA, or both. TCDD treatment alone enhanced CYP1A1 promoter-driven luciferase activity nearly 28-fold (Fig. 4A, assay 1). As expected (13), overexpression of GRIP1 enhanced AHR function in a dose-dependent and TCDD-dependent manner (assays 2–5). CoCoA expression increased TCDD-dependent reporter gene activity up to 5-fold (assays 6–9). This stimulation of AHR-ARNT activity was dependent on the amount of CoCoA, and the magnitude of stimulation was similar to that produced by GRIP1 under the same conditions. Despite the fact that CoCoA binds to AHR in a ligand-independent manner (Fig. 1A), the effect of CoCoA on AHR-mediated transactivation was TCDD-dependent. When CoCoA was co-expressed with GRIP1, an additive induction of AHR-ARNT-mediated transactivation was observed (assays 10–11). These results suggest that GRIP1 and CoCoA both interact directly with AHR-ARNT, function as primary coactivators, and make distinct contributions to AHR/ARNT-mediated transcriptional activation.

Although p160 coactivators contain an N-terminal bHLH-PAS domain, they do not utilize this domain to interact with AHR and ARNT; instead a C-terminal region of p160 proteins, just proximal to the p300/CBP binding AD1 domain, binds to the bHLH-PAS domains of AHR and ARNT (13). Therefore, we tested whether a GRIP1ΔN mutant lacking the bHLH-PAS domain could enhance AHR-ARNT function and cooperate with CoCoA. The GRIP1ΔN mutant enhanced AHR-ARNT function in a dose-dependent manner (Fig. 3B, assays 4 and data not shown). Furthermore, coexpression of CoCoA with the GRIP1ΔN mutant further potentiated the activity of AHR (Fig. 3B, assays 8–9). Thus, the bHLH-PAS domain of GRIP1 is not required for the coactivator function of CoCoA with AHR. These data are consistent with the conclusion that CoCoA interacts directly as a primary coactivator with AHR and ARNT. This result contrasts starkly with the secondary coactivator function of CoCoA with NRs, which depends entirely on the presence of a p160 coactivator with an intact N-terminal region (17).
CoCoA as a Coactivator for AHR and ARNT—CoCoA was initially identified as a novel type of NR coactivator with a coiled-coil domain (17). CoCoA binds to the bHLH-PAS domain of p160 coactivators but not directly to NRs, and the ability of CoCoA to enhance the activity of steroid receptors is highly dependent on the presence of a p160 coactivator with an intact N-terminal bHLH-PAS domain. By these characteristics, CoCoA is classified as a secondary coactivator for nuclear receptors (16). In contrast, CoCoA bound to AHR and ARNT in vitro and in vivo and functioned as a coactivator for AHR and ARNT without co-expression of p160 coactivators or any other exogenously expressed proteins (Figs. 1 and 3). Thus, CoCoA binds indirectly to NRs and functions as a secondary coactivator for them but appears to bind directly to AHR-ARNT and serves as a primary coactivator for AHR-ARNT.

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activity of a coactivator for AHR-ARNT under those conditions. Under more physiologically relevant conditions endogenous CoCoA was efficiently recruited together with AHR to the endogenous CYP1A1 promoter in a TCDD-dependent fashion (Fig. 5) and was required for efficient TCDD induction of the endogenous CYP1A1 gene by AHR and for the autonomous transcriptional activation activity of ARNT (Fig. 6). These findings demonstrate that CoCoA is a physiologically relevant part of transcriptional activation by AHR-ARNT.

Interestingly, we observed that the CoCoA mRNA level was up-regulated more than 2-fold by TCDD. Obviously, the resulting increase in CoCoA may further enhance AHR-ARNT activity. The regulation of CoCoA by ligand-activated AHR-ARNT is an additional physiological link between CoCoA and AHR-ARNT. The mechanism by which AHR-ARNT regulates CoCoA levels may involve direct binding of AHR-ARNT to the CoCoA gene promoter, since a putative AHR-ARNT binding sequence occurs within the proximal CoCoA promoter. Thus CoCoA and AHR-ARNT mutually regulate each other; AHR-ARNT regulates CoCoA levels, and CoCoA serves as a coactivator for AHR-ARNT.

Interaction of CoCoA with Multiple Classes of bHLH-PAS Proteins—The interaction between CoCoA and AHR appears to be direct and involves two distinct regions within AHR, the N-terminal bHLH-PAS domain and a second site within the C-terminal activation domain (Fig. 2). AHR bound CoCoA in a ligand-independent manner, suggesting that CoCoA may exist in a complex with AHR before ligand activation and after ligand binding travels with AHR to its target promoter. CoCoA and AHR are both recruited to the CYP1A1 promoter in a TCDD-dependent manner (Fig. 5), and CoCoA fails to enhance the activity of the CYP1A1 promoter in the absence of TCDD (Fig. 3). The ligand-independent association of AHR with CoCoA and other coactivators (13, 18–20) is in contrast to the interactions of many coactivators with NRs and may result from different structural organizations of AHR and NR proteins. Unlike the steroid receptors, where the ligand binding pocket and the important AF-2 activation function are part of the same structural domain, the major C-terminal activation domain of AHR is well separated from the N-terminal ligand binding domain; this may allow ligand-independent interactions between activation domain and coactivators.

In contrast to the situation with AHR, CoCoA interacts with the bHLH-PAS domain but not with the activation domain of ARNT (Fig. 2C). These observations are consistent with previous reports which indicate that deletion of the C-terminal activation domain of ARNT failed to have a significant effect on activation of a reporter gene under control of the CYP1A1 enhancer and promoter, leading to the conclusion that the activation domain of AHR is dominant over that of ARNT during transcriptional activation (24, 25).

In general, the bHLH-PAS superfamily can be divided into three subgroups; members of one group are regulated in their expression or activity by binding of ligands or by cellular con-
Implications of CoCoA as a Common Coactivator for NRs and for AHR-ARNT—The fact that CoCoA serves as a common coactivator for two different classes of DNA binding transcription factors suggests a novel avenue for cross-talk between these two signaling pathways. It is interesting to note that TCDD inhibits several estrogen-dependent biological responses, decreases cellular estrogen receptor (ER) and progesterone receptor levels (26), and inhibits transcription of estrogen-regulated genes (27). Conversely, 17β-estradiol (E2) can inhibit TCDD-induced reporter gene activity (28). The possible mechanisms proposed for inhibitory AHR-ER cross-talk include induction of inhibitory factors, enhanced E2 metabolism, proteasome-dependent degradation of ERs by non-genomic inhibitory effects of AHR, and competition for common nuclear coactivators (29). Recent studies report that TCDD-induced interactions between AHR and ERs enhance ubiquitylation of ERs and subsequent proteasome-dependent degradation of ERs (30).

NRs and AHR-ARNT have been reported to interact with many common coactivators and components of the transcription machinery, including CoCoA, p160 coactivators (13, 14), p300/CBP (31), BRG-1 (22), ERAP1/40 (12), RIP140 (19), basal transcription factors (32), and mediator complex (33). In addition, a recent study has shown that ARNT, the obligatory heterodimerization partner for AHR, also functions as a coactivator of ERα and ERβ (34). Some transcription factors have been reported to compete with one another for binding with limiting coactivators, resulting in mutually antagonistic effects (35, 36). Competition for binding and squelching of these limiting common coactivators could be one of the mechanisms for the anti-estrogenic activity of TCDD. Our results add an additional possibility that cellular availability of CoCoA may also be an important factor in regulating ER and AHR transcriptional activities.

Acknowledgments—We thank Drs. Oliver Hankinson and Timothy Beischlag for plasmids expressing mouse AHR, ARNT, and GAL4-ARNT, for CYP1A1-luciferase reporter plasmid, and for Hepa-1 cells. We thank Dan Gerke for expert technical assistance.

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