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Myb-binding Protein 1a Augments AhR-dependent Gene Expression*

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We have studied the mechanism by which an acidic domain (amino acids 515–583) of the aromatic hydrocarbon receptor (AhR) transactivates a target gene. Studies with glutathione *S*-transferase fusion proteins demonstrate that the wild-type acidic domain associates *in vitro* with Myb-binding protein 1a, whereas a mutant domain (F542A, I569A) does not. AhR-defective cells reconstituted with an AhR containing the wild-type acidic domain exhibit normal AhR function; however, cells reconstituted with an AhR containing the mutant acidic domain do not function normally. Transient transfection of Myb-binding protein 1a into mouse hepatoma cells is associated with augmentation of AhR-dependent gene expression. Such augmentation does not occur when Myb-binding protein 1a is transfected into AhR-defective cells that have been reconstituted with an AhR that lacks the acidic domain. We infer that 1) Myb-binding protein 1a associates with AhR, thereby enhancing transactivation, and 2) the presence of AhR's acidic domain is both necessary and sufficient for Myb-binding protein 1a to increase AhR-dependent gene expression.

The aromatic hydrocarbon receptor (AhR)[1] is an intracellular protein that mediates transcriptional responses to certain hydrophobic ligands, the most notorious of which is the widespread environmental contaminant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD, dioxin) (1–4). The liganded AhR heterodimerizes with a second protein, known as the AhR nuclear translocator (Arnt), to form a complex that activates transcription by binding to an enhancer in the vicinity of the TCDD-responsive target gene (5, 6). Both AhR and Arnt are prototypical members of the basic helix-loop-helix/Per-Arnt-Sim class of transcription factors, which regulate gene expression in response to a variety of environmental and developmental signals (7–11).

Much of our understanding of AhR/Arnt-dependent transcription stems from analyses of the TCDD-inducible *CYP1A1* gene in mouse hepatoma cells; this experimental system benefits from the availability of AhR-defective and Arnt-defective cells. Efficient reconstitution of such cells by retroviral infection permits analyses of AhR and Arnt mutants in a relatively physiological setting (12–14). Studies of *CYP1A1* gene regulation in mouse hepatoma cells reveal that exposure to TCDD leads to the binding of AhR/Arnt to an enhancer upsteam of the *CYP1A1* gene. The C-terminal portion of AhR (which contains several transactivation domains) communicates the induction signal to the neighboring promoter, which then assumes a more accessible chromatin structure and binds general transcription factors (12, 13). Such observations reveal that the transactivation domains of AhR facilitate enhancer-promoter communication by a process that involves changes in the structure of promoter chromatin and occupancy of promoter binding sites by the transcriptional machinery.

Here, we have studied AhR-dependent transactivation in more detail; we have focused on a relatively small (69 amino acid) domain of AhR that is rich in acidic residues and can transactivate the native chromosomal *CYP1A1* gene (13). Our observations indicate that this acidic activation domain (AAD) of AhR associates with a factor previously identified as Myb-binding protein 1a (Mybbp1a) and that Mybbp1a substantially augments the ability of AhR/Arnt to activate transcription. These findings reveal new aspects of AhR and Mybbp1a function.

EXPERIMENTAL PROCEDURES

Materials—The pGudLuc6.1 vector was provided by Dr. Michael S. Denison (University of California, Davis, CA); it contains an AhR/Arnt-dependent enhancer and the mouse mammary tumor virus promoter upstream of a firefly luciferase reporter gene (15). The QuikChange Site-Directed Mutagenesis Kit and *Pfu* DNA polymerase were purchased from Stratagene (La Jolla, CA). The pRL-CMV vector and Dual-Luciferase Report Assay System were purchased from Promega (Madison, WI). The retroviral vector pMFG was derived from the Moloney murine leukemia virus (16). The Phoenix-eco retroviral producer cell line (17) was provided by Dr. Garry Nolan (Stanford University). The pGEX-2T vector and glutathione-Sepharose were purchased from Amersham Biosciences. [α-^{32}]dCTP (3,000 Ci/mmol) and Renaissance Chemiluminescence Kit were purchased from PerkinElmer Life Sciences. The RNeasy Kit was from Qiagen (Valencia, CA). Reagents for SDS-PAGE and silver staining were from Bio-Rad. Hyperfilm MP was from Amersham Biosciences. Tissue culture reagents were from Life Invitrogen.

Cell Culture—Wild-type (Hepa1c1c7) and AhR-defective (Taoc1BP^{r}cl) mouse hepatoma cells were cultured as described previously (18). Phoenix cells were cultured as described previously (17).

Plasmid Construction—Mutations to alanine were made in AhR's acidic segment at Phe^{542} and Ile^{569} using the QuikChange Site-Directed Mutagenesis Kit (Stratagene) according to the manufacturer's instructions. Plasmid pGAhR$_{515–583}$ (13) was as used as a template for the sense and antisense mutation primers. Mutations were confirmed by nucleotide sequencing.

Wild-type and mutant pGAhR$_{515–583}$ plasmids were used as tem-

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[1] The abbreviations used are: AhR, aromatic hydrocarbon receptor; AAD(s), acidic activation domain(s); Arnt, AhR nuclear translocator; Mybbp1a, Myb-binding protein 1a; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; GST, glutathione *S*-transferase.

plates to PCR amplify sequences encoding AhR amino acids 515–583 for insertion into pMFGAhR$_{494}$ (13). Both the forward primer (5′-ACTACTGCAGCGGCCGCACTCTCTGGCGGCCCCTCAGAG-3′) and reverse primer (5′-ACTACTGCAGCGGCCGC**TCA**CAGGGAATCCTGCACGTAGGT-3′) contained *Not*I sites (underlined), and the reverse primer contained a stop codon (bold). The PCR products were digested with *Not*I and subcloned into the internal *Not*I site (amino acids 492–494) of AhR in plasmid pMFGAhR$_{494}$.

Wild-type and mutant pGAhR$_{515–593}$ (13) were also amplified for insertion into pGEX-2T, an expression plasmid for glutathione *S*-transferase fusion proteins. A linker sequence containing a *Bam*HI site was attached to the forward primer, and the reverse primer was linked to an *Eco*RI site. The resulting PCR products were ligated in-frame into *Bam*HI and *Eco*RI sites within the polylinker region of pGEX-2T, generating plasmids pGST-AAD and pGST-mutAAD.

Construction of the expression plasmid for Mybbp1a has been described previously (19).

Expression of GST Fusion Proteins and GST Pull-down Assays—GST fusion proteins were expressed in *Escherichia coli* by induction with 0.5 mM isopropyl β-D-thiogalactopyranoside. Cells were lysed 3 h after induction by five successive freeze-thaw cycles. After centrifugation, the lysates were incubated with GST-Sepharose beads (500 μl per 500-ml culture) for 30 min at room temperature. The beads were gently pelleted and then washed extensively with phosphate-buffered saline.

Whole-cell extracts were prepared from mouse hepatoma cells as described previously (20) and were incubated with GST fusion proteins (~10 μg) in NETN buffer (20 mM Tris (pH 8), 150 mM NaCl, 1 mM EDTA, and 0.5% Nonidet P-40) for 1 h at 4 °C with shaking. After the binding reaction, the beads were washed five times with binding buffer and then boiled in SDS sample buffer. The solubilized proteins were fractionated on SDS gels and visualized by silver staining. For protein sequencing, binding reactions were scaled up 10-fold, fractionated by SDS-PAGE, and transferred to Immobilon-P^{SQ} for protein microsequencing. Protein sequence determination was performed by the Protein/DNA Technology Center of the Rockefeller University (21, 22).

Transient Transfections—Wild-type or reconstituted AhR-defective mouse hepatoma cells were plated in 35-mm six-well tissue culture dishes and incubated overnight. Cells were co-transfected using a polybrene method (23) with 2 μg of pGudLuc6.1, 10 ng of pRL-Luc (expression plasmid for *Renilla* luciferase, used to control for transfection efficiency) (Promega), and 0, 0.5, 1.0, 2.5, or 5.0 μg of Mybbp1a expression plasmid. Twenty-four hours after transfection, luciferase activities were determined using the Dual-Luciferase Reporter Assay System (Promega) according to the manufacturer's instructions. Light production was measured using a Lumat LB 9507 luminometer. All experiments were performed at least three times, and the data are expressed as mean ± S.E.

Retroviral Expression of AhR—Five micrograms of pMFGAhR, pMFGAhR$_{494}$, pMFGAhR$_{494/515–583}$, and the pMFGAhR$_{494–515–583}$ mutants were transfected into the ectotropic packaging cell line, Phoenix, as described previously (17). Recovery of retroviruses and infection of AhR-defective mouse hepatoma cells was carried out as described previously (12).

Analysis of CYP1A1 Gene Expression—Wild-type, AhR-defective, and reconstituted mouse hepatoma cells were grown to ~80% confluence in 100-mm tissue culture dishes and were treated with 1 nM TCDD or 0.1% Me_2SO for 18 h. Total RNA was isolated using RNeasy spin columns (Qiagen). Total RNA (5 μg) was fractionated on 1.2% agarose-2.2 M formaldehyde gels, transferred to Nytran by capillary blotting in 20 × SSC, and cross-linked to the membrane in a UV Stratalinker 2400 (Stratagene). Blots were hybridized with ^{32}P-labeled CYP1A1 or actin cDNA overnight at 55 °C using ExpressHyb hybridization solution (CLONTECH). Blots were washed as described previously (24) and then autoradiographed with Hyperfilm MP (Amersham Biosciences).

Immunoblotting Analysis—Whole-cell extracts were prepared from wild-type, AhR-defective, and reconstituted cells as described above. Forty micrograms of cellular proteins were dissolved in 2× Laemmli sample buffer (Bio-Rad), fractionated by SDS-PAGE, and transferred to a polyvinylidene difluoride membrane. Blots were incubated in blocking buffer (20 mM Tris (pH 7.6), 137 mM NaCl, 0.1% Tween 20 (TBS-T) containing 5% nonfat milk) overnight at 4 °C. Incubation with primary antibody (anti-AhR, 1:2000) (25) was carried out for 1 h at room temperature. After several washes in blocking buffer, blots were incubated with secondary antibody (anti-mouse-HRP, 1:2000) for 1 h at room temperature. After washing in TBS-T, blots were developed using the Renaissance Chemiluminescence Kit (PerkinElmer Life Sciences) and visualized on Hyperfilm MP.

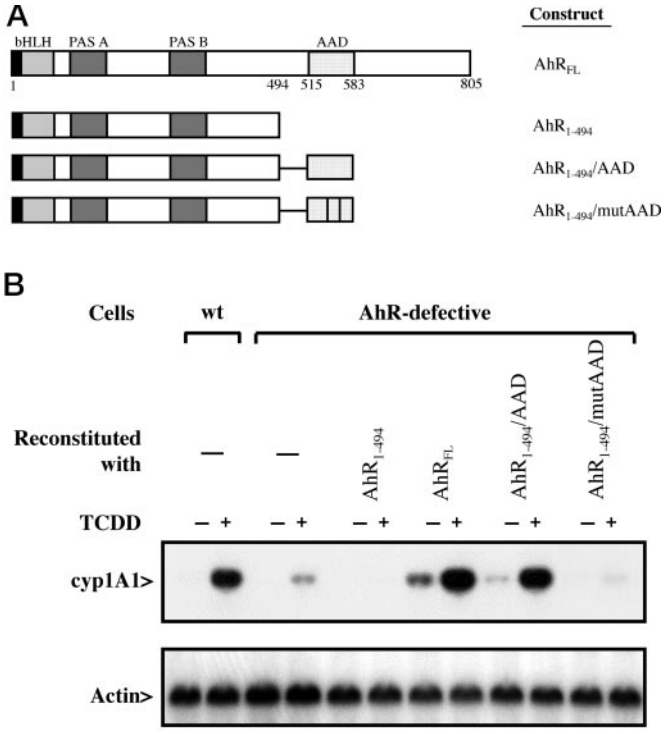

FIG. 1. **Structure and function of AhR constructs.** *A*, structural representation of AhR constructs. *B*, function of AhR constructs. AhR-defective mouse hepatoma cells were reconstituted by retroviral infection with the indicated AhR constructs, and the response of the *CYP1A1* gene to TCDD (1 nM, 24 h) was measured by Northern blotting.

RESULTS

Identification of a Protein That Interacts with AhR's AAD—We envision that transactivation by AhR involves protein-protein interactions that facilitate communication between AhR/Arnt heterodimers bound at an enhancer and other transcription factors that interact with the cognate promoter. To analyze the mechanism of transactivation in further detail, we used a GST pull-down technique to identify proteins that bind to the wild-type AAD but not to a mutant AAD that fails to transactivate. For the mutant AAD, we targeted two hydrophobic residues in regions previously shown to be important for AAD function (14). The mutant contains alanine substitutions at Phe^{542} and Ile^{569} but is otherwise identical to the wild-type AAD (aa 515–583). We fused the wild-type or mutant AAD to AhR's N-terminal half (aa 1–494) to generate AhR$_{1–494}$/AAD and AhR$_{1–494}$/mutAAD, respectively (Fig. 1*A*).

To assess the function of the wild-type and mutant constructs, we introduced them into AhR-defective cells by retroviral infection and used Northern blotting to measure the response of the native chromosomal *CYP1A1* target gene to TCDD. Positive and negative control experiments reveal that reconstitution of AhR-defective cells with full-length AhR restores responsiveness of the *CYP1A1* gene to TCDD, whereas reconstitution with AhR$_{1–494}$ does not (Fig. 1*B*). Reconstitution of AhR-defective cells with the AhR$_{1–494}$/AAD construct restores TCDD-responsiveness to approximately wild-type levels; in contrast, cells reconstituted with AhR$_{1–494}$/mutAAD fail to respond to TCDD (Fig. 1*B*). Immunoblotting experiments indicate that both the wild-type and mutant constructs are expressed at nearly identical levels in the reconstituted cells. Therefore, the failure of the mutant to transactivate is not due to underexpression of the mutant protein (data not shown). These findings extend our previous mutational analysis of AhR's AAD (14) by identifying a double point mutation that

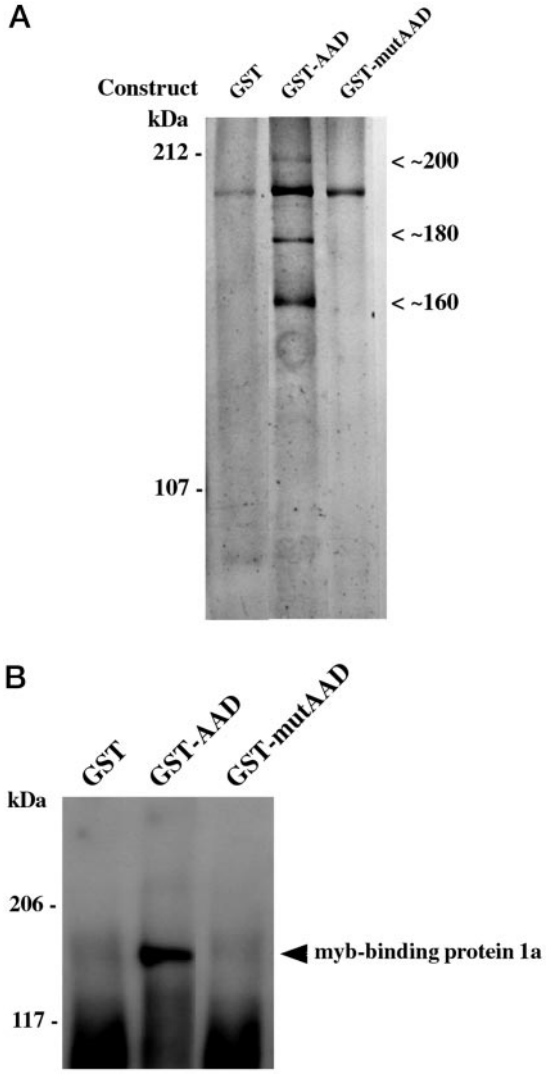

FIG. 2. **Identification of Myb-binding protein 1a as a protein that associates with the AAD of AhR.** *A*, GST pull-down experiments. The indicated GST-AhR fusion proteins were used to isolate interacting proteins, which were fractionated by SDS-PAGE and identified by silver staining. *B*, immunoblotting. Proteins interacting with the indicated GST-AhR fusion proteins were fractionated by SDS-PAGE, transferred to a polyvinylidene difluoride membrane, and identified by immunoblotting, using anti-Mybbp1a as the primary antibody.

abolishes function and provides a useful negative control for GST pull-down experiments.

We constructed GST fusion proteins containing either the wild-type or mutated AAD, attached the fusion proteins to glutathione-Sepharose beads, and allowed the beads to interact with extracts prepared from mouse hepatoma cells. Interacting proteins were purified and analyzed by SDS-PAGE and silver staining. Our findings reveal three proteins, with molecular masses of about 160, 180, and 200 kDa, that interact with the GST-AAD fusion protein but not with the GST-mutAAD fusion protein (Fig. 2*A*). We isolated enough of the most prominent (~160 kDa) AAD-interacting protein to permit its microsequencing; the data revealed that the sequences of two tryptic peptides were identical to sequences within Mybbp1a, a nuclear protein that interacts with c-Myb (19).

We confirmed the identity of the AAD-interacting protein in immunoblotting experiments using an anti-Mybbp1a antibody. Our findings indicate the presence of an immunoreactive ~160-kDa band in pull-down eluates from GST-AAD, but not in eluates from GST-mutAAD or GST alone (Fig. 2*B*). In addition,

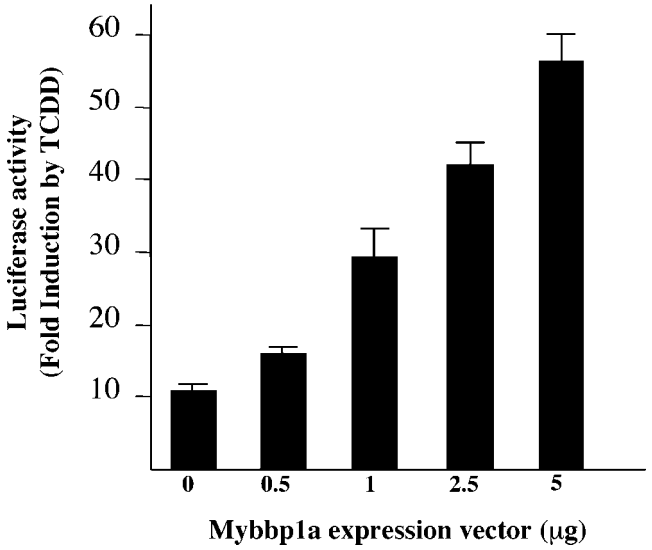

FIG. 3. **Increasing Mybbp1a expression augments AhR/Arnt function.** Mouse hepatoma cells were co-transfected with an AhR/Arnt-dependent firefly luciferase reporter gene, an expression plasmid for *Renilla* luciferase (to control for transfection efficiency), and the indicated amounts of a Mybbp1a expression vector. Luciferase activity was measured in uninduced and TCDD-induced (1 nM, 24 h) cells, and firefly luciferase activity was normalized to *Renilla* luciferase activity.

the immunoreactive band co-localized with the 160 kDa silver-stained band in a gel run in parallel (data not shown). Together, these findings imply that Mybbp1a interacts with the wild-type AAD but not with the mutant AAD. It is notable that the inability of Mybbp1a to interact with the mutant AAD is associated with loss of transactivation capability in the mutant (Fig. 1). This observation tends to implicate Mybbp1a in the transactivation function of the AAD.

Effect of Mybbp1a on AhR-mediated Gene Expression—The above findings led us to ask whether Mybbp1a affects the transactivation capability of AhR's AAD. To address this issue, we co-transfected mouse hepatoma cells with increasing amounts of a Mybbp1a expression vector together with a dioxin-responsive AhR/Arnt-dependent firefly luciferase reporter construct (pGudLuc) and measured TCDD-inducible luciferase activity in the transfected cells. Our findings (Fig. 3) reveal that transfections with increased amounts of Mybbp1a expression vector are associated with increased responsiveness of the reporter gene to TCDD. For example, in cells that contain no Mybbp1a expression vector, TCDD induces luciferase activity about 11-fold; in contrast, at the highest level of Mybbp1a expression vector used, TCDD induces luciferase activity about 56-fold. Thus, in this experimental setting, Mybbp1a can increase the responsiveness of an AhR-dependent gene by (at least) a factor of five.

The results of the expression studies (Fig. 3), together with those of the pull-down experiments (Fig. 2), imply that Mybbp1a influences gene expression via AhR's AAD. To test this idea directly, we used retroviral vectors to reconstitute AhR-defective cells with either AhR_{1-494}/AAD, full-length AhR (as a positive control), or AhR_{1-494} (as a negative control), and we established clonal strains of each reconstituted cell type. Immunoblotting studies confirmed that expression of the AhR constructs in each of the reconstituted cell strains is similar to that of AhR in wild-type cells (data not shown). We then transiently transfected these strains with the AhR/Arnt-dependent firefly luciferase reporter construct (pGudLuc), to document that the augmentation of AhR-dependent gene expression by Mybbp1a requires the AAD. The positive and negative controls reveal, as expected, that Mybbp1a augments the response of

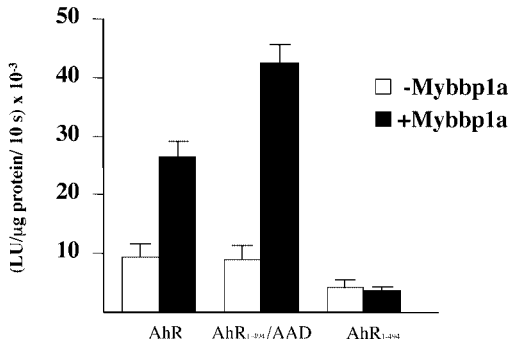

FIG. 4. **Augmentation of AhR/Arnt function by Mybbp1a requires the AAD of AhR.** AhR-defective cells were reconstituted by retroviral infection with the indicated AhR constructs, and clonal strains were established. Each strain was co-transfected with an AhR/Arnt-dependent luciferase reporter gene either with or without a Mybbp1a expression vector, as indicated. Luciferase activity was measured in TCDD-induced (1 nM, 24 h) cells, normalized to protein concentration in each of the sublines, and expressed as specific activity. *LU*, light units.

the reporter gene in cells reconstituted with full-length AhR but not in cells reconstituted with AhR$_{1-494}$. Notably, in cells reconstituted with AhR$_{1-494}$/AAD, Mybbp1a augments luciferase expression as effectively as it does in the positive control cells (Fig. 4). These findings imply that the AAD is both necessary and sufficient for Mybbp1a to augment AhR-dependent gene expression.

DISCUSSION

To better understand the mechanism by which AhR transactivates its target genes, we identified Mybbp1a as a factor that associates with AhR's AAD *in vitro* and augments AhR function *in vivo*. Our findings are consistent with previous observations that Mybbp1a may influence transactivation in other systems (19). Prior analyses of *CYP1A1* gene regulation indicate that the C-terminal portion of AhR mediates enhancer-promoter communication, producing an accessible chromatin structure that facilitates promoter occupancy (12, 13). The findings in this paper imply that Mybbp1a participates in this process.

We have shown previously that hydrophobic residues that are clustered in two regions of AhR's acidic segment are important for transactivation function (14). Here, we observe that mutation of Phe^{542} and Ile^{569} within the AAD abolishes not only its association with Mybbp1a but also its transactivation capability. These findings imply that hydrophobic forces are important both for the association between the two proteins and for transactivation function. Previous studies imply that Mybbp1a binds to c-Myb and to c-Jun via leucine zipper-like motifs (19, 28). However, AhR's AAD does not contain a leucine zipper; therefore, its association with Mybbp1a must involve a different type of interaction. This conclusion is consistent with other findings which imply that Mybbp1a influences Myb-dependent and AhR-dependent gene regulation by different mechanisms. For example, Mybbp1a associates with a negative regulatory domain in the Myb protein (19). In contrast, we find that Mybbp1a interacts with a transactivation domain of AhR. Furthermore, overexpression of Mybbp1a fails to alter Myb-dependent gene expression (19). In contrast, we find that overexpression of Mybbp1a augments AhR-dependent transcription. Taken together, these observations imply that Mybbp1a can utilize several different molecular mechanisms to influence gene expression.

Our GST pull-down experiments reveal that Mybbp1a can associate with AhR's AAD *in vitro* in the absence of TCDD. Therefore, we infer that TCDD is not required to induce a factor(s) that facilitates the Mybbp1a-AhR interaction. The constitutive interaction observed *in vitro* may not occur in intact cells, because, for the most part, the two proteins occupy different subcellular compartments; the unliganded AhR is cytoplasmic, while Mybbp1a is found in the nucleolus and in the nucleoplasm (19). It is conceivable that AhR interacts with Mybbp1a in the cytoplasm because Mybbp1a exhibits nuclear-cytoplasmic shuttling.[2] However, at any one time, most of the Mybbp1a is in the nucleus. Because of such compartmentalization, we envision that the two proteins do not have an opportunity to associate *in vivo* until the AhR enters the nucleus following exposure of cells to TCDD or another ligand.

Our studies reveal that increased expression of Mybbp1a substantially augments the response of an AhR/Arnt-dependent reporter gene to TCDD. This observation implies that the availability of Mybbp1a can be a limiting factor for maximal AhR/Arnt function. We envision that the restricted availability of Mybbp1a reflects its localization primarily in the nucleolus (19). The mechanism by which Mybbp1a augments AhR/Arnt function remains to be determined. We hypothesize that Mybbp1a contributes via protein-protein interactions to the formation of productive transcriptional complexes at AhR/Arnt-dependent promoters. This process could involve recruitment and/or stabilization of any of numerous factors that participate in the transcription of genes in chromatin (29–33). In this regard, we note that Mybbp1a contains several so-called LCD motifs, which have been implicated in protein-protein interactions involved in inducible gene expression in other systems (20, 34–36). Our experiments do not reveal whether Mybbp1a is essential for AhR/Arnt function; studies in Mybbp1a-defective cells could address this issue in the future.

Our studies re-emphasize the concept that AhR has a modular organization and that different domains of AhR subserve different functions. Our observation that the AAD of AhR can substitute functionally for the entire C-terminal portion of AhR (which contains several transactivation domains) suggests that the C-terminal portion exhibits redundancy with respect to its transactivation capability. One possible advantage of such redundancy is that it might improve the ability of AhR/Arnt to communicate with transcriptional promoters that differ in their cognate binding proteins. In this respect, it is notable that a second, glutamine-rich transactivation domain within AhR's C-terminal portion probably interacts with proteins that are different from those that interact with the AAD (37, 38). Given this situation, we speculate that the AAD and the glutamine-rich domain of AhR preferentially communicate with different sets of transcriptional promoters. This may be an interesting area for future research.

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