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Aryl hydrocarbon receptor-mediated suppression of GH receptor and Janus kinase 2 expression in mice

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Abstract Differential mRNA display revealed that a cDNA encoding the major urinary protein 2 (MUP2) that belongs to the lipocalin superfamily was absent in livers of mice treated with 3-methylcholanthrene (MC). The expression of MUP2 is known to be stimulated by growth hormone (GH), through the GH receptor (GHR), Janus kinase 2 (JAK2) and signal transducer and activator of transcription 5 (STAT5) signal transduction pathway. Since MC is an aryl hydrocarbon receptor (AhR) ligand, the effects of MC treatment on the expression of GHR, JAK2 or STAT5 in the livers of wild-type or AhR-null mice were examined. The result indicated that the expression of GHR and JAK2 mRNA was greatly decreased by MC in wild-type mice but not in AhR-null mice. In addition, the binding activity of STAT5 bound to STAT5-binding element was reduced after MC treatment in wild-type mice but not in AhR-null mice. Based on these results, we conclude that the suppression of MUP2 mRNA expression by MC is caused by the AhR-mediated disruption of the GH signaling pathway. Possible mechanism(s) by which exposure to aromatic hydrocarbons causes a decrease in the body weight of mice, which has been referred to as wasting syndrome, will also be discussed.

Key words: Aryl hydrocarbon receptor; Growth hormone receptor; 3-Methylcholanthrene; Janus kinase 2; Major urinary protein; Signal transducer and activator of transcription 5; Wasting syndrome

1. Introduction

Exposure to halogenated aromatic hydrocarbons such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related polycyclic aromatic hydrocarbons (PAHs) results in a variety of biological responses including wasting syndrome, epithelial hyperplasia, teratogenesis, tumor promotion and the induction of enzymes responsible for the metabolism of xenobiotics, such as cytochrome P450 (CYP) [1–5]. It is the consensus view that most of the biological responses to TCDD and related PAHs are mediated by a cytosolic protein designated the aryl hydrocarbon receptor (AhR), which exists in the cytosol as a part of a complex that has a molecular mass of about 280 kDa [6,7]. Upon binding of TCDD with AhR, AhR dissociates from the above complex and translocates to the nucleus where it heterodimerizes with a structurally related protein, called the AhR nuclear translocator (Arnt) [8]. The heterodimeric AhR/Arnt complex binds to a 5-bp sequence, named xenobiotic-responsive element (XRE) (5′-GCGTG-3′), located within the 5′-flanking region of the AhR target genes, *CYP1A1*, *CYP1A2* and *CYP1B1* [9].

A phenomenon known as wasting syndrome is observed in wild-type (WT) mice treated with TCDD but not in AhR-null mice treated with TCDD [10]. In addition, teratogenesis such as cleft palate and hydronephrosis is seen upon treatment of dams with TCDD [4,10], while AhR-null mice do not exhibit teratogenesis after treatment with this agent [10]. These findings suggest that the toxicities seen with TCDD are mediated by AhR. However, the AhR target genes involved in the wasting syndrome and teratogenesis have not yet been elucidated.

To determine causal genes for the toxicity of dioxins and PAHs, we examined molecular changes in gene expression profiles caused by treatment of mice with 3-methylcholanthrene (MC) by using differential mRNA display. We found a cDNA that disappeared upon treatment of mice with MC. This cDNA encoded major urinary protein 2 (MUP2), which is a group of closely related proteins secreted into mouse urine [11] and known to be a member of the lipocalin superfamily of proteins [12]. The expression of MUP2 is thought to be mediated by the growth hormone (GH) [13,14]. Signal transduction pathway binding of GH to the GH receptor (GHR) promotes the association of the GHR with the Janus kinase 2 (JAK2) and tyrosyl phosphorylation of JAK2. Then activated JAK2 phosphorylates the tyrosine residues of a signal transducer and activator transcription (STAT) protein. The homodimer of the STAT or heterodimer of STAT protein with other factor(s) is found in the cytoplasm. The complex then translocates to the nucleus, and then binds to target sequences. Supporting this idea, STAT5 has been reported to participate in the GH-induced expression of MUP2, cytokine-inducible SH2-containing protein (CIS) or α-whey acidic protein (WAP) [15–17].

In the present study, we found that the expression of GHR

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Abbreviations: AhR, aryl hydrocarbon receptor; Arnt, AhR nuclear translocator; CIS, cytokine-inducible SH2-containing protein; CYP, cytochrome P450; EMSA, electrophoretic mobility shift assay; GAS, γ-interferon-activated site; GH, growth hormone; GHR, growth hormone receptor; JAK2, Janus kinase 2; MC, 3-methylcholanthrene; MUP, major urinary protein; PAH, polycyclic aromatic hydrocarbon; PCR, polymerase chain reaction; RT, reverse transcription; STAT, signal transducer and activator of transcription; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; WAP, α-whey acidic protein; WT, wild-type; XRE, xenobiotic-responsive element

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and JAK2 mRNAs was inhibited by MC, resulting in a decrease in the binding activity of STAT5 for the STAT5-binding site. We discuss the possible mechanism(s) by which exposure to PAHs leads to a decrease in body weight, which is known as the wasting syndrome.

2. Materials and methods

2.1. Animal treatment

Male 7-week-old C57BL/6J mice (Sankyo Experimental Animals, Tokyo, Japan) and AhR-null mice [18] were treated with MC (Sigma, St. Louis, MO, USA) dissolved in corn oil at a dose of 80 mg/kg/day intraperitoneally once daily for 2 days. Twenty-four hours after the last administration, the mice were killed, and the livers were removed and immediately used for the following experiments.

2.2. Differential mRNA display

Total RNAs were prepared from the livers of mice by the guanidinium/cesium chloride method [19]. Reverse transcription polymerase chain reaction (RT-PCR)-based differential mRNA display was performed by using a fluorescence differential display kit (Takara, Kyoto, Japan) essentially according to the manufacturer's instructions [20] with minor modifications. Briefly, total RNA (0.5 μg) and the two-base-anchored 5′-fluorescein-labeled oligo(dT) primer (5′-T_{13-16}AC-3′) were used for RT reaction. cDNA was synthesized by means of PCR using an arbitrary primer (5′-CTGCTTGATG-3′). The PCR products were separated on a 6% DNA sequencing gel and analyzed by autofluorography (FLA2000, Fuji Film, Tokyo, Japan). Differentially expressed cDNAs were recovered from the gel, and then amplified using the same PCR primers. Amplified cDNAs were subcloned into the pGEM-T® Easy Vector (Promega, Madison, WI, USA) and transformed into competent *Escherichia coli* cells. Plasmids which contained inserts were subjected to sequencing. Using a Bigdye primer cycle sequencing kit (PE Applied Biosystems, Foster City, CA, USA) on an ABI 310 automated sequencer (PE Applied Biosystems), a sequence similar to the isolated cDNA was sought by using the BLAST 2.1 program.

2.3. Northern blot analysis

Total RNAs were prepared from the livers of WT mice or WT mice treated with MC as previously reported [20]. A part of MUP2 cDNA [11] (593–774, relative to the initiation codon) was used as a probe. The entire coding regions of murine CIS and WAP cDNAs were obtained by RT-PCR as described elsewhere [21,22]. Total RNA (20 μg) was electrophoresed in a 0.8% agarose gel containing 18% formaldehyde and was transferred to a nylon membrane (Nytran N, Schleicher and Schuell, Dassel, Germany). The membrane was hybridized with ^{32}P-labeled cDNA by using DNA labeling system (Nippon Gene, Tokyo, Japan). Hybridization was carried out by the method as previously described [23]. The membrane was washed twice with 1×saline sodium citrate containing 0.2% sodium dodecyl sulfate at 50°C for 30 min.

2.4. RT-PCR

Determining the expression levels of mRNAs for GHR, JAK2 and STAT5, RT-PCR using total RNAs prepared from the livers of mice was carried out as follows. Briefly, total RNA (3 μg) was mixed with 50 μl of RNA–primer mixture (oligodeoxythymidylic acid primer (0.5 μg), a Moloney murine leukemia virus reverse transcriptase (20 U) (Toyobo, Tokyo, Japan), RNase inhibitor (20 U) (Takara, Tokyo, Japan), 0.5 mM each of four deoxynucleoside triphosphates), and incubated at 37°C for 60 min. PCR was performed in 50 μl reaction mixture (1.5 mM $MgCl_2$, 0.2 mM each of four deoxynucleoside triphosphates, each primer (50 pmol), AmpliTaq Gold polymerase (2.5 U) (Perkin Elmer, Norwalk, CT, USA), 10×AmpliTaq reaction buffer (5 μl) (Perkin Elmer)) containing cDNA synthesized by RT (1 μl). The reaction mixture was incubated at 94°C for 12 min. The reaction was performed in 30–35 cycles at 94°C for 1 min, at 55°C for 1 min 10 s, and at 72°C for 1 min 30 s. The PCR products were subjected to a 2% agarose gel, and then visualized by ethidium bromide staining. The sequences of oligonucleotide primers were as follows. Forward primers for murine STAT5, GHR, JAK2 and β-actin were 5′-GATCGGAATTCCCAGAAGGAT-3′, 5′-AATGCAGATGTTCTGAAGGGA-3′, 5′-GACGTACAGTTATATTGTGAT-3′, and 5′-CAACTGGGACGACATGGAGAA-3′, respectively [24]. Reverse primers for murine STAT5, GHR, JAK2 and β-actin were 5′-TGCTGTTGTAGTCCTCGAGG-3′, 5′-ATACTTGCTGTCTCAGACATCT-3′, 5′-AACTGTAATGCTAATGCCAGG-3′, and 5′-CATCTCCTGCTCGAAGTCTAG-3′, respectively [24].

2.5. Preparation of liver homogenates and electrophoretic mobility shift assay (EMSA)

Livers (1 g) were homogenized with three strokes in 10 ml of homogenizing buffer (10 mM Tris–HCl (pH 7.4), 1 mM EDTA, 250 mM sucrose, 1 mM sodium orthovanadate, 10 mM sodium fluoride and 100 μM phenylmethylsulfonyl fluoride) and centrifuged at 9000×*g* for 15 min. The supernatant was used as liver homogenates for the following experiments. Protein concentration was determined using a protein assay kit (Bio-Rad, Hercules, CA, USA) [25]. EMSA was performed with 20 μl of a reaction mixture containing 25 mM HEPES (pH 7.9), 4% Ficoll, 40 mM KCl, 0.5 mM dithiothreitol, 0.1 mM EGTA, 1 mM $MgCl_2$, poly[dI-dC] (1 μg), carrier DNA (1 μg), 5% glycerol, liver homogenates (15 μg) and ^{32}P-labeled probe DNA (5×10^4 cpm). The mixture was incubated at room temperature for 20 min, and then further incubated for 10 min on ice. The DNA-binding complex was electrophoresed in a 4% polyacrylamide gel. Oligonucleotide primers used as probes are as follows: STAT5 consensus sequence (rat β-casein γ-interferon-activated site (GAS) element) [26], 5′-GATCAGATTTCTAGGAATTCAATCC-3′ and 5′-GATCGGATTGAATTCCTAGAAATCT-3′.

2.6. Antibodies

Antibodies against STAT5a or STAT5b proteins were purchased from Santa Cruz Biotechnology (Santa Cruz, CA, USA). A supershift assay was performed using these antibodies as follows. After incubation of probe DNA with liver homogenates as described above, antibodies were added to the reaction mixture and incubated at room temperature for 10 min. The mixture was then incubated for 10 min on ice and the products subjected to EMSA.

3. Results and discussion

To monitor molecular alterations caused by treatment of mice with MC, differential mRNA display using total RNAs prepared from both the livers of WT mice and WT mice treated with MC was performed (Fig. 1). A cDNA band with the size of 1.35 kb (designated A45) was present in untreated mice but not in MC-treated mice. This band was recovered from a gel and subjected to sequence analysis. A data base search using the BLAST 2.1 program revealed that the

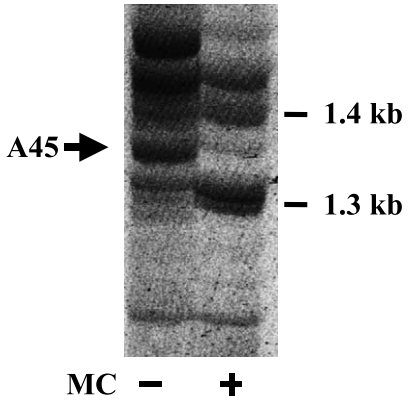

Fig. 1. Loss of a cDNA band by treatment of mice with MC as detected by differential mRNA display. Male C57BL/6J mice were treated with MC dissolved in corn oil at a dose of 80 mg/kg/day intraperitoneally once daily for 2 days. Twenty-four hours after the last injection, these mice were killed, and the livers were removed to prepare RNAs. Total RNA (0.5 μg) was converted to cDNA and differential display was performed. Samples were run on a 6% polyacrylamide/8 M urea gel.

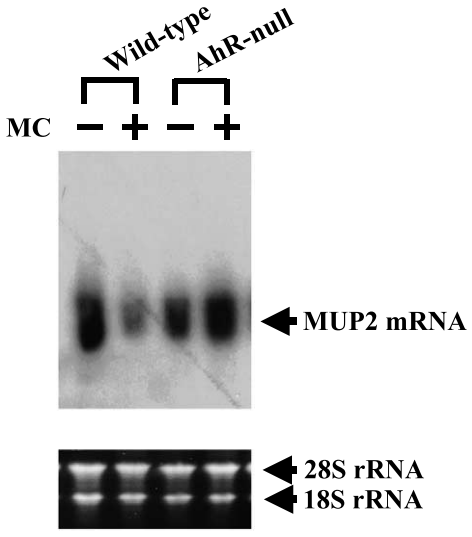

Fig. 2. Suppression of MUP2 expression by MC. WT and AhR-null mice were treated with MC and a portion (20 μg) of total RNA was subjected to Northern blot analysis. The position of migration of MUP2 mRNA is indicated by an arrow (upper panel). An identical blot was stained with ethidium bromide to verify equal RNA loading (lower panel).

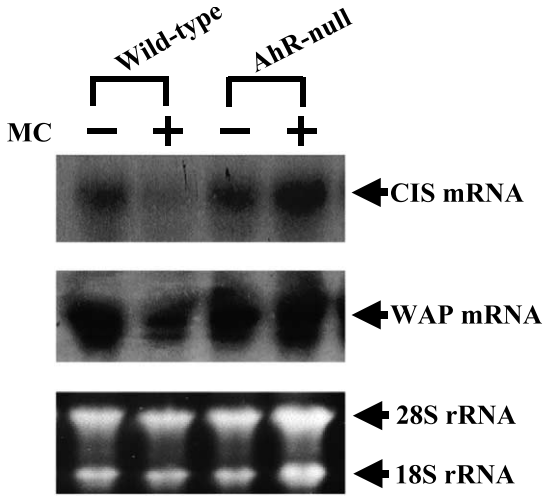

Fig. 3. Down-regulation of the expression of CIS and WAP by treatment of mice with MC. Total RNA (20 μg) was subjected to Northern blot analysis. The mRNAs encoding CIS or WAP are indicated by arrows (upper and middle panels). An identical blot was strained with ethidium bromide to verify the amounts of RNA loaded (lower panel).

sequence of clone A45 was identical to that of the murine MUP2 cDNA (data not shown). MUP2 is a member of the major urinary protein (MUP) gene family [11]. MUPs are a group of closely related pheromone carriers secreted into mouse urine [27]. MUPs are a class of lipocalin proteins encoded by a family of about 35–40 genes that exhibit sequence conservation of at least 85%, both in the transcribed and in the flanking sequences [12,28]. In male liver, most MUPs belong to the group 1 MUP gene family. MUP2 is a major isoform of group 1 MUP gene product in C57BL/6 mice [11] and is reported to be induced by GH [14].

To further confirm that the expression of MUP2 mRNA was suppressed by MC, we carried out Northern blot analysis using murine MUP2 cDNA as a probe and total RNAs prepared from the livers of untreated and MC-treated mice (Fig. 2). Consistent with the results shown in Fig. 1, the expression of MUP2 mRNA was clearly decreased by MC. In addition, to examine whether or not the decreased expression of MUP2 mRNA by MC was mediated by AhR, AhR-null mice were also treated with MC (Fig. 2). The result showed that the expression level of MUP2 mRNA was not reduced by treatment of AhR-null mice with MC. Thus, it appeared that the suppression of the expression of MUP2 mRNA by MC was dependent on AhR. Since there is a possibility that the MUP2 cDNA probe can be hybridized with other group 1 MUP gene products due to the high degree of homology, the band detected using the MUP2 cDNA probe may contain other MUP isoforms [11,12].

It is of particular interest to note that expression of the MUP2 gene is stimulated by the GH signal transduction pathway, through GHR, JAK2 and STAT5 [1,14]. GH is known to induce the expression of CIS and WAP, which encodes a negative regulator of signaling through cytokine receptor and a group of milk proteins related to mammary gland development, in addition to MUP2 [15,16,21]. If the GH signal is affected by MC, then expression of other GH-regulated genes, such as CIS and WAP, should be down-regulated by MC. To explore this possibility, we compared the expression levels of CIS and WAP mRNAs in livers from untreated and MC-treated mice (Fig. 3). As noted in the expression of MUP2 mRNA, the expression of mRNA for CIS and WAP was also down-regulated by MC. Due to the possibility that down-regulation of expression of mRNAs encoding CIS and WAP by MC was mediated by AhR, the same experiment was performed with AhR-null mice (Fig. 3). Indeed, the expression of CIS and WAP mRNAs was unaffected by MC in AhR-null mice. These results suggest that GH signal transduction may be disrupted by MC dependent on AhR.

As noted above, JAK2 and STAT5, through the GHR, mediate the stimulation of the MUP2, CIS and WAP genes by GH. Thus, we examined the effects of MC treatment on

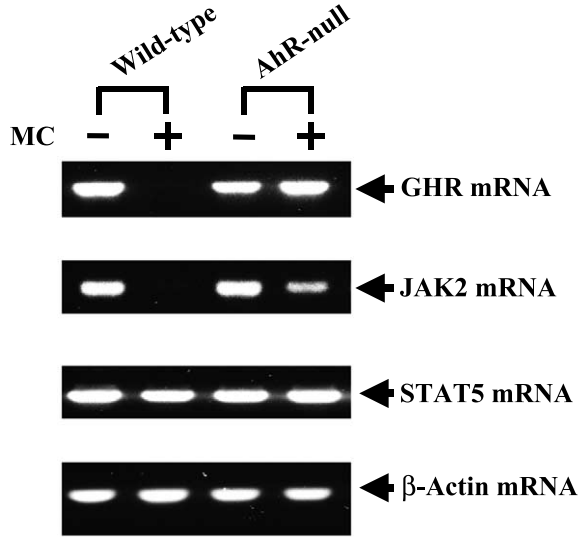

Fig. 4. Effects of MC on the expression of mRNAs for GHR, JAK2 and STAT5. Total RNA (3 μg) was subjected to RT-PCR. The mRNAs encoding GHR, JAK2 and STAT5 are indicated by arrows. RT-PCR for β-actin was used to check equal loading of cDNA samples.

the expression levels of mRNAs encoding GHR, JAK2 and STAT5. As shown in Fig. 4, the expression of both GHR and JAK2 mRNAs as determined by RT-PCR was inhibited by MC, although the expression of STAT5 was unaffected. These alterations in the expression of GHR and JAK2 mRNAs were not seen in AhR-null mice. Thus, it appeared that down-regulation of the expression of GHR and JAK2 mRNA by MC was also mediated by AhR.

It was reported that STAT5 activated by JAK2 mediated tyrosyl phosphorylation to bind to a STAT5-binding site. As shown in Fig. 4, we found that the expression of STAT5 was not altered by MC. From these lines of evidence, it was expected that the amounts of STAT5 bound to the STAT5-binding site were reduced by MC. Thus, we performed EMSA using the STAT5 consensus sequence [26] as a probe and liver homogenates from untreated and MC-treated mice (Fig. 5). A band appeared using the STAT5 consensus sequence and liver homogenates from untreated mice. This band was supershifted by the presence of antibodies to STAT5a or STAT5b, indicating that the band is derived, at least in part, from the STAT5a/STAT5b heterodimer. The binding of the homodimer or heterodimer of STAT5a and/or STAT5b to the STAT5 consensus sequence was diminished by MC. To further confirm that the reduced binding of STAT5 caused by MC was mediated by AhR, liver homogenates from AhR-null mice or AhR-null mice treated with MC were applied to EMSA (Fig. 5). As expected, the binding of STAT5 to STAT5-binding element was not altered in AhR-null mice. Based on these results, we confirmed that the reduction of the expression of GHR and JAK2 mRNAs by MC attenuates the binding activity of STAT5 for the STAT5-binding element, thus resulting in down-regulation of the expression of MUP2, CIS and WAP mRNAs.

MUP plays important roles in individual recognition, territorial marking and sex behavior [29]. Since it is reported that cognitive function and reproductive behavior are disrupted by polychlorinated biphenyls and TCDD in humans and laboratory animals [30–32], the suppression of MUP expression by

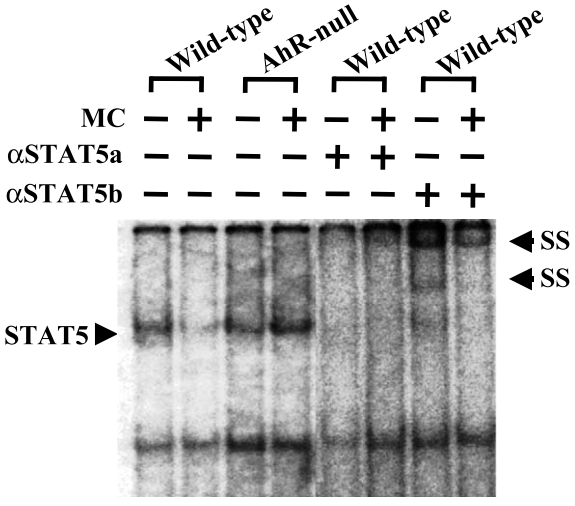

Fig. 5. Decreased binding of STAT5 to STAT5-binding element by treatment of mice with MC. A ^{32}P-labeled double-stranded STAT5 consensus sequence (rat β-casein GAS element) [28] was incubated with liver homogenates (15 μg) prepared from WT or AhR-null mice in the presence or absence of antibodies against STAT5a (αSTAT5a) or STAT5b (αSTAT5b). SS, supershifted band.

PAHs may occur in the behavioral changes. The PAH-induced repression of WAP may influence the process of mammary gland development, because it is known that the development and proliferation of terminal end buds is impaired by exposure to AhR ligands in rodents [33,34]. CIS encodes a negative regulator of signaling through cytokine receptor. Thus, the down-regulation of CIS expression may lead to disruption of cytokine signaling.

The suppression of MUP2 expression by MC was apparently mediated by AhR. However, there are no apparent XREs within the promoter region up to 869 bp of the murine MUP2 gene [11]. In addition, XREs were also absent in the promoter region of the CIS [17] and WAP genes (GenBank accession number U38816). Thus, these observations suggest that the suppression of MUP2, CIS and WAP expression by MC is due to the suppression of the expression of GHR and JAK2 mRNAs.

Searching for a possible XRE sequence(s), we found several possible XREs in the promoter regions (L1–L4) of the murine GHR gene [35,36]. A possible XRE sequence was also located within a V1 promoter region necessary for the liver-specific expression of the human GHR gene [37,38]. Thus, AhR may affect the liver-specific transcription of the human GHR gene through XREs. The mechanism for the repression of GHR expression is currently under examination. Unlike GHR, the promoter region of the JAK2 gene [39] did not contain any obvious XREs. Thus, the expression of JAK2 may be indirectly regulated by AhR on the GHR. We identified possible XREs in the 5′-upstream region of the STAT5a and STAT5b genes. However, these XREs may not function as *cis*-acting elements to modulate the expression of STAT5 genes, since the expression of STAT5 was unaffected by MC.

The amounts of binding of STAT5a/STAT5b homo- or heterodimer were reduced by MC. This context should be noted in that STAT5a- and STAT5b-null mice showed a slower growth rate than WT mice, and were smaller in size [15,40,41]. It was reported that exposure to PAHs causes a decrease in body weight, which is called the wasting syndrome [4]. Thus, it is tempting to speculate that the decrease in body weight by exposure to PAHs may be explained, at least in part, by the AhR-mediated disruption of the GH signaling pathway. The GH signaling pathway also plays an important role in skeletal growth [42]. Interestingly, it was reported that PAHs and TCDD inhibited GH-induced proliferation and differentiation of osteoblasts via AhR [43,44]. Therefore, AhR-mediated suppression of the GH signaling pathway may also account for the abnormality of bone formation induced by PAHs and TCDD.

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