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The aryl hydrocarbon receptor regulates the expression of *TIPARP* and its *cis* long non-coding RNA, *TIPARP-AS1*

Giulia Grimaldi [a], Sharanya Rajendra [b], Jason Matthews [a, b, *]

[a] Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada
[b] Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway

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ABSTRACT

The aryl hydrocarbon receptor (AHR) is a ligand-activated transcription factor and member of the basic helix-loop-helix-PAS family. AHR is activated by numerous dietary and endogenous compounds that contribute to its regulation of genes in diverse signaling pathways including xenobiotic metabolism, vascular development, immune responses and cell cycle control. However, it is most widely studied for its role in mediating 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) toxicity. The AHR target gene and mono-ADP-ribosyltransferase, TCDD-inducible poly-ADP-ribose polymerase (TIPARP), was recently shown to be part of a novel negative feedback loop regulating AHR activity through mono-ADP-ribosylation. However, the molecular characterization of how AHR regulates *TIPARP* remains elusive. Here we show that activated AHR is recruited to the *TIPARP* promoter, through its binding to two genomic regions that each contain multiple AHR response elements (AHREs), AHR regulates the expression of both *TIPARP* but also *TIPARP-AS1*, a long non-coding RNA (lncRNA) which lies upstream of *TIPARP* exon 1 and is expressed in the opposite orientation. Reporter gene and deletion studies showed that the distal AHRE cluster predominantly regulated *TIPARP* expression while the proximal cluster regulated *TIPARP-AS1*. Moreover, time course and promoter activity assays suggest that TIPARP and *TIPARP-AS1* work in concert to regulate AHR signaling. Collectively, these data show an added level of complexity in the AHR signaling cascade which involves lncRNAs, whose functions remain poorly understood.

1. Introduction

The aryl hydrocarbon receptor (AHR) is a basic helix-loop-helix/period-ARNT-single-minded ligand-activated transcription factor essential in mediating the adaptive responses to xenobiotics. It is activated by the environmental contaminant, 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) but also by numerous other endogenous and dietary compounds [1]. Ligand binding initiates the nuclear translocation of cytosolic AHR where it heterodimerizes with the aryl hydrocarbon receptor nuclear translocator (ARNT). The heterodimer binds to aryl hydrocarbon response elements (AHREs; 5′-TnGCGTC-3′) located within the regulatory regions of its targeted genes, including cytochrome P450 1A1 (*CYP1A1*), AHR repressor (*AHRR*) and TCDD-inducible poly-ADP-ribose polymerase (*TIPARP*; also known as, PARP7/ARTD14) [2,3]. Binding of the AHR/ARNT complex to the DNA leads to recruitment of co-regulatory proteins resulting in modulation of gene expression. Although the AHR is essential in mediating the toxicity of TCDD and structurally-related compounds [4], it also plays a critical role in development and in the maintenance of tissue homeostasis [5]. Moreover, AHR regulates immune functions, inflammation, stem differentiation and plays a role in cancer [6]. Because of its wide physiological and pathophysiological roles, AHR has emerged as an important pharmacological target [7].

TIPARP is one of many TCDD-induced target genes that are part of the AHR dependent transactivation cascade, sometimes referred to as the AHR gene battery [8]. It is a member of the poly-adenosine diphosphate (ADP)-ribose polymerase (PARP) family. PARPs use nicotinamide adenine dinucleotide (NAD^+) as a substrate to transfer one molecule of ADP-ribose, mono-ADP-ribosylation, or several ADP-ribose moieties, poly-ADP-ribosylation, to specific amino acid residues on themselves and/or on target proteins [9]. TIPARP mono-ADP-ribosylates itself and other proteins, including histones and AHR [3,10]. Although TIPARP's exact cellular role remains unknown, it has been reported to regulate pluripotency of

* Corresponding author. Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Sognsvannsveien 9, 0372 Oslo, Norway.
E-mail address: jason.matthews@medisin.uio.no (J. Matthews).

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embryonic stem cells, cellular responses to viral infection and is a downstream target of platelet derived growth factor receptor activation [11–13]. We recently reported that *Tiparp*$^{-/-}$ mice exhibit increased AHR responsiveness and increased sensitivity to dioxin-induced toxicity and wasting syndrome, confirming that TIPARP is a repressor of AHR activity [10].

Long noncoding RNAs (lncRNAs) are a class of transcribed, but not translated, RNA molecules greater than 200 bp. They are poorly conserved and their molecular mechanisms and functions are still not fully understood [14]. However, they have been shown to be implicated in a wide range of processes and operate via different mechanisms. They regulate the recruitment of transcriptional regulatory complexes to chromatin, RNA maturation and transport, and protein synthesis [15,16].

AHR regulates various noncoding RNAs, which play roles in AHR-dependent signaling pathways. In zebrafish, AHR2 (the orthologue of mammalian AHR) strongly upregulates the lncRNA, *slincR*, which silences the adjacently located *sox9b* gene by acting as an RNA macromolecule. *SlincR* is essential for development as reduced expression leads to altered neurological responses [17]. Chronic cigarette smoke exposure regulates pulmonary and miRNAs by activating AHR [18], while fine particulate matter (PM2.5) may illicit its toxicological response by activating a series of lncRNAs via AHR [19]. Taken together this data highlight additional players in gene regulation via the AHR pathway.

Both mouse and human express a long non-coding RNA, which lies upstream of exon 1 and is expressed in the opposite orientation compared to *TIPARP* mRNA, referred to as *TIPARP antisense RNA 1* (*TIPARP-AS1*). In mouse, this lncRNA is known to be induced by Ahr in response to xenobiotics [20]. A genome-wide study in HeLa cells placed *TIPARP-AS1* as an early response gene following oxidative stress. However, whether *TIPARP-AS1* contributes to the regulation of *TIPARP* expression or whether it is involved in AHR signaling remains unknown [20].

Here we characterize the regulation of *TIPARP* and investigate the regulation of the lncRNA, *TIPARP-AS1*, by AHR. Overall our findings show that AHR directly regulates both *TIPARP* mRNA but also *TIPARP-AS1* revealing an additional complexity in the AHR-TIPARP signaling axis.

2. Materials and methods

2.1. Chemicals

TCDD was purchased from Wellington Laboratories (Guelph, ON, Canada). Dimethyl sulfoxide (DMSO), cell culture media, fetal bovine serum (FBS) and trypsin were purchased from Sigma-Aldrich (St. Louis, MO, USA). All other reagents were of the highest quality available from commercial vendors.

2.2. Plasmids

The regulatory region of human *TIPARP* spanning 4.2 kb and various truncations of this region were PCR amplified from genomic DNA from MCF-7 cells. The amplicons were then digested with BglII and KpnI and then ligated into BglII and KpnI sites of the pGL3 Basic vector (Promega, Madison, WI, USA) or in the case of AHRE cluster I, AHR cluster II and AHRE cluster II R.C. in pGL3 promoter vector (Promega, Madison, WI, USA). The TIPARP-AS1 overexpression vector was created by PCR amplifying a partial TIPARP-AS1 sequence from commercial human genomic DNA (Roche, Basel Switzerland). The product was digested with MscI and KpnI and then ligated into the Kpn1 and internal MscI site in the pGL3 TIPARP 4.2 kb vector. The complete TIPARP-AS1 sequence was excised with KpnI and HindIII and subcloned into the similarly digested pCDNA3.1(+) vector (Thermo Fisher Scientific, Waltham, MA, USA). Primer sequences are available upon request.

2.3. Cell culture

MCF-7 human breast carcinoma cells and HuH7 human hepatoma cells were purchased from ATCC (Manassas, VA, USA). MCF-7 *AHR*^{ko} cells were obtained by ZFN-mediated AHR gene knockout and described elsewhere [21]. All cells were cultured in low-glucose Dulbecco's Modified Eagle's Media (DMEM; glucose 1 g/L) supplemented with 10% FBS and 1% (w/v) penicillin/streptomycin (P/S). They were maintained at 37 °C with 5% CO_2 and sub-cultured every 2–3 days or when cells reached 80% confluency.

2.4. Chromatin immunoprecipitation

MCF-7 and MCF-7 *AHR*^{ko} cells were plated in a 10 cm culture dish, after 24 h the media was changed to DMEM low glucose phenol red free media with 5% (v/v) dextran/coated charcoal (DCC)-stripped FBS and 1% P/S. After 48 h they were treated with 10 nM TCDD for the indicated time. ChIP assays were done as previously described [22] using 1 μg of anti-AHR (H-211) (Santa Cruz Biotechnology, Santa Cruz, CA) or anti-ARNT (H-172) (Santa Cruz). Isolated DNA was quantified by qPCR using SsoFast EvaGreen SYBR Supermix (Biorad, Hercules, CA).

2.5. Transient transfection and reported gene assay

MCF-7 and MCF-7 *AHR*^{ko} were transfected with 500 ng of the reporter gene constructs containing truncations of *TIPARP* regulatory region or the empty vector. Cells were also transfected with 100 or 400 ng pRC CMV2 AHR and 100 or 400 ng ARNT-FLAG-pcDNA4B or 700 or 800 ng pcDNA. HuH7 cells were transfected with the indicated amounts of pEGFP1-C2-TiPARP and/or pCDNA3.1-TPAS-1 or pCDNA3.1 as well as 200 ng pGudLuc, a CYP1A1-regulated gene activity vector (kindly provide by Michael Denison University of California Davis). All cell lines were transfected with 100 ng pEGFP-C2 and 200 ng pCH110-β-Gal or 100 ng pRenilla-SV40 to normalize for transfection efficiency. Transfections were done using Lipofectamine LTX or Lipofectamine 2000 (Thermo Fisher Scientific, Waltham, MA). After 8 h of transfection cells were treated with DMSO or 10 nM TCDD for 16 h before measuring activity with Luciferase Assay System or the Dual-Luciferase Reporter Assay System (Promega, Madison, WI).

2.6. RNA isolation and qPCR

Cells were seeded in 6-well plates 24 h prior to treatment with 10 nM TCDD for the indicated time. RNA was isolated with Aurum Total RNA Mini Kit (Biorad) following the manufacturer's instruction. RNA was reverse transcribed using either SuperScript III (Invitrogen) or High-Capacity cDNA Reverse Transcription Kit (Thermo Scientific). Transcripts levels were quantified by qPCR using SsoFast EvaGreen SYBR supermix (Biorad). All primers sequences are available upon request.

2.7. Statistics

All data are expressed as mean ± standard error of the mean (SEM). A One-way Analysis of Variance (ANOVA) with Tukey's multiple comparisons test or Student's t-test were used to determine statistical significance ($p < .05$) using GraphPad Prism 5 and Microsoft Excel.

3. Results

3.1. Ligand-induced AHR recruitment to the TIPARP promoter

The human *TIPARP* gene, located on chromosome 3, is composed of 6 exons, exons 2–5 code for the full-length protein with a molecular weight of 76 kDa. Previous genome wide ChIP-chip and ChIP-sequencing studies identified the ligand-dependent recruitment of AHR to two unique sites upstream of the *TIPARP* gene [23,24]. Transcription factor binding site analysis of two AHR bound regions using Genomatix (http://www.genomatix.de/), identified 4 AHREs in one AHR bound sequence and 2 in the other, which we refer to as AHRE cluster I and cluster II, respectively (Fig. 1A).

TCDD-induced recruitment of AHR to each cluster was confirmed using ChIP-qPCR (Fig. 1B). Here we used the well-

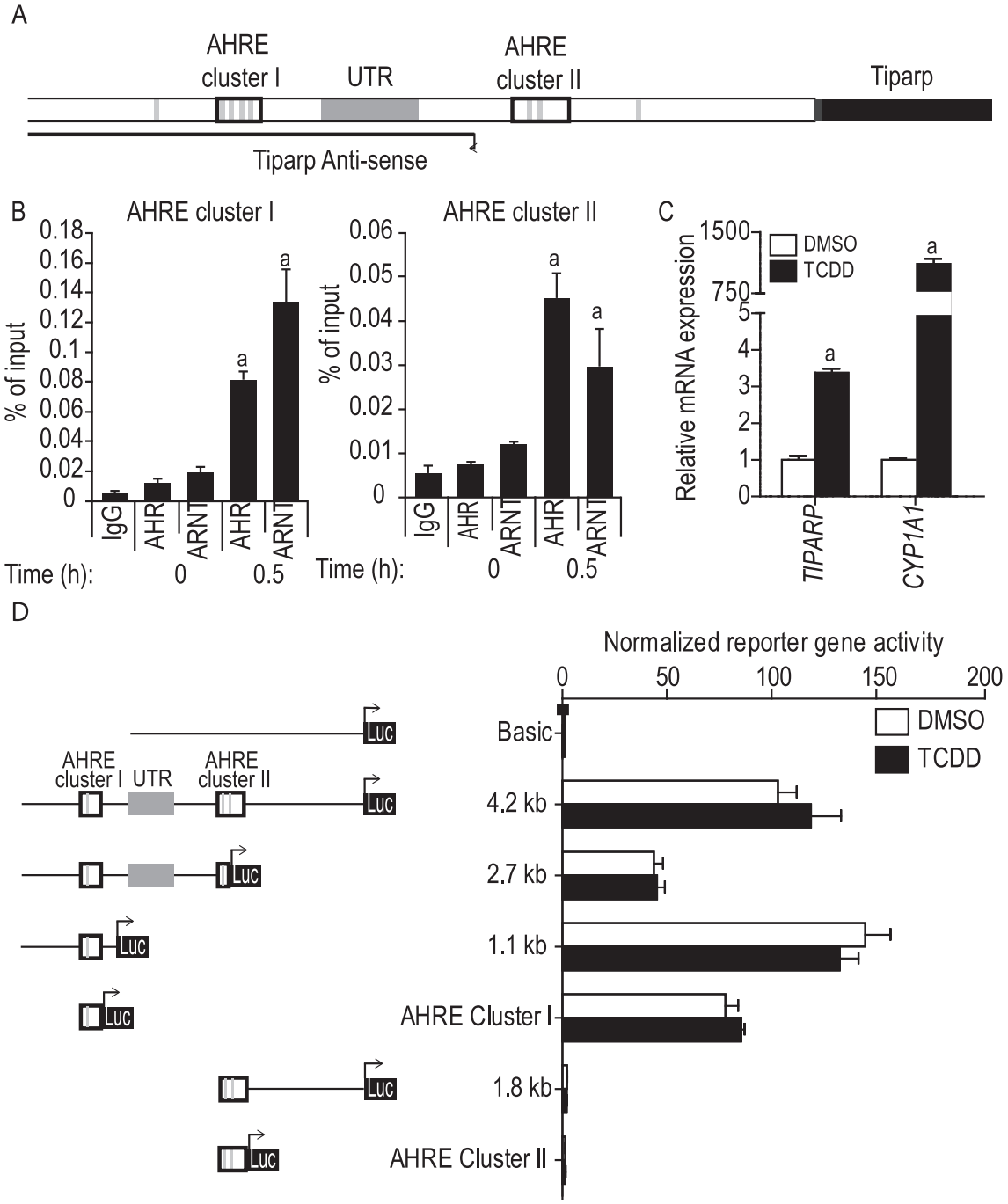

Fig. 1. *TIPARP* promoter has two clusters of AHREs to which AHR binds. **A.** Schematic representation of the human *TIPARP* promoter. MCF-7 cells were treated with 10 nM TCDD **B.** Recruitment of AHR to the two AHRE clusters on the *TIPARP* promoter. Recruitment levels significantly greater ($p < .05$) than untreated cells are denoted with a lowercase letter a. **C.** Activation of the AHR pathway and upregulation of *TIPARP* and *CYP1A1*. Cells were treated for 18 h with TCDD. Gene expression levels were normalized to DMSO treated cells, *a* denotes greatly significant ($p < .05$) changes in gene expression upon TCDD treatment. **D.** MCF-7 cells were transfected with reporter gene constructs containing truncations of *TIPARP* regulatory region or the empty vector. Cells were then treated with TCDD for 18 h. All the data shown are the mean of three experiments and the error bars represent the S.E.M.

characterized breast cancer cell line MCF-7 because it expresses AHR and ARNT and is routinely used to study AHR signaling [22]. Cells were treated for 0.5 h with 10 nM TCDD and recruitment of AHR and ARNT to AHRE cluster I and cluster II was determined. Significant enrichment of AHR and ARNT to both regions was observed (Fig. 1B). A higher percentage of AHR binding occurred at cluster I compared with cluster II, suggesting an increased number of AHR molecules at that region. As previously reported, expression levels of *TIPARP* and *CYP1A1*, a marker of AHR pathway activation, increased following TCDD treatment (Fig. 1C).

To determine which AHREs contributed to *TIPARP* regulation various luciferase vectors containing all or fragments of a 4.2 kb upstream regulatory region were made. The constructs were transfected into MCF-7 cells treated with DMSO or 10 nM TCDD for 18 h. All the constructs containing the AHRE cluster I, which included the full length 4.2 kb promoter, a 2.7 kb, and a 1.1 kb truncated region and just the AHRE cluster I, showed high levels of constitutive reporter gene activity. Despite the recruitment of AHR to cluster II, the two truncations containing cluster II failed to exhibit any TCDD-dependent increases in reporter gene activity (Fig. 1D). This suggested that cluster I was important in regulating *TIPARP* expression even though TCDD failed to enhance luciferase activity in any of the constructs tested. To further investigate the AHR and TCDD-dependent regulation of *TIPARP* and to exclude the possibility that the high constitutive activity of *TIPARP* promoter fragments containing cluster I was not due to AHR activation by ligands in the cell culture medium [25], we tested the *TIPARP* promoter deletions in MCF-7 *AHR*^{ko} cells [21]. The transfected *TIPARP* promoter constructs containing cluster I also showed high constitutive luciferase expression in MCF-7 *AHR*^{ko} cells (Fig. 2A), implying

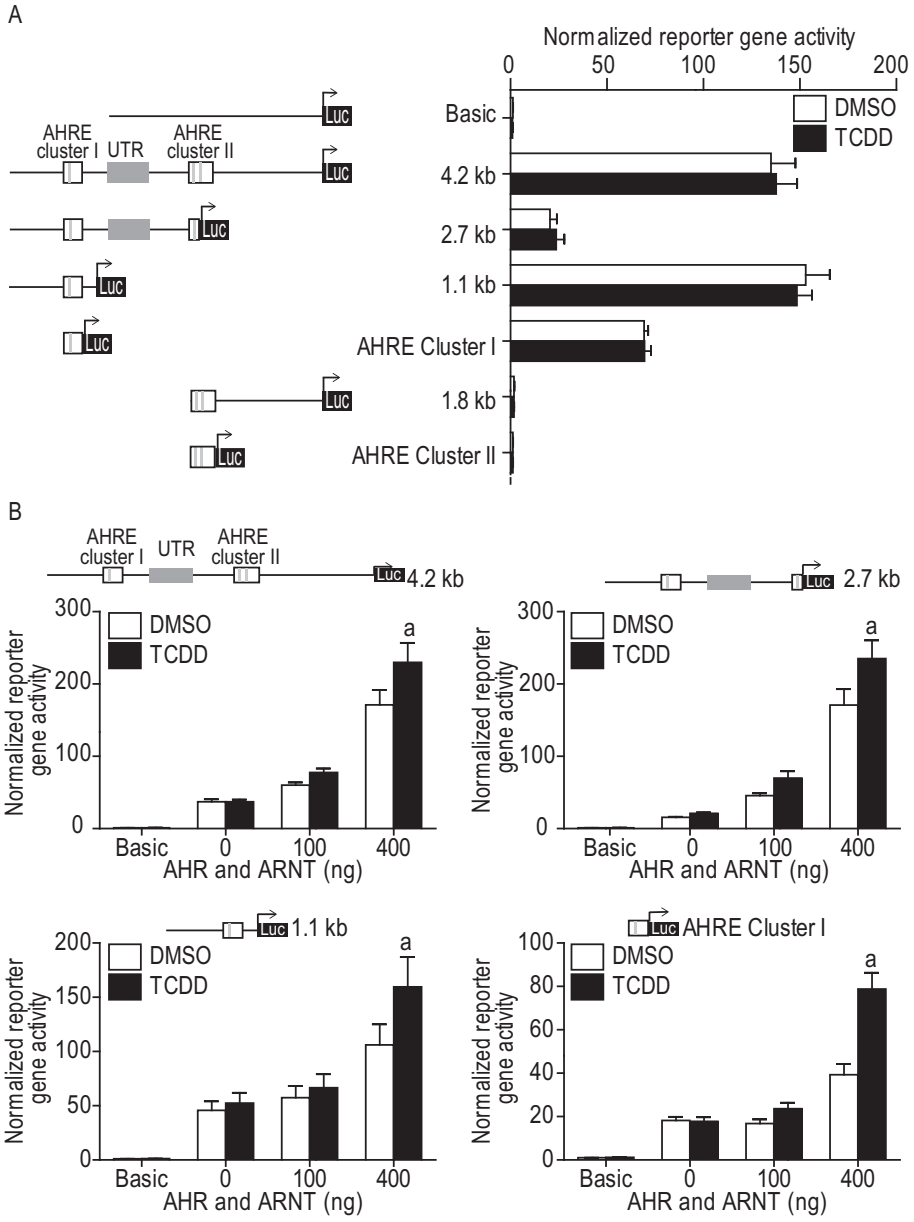

Fig. 2. AHRE cluster I is also regulated by transcription factors other than AHR. MCF-7 *AHR*^{ko} cells transfected with reporter gene constructs containing truncations of *TIPARP* regulatory region or the empty vector and treated for 18 h with 10 nM TCDD. **A.** All truncations containing cluster I show elevated basal activity. There is no activity on the constructs bearing only cluster II. **B.** MCF-7 *AHR*^{ko} cells were also transfected with increasing concentrations of AHR and ARNT. Overexpression of AHR and ARNT showed a significant ($p < .05$) increase of reported gene activity upon TCDD treatment compared to DMSO treatment, denoted by *a*. All the data shown are the mean of three experiments and the error bars represent the S.E.M.

that other transcription factors also bind this region. No significant increases in luciferase activity were observed with *TIPARP* promoter constructs containing cluster II. Transfection of 4.2 kb, 2.7 kb, and 1.1 kb construct in MCF-7 *AHR*^{ko} cells with increasing amounts of AHR and ARNT and treated with TCDD resulted in a significant TCDD-dependent increase in luciferase assay (Fig. 2B–E).

The lack of TCDD-dependent increases in reporter gene activity from TIPARP promoter deletion that only contained cluster II was intriguing and suggested that either AHR recruitment to the region was nonproductive or that binding of AHR to cluster II regulates another gene. The AHRE cluster II is located 35 bp upstream of *TIPARP-AS1* expressed on the negative strand (Fig. 1A). *TIPARP-AS1* encodes a 2556 bp linear lncRNA of unknown function that overlaps with the untranslated exon 1 of *TIPARP*. To test if AHR regulates *TIPARP-AS1*, we cloned the *TIPARP-AS1* (*TPAS*) promoter, which included the −1517 to −2059 region relative to *TIPARP* start site. The reverse complement of cluster II (cluster II RC) was also cloned into a luciferase vector to test if this region acted as an enhancer to regulate *TIPARP-AS1* expression. The *TIPARP-AS1* promoter and the cluster II RC exhibited higher level of constitutive activity compared with 1.8 kb region containing cluster II. TCDD treatment caused a small, but significant, increase in cluster II RC-mediated luciferase activity. No TCDD-dependent increases were observed for *TIPARP-AS1* promoter (Fig. 3A). High constitutive activity of the *TIPARP* promoter and cluster II R.C. vectors was also observed in transfected MCF-7 *AHR*^{ko} cells, and as expected the TCDD-dependent increase in cluster II R.C.-mediated luciferase activity was only observed after overexpression of AHR and ARNT in MCF-7 *AHR*^{ko} cells (Fig. 3B). However, overexpression of AHR and ARNT failed to increase *TPAS* promoter driven luciferase activity in the presence of TCDD. Taken together these results suggest that AHR binding to cluster II regulates *TIPARP-AS1* rather than *TIPARP* mRNA expression levels.

3.2. Temporal mRNA expression

To determine the effect of AHR activation in regulating both *TIPARP* mRNA and *TIPARP-AS1* levels we did a time course expression analysis in TCDD-treated MCF-7 cells. A significant increase in the *TIPARP-AS1* expression was observed 45 min (Fig. 4A). Peak expression of *TIPARP-AS1* preceded that of *TIPARP*, which occurred after 1.5 h before declining. *CYP1A1* levels were still increasing at the end of the time-course (3 h) as expected. No increases were observed in TCDD treated MCF-7 *AHR*^{ko} cells (Fig. 4B).

To test the role of *TIPARP-AS1* in TIPARP-dependent repression of AHR signaling, we did CYP1A1-regulated reporter gene studies in HuH7 human hepatoma cells. In agreement with previous studies [3], increasing concentrations of TIPARP reduced TCDD-dependent increases in luciferase activity (Fig. 4C). Overexpression of *TIPARP-AS1* had no effect on TCDD-induced reporter gene activity (Fig. 4D). However, overexpression of *TIPARP-AS1* improved the ability of TIPARP to repress CYP1A1-regulated luciferase activity (Fig. 4E).

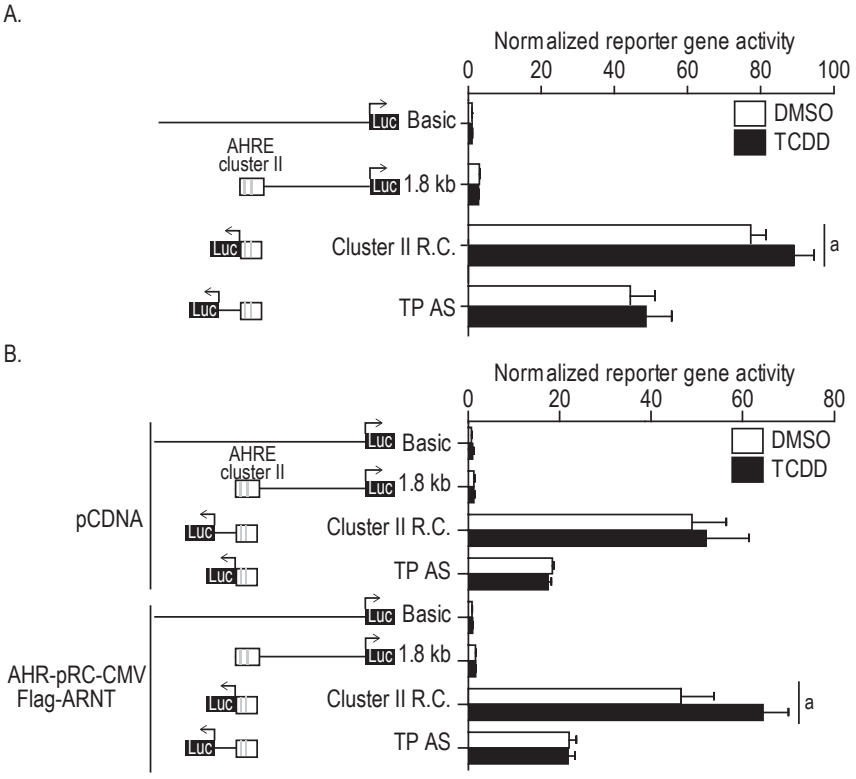

Fig. 3. AHRE cluster II regulates *TIPARP-AS1* rather than *TIPARP*. MCF-7 (**A**) and MCF-7 *AHR*^{ko} (**B**) cells transfected with reporter gene constructs containing truncations of *TIPARP* regulatory region containing cluster II and cloned in the reverse complement or the empty vector and treated for 18 h with 10 nM TCDD. **A.** In MCF-7 cells when AHRE cluster II is cloned in the reverse complement there is high basal gene reporter activity, suggesting that AHRE cluster II regulates *TIPARP-AS1*. The vector containing only the AHRE cluster II also shows significant ($p < .05$) increase of reported gene activity upon TCDD treatment compared with DMSO. **B.** Transfection of MCF-7 *AHR*^{ko} cells with AHRE cluster II cloned in the reverse complement showed elevated basal activity. Overexpression of AHR and ARNT showed a significant ($p < .05$) increase of reported gene activity upon TCDD treatment compared with DMSO treatment, denoted *a*. All the data shown is the mean of three experiments and the error bars represent the S.E.M.

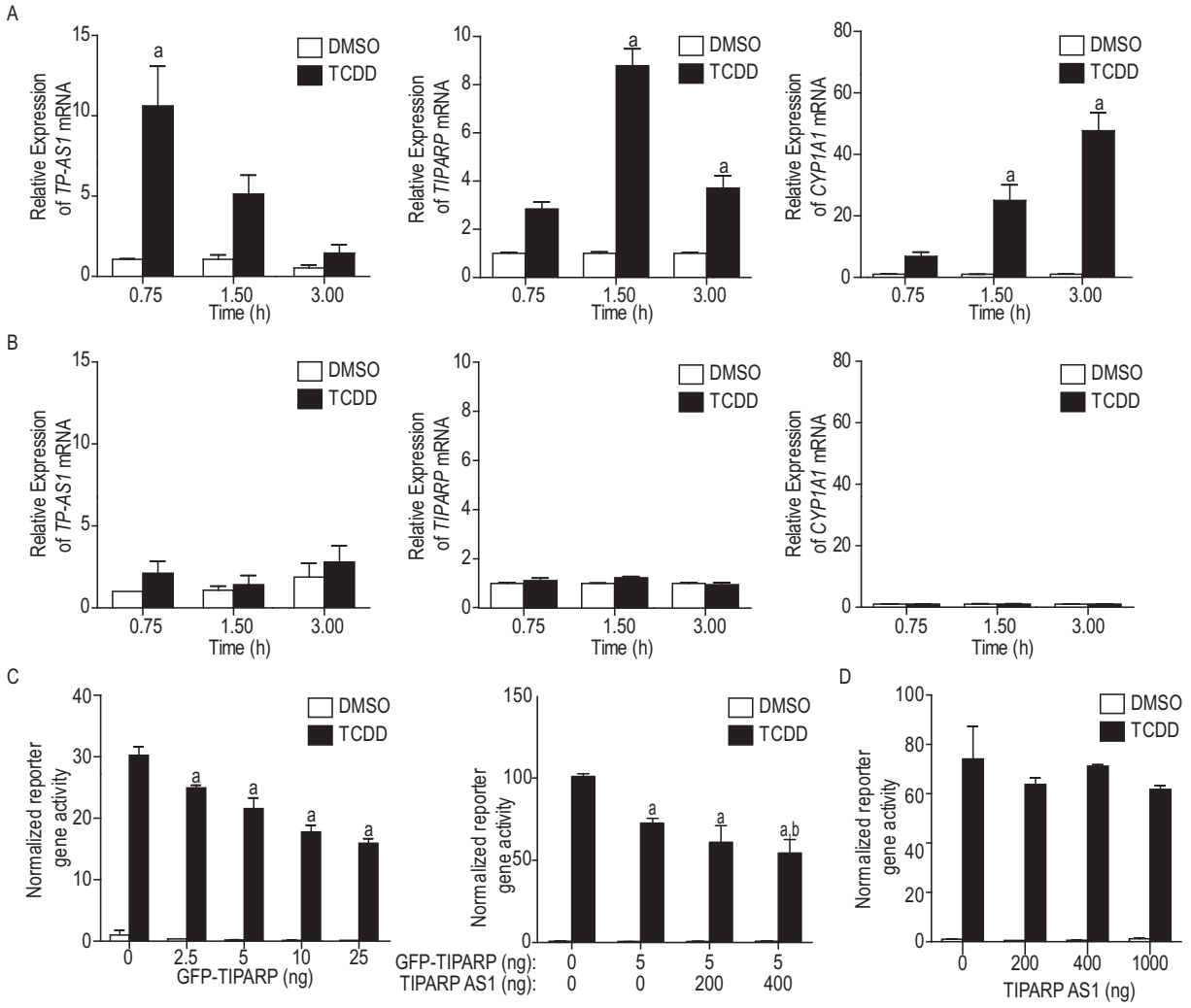

Fig. 4. *TIPARP* and *TIPAR- AS1* work in concert to regulate AHR signaling. **A.** MCF-7 cells were treated for 18 h with 10 nM TCDD. *TIPARP-AS1* gene expression (left panel) peaks earlier than *TIPARP* (middle panel) following dioxin treatment. Gene expression levels were normalized to DMSO treated cells, *a* denotes greatly significant ($p < .05$) changes in gene expression upon TCDD treatment. **B.** MCF-7 AHR^{ko} cells were treated for 18 h with 10 nM TCDD. A lack of AHR results in no upregulation of *TIPARP-AS1* (right panel), *TIPARP* (middle panel) or *CYP1A1* (right panel). **C.** Huh7 cells were transfected with pGudLuc, a CYP1A1-regulated luciferase activity vector and increasing concentrations of pGFP-TIPARP and/or TIPARP-AS1 overexpression plasmids or pEGFP. Cells were then treated with TCDD for 18 h. Increasing amounts of TIPARP reduced luciferase activity (left panel). Overexpression of *TIPARP-AS1* enhanced TIPARP-dependent repression of reporter gene activity. Significant decrease ($p < .05$) in luciferase activity in cells transfected with pGFP-TIPARP or pGFP-TIPARP-AS1 compared to those transfected with pEGFP are denoted *a*. *b* indicates a significant decrease ($p < .05$) in luciferase activity in cells transfected with both with pGFP-TIPARP or TIPARP-AS1 compared to those transfected with pGFP-TIPARP alone. All the data shown are the mean of three experiments and the error bars represent the S.E.M.

This suggests that TIPARP and *TIPAR- AS1* work in concert to regulate AHR signaling.

4. Discussion

Previous work by our group has shown that TIPARP negatively regulates AHR through a novels negative feedback loop, where increased levels of TIPARP repress AHR activity in a process that requires TIPARP catalytic activity [3]. We also showed that loss of *Tiparp* expression in mice increases their sensitivity to TCDD-dependent toxicity [10]. Here we show that AHR binds to the *TIPARP* promoter region where it drives the expression of *TIPARP* mRNA levels, but also the lncRNA, *TIPARP-AS1*.

Characterization of the upstream regulatory region of the *TIPARP* promoter revealed two clusters of AHR response elements, with the more distal (cluster I) showing strong recruitment of AHR after TCDD exposure. AHRE cluster II is located downstream of the untranslated exon of *Tiparp* (which overlaps the lncRNA) and is positioned between *TIPARP AS-1* and *TIPARP*. Reporter gene assays showed that the AHRE cluster I drives basal levels of *TIPARP* expression but this is not enhanced by dioxin treatment, AHRE cluster II did not show any basal or treatment induced expression of the reporter gene when cloned in the same orientation as *TIPARP*. However, when cloned in the reverse complement orientation it showed significantly greater reporter activity. The presence of basal reporter activity also in MCF-7 AHR^{ko} cells indicates that there are other transcription factors involved in this regulation. AHR is required for the TCDD-dependent increase of both *TIPARP* and its *cis*-antisense RNA since, no changes were observed in treated AHR^{ko} cells. This is also conserved in the mouse, where Ahr binding to an AHRE cluster positioned in the first intron of the *Tiparp* gene and upstream of the *Tiparp-as1* (*4931440P22Rik*) modulates expression of both the protein-coding mRNA and the lncRNA [20]. It is estimated that approximately 40% of the mouse and human transcripts form complex loci with *cis*-antisense transcript pairs, with the majority involving ncRNAs [26]. Our study provides another

example of the impact of lncRNA on gene regulation and transcription factor function.

We show that *TIPARP-AS1* peak expression precedes that of *TIPARP* in response to dioxin. This suggests a regulatory role for the *cis*-antisense lncRNA, *TIPARP-AS1* in regulating transcription of the TIPARP mRNA. In support of this, we found that overexpression of *TIPARP-AS1* enhanced TIPARP's ability to regulate genes such as *CYP1A1* suggesting that the lncRNA plays an important role in regulating TIPARP-mediated AHR signaling. Although the molecular mechanism of this cooperation and the precise function of *TIPARP-AS1* still remain elusive. Further studies investigating how other pathways regulate *TIPARP-AS1* and whether the two types of RNA always form a transcriptional unit will help dissect the overlapping and independent mechanisms through which TIPARP operates.

Declaration of interest

The authors have nothing to declare.

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