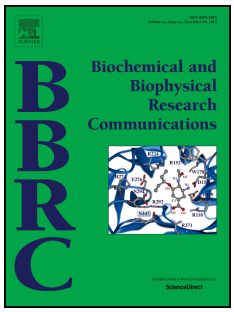
Accepted Manuscript



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

Giulia Grimaldi, Sharanya Rajendra, Jason Matthews

PII: S0006-291X(17)32513-5

DOI: 10.1016/j.bbrc.2017.12.113

Reference: YBBRC 39113

To appear in: *Biochemical and Biophysical Research Communications*

Received Date: 5 December 2017

Accepted Date: 20 December 2017

Please cite this article as: G. Grimaldi, S. Rajendra, J. Matthews, The aryl hydrocarbon receptor regulates the expression of *TIPARP* and its *cis* long non-coding RNA, *TIPARP-AS1*, *Biochemical and Biophysical Research Communications* (2018), doi: 10.1016/j.bbrc.2017.12.113.

The Aryl Hydrocarbon Receptor regulates the expression of *TIPARP* and its *cis* long non-coding RNA, *TIPARP-AS1*.

Giulia Grimaldi[1], Sharanya Rajendra[2] and Jason Matthews[1,2,*].

[1]Department of Pharmacology and Toxicology, University of Toronto, Toronto, Canada. [2]Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Oslo, Norway.

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.

Keywords 2,3,7,8-tetrachlorodibenzo-p-dioxin, TCDD-inducible poly-ADP-ribose polymerase, long non-coding RNA, aryl hydrocarbon receptor

[*]Corresponding author: Jason Matthews, Department of Nutrition, Institute of Basic Medical Sciences, University of Oslo, Sognsvannsveien 9 0372 Oslo, Norway.

Email: jason.matthews@medisin.uio.no