OPEN ACCESS

Scientific Letters

II TOXRUN
International Congress 2023
27-28 April, 2023 | Porto, Portugal

Poster 52

T(AHR)getting the AHR: mapping the road of a xenobiotic sensor, from disease to a therapeutic target

I. Castro-Almeida [1,2,3,*], A. Janowska [4,5], R. Saitch [4], Y. Lian [4], A. Delgado [6], J. Protze [7] and P. Moura-Alves [1,2,4]

[1] IBMC, Instituto de Biologia Molecular e Celular, Universidade do Porto, Porto, Portugal
[2] I3S, Instituto de Investigação e Inovação em Saúde, Universidade do Porto, Porto, Portugal
[3] Departamento de Química, Universidade de Aveiro, Aveiro, Portugal
[4] Ludwig Institute for Cancer Research, Nuffield Department of Clinical Medicine, University of Oxford, Oxford, United Kingdom
[5] Cancer Research UK Cambridge Institute, University of Cambridge, Cambridge, United Kingdom
[6] Novo Nordisk Foundation Center for Biosustainability (NNF CfB), Technical University of Denmark, Kongens Lyngby, Denmark
[7] Leibniz-Forschungsinstitut für Molekulare Pharmakologie (FMP), Berlin, Germany

* Correspondence: ialmeida@i3s.up.pt

Abstract

Background: The aryl hydrocarbon receptor (AHR) is a highly conserved ligand-dependent transcription factor, which recently gained recognition, beyond its role as a toxicity sensor, as a major player in different biological circumstances [1]. Our group and others have shown that AHR modulation in different scenarios, including by therapeutic drugs, impacts disease outcomes and treatment efficacy, in conditions such as cancer and bacterial infections [1-3]. For example, therapeutic drugs designed to target other molecules also bind to and modulate AHR activity [1,2]. Albeit, the extent of clinically approved drugs with AHR modulatory properties and the elicited AHR functions is largely unknown. **Objective:** Identify drugs with AHR modulatory properties. **Methods:** The AHR modulatory properties of 3178 drugs were examined using a luciferase cell reporter assay, *in silico* binding studies, and data analysis, through Ingenuity Pathway Analysis and data mining [2,4,5]. **Results:** We unbiasedly identified 228 hits as potential AHR agonists or antagonists (including known AHR ligands, validating our approach) and calculated the respective EC50s or IC50s. Next, AHR modelling studies predicted 53 agonists and 31 antagonists to bind to AHR. According to the data analysis, we classified the hits according to their roles in different pathways, diseases, and targets. We decided to initially focus on drugs with known roles in cancer or infection. An anticancer and anti-infection molecule is currently being tested for its AHR modulatory properties, and for the assessment of the AHR role(s) in its therapeutic mechanism and drug-resistance phenotypes. Further validation studies will involve *in vitro* and *in vivo* approaches (e.g. in zebrafish). **Conclusions:** In all, we aim to gain a deeper understanding of the biology of AHR in disease and its role in resistance mechanisms and identify potential repurposing drugs to target this receptor, paving the ground for future therapeutic approaches.

Keywords: aryl hydrocarbon receptor; disease; drug therapy; drug resistance

Acknowledgments

Project supported by John Fell Fund, University of Oxford; Ludwig Institute for Cancer Research – Core Award; and H2020-WIDESPREAD-2018-951921 – ImmunoHUB.

References

1. Corre, S. *et al.* Sustained activation of the Aryl hydrocarbon Receptor transcription factor promotes resistance to BRAF-inhibitors in melanoma. *Nat. Commun.* **2018**, *9*, 4775.

2. Puyskens, A. *et al.* Aryl Hydrocarbon Receptor Modulation by Tuberculosis Drugs Impairs Host Defense and Treatment Outcomes. *Cell Host Microbe* **2020**, *27*, 238-248.e7.
3. Murray, I. A., Patterson, A. D. & Perdew, G. H. Aryl hydrocarbon receptor ligands in cancer: friend and foe. *Nat. Rev. Cancer* **2014**, *14*, 801–814.
4. Moura-Alves, P. *et al.* AhR sensing of bacterial pigments regulates antibacterial defence. *Nature* **2014**, *512*, 387–392.
5. Moura-Alves, P. *et al.* Host monitoring of quorum sensing during Pseudomonas aeruginosa infection. *Science* **2019**, *366*, eaaw1629.