Which are the Keystones in the Dynamic AHR-CYP1A1 Signaling Network?

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To the Editor,

Kyoreva and co-workers demonstrated recently that the enzymatic activity of CYP1A1 is a critical regulator of skin inflammation (Kyoreva et al., 2021). In a commentary by van den Bogaard and Perdew, these authors are focussing on the potential relationship between CYP1A1 and the role of a natural AHR ligand under the paragraph “Identification of the natural AHR ligand pool in the skin: Needles in a haystack?” (van den Bogaard and Perdew, 2021).

The authors bring up some basic questions related to the potential role of CYP1A1 in the loss of AHR activation in relation to the “natural AHR ligand pool” e.g. which AHR ligands are present in and on our skin, which of them are CYP1A1 substrates, and what is their source.

There are several indoles and tryptophan derivatives in the human skin, some of which are high-affinity AHR ligands e.g., indolo[3,2-b]carbazole (ICZ) and 6-formylindolo[3,2-b]carbazole (FICZ) formed from the commensal yeast Malassezia, or by photooxidation or oxidation by hydrogen peroxide (Magiatis et al., 2013, Schallreuter et al., 2012, Smirnova et al., 2016). When the authors discuss photooxidation they mention that it has been known for a long time that UVR generates high-affinity ligands for AHR. However, they citing one report only (Youssef et al., 2019) demonstrating that FICZ accounts for only a small part (0.02%) of the generated photoproducts after UVB exposure, which apparently in their opinion would imply that it would be of minor biological relevance. This might be misleading. Firstly, FICZ is such a potent AHR ligand that it activates the receptor in picomolar concentrations. Secondly, the other formation pathways mentioned above, including FICZ generation from UVA and visible light would also contribute to the amount of ligand in the skin. Thus, UVB is not the only producer of FICZ in the skin, and its bioavailability would be well in the concentration range for efficient AHR activation.

The authors also suggest that other sources of AHR ligands in the skin should be considered. The suggestion is worthwhile, but their example, oxidized photoproducts of squalene that can activate AHR, does not seem to be the obvious choice since there are no indications of ligand-dependent receptor activation, which should be the key criterion. It seems more appropriate to start with the most powerful ligand for AHR, FICZ, the needle already found in the haystack. Several pathways from tryptophan to FICZ have been identified, involving in addition to microbial enzymes also common mammalian/human enzymes providing the precursors indole-3-pyruvate and indole-3-acetaldehyde (Smirnova et al., 2016). The presence of FICZ...
metabolites in humans (Wincent et al., 2009) further underscores the relevance of determining the sources of FICZ, in different organs, and cell types in humans.

In the study by Kyoreva et al., it was found that the CYP1A1 enzymatic activity was a critical regulator of the AHR signaling in the context of skin inflammation (Kyoreva et al., 2021). In 1985, Nebert and co-workers proposed a role of an endogenous AHR ligand that could be metabolized by CYP1A (Hankinson et al., 1985). Other reports followed providing further support for the existence of a possible feedback mechanism in which the enzyme CYP1A and CYP1B families can metabolically alter putative endogenous ligand(s). When the authors discuss "the natural AHR ligand pool" and the potential role of CYP1A1 in the depletion of a natural ligand they raise the question of which of the ligands are CYP1A1 substrates. It is known that FICZ is effectively metabolized by CYP1A1 and the best CYP1A1 substrate identified so far and CICZ the chemically related skin ligand is also a good substrate for CYP1A1 (Wei et al., 1998, Wincent et al., 2009). It, therefore, seems that FICZ would be the important link in the AHR-CYP1A1 feedback regulation. However, van den Bogaard and Perdew do not mention these data at all in relation to their alternative, i.e. that AHR ligand depletion could be the result of elevated kynureninase levels in psoriasis resulting in a depletion of kynurenine (KYN). KYN itself is not an AHR ligand, and it doesn’t seem to be metabolized by CYP1A1 and therefore not able to form a part of an AHR-CYP1A1 negative feedback loop, which, after all, would be an efficient regulatory pathway and offers the simplest explanation.

Additionally, the chemical analysis of FICZ might be difficult in complex biological matrices in the presence of larger amounts of related substances. In many cases, neither FICZ nor its unstable precursors indole-3-acetaldehyde or indole-3-pyruvate have been analyzed or found instead, the corresponding stable end products indole-3-aldehyde and indole-3-acetic acid are identified (Sadik et al., 2020, Zelante et al., 2013). There are no indications that these two substances are high-affinity AHR ligands but they might or might not contribute to an indirect AHR activation, but data are scarce. On the other hand, it’s more likely that FICZ may have been formed from their common precursor indole-3-acetaldehyde.

It is becoming clearer and clearer that AHR signaling in different organs and cell types has biological functions and it is now essential to elucidate in detail the relationship between the endogenous ligands, AHR, and CYP1A1 pathway to this signaling. Data concerning endogenous AHR ligands beyond FICZ (and CICZ) are scarce and the existence of such ligands is highly speculative in nature and that therefore data related to endogenous AHR ligands should be interpreted and discussed with greater care than previously done. For these reasons, studies on the nature of endogenous AHR ligands beyond FICZ and CICZ are also important as are studies that further characterize the role of these known endogenous AHR ligands in cutaneous biology.

Conflict of Interest

The author states no conflict of interest.


