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

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TO THE EDITOR

Kyoreva et al. (2021) showed recently that the enzymatic activity of CYP1A1 is a critical regulator of skin inflammation. In a commentary by van den Bogaard and Perdew (2021), these authors are focusing 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?"

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", for example, 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, for example, indolo(3,2-b) carbazole 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 cited one report only (Youssef et al., 2019) showing 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. First, FICZ is such a potent AHR ligand that it activates the receptor in picomolar concentrations. Second, the other formation pathways mentioned earlier, 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 because 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. (2021), it was found that CYP1A1 enzymatic activity was a critical regulator of the AHR signaling in the context of skin inflammation. In 1985, Hankinson et al. (1985) proposed a role of an endogenous AHR ligand that could be metabolized by CYP1A. Other reports followed, providing further support for the existence of a possible feedback mechanism in which the enzymes CYP1A and CYP1B 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, indolo(3,2-b)carbazole-6-carboxylic acid, the chemically related skin ligand, is also a good substrate for CYP1A1 (Wei et al., 1998; Wincent et al., 2009). Therefore, it seems that FICZ would be the important link in the AHR–CYP1A1 feedback regulation. However, van den Bogaard and Perdew (2021) do not mention these data at all in relation to their alternative, that is, that AHR ligand depletion could be the result of elevated kynureninase levels in psoriasis, resulting in a depletion of kynurenine. Kynurenine itself is not an AHR ligand, and it does not 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.

In addition, 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. In contrast, it is 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 indolo[3,2-b] carbazole) are scarce, and the existence of such ligands is highly speculative in nature, and 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 indolo(3,2-b)carbazole are also important as are studies that further characterize the role of these known endogenous AHR ligands in cutaneous biology.

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CONFLICT OF INTEREST
The author states no conflict of interest.

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REFERENCES

Hankinson O, Andersen RD, Birren BW, Sander F, Negishi M, Nebert DW. Mutations affecting the regulation of transcription of the cytochrome P1-450 gene in the mouse Hepa-1 cell line. J Biol Chem 1985;260:1790−5.

Kyoreva M, Li Y, Hoosenally M, Hardman-Smart J, Morrison K, Tosi I, et al. CYP1A1 enzymatic activity influences skin inflammation via regulation of the AHR pathway. J Invest Dermatol 2021;141:1553−1563.e3.

Magiatis P, Pappas P, Gaitanis G, Mexia N, Melliou E, Galanou M, et al. Malassezia yeasts produce a collection of exceptionally potent activators of the Ah (dioxin) receptor detected in diseased human skin. J Invest Dermatol 2013;133:2023−30.

Sadik A, Somarribas Patterson LF, Öztürk S, Mohapatra SR, Panitz V, Secker PF, et al. IL4I1 is a metabolic immune checkpoint that activates the AHR and promotes tumor progression. Cell 2020;182:1252−1270.e34.

Schallreuter KU, Salem MA, Gibbons NC, Maitland DJ, Marsch E, Elwary SM, et al. Blunted epidermal L-tryptophan metabolism in vitiligo affects immune response and ROS scavenging by Fenton chemistry, part 2: epidermal H2O2/ONOO(−)-mediated stress in vitiligo hampers indoleamine 2,3-dioxygenase and aryl hydrocarbon receptor-mediated immune response signaling. FASEB J 2012;26:2471−85.

Smirnova A, Wincent E, Vikström Bergander L, Alsberg T, Bergman J, Rannug A, et al. Evidence for new light-independent pathways for generation of the endogenous aryl hydrocarbon receptor agonist FICZ. Chem Res Toxicol 2016;29:75−86.

van den Bogaard EH, Perdew GH. The enigma of AHR activation in the skin: interplay among ligands, metabolism, and bioavailability. J Invest Dermatol 2021;141:1385−8.

Wei YD, Helleberg H, Rannug U, Rannug A. Rapid and transient induction of CYP1A1 gene expression in human cells by the tryptophan photoproduct 6-formylindolo[3,2-b] carbazole. Chem Biol Interact 1998;110:39−55.

Wincent E, Amini N, Luecke S, Glatt H, Bergman J, Crescenzi C, et al. The suggested physiologic aryl hydrocarbon receptor activator and cytochrome P4501 substrate 6-formylindolo[3,2-b]carbazole is present in humans. J Biol Chem 2009;284:2690−6.

Youssef A, von Koschembahr A, Caillat S, Corre S, Galibert MD, Douki T. 6-formylindolo[3,2-b] carbazole (FICZ) is a very minor photoproduct of tryptophan at biologically relevant doses of UVB and simulated sunlight. Photochem Photobiol 2019;95:237−43.

Zelante T, Iannitti RG, Cunha C, De Luca A, Giovannini G, Pieraccini G, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. Immunity 2013;39:372−85.