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Commentary

Beyond toxicology: Aryl hydrogen receptor role in physiology

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Aryl hydrocarbon receptor (AHR) was initially discovered as a cellular protein involved in the detoxification of xenobiotic compounds. Recently, Kou and Dai [1] wrote a concise review on AHR, summarizing advances in several important areas of mammalian physiology including cardiovascular, gastrointestinal, integumentary, nervous, and immunomodulatory systems. Given the importance of AHR and our increased understanding of its physiological roles, it is necessary to highlight a few key aspects of AhR in normal development and metabolic homeostasis that have not been extensively discussed.

In the angiogenesis section of the review, Kou and Dai compared the phenotypic similarities and differences in AHR-deficient rat and mice. They noticed significant differences in AHR-mediated transcriptional regulation between rat and mice with AHR deficiency. Significantly, the differences are more pronounced between human and rodents. It has been shown that human AHR and its mouse counterpart display a ten-fold difference in their sensitivity to 2,3,7,8 -Tetrachlorodibenzo-p-dioxin (TCDD) and that the difference may be partly attributed to the structural basis, as there is only a 58% similarity in the transactivation domain [2]. It is conceivable that the sensitivity of mouse AHR to endogenous ligands would differ from that of human AHR. Therefore, we need to keep in mind that the efficacy of an AHR-targeting drug based on results of rodent models would unlikely be achieved in humans.

The importance of AHR in the circadian rhythm has not been widely recognized. In the above-mentioned review, Kou and Dai discussed the fact that AHR has a Per-ARNT-Sim (PAS) domain that is involved in mediating its association with circadian proteins. They also discussed that recruitment of circadian proteins by the PAS domain may serve as a possible molecular mechanism for AHR to regulate the circadian rhythm. However, AHR may play an additional role in circadian rhythm regulation via different pathways. For example, AHR activity and its downstream signals can be highly impacted by the outcome of melatonergic and tryptophan catabolite pathways. L-tryptophan is converted by tryptophan hydroxylase to L-5OH-tryptophan and then to serotonin. Besides functioning as an important neurotransmitter, serotonin can be metabolized to melatonin in the pineal gland of the brain during the night-time, which in turn regulates the circadian rhythms [3,4]. In this process, AHR is not only activated by L-kynurenine but also modulated by serotonin via a serotonin transporter-dependent mechanism [5].

In the review article, Kou and Dai extensively discussed a relatively weak connection between AHR signaling and wound healing. On the other hand, it is well known that acute exposure to TCDD causes chloracne, a pathological skin condition, thus directly linking the AHR signaling pathway to skin biology. The weak connection can be partly explained by the level of AHR expression that significantly varies in different layers of keratinocytes. Skin keratinocytes are roughly divided into two layers: (i) the basal layer consisting of highly proliferative epidermal stem cells and (ii) the spinous and granular layer consisting of fully differentiated cells. AHR expression is high in the granular layer but low in the basal layer, and wound-healing is closely linked to the basal layer which controls the proliferation of epidermal cells [6]. Therefore, the role of AHR in wound-healing cannot be underestimated. It has been reported that activation of Src, a molecular chaperone of AHR in the cytoplasm, improves wound-healing, which is associated with activation of its downstream components including the phosphoinositide 3-kinase (PI3K) or extracellular signal-

regulated kinases 1/2 (ERK1/2) [7,8]. Moreover, inflammation, one of important phases in skin wound-healing process, is closely connected to the AHR signaling pathway. A recent study reveals that an accelerated rate of wound-healing is observed in AHR-deficient mice compared with that of wild-type mice, which is likely due to decreased inflammation as the result of AHR ablation [9].

With the discovery of an ever-increasing number of endogenous ligands, AHR has been recognized to have important roles in several aspects of human physiology. Obviously, AHR physiological functions are not just limited to those aspects summarized in the review. No doubt, further studies will reveal new roles of AHR in human development and normal homeostasis.

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