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The aryl hydrocarbon receptor as a moderator of host-microbiota communication

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Abstract

The aryl hydrocarbon receptor (AHR) is an important component of the host-microbiota communication network. Comparisons of wild-type and *Ahr*-null mice as well as from exposure studies with potent AHR ligands (e.g., 2,3,7,8-tetrachlorodibenzo-p-dioxin) have provided compelling evidence that the AHR may be a master regulator of the host-microbiota interaction thus helping to shape the immune system and impact host metabolism. Metabolomics and sequenced-based microbial community profiling, two recent technological advances, have helped to solidify this host-microbiota signaling concept and identified not only how specific ligands generated by the host and by the microbiota can activate the AHR, but also how activation/disruption of the AHR can influence and shape the microbiota. We are just beginning to understand how the temporal nature and tissue- and microbiota-specific generation of AHR ligands contribute to many AHR-dependent processes. In this review, we focus on several recent advances where metabolomics and characterization of the microbiota structure and function have generated new perspectives by which to evaluate AHR activity.

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1. Introduction

The aryl hydrocarbon receptor (AHR) is a key regulator of the response to drugs and toxicants, is important in immune system development and homeostasis (reviewed in [1]), and, more recently, AHR activity has been reported to modulate the microbiota residing on the skin [2] and in the gut [3–5]. The diverse roles of the AHR are driven in large part by a similarly diverse set of ligands (reviewed in [6]) including xenobiotics (e.g., environmental contaminants such as 2,3,7,8-tetrachlorodibenzo-p-dioxin [TCDD], benzo[a]pyrene), diet-derived chemicals (e.g., flavonoids and indoles), endogenous (e.g., 6-formylindolo[3,2-b]carbazole [FICZ]), and bacterial-associated or -produced metabolites (e.g., phenazines, tryptophan catabolites). Within the last ten years we have witnessed a renewed interest in the AHR moving beyond its well-studied role as a xenobiotic sensor to new roles that have implications in host metabolism, barrier organ function (reviewed in [7]), and, importantly, to roles that may represent new therapeutic targets for several human diseases including cancer and obesity [8].

Understanding the AHR has been advanced through the development of tools including mouse models, highly sensitive reporter cell lines, and through the generation and characterization of diverse AHR ligands with differential affinity. In particular, the strategic use of tissue-specific knockout mice [9] (generated in the low affinity Ahr^d background) has clarified the role of AHR in different tissue compartments including immune cell populations, hepatocytes, keratinocytes, and the intestinal epithelium. However, differences in ligand binding affinity between the various *Ahr* alleles in mice (Ahr^d vs Ahr^b) and important species differences between human, mouse, and other model organisms have yet to be fully reconciled in the literature [10] and (reviewed in [11]). Sensitive reporter lines have helped not only to identify new AHR ligands but have also been instrumental for monitoring low-level exposure to toxic environmental AHR ligands [12]. Despite these incredibly valuable tools, our knowledge of the quantity, identity, and ultimate distribution of AHR endogenous as well as exogenous ligands throughout the body remains limited.

With cutting-edge tools including metabolomics (i.e., chemical fingerprinting) and sequenced-based microbial community profiling, new and exciting roles for the AHR are beginning to unfold. In this review we highlight and discuss how metabolomics and characterization of the microbiota has helped to advance understanding of AHR activity and function, and provide our vision for ways to clarify the role of AHR in modulating the host-microbiota relationship.

2. AHR and metabolomics

Metabolomics has accelerated numerous discoveries in the fields of toxicology, drug metabolism, and receptor

biology [13–15]. For example, metabolomics has been instrumental in uncovering the important contribution of the gut microbiota to host metabolism [16] and has provided detailed metabolic maps of AHR ligands [17]. Metabolomics is typically conducted by hyphenated techniques such as liquid or gas chromatography coupled with mass spectrometry and by nuclear magnetic resonance spectroscopy (NMR). It is important to emphasize that given the varied physicochemical properties of chemicals making up the metabolome numerous platforms are required, which is especially true when considering the diverse array of known AHR ligands (reviewed in [18]). Below we critically evaluate the contributions that metabolomics has made to the AHR field by examining reports from mouse models and human studies.

2.1. Mouse models

Metabolomic studies are profoundly impacted by age, sex, diet, lifestyle, and environmental exposures (reviewed in [13]). Therefore, mouse models are essential to study the metabolic impact of AHR activation without the influence of confounding factors. Many of the early metabolomic studies with AHR surround the prototypical AHR ligand TCDD at generally high doses. For example, Matsubara and colleagues [19] examined the dose- and time-dependent impact of TCDD on the mouse serum metabolome. The authors gave TCDD to C57Bl/6N mice via intraperitoneal injection (10 μg/kg and 200 μg/kg) and using ultra-high pressure liquid chromatography coupled with quadrupole time-of-flight mass spectrometry (UHPLC-QTOFMS) were able to identify specific upregulation of azelaic acid monoesters, which was attributed to downregulation of hepatic carboxylesterase 3 (CES3) activity. It was concluded that downregulation of CES3 was associated with steatohepatitis which is commonly observed with high doses of TCDD and related environmental contaminants. Other examples using high dose TCDD include comparison of C57Bl/6 and DBA/2 mice (representing the high affinity and low affinity alleles, respectively) exposed to TCDD (20 μg/kg p.o. daily for 7 days) [20]. The authors identified using QTOFMS-based metabolomics significant accumulation of liver fatty acids and lysophosphocholines in the high affinity C57Bl/6 mice. The DBA/2 mice exhibited a significant, but blunted response to TCDD exposure. Similarly, a series of studies elegantly examined the longitudinal metabolic perturbations associated with TCDD-associated fibrosis in female C57Bl/6 mice using a variety of high throughput techniques including microarray, RNA-seq, and metabolomics [21–23]. Mice were given TCDD via gavage at doses ranging from 0.01 μg/kg to 30 μg/kg every four days over a period of 28 or 92 days. Using a targeted metabolite profiling approach, the authors report that TCDD exposure significantly perturbed many metabolic pathways including glycogen, amino acid, TCA, and lipid metabolism; however, significant changes were only observed at doses >1 μg/kg. In addition, ^{1}H NMR-based metabolomic studies of male wild-type and *Ahr*$^{-/-}$ C57Bl/6J mice treated with 24 μg/kg 2,3,7,8-tetrachlorodibenzofuran (TCDF), another typical environmental AHR ligand, demonstrated that TCDF exposure profoundly affects host metabolic pathways such as hepatic lipogenesis, glucose and energy metabolism, and de novo fatty acid biosynthesis [3,24].

Collectively, these as well as other investigations of AHR activation point to a central role for AHR in hepatic lipid metabolism [25,26]. However, interpreting these data in contexts outside of industrial accidents or intentional poisonings remains challenging given that TCDD burden can be orders of magnitude greater than what might be found in the general population. Therefore, studies with TCDD as well as other relevant environmental AHR ligands including polychlorinated biphenyls and polycyclic aromatic hydrocarbons should be investigated as doses resembling those found in the general population to best appreciate their metabolic impact. Longitudinal dose–response studies comparing the most toxic AHR ligands (e.g., TCDD) with those generally considered potentially important for health (e.g., indole-3-carbinol, a breakdown product of the glucosinolate glucobrassicin found in cruciferous vegetables) would be invaluable to differentiate the metabolic effects of AHR-mediated toxicity from AHR health promoting effects (Fig. 1).

2.2. Human studies

To date, there have been only a few studies that have attempted to identify how exposure to environmental AHR ligands influences the metabolome. For example, the serum metabolome from 81 Dutch chlorophenoxy herbicide factory workers and 63 non-exposed workers was measured via UHPLC-QTOFMS [27]. While significant differences in blood TCDD concentrations were observed (2.09 parts per trillion [ppt] compared with 0.44 ppt), the authors reported that no metabolic features (here a metabolic feature is defined as a mass and retention pair that has not been structurally elucidated) survived false discovery rate correction. Limitations of the study included its retrospective nature (workers were exposed from 1953 to 1969 but blood was sampled in 2007–2008), differences in age between the exposed and non-exposed cohorts, and the rather limited metabolomic analysis (the samples were only analyzed by one platform in a single ionization mode). A retrospective urinary metabolomic investigation was conducted in Czech factory workers producing the herbicide trichlorophenol acetic acid [28]. Using UHPLC-QTOFMS-based metabolomics, the authors report significant alterations in steroid and bile acid metabolism and interestingly were able to find a subset

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