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Michael C. Petriello
University of Kentucky, michaelcpetriello@gmail.com

Jessie B. Hoffman
University of Kentucky, jessie.hoffman@uky.edu

Andrew J. Morris
University of Kentucky, a.j.morris@uky.edu

Bernhard Hennig
University of Kentucky, bhennig@uky.edu

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Emerging Roles of Xenobiotic Detoxification Enzymes in Metabolic Diseases

Review

Michael C. Petriello, Jessie B. Hoffman, Andrew J. Morris* and Bernhard Hennig*

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Abstract: Mammalian systems have developed extensive molecular mechanisms to protect against the toxicity of many exogenous xenobiotic compounds. Interestingly, many detoxification enzymes, including cytochrome P450s and flavin-containing monooxygenases, and their associated transcriptional activators [e.g. the aryl hydrocarbon receptor (AhR)], have now been shown to have endogenous roles in normal physiology and the pathology of metabolic diseases. This mini-review will focus on two such instances: the role of flavin-containing monooxygenase 3 (FMO3) in the formation of the cardiometabolic disease biomarker trimethylamine-N-oxide (TMAO) and the role of AhR as a sensor of endogenous ligands such as those generated by the gut microbiota. Understanding the roles of xenobiotic sensing pathways in endogenous metabolism will undoubtedly lead to a better understanding of how exposure to environmental pollutants can perturb these physiological processes.

Keywords: cardiovascular disease; dioxin; FMO3; metabolic pathologies; TMAO.

*****Corresponding authors: Andrew J. Morris,** Superfund Research Center, University of Kentucky, 900 S. Limestone Street, Lexington, KY 40536, USA; Lexington Veterans Affairs Medical Center, Lexington Kentucky, USA; and Division of Cardiovascular Medicine, College of Medicine, University of Kentucky, Lexington, KY 40536, USA, E-mail: a.j.morris@uky.edu; and **Bernhard Hennig,** Superfund Research Center, University of Kentucky, 900 S. Limestone Street, Lexington, KY 40536, USA; and Department of Animal and Food Sciences, College of Agriculture, Food and Environment, University of Kentucky, Lexington, KY 40536, USA, Phone: +1 859-218-1343, Fax: +1 859-257-1811, E-mail: bhennig@uky.edu
Michael C. Petriello: Superfund Research Center, University of Kentucky, 900 S. Limestone Street, Lexington, KY 40536, USA; Department of Animal and Food Sciences, College of Agriculture, Food and Environment, University of Kentucky, Lexington, KY 40536, USA; and Lexington Veterans Affairs Medical Center, Lexington Kentucky, USA
Jessie B. Hoffman: Superfund Research Center, University of Kentucky, 900 S. Limestone Street, Lexington, KY 40536, USA; and Department of Pharmacology and Nutritional Sciences, College of Medicine, University of Kentucky, Lexington, KY 40536, USA

Introduction

Humans are exposed to multiple endogenous and xenobiotic compounds that if left unmodified and excreted could impact cellular physiology, leading to detrimental pathological outcomes. Fortunately, mammalian systems have evolved multiple signaling systems, including the well-studied nuclear factor (erythroid-derived 2)-like 2 (Nrf2) and aryl hydrocarbon receptor (AhR) pathways, among others, which aide in the detoxification, elimination, and increased endogenous antioxidant buffering capacity against the toxicity of chemical compounds. Two major classes of detoxification enzymes, cytochrome P450s (CYPs) and flavin-containing monooxygenases (FMOs), are known to modify multiple drugs and environmental pollutants, generating more readily excreted polar metabolites, but emerging data now implicate these xenobiotic-metabolizing enzymes in the metabolism of endogenously formed or diet-derived compounds that are themselves associated with disease pathologies. Here, we briefly outline the importance of studying such endogenous roles by focusing on FMO3's broad impact on metabolism and cardiovascular disease risk as well as the interplay between gut microbiota and AhR-CYP1A1 signaling.

Emerging roles of FMO3 in cardiometabolic disease

Flavin-containing monooxygenases are a major class of enzymes responsible for oxidizing multiple substrates including many commonly administered amine- and sulfate-containing drugs (1, 2). FMO3 is the primary isoform found in the liver, and thus has garnered much attention because of its role in drug metabolism and drug-drug interactions. FMO3 expression is modulated by multiple transcription factors (e.g. AhR, FXR, C/EBPbeta) and steroid hormones, but inter-species differences are evident (3–6). Interestingly, female mice and humans display significantly more FMO3 at baseline levels than their male counterparts, although the differences in mice are more robust (7). Multiple genetic mutations in the FMO3 gene locus

have been discovered in human populations, with the most severe causing a loss of function of the enzyme product in an autosomal recessive manner. The most obvious phenotypic difference in rare individuals who are homozygous for loss of function of FMO3 alleles is a distinct fishy body odor known as trimethylaminuria, named for the malodourous compound, trimethylamine (TMA), that FMO3 normally quickly metabolizes (8). It is now known that the formation of TMA and oxidation product trimethylamine-N-oxide (TMAO) is reliant on the gut microbiota-dependent metabolism of dietary precursors such as choline and carnitine (9, 10). Previously, it was believed that the FMO3 product TMAO was a benign compound, but emerging data now implicate TMAO's importance as a biomarker or possibly causative contributor to coronary artery disease, diabetes, and kidney disease risks (7, 10–13).

Circulating TMAO is garnering much attention as a biomarker of multiple cardiometabolic diseases including coronary artery disease (CAD), type 2 diabetes, and kidney disease (7, 10–12, 14–17). First implicated as a biomarker of human disease in 2013, Hazen's group at the Cleveland Clinic described that TMAO could be formed in a gut-microbe-dependent manner from dietary sources like eggs, and also showed that people with higher TMAO were more likely to experience a heart attack or a related ailment (10). This work has been widely cited because it was one of the first studies to show that bacteria living in the gut could create a compound that, at the least, was a biomarker of the leading cause of death in the United States, cardiovascular disease. Since then, there have been some reports implicating TMAO as a causative agent of inflammation and disease pathology (12, 17–19). For example, TMAO was shown to alter nuclear factor-kappa B (NF-κB) signaling in both endothelial and smooth muscle cells, leading to a pro-inflammatory response (19). Not all data currently support this hypothesis that increased TMAO is detrimental to human health. In fact, seafood is known to be a good source of TMAO and related substrates, but dietary intake of certain fish has been linked to protection against cardiovascular disease. Thus, other factors may be more important in mechanistically explaining this observed link between TMAO and human disease, such as alteration of gut microbiota diversity or regulation of FMO3.

Although TMAO may have its own pro-atherosclerotic or pro-inflammatory characteristics, emerging evidence now implicates a role of FMO3 in cardiometabolic disorders independent of TMAO. Using genetically modified mouse models or anti-sense oligo nucleotide silencing (ASO), at least three independent laboratories have now shown that FMO3 plays important roles in reverse cholesterol transport, glucose and insulin signaling, lipid metabolism, and metabolic dysfunction (7, 9, 20, 21). Shih et al. showed that a decrease in FMO3 lowered circulating TMAO as well as reduced plasma and liver levels of glucose and lipids in a mouse model highly susceptible to atherosclerosis (21). Similar work extended these observations to show that ASO-mediated silencing of FMO3 altered cholesterol transport; FMO3 downregulation resulted in an apparent preference for transintestinal cholesterol excretion (TICE), promotion of macrophage reverse cholesterol transport (RCT), a repression of biliary cholesterol levels, and decreased intestinal cholesterol absorption (20). Finally, multiple epidemiological and preclinical studies have shown that metabolic disorders, such as diabetes, and cardiovascular disease/atherosclerosis are interconnected, and FMO3 may be a critical mediator of these observed associations. In a mouse model of diabetes, FMO3-ASO treatment resulted in increased glucose sensitivity via alterations of key metabolic control genes including FOXO1 and SREBP-2 (7). Additionally, it was shown that FMO3 can be inhibited by insulin in vitro, and FMO3 expression was increased in obese/insulin-resistant clinical patients (7). Most of the discussed work implicating FMO3 and cardiometabolic signaling was completed using ASO technology in mouse models highly susceptible to diseases (e.g. LDLr -/- or LIRKO mice), so it will be important to recapitulate these findings in wild-type and FMO3 knockout animals. Multiple research groups have shown that AhR may transcriptionally regulate FMO3, which may provide evidence linking AhR, TMAO, and cardiometabolic diseases.

Emerging roles of AhR signaling in metabolic function

AhR is a ligand-activated transcription factor involved in xenobiotic metabolism with a binding pocket capable of interacting with a variety of endogenous and exogenous ligands (22). AhR was first characterized as a receptor for dioxins like 2,3,7,8-tetra-chlorodibenzo-p-dioxin (TCDD), but additional environmental agonists including halogenated hydrocarbons (HAHs) and polycyclic aromatic hydrocarbons (PAHs) have also been identified and studied. In its inactive state, AhR is located within the cytoplasm as a component of a large protein complex that includes a dimer of heat shock protein 90 (Hsp90) and the co-chaperone protein X-associated protein 2 (XAP2) (22, 23). Upon binding of an agonist, the AhR complex translocates to the nucleus where it dimerizes

with the AhR nuclear translocator (ARNT). Upon this dimerization, AhR and ARNT can bind to specific DNA sequences contiguous to promoter regions called "xenobiotic responsive elements" (XREs) (22, 23). The subsequent recruitment of co-activators by AhR and ARNT can lead to the transcription of numerous genes involved in xenobiotic metabolism such as the phase I, phase II, and phase III drug-metabolizing enzymes (22). The primary function of this increase in expression and induction of drug-metabolizing enzymes is to assist in the metabolism and clearance of the initial AhR ligands; however, it has been observed that during this metabolism, certain pro-inflammatory pathways can be activated that contribute to the development of chronic inflammatory diseases (22–24).

Dioxin-like pollutants, including PCBs, are potent ligands of AhR, and their interaction can influence outcomes related to cardiometabolic disease (25, 26). Within vascular endothelial cells, activation of AhR by coplanar PCBs (e.g. PCB 126 and PCB 77) contributes to a CYP1A1-facilitated uncoupling mechanism resulting in an increase in reactive oxygen species (ROS) (27). Subsequently, these elevated levels of ROS contribute to dysregulation of the cellular redox status, which can lead to activation of NF-κB and induction of pro-inflammatory molecules, including cytokines, chemokines, and cell adhesion molecules (28, 29). Preclinical data have indicated that these PCB-induced pollutants increase ROS, and activation of pro-inflammatory pathways can contribute to the development of atherosclerosis and cardiovascular diseases (28, 29). There are also a few human studies linking genetic polymorphisms in key AhR-related genes (e.g. CYP1A1) to increased risk of cardiovascular disease and metabolic disease risk factors (30, 31).

While AhR has been classically characterized as a mediator of xenobiotic metabolism of organic pollutants, emerging research now points to numerous other metabolic and developmental impacts of AhR and CYP1A1 (32). Much of our understanding of the endogenous functions of AhR comes from studies involving AhR null mice. AhR null mice, as expected, are resistant to dioxin-like pollutant toxicity (33). However, compared to their wild-type counterparts, AhR null mice have smaller livers, delayed growth, and exhibit cardiovascular and fertility abnormalities, thus suggesting roles of AhR that extend beyond xenobiotic metabolism (34, 35).

Interestingly, AhR null mice also display altered energy expenditure and fibroblast growth factor 21 (FGF21) expression, changes in body weight, and differential glucose/insulin signaling (36–40).

It has been observed that AhR activation can occur in the absence of exogenous ligands, thus suggesting the presence of endogenous ligands of AhR (41). Several of the known endogenous ligands of AhR are derived, via various mechanisms, from the amino acid tryptophan. For example, 6-formylindolo(3,2-b)-carbazole (FICZ) is produced from tryptophan mediated by UV-light degradation and has been shown to be a strong activator of AhR (42). Furthermore, L-kynurenine, a metabolite of tryptophan utilized in the production of niacin, exhibits high affinity for AhR and has been observed to be involved in modulating immune responses (e.g. mast cell activation) (43) and promoting tumor cell survival (44). Interestingly, commensal bacteria have also been demonstrated to be involved in the production of tryptophan and appear to monitor and regulate tryptophan levels based on dietary intakes (45). Furthermore, there is evidence that certain bacteria can metabolize tryptophan into AhR ligands, such as those discussed above. For example, the bacterial species *Lactobacillus reuteri* (46) and *Lactobacillus bulgaricus* (47) are capable of producing the AhR ligand indole-3-aldehyde, which has been demonstrated to be involved in immune responses within the intestines. Additionally, indole-3-aldehyde-mediated AhR activation contributes to interleukin-22 (IL-22) transcription and mucosal responses that allow for gut microbial diversity and also protects against detrimental fungal colonization (e.g. *Candida albicans*) and inflammation (46). Due to the varying responses elicited by the discussed endogenous AhR ligands, further research is needed to further our understanding of the roles of AhR that extend beyond xenobiotic metabolism and the ways in which responses may be modulated for therapeutic interventions.

Cardiovascular disease and other metabolic pathologies are known to be ailments related to chronic inflammation. Importantly, recent studies have noted that AhR has functions in the regulation of immunity and inflammation (48). In support of this, AhR null mice exhibit immune system defects, including spleen enlargement and alterations in lymphocyte numbers within the spleen (34, 35). It also appears that AhR is important in regulating T cell differentiation and maintaining the balance between regulatory T cells and pro-inflammatory IL-17-secreting T cells (49). In addition to the role of AhR on T cells, recent studies suggest that the AhR pathway also affects B cell differentiation and antibody production (32). For example, dioxin exposure to activated B cells results in suppression of B cell differentiation, and is believed to be mediated through the AhR target Bach2 (50). Furthermore, it appears that AhR has important functions in protection against pathogenic bacterial infections, as AhR

null mice display increased sensitivity to the pathogenic gram-positive bacterium *Listeria monocytogenes* (51).

Within the gut, AhR is highly expressed in both immune and non-immune cells and is believed to play a role in maintaining intestinal homeostasis. It has been demonstrated that activation of AhR via dietary ligands, including indole-3-carbinol, derived from the metabolism of vegetables such as broccoli and brussel sprouts, is required for the innate immune response of intraepithelial lymphocytes and IL-22-secreting lymphoid cells (52, 53). Furthermore, AhR null mice have reduced numbers of these innate immune cells, making them more vulnerable to colitis and bacterial infection (54). In mice with dextran sulfate sodium (DSS)-induced colitis, administration of the endogenous AhR ligand FICZ attenuated colitis and reduced levels of pro-inflammatory cytokine production while stimulating IL-22 production (55). Similarly, immune cells isolated from the gut of humans with Crohns disease have low expression of AhR, and treatment with AhR ligands has been demonstrated to reduce levels of pro-inflammatory cytokines and increase IL-22 (55).

Due to the multi-faceted role of AhR in metabolism, energy balance, and inflammation, further research on how the various endogenous and exogenous AhR ligands may differentially regulate these cellular processes is needed. Overall, it appears that the AhR signaling pathway functions more than just a xenobiotic sensor and rather is capable of integrating signals from a variety of sources to produce responses that are modifiable based on an individual's environment.

Conclusion

Exposure to persistent environmental pollutants has been associated for many years with increased risk of developing many chronic diseases including cardiovascular disease and diabetes. Using preclinical and cell culture studies, toxicologists have identified multiple causative mechanisms of toxicant-induced disease, including increased cellular oxidative stress, endocrine hormone disruption, and chronic induction of inflammation. It is now becoming clear that many enzymes and genes historically studied for their detoxification and xenobiotic-sensing capabilities may also have evolved critical endogenous processes that, if altered, can lead to metabolic dysfunction. FMO3, a well-studied drug-metabolizing enzyme, now has been shown to be critically important in the production of the cardiometabolic disease biomarker TMAO, and may also have roles in glucose and cholesterol signaling. Similarly,

the dioxin-sensing transcription factor AhR has now been shown to be activated by multiple endogenous ligands, many of which are formed by the gut microbiota, and has basal roles in metabolism and energy expenditure. Interactions between toxicology, nutrition, and cardiometabolic diseases are becoming increasingly more evident, and the important endogenous roles for both AhR and FMO3 are an example of the critical necessity to reevaluate pollutant-related signaling pathways to understand previously underappreciated biological phenomena related to environmental insults and disease risks.

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