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Special Section on Perspective on Drug Metabolism and Disposition, Part I—Minireview

Fifty Years of Aryl Hydrocarbon Receptor Research as Reflected in the Pages of *Drug Metabolism and Disposition*

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ABSTRACT

The induction of multiple drug-metabolizing enzymes by halogenated and polycyclic aromatic hydrocarbon toxicants is mediated by the aryl hydrocarbon receptor (AHR). This fascinating receptor also has natural dietary and endogenous ligands, and much is now appreciated about the AHR's developmental and physiologic roles, as well as its importance in cancer and other diseases. The past several years has witnessed increasing emphasis on understanding the multifaceted roles of the AHR in the immune system. Most would agree that the "discovery" of the AHR occurred in 1976, with the report of specific binding of a high affinity radioligand in mouse liver, just three years after the launch of the journal *Drug Metabolism and Disposition* (DMD) in 1973. Over the ensuing 50 years, the AHR and DMD have led parallel and often intersecting lives. The overall goal of this mini-review is to provide a decade-by-decade overview of major historical landmark discoveries in the AHR field and to highlight the numerous contributions made by publications appearing in the pages of DMD. It is hoped that this historical tour might inspire current and future research in the AHR field.

SIGNIFICANCE STATEMENT

With the launch of *Drug Metabolism and Disposition* (DMD) in 1973 and the discovery of the aryl hydrocarbon receptor (AHR) in 1976, the journal and the receptor have led parallel and often intersecting lives over the past 50 years. Tracing the history of the AHR can reveal how knowledge in the field has evolved to the present and highlight the important contributions made by discoveries reported in DMD. This may inspire additional DMD papers reporting future AHR landmark discoveries.

Introduction

The aryl hydrocarbon receptor (AHR) is an intracellular protein that binds halogenated aromatic hydrocarbons (HAHs) such as 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and polycyclic aromatic hydrocarbons (PAHs) such as 3-methylcholanthrene (MC) and benzo[*a*]pyrene (B[*a*]P) (Okey, 2007). Most AHR ligands are toxic, carcinogenic environmental pollutants; however, there are also natural dietary and endogenous ligands (Nguyen and Bradfield, 2008). Many of the molecular details of AHR function have been derived from studies of the classic paradigm involving induction of the cytochrome P450 (P450) gene, *CYP1A1*, as illustrated in Fig. 1. In its unliganded state, the AHR resides in the cytoplasm in a complex with chaperones: a dimer of the 90-kDa heat shock protein (hsp90), p23, and a ~37-kDa immunophilin-related protein known as AHR-interacting protein (AIP). Ligand binding transforms the AHR into its activated nuclear form, a heterodimer of the AHR with the AHR nuclear translocator (ARNT). This heterodimer binds to specific *cis*-acting DNA enhancer sequences known as dioxin-responsive elements (DREs) in the 5′-flanking region of the *CYP1A1* gene, resulting in recruitment of transcriptional co-activators, altered histone acetylation, and chromatin remodeling.

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ABBREVIATIONS: AFB_1, aflatoxin B_1; AHH, aryl hydrocarbon hydroxylation; AHR, aryl hydrocarbon receptor; AHRR, AHR repressor; AIP, AHR-interacting protein; AKR, aldo-keto reductase; ALDH, aldehyde dehydrogenase; ARNT, AHR nuclear translocator; B[*a*]A, benzo[*a*]anthracene; B[*a*]P, benzo[*a*]pyrene; BCRP, breast cancer resistance protein; βNF, β-naphthoflavone; CAR, constitutive androstane receptor; DEX, dexamethasone; DMD, Drug Metabolism and Disposition; DRE, dioxin-responsive element; EROD, 7-ethoxyresorufin O-deethylation; FICZ, 6-formylindolo[3,2-*b*]carbazole; FMO, flavin-containing monooxygenase; GH, growth hormone; GR, glucocorticoid receptor; HAH, halogenated aromatic hydrocarbon; hsp90, 90-kDa heat shock protein; I3C, indole-3-carbinol; MC, 3-methylcholanthrene; MDR, multidrug resistance; MRP, multidrug resistance-associated protein; NQO, NAD(P)H-quinone oxidoreductase; OATP, organic anion-transporting polypeptide; P450, cytochrome P450; PAH, polycyclic aromatic hydrocarbon; PB, phenobarbital; PCB, polychlorinated biphenyl; POR, NADPH-cytochrome P450 oxidoreductase; PXR, pregnane X receptor; RT-PCR, reverse transcription polymerase chain reaction; SULT, sulfotransferase; tBHQ, *t*-butylhydroquinone; TCB, 3,3′,4,4′-tetrachlorobiphenyl; TCDD, 2,3,7,8-tetrachlorodibenzo-*p*-dioxin; TCDF, 2,3,7,8-tetrachlorodibenzofuran; TEF, toxic equivalency factor; TiPARP, TCDD-inducible poly(ADP-ribsose) polymerase; UGT, UDP-glucuronosyltransferase.

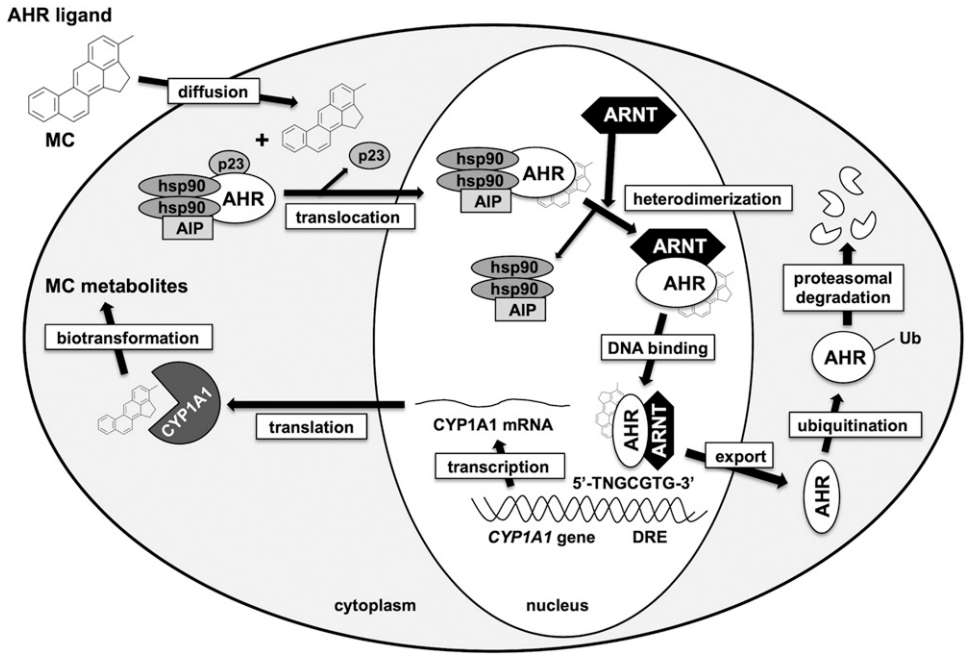

Fig. 1. The classic mechanistic paradigm for AHR-mediated induction of *CYP1A1*. Steps are described in the text and include entry of an agonist ligand (MC shown here) into the cell by diffusion; binding of ligand to the cytoplasmic AHR complex, nuclear translocation and chaperone dissociation, heterodimerization with ARNT, heterodimer binding to DRE sequences and transcriptional regulation of *CYP1A1*, translation of mRNA into functional CYP1A1 protein that biotransforms the inducing ligand, export of AHR from the nucleus and its ubiquitination and proteasomal degradation.

The result is increased transcription of the *CYP1A1* gene, enhanced synthesis of CYP1A1 mRNA and functional protein, with catalytic activity commonly assessed as aryl hydrocarbon hydroxylation (AHH) or 7-ethoxyresorufin O-deethylation (EROD). Acute ligand treatment often triggers AHR nuclear export, ubiquitination, and proteasomal degradation.

The purpose of this mini-review is to provide a decade-by-decade overview of major historical landmark discoveries in the AHR field and to illustrate the important contributions that have derived from work published in *Drug Metabolism and Disposition* (DMD). Interested readers are directed to the following sources for comprehensive tables and figures showing timelines of AHR major milestone discoveries (Okey, 2007; Gasiewicz and Henry, 2012; Nebert, 2017), AHR ligands (Nguyen and Bradfield, 2008; Stevens et al., 2009; DeGroot et al., 2012), and AHR target genes (Boverhof et al., 2006; Boutros et al., 2008; Stevens et al., 2009).

The 1970s

Long before the 1970s, we must recognize as a key foundation of the AHR field the discovery of "MC-type" induction, in which prior exposure of rodents to MC could increase the synthesis of microsomal enzymes capable of biotransforming the inducing chemical and other substrates (Conney et al., 1956). Major landmarks in AHR research during the 1970s include characterization of differences at the *Ah* locus between the "responsive" C57BL/6 mouse strain and the "nonresponsive" DBA/2 mouse strain (Gielen et al., 1972), identification of TCDD as a much more potent AHH inducer than PAHs such as MC (Poland and Glover, 1974), the use of [^{3}H]TCDD to demonstrate specific binding to the mouse hepatic AHR (Poland et al., 1976), and the discovery of AHR translocation from the cytoplasm to the nucleus (Okey et al., 1979).

The inaugural DMD issue was published in January 1973 and featured presentations from the Second Symposium on Microsomes and Drug Oxidations held at Stanford University in July 1972. A report from the Nebert group discussed genetic differences at the *Ah* locus between responsive and nonresponsive mouse strains as assessed by AHH induction, and the text included the prescient speculation that "the inducer acts at some subcellular site (*question mark*), thereby causing synthesis of induction-specific RNA and protein—regulated in some manner, at least in certain mouse strains, by the dominant *Ah* allele" (Nebert et al., 1973). In a few short years, this "*question mark*" would be definitively identified as the AHR. The inaugural issue also contained a report of induction of AHH activity in human foreskins cultured in the presence of B[*a*]P or benz[*a*]anthracene (B[*a*]A) (Alvares et al., 1973). The following year saw a report of EROD activity as a direct fluorimetric assay of microsomal P450s preferentially induced by MC (Burke and Mayer, 1974). A strong correlation was reported between the AHH activities in human lymphocyte cultures and plasma half-lives of antipyrine and phenylbutazone (Kellermann et al., 1975). Studying MC induction in several inbred mouse strains, researchers found that AHH activity was under similar regulatory control as phenacetin O-dealkylation (Poppers et al., 1975), which would eventually become a diagnostic marker activity for CYP1A2. Closing out the decade in DMD, a fascinating report showed that 2,3,7,8-tetrachlorodibenzofuran (TCDF) as a contaminant in a commercially available 99% pure polychlorinated biphenyl (PCB) isomer was the inducer of rat hepatic AHH activity (Goldstein et al., 1978).

The 1980s

Landmark discoveries during the 1980s include the demonstration that TCDD toxicity segregates with the *Ah* locus (Poland and Glover, 1980), early quantitative structure-activity relationships for AHR ligands (Bandiera et al., 1984), comparisons of the physicochemical properties of the cytosolic versus nuclear AHR forms (Gasiewicz and Bauman, 1987), initial characterization of the highly TCDD-resistant Han/Wistar (Kuopio) rat strain (Pohjanvirta et al., 1987), identification of the human AHR by ligand binding (Manchester et al., 1987), and discovery of

6-formylindolo[3,2-*b*]carbazole (FICZ) as a candidate endogenous ligand (Rannug et al., 1987). The final years of the decade saw the definition of the DRE nucleotide sequence (Denison et al., 1988), identification of hsp90 as a component of the AHR cytosolic complex (Perdew, 1988), and demonstration of a low affinity AHR in the nonresponsive DBA/2 mouse (Okey et al., 1989).

During the decade of the 1980s, DMD featured several interesting and important publications related to the AHR field. Three Bernard B. Brodie Award Lecture articles were particularly relevant to this topic. Donald Jerina reviewed the metabolism of aromatic hydrocarbons by P450s and epoxide hydrolases (Jerina, 1983). Among other topics, Gilbert Mannering's article contained the fascinating story of using phenobarbital (PB)- and MC-treated rats to derive some of the earliest evidence for distinct forms of P450s (Mannering, 1986). Daniel Nebert provided a wonderful historical overview of the first two decades of research on the *Ah* locus and the AHR (Nebert, 1988).

Some DMD papers further explored MC-type induction in rat and rabbit liver. Immunohistochemistry revealed induction of P450a (CYP2A1) by MC in mature female and immature male and female rats but not mature male rats (Moody et al., 1983). In vivo treatment of rats with MC or a PCB mixture (Aroclor 1254) increases the metabolism of 8-hydroxymethylbenz[*a*]anthracene to the 8,9-dihydrodiol (Yang et al., 1984). In vivo treatment of rats with MC increases in vitro liver microsomal theobromine metabolism and in vivo theobromine elimination (Shively and Vesell, 1987) and hepatic microsomal conversion of the antiarrhythmic amiodarone to desethylamiodarone (Young and Mehendale, 1987). In vivo treatment of rats with β-naphthoflavone (βNF) increases in vitro liver microsomal 8-methoxypsoralen metabolism and in vivo total clearance of 8-methoxypsoralen (Mays et al., 1987). In vivo treatment of rats with nafimidone alcohol, the major metabolite of the anticonvulsant nafimidone, increases hepatic EROD activity, consistent with MC-type induction (Rush et al., 1987). N-Benzylimidazole displays both MC- and PB-type induction of phase I and II enzymes in rat liver (Papac and Franklin, 1988). MC protects rats from acute *trans*-4-acetylaminostilbene toxicity by increasing the rate of phase II conjugation pathways of inactivation relative to oxidative activation (Pfeifer and Neumann, 1988). Hind-limb ischemia secondary to infrarenal aortic ligation (as a model of traumatic injury) results in induction of hepatic EROD activity and P-448 content, in contrast to a decrease in other P450 activities (Griffeth et al., 1984). In vivo treatment of rats with βNF causes selective down-regulation of androgen-dependent testosterone hydroxylation activities (Shiverick, 1981). In vivo treatment of rabbits with βNF increases the rate of B[*a*]P fluorescence elimination from individual hepatocytes based on microspectrofluorometry (Massey et al., 1986).

Several DMD papers exploited genetic differences at the *Ah* locus between responsive C57BL/6 mice and nonresponsive DBA/2 mice. Examples included induction of theophylline clearance by βNF or MC (Betlach and Tozer, 1980); induction of 2,5-diol formation from biphenyl by βNF (Halpaap-Wood et al., 1981); a comparison of the metabolism of two antitumor ellipticines (Roy et al., 1985); and a stronger AHH induction by MC in C57BL/6 mice, studied here as fast acetylators, than in slow acetylator A/J mice (Elves et al., 1985).

Some publications featured an extrahepatic focus. There are age-dependent differences in rat skin AHH inducibility by topically applied MC (Mukhtar and Bickers, 1983). Treatment of rabbits with TCDD induces the 7-hydroxylation of 2-acetylaminofluorene in most lung cell fractions separated by elutriation (Minchin et al., 1985). The PCB metabolite 4,4'-bis(methylsulfonyl)-2,2',5,5′-tetrachlorobiphenyl binds to protein residing in club and goblet-like cells in lung and the apical region of proximal tubular cells in kidney (Brandt et al., 1985), and these methylsulfonyl-PCBs bind with high affinity to secretory 13-kDa protein in rat lung club cells (Lund et al., 1988). Immunohistochemistry was used to define the regional and cellular selectivities shown in mouse lung for the major MC-inducible P450 forms (Forkert et al., 1989). Extrahepatic PAH metabolism and DNA binding featured in the following DMD papers. Comparison of B[*a*]P covalent binding in perfused rat lung following systemic versus intratracheal dosing reveals a partial protective effect of liver (Foth et al., 1984). Capsaicin, an active principle in hot peppers, inhibits B[*a*]P metabolism and DNA binding in mouse and human keratinocytes (Modly et al., 1986). In vivo treatment of pregnant rats with βNF or MC induces B[*a*]P metabolism and DNA binding catalyzed by microsomes from the vascular labrynth zone tissues of rat placenta (Salhab et al., 1986). Topical application of MC to neonatal BALB/c mice causes maximal induction of PAH metabolism and DNA binding in the epidermal skin compartment (Das et al., 1986).

A few DMD papers had a glucuronidation focus. Several AHR activators (MC, B[*a*]P, TCDD) increase rat hepatic levels of UDP-glucuronic acid, and this may influence glucuronidation (Watkins and Klaassen, 1983). Stereoselective glucuronidation of oxazepam can provide evidence for distinction between quite similar inducers such as MC and βNF (Yost and Finley, 1985). B[*a*]A induces EROD activity and UDP-glucuronosyltransferase (UGT) activity toward 3-hydroxy B[*a*]P in rat hepatocytes (Forster et al., 1986). The disposition of HAHs was also a prominent topic. The disposition of [^{3}H]TCDD was compared in responsive versus nonresponsive mouse strains (Gasiewicz et al., 1983). The use of congenic mouse strains that differ at the *Ah* locus showed that the distribution and excretion of TCDD is mainly governed by the total genetic background rather than the allele at the *Ah* locus (Birnbaum, 1986). Studies of isolated hepatocytes from C57BL/6 and DBA/2 mice showed that uptake and metabolism of TCDD are not correlated with genetic differences at the *Ah* locus (Shen and Olson, 1987). Studies of isolated hepatocytes from rat and hamster, a species highly resistant to TCDD, showed that the effects of inducers (MC and TCDD) and inhibitors on metabolism of TCDD and B[*a*]P reveal species differences in the substrate specificity of P-448 involved in TCDD metabolism (Wroblewski and Olson, 1988).

The remaining important DMD papers from the 1980s fall under the heading "of fish and men." In terms of fish, waterborne B[*a*]P exposure of freshwater *Poeciliopsis* species increases hepatic AHH and EROD activities (Goddard et al., 1987), and dietary MC or B[*a*]P causes preferential induction of intestinal AHH and EROD activities in spot, a marine teleost (van Veld et al., 1988). In terms of humans, an early study showed a weak but significant correlation between AHH activity in human liver biopsy samples and in vivo antipyrine half-life or clearance (Pelkonen et al., 1980). The 4-hydroxylation of 17β-estradiol was induced in human placental microsomes from smokers, but the correlation with AHH activity shows an unusual threshold-type relationship (Juchau et al., 1982). Metabolism of 7,12-dimethylbenz[*a*]anthracene and DNA adduct formation were studied in human fetal kidney and intestinal cells in culture (Oravec et al., 1985). Theobromine plasma clearance was shown to be higher in smokers versus nonsmokers due to induction of multiple metabolic pathways, particularly 7-demethylation (Miners et al., 1985). Finally, studies in human liver microsomes characterized the biotransformation of caffeine, paraxanthine, theophylline, and theobromine by PAH-inducible P450s (Campbell et al., 1987).

The 1990s

This decade witnessed a noticeable acceleration of AHR research as new molecular tools and approaches became available. Many landmark discoveries can be highlighted. There was introduction of the toxic equivalency factor (TEF) approach to the risk assessment of dioxin-like chemicals acting through the AHR (Safe, 1990). The early 1990s saw the demonstration that the transformed AHR is heteromeric (Elferink

et al., 1990), and this was followed quickly by the purification of AHR protein (Bradfield et al., 1991), the raising of polyclonal antibodies to the AHR (Poland et al., 1991), and cloning of the AHR cDNAs from mouse (Burbach et al., 1992; Ema et al., 1992) and human (Dolwick et al., 1993). Discovery of ARNT revealed the identity of the AHR's nuclear heterodimerization partner (Reyes et al., 1992). Further molecular dissection revealed the arrangement of the AHR's functional domains (Fukunaga et al., 1995), and the generation of *Ahr*-null mice provided definitive evidence of the AHR's role in toxic responses to xenobiotics and developmental processes (Fernandez-Salguero et al., 1995; Schmidt et al., 1996; Mimura et al., 1997). Germ-line deletion of *Arnt* in mice was shown to result in embryonic lethality due to defective angiogenesis (Kozak et al., 1997; Maltepe et al., 1997). The remaining components of the AHR cytosolic complex were identified as a ~37-kDa immunophilin-related protein designated by various groups as AIP (Ma and Whitlock, 1997), AHR-associated protein 9 (Carver and Bradfield, 1997), or hepatitis B virus X-associated protein 2 (Meyer et al., 1998), along with p23 (Kazlauskas et al., 1999). To close the decade, acute ligand treatment was shown to result in ubiquitination and proteasomal degradation of AHR protein (Davarinos and Pollenz, 1999; Roberts and Whitelaw, 1999).

DMD featured Brodie Award Lecture articles by Wayne Levin and Fred Guengerich during the 1990s. The Levin review discussed the early observation that the spectral maximum of the ferrous carbonyl complex was at ~448 nm (instead of 450 nm) for microsomes from MC-treated rats and the subsequent purification and raising of antibodies against the major constitutive, PB- and MC-inducible rat liver P450s (Levin, 1990). A pertinent aspect of the Guengerich review was the role of the major PAH-inducible human P450s (CYP1A1 and 1A2) in carcinogen activation (Guengerich, 1993). Alan Poland reported on an ASPET-sponsored colloquium titled "Receptor-Acting Xenobiotics and Their Risk Assessment" held in October 1995; this meeting was stimulated by the release of the U.S. Environmental Protection Agency draft risk assessment of TCDD, the first for a xenobiotic exerting its toxic effects via a receptor (Poland, 1996). The Anthony Y.H. Lu Commemorative Issue of DMD appeared in December 1998 and contained a review from the Gonzalez group highlighting the toxic responses and developmental and physiologic processes mediated by the receptor observed during the first few years after generation of *Ahr*-null mice (Gonzalez and Fernandez-Salguero, 1998). This same issue also contained a report on an ASPET symposium titled "Physiological and Pathophysiological Regulation of Cytochrome P450" held at Experimental Biology 1998; in this report, the Tukey group discussed the role of signal transduction in AHR-mediated transcriptional activation of the *CYP1A1* gene (Morgan et al., 1998).

Further work on mouse strain differences showed that PB induced CYP1A2 at the mRNA, protein, and enzyme activity levels in mouse strains that are either responsive or nonresponsive to PAHs (Sakuma et al., 1999). Several DMD papers in the 1990s continued to characterize MC-type induction in rat liver. In MC-treated rats, formation clearance of 4-hydroxyantipyrine and metabolic clearance of theophylline are strongly correlated (Groen et al., 1992). Distinct mechanisms are involved in the induction of NAD(P)H-quinone oxidoreductase (NQO) in liver and kidney by arsenite versus βNF (Falkner et al., 1993). The potent AHR agonist, TCDD, was shown to decrease biliary excretion of total thiol-derived sulfur and reduced glutathione (Madhu et al., 1993). Studies of the modulation by glucocorticoids of induction responses to TCDD, B[*a*]A, and *t*-butylhydroquinone (tBHQ) revealed regulation of *Ah* battery genes via AHR-dependent and -independent processes in cultured rat hepatocytes (Xiao et al., 1995). The biphasic kinetics for the metabolism of the β-adrenoceptor blocker, bunitrolol, in microsomes from MC-treated rats are due to the involvement of both CYP1A1 and a CYP2D subfamily enzyme (Fujita et al., 1996). Caffeine, not polyphenols, is the component in tea responsible for induction of CYP1A2 protein and activity in rat liver (Chen et al., 1996). Among hydroxymethylglutaryl-coenzyme A reductase inhibitors tested, fluvastatin is unique in showing CYP1A1 inducing properties in primary cultured rat hepatocytes and in rat liver (Kocarek and Reddy, 1996). Among proton pump inhibitors, pantoprazole shows less CYP1A induction in rat liver compared with omeprazole or lansoprazole (Masubuchi et al., 1997). Using 7-ethoxycoumarin O-deethylation as a marker activity, rat liver slices underestimate the effects of the inducer βNF compared with isolated hepatocytes and hepatic microsomes (Carlile et al., 1999). Finally, four DMD papers focused on indole-3-carbinol (I3C), an AHR activator found in cruciferous vegetables. Both βNF and I3C inhibit aflatoxin B_1 (AFB_1) carcinogenesis, at least partly, by inducing P450s and enhancing net production of less toxic, hydroxylated AFB_1 metabolites (Stresser et al., 1994a). I3C, and βNF to a lesser degree, protect against AFB_1 carcinogenesis by inducing glutathione S-transferases with high activity toward AFB_1 *exo*-epoxide, thereby decreasing DNA adducts (Stresser et al., 1994b). The disposition of I3C and its metabolites was characterized in male rats (Stresser et al., 1995), and I3C was shown to inhibit the activity and expression of flavin-containing monooxygenase (FMO)-1 in rat liver and intestine (Larsen-Su and Williams, 1996).

DMD papers from the 1990s with an extrahepatic focus included the report that the relative inducibility of CYP1A1 and EROD activity, but not NQO, in skin by dibenz[*a,c*]anthracene is regulated as a function of epidermal differentiation (Reiners et al., 1992). The induction of CYP1A1 mRNA by B[*a*]A and βNF was also characterized in rat epidermis and cultured human epidermal keratinocytes (Khan et al., 1992). Expression of CYP1A1 and 1A2 mRNA is enhanced in rat renal tissue after exposure to MC or pyridine (Kim et al., 1995). The inducibility of rat small intestinal CYP1A1 by βNF diminishes from duodenum to ileum, and intestinal induction is more sensitive to oral versus intraperitoneal βNF (Zhang et al., 1996). Interestingly, the decrease in CYP1A1 inducibility from duodenum to ileum parallels the AHR protein levels (Zhang et al., 1997). The induction of rat CYP1A1 by intraperitoneal βNF is much greater in airways and lung parenchyma compared with liver or trachea (Lee et al., 1998). Finally, dose-dependent induction of CYP1A by nicotine feeding was characterized in rat lung, kidney, and liver (Iba et al., 1999).

In terms of glucuronidation, treatment of rat hepatocytes with MC induces a high affinity phenol UGT, shifting benzene metabolism toward the production of less toxic metabolites (Schrenk and Bock, 1990). In human colon carcinoma Caco-2 cells, TCDD induces UGT1A6 and 1A9, whereas tBHQ induces UGT1A6, 1A9, and 2B7 (Münzel et al., 1999). DMD papers examining HAH disposition included the report that, at two days following dosing, less than 0.1% of an immunosuppressive dose of [^{3}H]TCDD is distributed to mouse spleen (Neumann et al., 1992). Decreased AHR-mediated toxicity following oral administration of 3,3′,4,4'-tetrachloroazobenzene versus TCDD is largely due to extensive azo reduction and limited systemic absorption (Pillai et al., 1996). Similarly, for 3,3′,4,4'-tetrachloroazoxybenzene, decreased toxicity is mainly due to reduced absorption and enhanced elimination of metabolites (Ziegler et al., 1996). The effects of age, sex, and pharmacologic agents on rat biliary elimination of TCDD were characterized (Jackson et al., 1998). With respects to PAHs, rat Kupffer cells were shown to act as a reservoir for B[*a*]P, reducing access to drug-metabolizing enzymes in the hepatic parenchymal cells (Zhong et al., 1994).

Work with human cellular models showed PAH inducibility of CYP1A enzyme activities in three long-term normal human hepatocyte lines cocultured with rat liver epithelial cells (Roberts et al., 1993) and strong induction of EROD activity by MC in primary human hepatocyte cultures (Donato et al., 1995). Studies with diverse species included monkey, chicken, and fish. Oral treatment of cynomolgus monkeys with βNF induces hepatic CYP1A1/2 proteins and associated activities such as

EROD and caffeine N3-demethylation (Bullock et al., 1995). In chick embryo hepatocytes, different TCDD-inducible CYP1-related P450s are responsible for arachidonic acid epoxygenation and AHH activity (Paroli et al., 1994), and the arachidonic acid epoxygenase (CYP1A5) is mainly responsible for uroporphyrinogen oxidation induced by AHR ligands in chicken liver and kidney (Sinclair et al., 1997). Induction of CYP1A1 in liver and extrahepatic tissues of the marine teleost scup by 3,3′,4,4’-tetrachlorobiphenyl (TCB) and TCDF was studied by immunohistochemistry (Smolowitz et al., 1991), and AHR-regulated CYP1A enzymes were found to be involved in TCB metabolism in this fish species (White et al., 1997). CYP1A-dependent EROD and AHH activities are induced by dietary βNF in the intestine, but not liver, of channel catfish (James et al., 1997).

The 2000s

Achievement of important milestones in AHR research continued apace during the first decade of the new millennium. The adoption of genome-wide approaches to the analysis of the transcriptome dramatically expanded the repertoire of genes up- and down-regulated by the activated AHR, and only a few of the early examples are cited here (Puga et al., 2000; Frueh et al., 2001; Thomas et al., 2001; Boverhof et al., 2006). The AHR repressor (AHRR) was discovered and characterized as a negative regulator of AHR signaling (Baba et al., 2001). Several novel and informative genetically modified mouse models were generated and characterized: mice with a constitutively active AHR (McGuire et al., 2001), *AHR*-humanized mice (Moriguchi et al., 2003), and mice carrying a mutation in the AHR’s nuclear localization signal (Bunger et al., 2003) or DNA-binding domain (Bunger et al., 2008). There was growing attention to the role of the AHR in the immune system, characterized by the seminal study showing control of T_{reg} and T_H17 differentiation by the AHR (Quintana et al., 2008).

The total annual page count for DMD and the number of papers related to the AHR appearing in the journal both reached peaks during the 2000s (Fig. 2). DMD featured several mini-reviews, symposium reports, and perspectives articles of relevance to the AHR field during the 2000s. A mini-review reported on a symposium titled “Molecular Regulation of Genes Encoding Xenobiotic-Metabolizing Enzymes: Mechanisms Involving Endogenous Factors” held in Boston in 2000; this included a report from the Elferink group discussing the implications of AHR and retinoblastoma protein interactions for cell cycle control (Hines et al., 2001). The same meeting featured a symposium titled “Glucuronidation and the UDP-Glucuronosyltransferases in Health and Disease”; this symposium paper included reports from the Guillemette group on human UGT

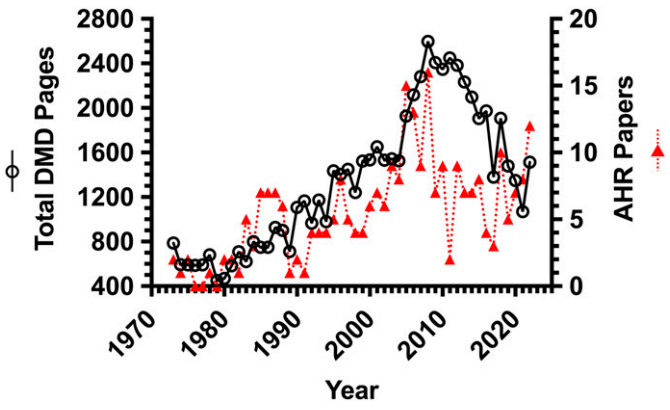

Fig. 2. A year-by-year timeline showing the total DMD pages published and the number of DMD articles related to AHR. Publications cover the history of DMD from Vol. 1, Issue 1 (January 1973) to Vol. 50, Issue 12 (December 2022), inclusive.

polymorphisms and smoking-related cancers, the Wells group on UGT deficiency as a determinant of B[*a*]P toxicity, and the Ritter group on PAH exposure as a cause of variation in UGT1A1 and 1A6 levels (Wells et al., 2004). A report on an ASPET symposium titled “Transcriptional Suppression of Cytochrome P450 Genes by Endogenous and Exogenous Chemicals” held at Experimental Biology 2003 included our work on the transcriptional down-regulation of the male-specific growth hormone (GH) pulse-regulated rat hepatic *CYP2C11* by PAHs and HAHs via an incompletely understood mechanism that involves the AHR (Riddick et al., 2004). A review article published as a tribute to James R. Gillette included consideration of the induction of small intestinal CYP1A1 and other drug-metabolizing enzymes by AHR activators (Kaminsky and Zhang, 2003). A mini-review on metabolism-based drug-drug interactions featured discussions of how various aspects of AHR biology influence interindividual variability in CYP1A inducibility (Tang et al., 2005). A perspectives article covered the important topic of CYP1A induction and human risk assessment (Ma and Lu, 2007). The year 2008 was memorable for ASPET, and centennial perspectives articles focused on drug metabolism research included discussion of historical landmarks in the discovery of MC-type induction and the early characterization of the AHR system (Murphy, 2008a) and the continuing evolution of the AHR field into the realm of endogenous ligands (Murphy, 2008b). Perspectives from the Pharmaceutical Research and Manufacturers of America included surveys of current practices for in vitro assays of P450 inducers acting via the AHR and clinical drug-drug interaction studies involving CYP1A2 induction (Bjornsson et al., 2003; Chu et al., 2009).

Further characterization of MC-type induction in rat liver appeared in DMD research articles during this decade. I3C and a major acid condensation product, 3,3′-diindolylmethane, decrease rat hepatic FMO1 protein and enzyme activities while inducing P450 activities (Katchamart et al., 2000). Induction of CYP1A1 mRNA levels by βNF in cultured rat hepatocytes was characterized using real-time reverse transcription polymerase chain reaction (RT-PCR) and the RNA invasive cleavage assay (Burczynski et al., 2001). Taqman-based real-time RT-PCR was used to confirm CYP1A1 and 1A2 induction in rat liver by βNF, and the technique was used to estimate the inductive potential of drug candidates undergoing rodent toxicity evaluation (Baldwin et al., 2006). The suspected human carcinogen, 3-nitrobenzanthrone and its metabolite, 3-aminobenzanthrone, induce rat hepatic NQO1 and CYP1A, thereby promoting DNA adduct formation (Stiborová et al., 2006). Multiple DREs were implicated in the constitutive and MC-inducible expression of rat hepatic aldehyde dehydrogenase ALDH3A1 (Reisdorph and Lindahl, 2007). The anticancer drug ellipticine modulates its own metabolic detoxification and DNA adduct formation by inducing rat hepatic CYP1A1 and 1A2 (Aimová et al., 2007).

Mouse animal and cellular models were a focus for AHR research in several DMD papers. Treatment of mice with βNF causes strong induction of CYP1A1 protein in endothelial cells of blood-brain interfaces and a corresponding increase in irreversible binding of [^{3}H]7,12-dimethylbenz[*a*]anthracene (Granberg et al., 2003). MC induces human CYP1A2 mRNA and protein in chimeric mice with humanized liver (Katoh et al., 2005). TCDD triggers AHR-dependent induction of mouse hepatic FMO2 and FMO3 mRNAs (Celius et al., 2008). Mice with liver-specific deletion of β-catenin show decreased AHR mRNA levels and diminished induction of AHR target genes by MC (Braeuning et al., 2009). Inoculation of human hepatocellular carcinoma cells into athymic nude mice has little impact on basal hepatic AHR mRNA levels and induction of AHR target genes by MC (Sugawara et al., 2009). Mercury and lead increase, whereas copper decreases, constitutive and TCDD-inducible expression of NQO1 and glutathione S-transferase Ya mRNAs in mouse Hepa-1 cells via a transcriptional mechanism (Korashy and El-Kadi, 2006). Vanadium interferes

with TCDD-induced transcriptional activation of *CYP1A1* in mouse Hepa-1 cells (Anwar-Mohamed and El-Kadi, 2008).

DMD papers with an extrahepatic focus included the report that mouse small intestinal CYP1A1 protein shows higher inducibility by βNF proximally with decreasing induction distally, and induction is stronger in C57BL/6 versus 129/Sv mice (Zhang et al., 2003). βNF (van de Kerkhof et al., 2005) and several other AHR activators (van de Kerkhof et al., 2007) induce CYP1A-dependent 7-ethoxycoumarin O-deethylation in rat small intestinal and colon precision-cut slices. βNF induces CYP1A1 and UGT1A6 mRNA levels in precision-cut slices from human proximal jejunum and colon (van de Kerkhof et al., 2008). The C57BL/6 versus DBA/2 mouse strain difference was used to demonstrate that CYP1A1 induction by βNF in white adipose tissue is AHR-mediated (Yoshinari et al., 2006).

Regarding glucuronidation, MC induces UGT activity toward thyroxine in rat hepatocytes, but the response is not potentiated by dexamethasone (DEX), as is the case for UGT1A6 induction (Jemnitz et al., 2000). The dietary flavonoid chrysin, a relatively weak AHR agonist, induces UGT1A1 in HepG2 cells (Walle et al., 2000). Comparisons of 22 flavonoids in HepG2 cells suggest that UGT1A1 induction by these compounds occurs via a novel non-AHR-mediated mechanism (Walle and Walle, 2002). Treatment of primary human hepatocytes with MC induces estradiol-3-glucuronidation in four of five donors (Soars et al., 2004). In contrast to the AHR-activating PCB mixture Aroclor 1254, treatment of rats with various catechols produces little effect on their own hepatic glucuronidation (Elovaara et al., 2004). Immunoactivation of rat peritoneal macrophages induces UGT1A7 mRNA and glucuronidation of 3-hydroxy-B[*a*]P (Tochigi et al., 2005). A comparison of Wistar versus UGT1A-deficient Gunn rats showed that the decrease in serum thyroxine levels caused by the PCB mixture Kanechlor-500 is mostly due to thyroxine tissue accumulation rather than UGT induction (Kato et al., 2007). The AHR activator 1,7-phenanthroline induces CYP1A1 and UGT1A6 in rats fed a standard diet or a high-fat/high-sucrose diet; the diet also had no effect on hepatic AHR and ARNT protein levels, and AHR and ARNT showed no sex differences (Osabe et al., 2008). The proximity of a DRE to a glucocorticoid-responsive element in the 5′-flanking region of rat *UGT1A6* is involved in the diminished glucocorticoid induction following AHR activation (Falkner et al., 2008).

There was a large increase in the number of DMD papers dealing with the human AHR system during the 2000s. CYP1B1, an AHR target, is commonly expressed in human lung at the mRNA and protein levels, and this is likely important for lung carcinogen metabolism (Spivack et al., 2001). The *CYP1B1*3/*3* genotype is associated with decreased mRNA expression in human leukocytes, CYP1B1 levels are higher in females versus males, and tobacco smoke does not alter CYP1B1 levels (Helmig et al., 2009). AHR, ARNT, and CYP1A1 mRNA levels in lymphocytes from healthy subjects show strong correlations (Siest et al., 2008). The human AHR variants K401R and N487D display decreased transcriptional activity in response to MC, βNF, and omeprazole, mainly through decreased protein expression due to accelerated proteasomal degradation (Koyano et al., 2005). In a study with precision-cut human liver slices, βNF induced CYP1A2 protein levels but CYP1A1 protein was not detected before or after treatment with model inducers (Edwards et al., 2003). DNA binding of B[*a*]P is associated with CYP1A1 and 1B1 induction in bioengineered human gingival epithelial tissue constructs (Walle et al., 2006). The sequential metabolism of 2,3,7-trichlorodibenzo-*p*-dioxin by CYP1A1 and UGTs was characterized in human liver microsomes (Kasai et al., 2004). The AHR-inducible human CYP2S1 showed negligible activity in the metabolism of nicotine and bioactivation of several cigarette smoke lung carcinogens (Wang et al., 2005).

DMD published several studies that characterized the presence and functionality of the AHR in human cellular models. This includes work done with cultured primary human hepatocytes. Quantitative RT-PCR was used to characterize CYP1A1 induction by MC, omeprazole, and lansoprazole (Bowen et al., 2000). Strong induction of CYP1A2 by βNF was confirmed using data summarized from 62 hepatocyte preparations (Madan et al., 2003). The antitumor olivacine derivative S 16020 induces CYP1A2 protein, CYP1A-dependent enzyme activities, and its own metabolism (Pichard-Garcia et al., 2004). Reliable assessment of the induction of CYP1A2 enzyme activity, with phenacetin as probe, by omeprazole was shown using a substrate cassette strategy (Mohutsky et al., 2005). Induction of CYP1A2 mRNA, protein, and EROD activity by omeprazole was demonstrated in cryopreserved hepatocytes (Roymans et al., 2005). Simultaneous measurement of 23 human P450s confirmed strong induction of CYP1A1, 1A2, and 1B1 mRNA by MC (Girault et al., 2005). TCDD induces mRNA levels for multidrug resistance 1 (MDR1) and breast cancer resistance protein (BCRP) while down-regulating canalicular bile salt export pump and several sinusoidal transporters (Jigorel et al., 2006). Induction of CYP1A1 and 1A2 mRNA by omeprazole was confirmed in long-term cultures (Meneses-Lorente et al., 2007).

Work with HepG2 cells included the report that hazardous environmental metals (arsenic, lead, mercury, cadmium) decrease PAH-induced CYP1A1 activities (Vakharia et al., 2001). Arsenite decreases CYP1A1-mediated PAH bioactivation by down-regulating the transcriptional induction of *CYP1A1* by a prototypical PAH (Bessette et al., 2005). High-throughput screening of dietary flavonoids as inducers or AHR antagonists was conducted in HepG2 cells stably transfected with luciferase reporters under the control of the human *CYP1A1* promoter and 5′-flank (Allen et al., 2001). Although HepG2 cells display low P450 expression compared with primary human hepatocytes, both cell systems show comparable CYP1A1 and 1A2 mRNA inducibility by B[*a*]P and MC (Wilkening et al., 2003). Research with HepaRG cells showed induction of CYP1A1 and 1A2 mRNA and phenacetin O-deethylation activity by omeprazole (Kanebratt and Andersson, 2008b). The functional resemblance of HepaRG cells to primary human hepatocyte cultures was confirmed by comparing the basal expression of AHR mRNA and target genes such as CYP1A2 and the response to MC as a prototypical inducer (Aninat et al., 2006; Kanebratt and Andersson, 2008a). The responsiveness of HepaRG cells to induction of CYP1A2 activity by MC is well preserved for long culture times at confluence (Jossé et al., 2008). Using the Fa2N4 immortalized human hepatocyte cell line, omeprazole was shown to induce CYP1A2 activity with tacrine as a component of a probe substrate cocktail (Youdim et al., 2007). Fa2N4 cells display similar AHR levels compared with human hepatocytes and show strong induction of CYP1A2 mRNA and activity by omeprazole (Hariparsad et al., 2008).

Other human cell lines were important models for AHR research appearing in DMD. The transcriptional regulation and molecular function of the AHRR was characterized in human cell lines (Haarmann-Stemmann et al., 2007). The fluorinated benzothiazole 5F 203 induces CYP1A1, leading to increased metabolic activation and covalent binding to cellular macromolecules only in human cancer cell lines sensitive to the drug's cytotoxic effects (Brantley et al., 2004). Emodin, an active component of herbal laxatives, induces CYP1A1 and 1B1 mRNA, protein, and activities in the CL5 human lung adenocarcinoma cell line (Wang et al., 2001). Induction of CYP1A1 and 1B1 by B[*a*]P in T-47D human breast cancer cells is diminished by arsenite, possibly via a post-transcriptional mechanism involving decreased heme availability (Spink et al., 2002). TCDD-induced CYP1B1 mRNA and protein expression in MCF-7 human breast cancer cells is suppressed by 2,4,3′,5′-tetramethoxystilbene without altering AHR or ARNT mRNA levels (Chun et al., 2005).

DMD papers featuring diverse species included eel, swine, dog, guinea pig, and fish. B[*a*]P, TCB, and βNF induce CYP1A and EROD activity in the heart and swimbladder rete mirabile of the eel, with induction occurring in endothelium (Schlezinger and Stegeman, 2000). Immunoreactive homologs of CYP1A1 and 1A2 and enzyme activities were characterized following exposure of swine to a cocktail of inducers including βNF (Myers et al., 2001). Strong induction of CYP1A-dependent EROD activity was observed following in vivo treatment of beagle dogs with βNF and treatment of beagle dog hepatocyte cultures with βNF or MC (Graham et al., 2002). Compound I, an inhibitor of human kinase insert domain-containing receptor, induces its own metabolism and clearance in beagle dogs because it is both an inducer and a substrate for CYP1A (Gibson et al., 2005). The 5′-flanking region of the guinea pig *CYP1A2* gene was cloned and characterized for functional DRE sequences (Black and Quattrochi, 2004). Treatment of channel catfish with MC as a CYP1 inducer enhances formation of estrogenic metabolites from methoxychlor (Stuchal et al., 2006).

Several DMD publications reported the identification of novel AHR ligands. Compounds showing AHR activation in various experimental systems included metabolites of the tryptophan photoproduct FICZ (Bergander et al., 2003); the antioxidant tBHQ (Gharavi and El-Kadi, 2005; Schreiber et al., 2006); the antiandrogen flutamide (Coe et al., 2006); imidazole drugs from distinct therapeutic classes, for example, the aromatase inhibitor vorozole (Diani-Moore et al., 2006); the antiangiogenic agent TSU-68 (Kitamura et al., 2008); the calcium/calmodulin-dependent protein kinase kinase inhibitor STO-609 (Monteiro et al., 2008); and the glycogen synthase kinase inhibitor SB216763 (Braeuning and Buchmann, 2009). The Jun N-terminal kinase inhibitor SP600125 was characterized as an AHR antagonist (Joiakim et al., 2003).

The Klaassen group used the branched DNA signal amplification technology and other approaches to systematically characterize gene expression profiles in several contexts. These DMD papers included reports of rat hepatic P450 induction by MC and other prototypical inducers (Hartley and Klaassen, 2000); enhanced rat liver UGT activity toward thyroxine by MC and Aroclor 1254 via increased expression of UGT1A6 (Vansell and Klaassen, 2002); and induction of mRNAs encoding multidrug resistance-associated proteins MRP2, 3, 5, 6, and 7 (Maher et al., 2005) and organic anion-transporting polypeptides OATP2B1 and 3A1 (Cheng et al., 2005) in mouse liver by the AHR activators TCDD, PCB126, and βNF. Conversely, microsomal enzyme inducers, including multiple AHR ligands, were unable to increase rat MDR1 gene expression (Brady et al., 2002). Further studies documented induction of UGT1A3, 1A6, and 1A7 by AHR activators in the liver but not duodenum of rats (Shelby and Klaassen, 2006); peak hepatic AHR and ARNT mRNA levels around the light/dark transition (Zhang et al., 2009); and induction of mouse hepatic UGT1A1, 1A6, 1A9, and 2B35 and intestinal UGT1A6 and 1A7 by AHR activators (Buckley and Klaassen, 2009). Mouse AHR shows ubiquitous tissue distribution with no sex differences; hepatic AHR levels are induced by βNF, spironolactone, clofibrate, and butylated hydroxyanisole but not TCDD or PCB126, and AHR activation transcriptionally induces constitutive androstane receptor (CAR) and enhances induction of CAR target genes (Petrick and Klaassen, 2007).

Our laboratory used luciferase reporter plasmids driven by the rat *CYP2C11* promoter and 5′-flank to study down-regulation of this gene by PAHs and HAHs in cell culture models (Bhathena et al., 2002) and in rat liver in vivo (Sawaya and Riddick, 2008). We also reported the regulation of constitutive mouse hepatic P450s and GH signaling components by MC (Lee et al., 2006) and enhanced AHR expression and function by glucocorticoids in mouse Hepa-1 cells (Bielefeld et al., 2008).

The 2010s

The new decade was ushered in by landmark discoveries emphasizing the critical physiologic functions of the AHR in the immune system, including the characterization of kynurenine as a candidate endogenous ligand (Mezrich et al., 2010), the demonstration that AHR activation by kynurenine suppresses the antitumor immune response (Opitz et al., 2011), the key regulatory role of the AHR in the maintenance of intraepithelial lymphocytes in skin and intestine (Li et al., 2011), and the ability of natural dietary AHR ligands to stimulate the postnatal expansion of intestinal lymphoid cells, thereby contributing to intestinal homeostasis and protection against infection (Kiss et al., 2011). StemRegenin 1, an AHR antagonist, was shown to promote expansion of human hematopoietic stem cells (Boitano et al., 2010) and TCDD-inducible poly (ADP-ribose)polymerase (TiPARP/PARP7) was characterized as a transcriptional repressor of AHR, forming a negative feedback loop (MacPherson et al., 2013). Induction of TiPARP and related polymerases by TCDD causes NAD^+ loss and decreased activity of sirtuins, revealing a novel unifying mechanism for dioxin toxicities such as thymus atrophy and hepatosteatosis (Diani-Moore et al., 2017). AHR activation by endogenous tryptophan catabolites was shown to promote disease tolerance by controlling excess inflammation without compromising immunity (Bessede et al., 2014), and there was the demonstration that type I interferons generated in the central nervous system and gut microbial metabolites of dietary tryptophan act via the AHR in astrocytes to suppress central nervous system inflammation (Rothhammer et al., 2016). Finally, excessive CYP1A1-mediated degradation of AHR ligands in intestinal epithelial cells compromises intestinal immune function (Schiering et al., 2017) and tapinarof, an approved treatment of plaque psoriasis, exerts its anti-inflammatory effects via AHR activation (Smith et al., 2017).

In the 2010s decade, DMD featured several mini-reviews, symposium reports, commentaries, and perspectives articles with AHR relevance. A report on an ASPET symposium titled "Targeting Drug-Metabolizing Enzymes for Effective Chemoprevention and Chemotherapy" held at Experimental Biology 2009 included a report from the Williams group on the role of AHR-regulated CYP1B1 in chemoprevention of PAH transplacental carcinogenesis (Swanson et al., 2010). A symposium report from Experimental Biology 2012 titled "NADPH-Cytochrome P450 Oxidoreductase: Roles in Physiology, Pharmacology, and Toxicology" included a report from the Wolf group on the reductase conditional null mouse in which administration of an AHR agonist drives Cre-recombinase expression under control of a *CYP1A1* promoter, resulting in NADPH-cytochrome P450 oxidoreductase (POR) deletion either in liver or liver and gastrointestinal tract depending on the AHR activator and dose (Riddick et al., 2013). The Experimental Biology 2013 meeting generated a symposium report titled "Potential Role of Epigenetic Mechanisms in the Regulation of Drug Metabolism and Transport" featuring a report from the Hankinson group on the role of DNA methylation in differential AHR-mediated induction of CYP1A1 versus CYP1B1 by TCDD (Ingelman-Sundberg et al., 2013). A symposium titled "Physiological Regulation of Drug Metabolism and Transport" was held at Experimental Biology 2017, and the report from the Cui group included consideration of the regulation of hepatic and intestinal AHR target genes by tryptophan metabolites generated by intestinal microbiota (Morgan et al., 2018). A perspectives article considered pharmacokinetic herb-drug interactions involving induction of drug-metabolizing enzymes and transporters, using milk thistle and resveratrol as examples (Brantley et al., 2014). A minireview on miRNA pharmacoepigenetics included discussion of the modulation of AHR expression by miR-29 and miR-124, and ARNT by miR-24 (Yu et al., 2016). A "Special Section on Drug Metabolism and the Microbiome" from October 2015 featured a commentary introducing the concept that tryptophan metabolites produced by gut microbiota act

via the AHR to regulate host immune function and intestinal health (Swanson, 2015). This topic was developed further in mini-reviews showing that AHR-activating xenobiotics can also alter the intestinal microbiome composition (Klaassen and Cui, 2015) and discussing physiologic functions of AHR ligands derived from indole and tryptophan metabolism, encompassing dietary exposure, microbiota-derived products, host metabolism of indoles and tryptophan, and photo-oxidation of tryptophan (Hubbard et al., 2015). A "Special Section on New Models in Drug Metabolism and Transport" from November 2018 included mini-reviews addressing progress and challenges with using *CYP1A1/1A2*-humanized and *CYP1B1*-humanized mice in pharmacological and toxicological investigations (Bissig et al., 2018) and discussing transcriptional induction of the *UGT1A1* gene in *UGT1*-humanized mice (Chen and Tukey, 2018). Finally, a mini-review included discussion of using CRISPR-Cas9 to knock-in a luciferase reporter into the human *CYP1A1* locus in induced pluripotent stem cells, insert mutations or knock-out fish *AHR2* genes, and knock-out AHR in human and mouse cell models (Karlgren et al., 2018).

Additional aspects of MC-type induction in rat liver were covered in DMD papers published during the 2010s. βNF causes strong induction of CYP1A1 and moderate induction of UGT1A6 and CYP2B1 mRNAs in "Liverbeads," rat hepatocytes entrapped in an alginate matrix (Al Khansa et al., 2010). AHR mRNA is detected in rat olfactory mucosa along with strong induction of CYP1A1 by MC and Aroclor 1254 (Thiebaud et al., 2010). A mechanism-based mathematical model related βNF plasma concentrations, hepatic CYP1A1 and 1A2 mRNA levels, and EROD activity in rats (Chen et al., 2010). In cultured rat hepatocytes, arsenite decreases induction of CYP1A1 and 1A2 by TCDD via a mechanism involving decreased AHR nuclear accumulation, increased binding of cytosolic AHR to chaperones, and induction of heme oxygenase-1 (Anwar-Mohamed et al., 2012). In vivo treatment of rats with oxycodone increases hepatic AHR mRNA levels, but oxycodone and its major metabolites (noroxycodone and oxymorphone) are not direct AHR activators (Hassan et al., 2013). Recombinant rat CYP1A1 and 1A2 are active in converting arachidonic acid to terminal/subterminal hydroxyeicosatetraenoic acids, and these activities are induced by in vivo MC treatment in heart, lung, kidney, and liver and inhibited by α-naphthoflavone in lung and liver microsomes (El-Sherbeni and El-Kadi, 2014). Finally, destruction of serotonergic projections from raphe nuclei to the hypothalamus altered serum levels of multiple hormones and elevated rat hepatic CYP1A1 and 1A2 mRNA, CYP1A protein, and caffeine metabolism (Rysz et al., 2015).

DMD continued to feature important studies conducted in mice and mouse-derived cell models. Comparison of responsive C57BL/6 versus nonresponsive DBA/2 mice showed the decrease in serum thyroxine levels caused by PCB126 is due to induction of hepatic UGT activity toward thyroxine and enhanced hepatic accumulation of thyroxine (Kato et al., 2010). The reductase conditional null mouse, described earlier in this report, was used to study the role of hepatic P450s in DNA adduct formation by 2-amino-1-methyl-6-phenylimidazo[4,5-*b*] pyridine (Arlt et al., 2011). Using a cocktail of P450 probe drugs, including phenacetin for CYP1A2, in a single-mouse pharmacokinetic approach, the in vivo inhibitory effect of α-naphthoflavone and inductive effect of MC were confirmed (Jilek et al., 2017). In a mouse model humanized for multiple P450s, including CYP1A1 and 1A2, in vivo treatment with βNF enhanced CYP1A-mediated clearance of the epidermal growth factor receptor inhibitor osimertinib (Henderson et al., 2019). *CYP1A1/1A2*-humanized mice show constitutive and TCDD-inducible CYP1A2 expression in liver and TCDD-inducible CYP1A1 expression in liver, lung, and small intestine, and this model was used to develop a method to distinguish the contributions of human CYP1A1 versus 1A2 to the metabolism of model compounds (Kapelyukh et al., 2019). Multiple DREs in the distal 5′-flank of mouse *CYP1A2*, approximately 13 kb upstream, were shown to be involved in transcriptional activation by TCDD and MC in studies using primary cultures of mouse hepatocytes (Kawasaki et al., 2010). Studies of AHR relevance conducted in diverse species during the 2010s were limited to a single chick embryo paper: TCDD-inducible avian P450s (e.g., CYP1A5) convert arachidonic acid to epoxyeicosatrienoic acids, which can be converted by epoxide hydrolase to dihydroxyeicosatrienoic acids, and the hepatic ratio of the epoxy: dihydroxy metabolites is increased by cotreatment with TCDD and an inhibitor of soluble epoxide hydrolase (Diani-Moore et al., 2014).

The strong emphasis on studies relevant to the human AHR system continued in DMD publications during the 2010s. Human white adipose tissue shows basal expression of AHR mRNA with high constitutive levels of CYP1B1 and strong induction of CYP1A1 and 1B1 by TCDD and prochloraz (Ellero et al., 2010). A "Special Section on Epigenetic Regulation of Drug-Metabolizing Enzymes and Transporters" from October 2013 featured a study identifying correlations between levels of specific miRNAs for AHRR, CYP1A1, and 1A2 in human liver (Rieger et al., 2013). A "Special Section on Transporters in Drug Disposition and Pharmacokinetic Prediction" from May 2018 included a report of a significant correlation between AHR and BCRP mRNA levels in 137 term placentas from uncomplicated pregnancies (Bircsak et al., 2018).

Several studies using human liver-derived cellular models were published in DMD in this decade. In sandwich cultured human hepatocytes, omeprazole induces CYP1A2 mRNA and phenacetin O-deethylation, as well as CYP1A2 protein, as assessed via absolute quantitation by tandem mass spectrometry (Schaefer et al., 2012). In cryopreserved human hepatocytes, omeprazole induces CYP1A2 mRNA and EROD activity in all lots tested (Yajima et al., 2014). The endocannabinoid oleamide demonstrates neither agonist nor antagonist properties in an AHR-driven luciferase reporter in HepG2 cells and fails to induce CYP1A2 mRNA in primary human hepatocytes (Dovrtelova et al., 2018). A "Special Section on Pharmacokinetic and Drug Metabolism Properties of Novel Therapeutic Modalities" from October 2019 featured a report that five N-acetylgalactosamine-conjugated siRNAs failed to elicit AHR-mediated induction of CYP1A2 mRNA in primary human hepatocytes (Ramsden et al., 2019). Differentiated HepaRG cells over a 4-week period show stable basal AHR mRNA levels and induction of CYP1A2 mRNA and activity by omeprazole (Anthérieu et al., 2010). Using HepaRG cells as a model for nonalcoholic fatty liver disease and steatohepatitis, inflammatory conditions do not diminish AHR-mediated induction of CYP1A1 and 1A2 mRNAs by MC (Tanner et al., 2018). Lastly, treatment of HepaRG cells with TCDD decreased mRNA levels for multiple sulfotransferases, with the exception of SULT1C3 (Dubaisi et al., 2018). The functionality of AHR was confirmed in the HC-AFW1 human hepatocellular carcinoma cell line by induction of CYP1A mRNAs, CYP1A2 activity with phenacetin as probe, and an AHR-driven luciferase reporter by TCDD, βNF, and tBHQ (Braeuning et al., 2015).

Several other human cell lines formed important models for AHR research appearing in DMD. In human mammary epithelial MCF10A cultures, *p*-anilinoaniline, an inhibitor of an E2 ubiquitin-conjugating enzyme implicated in AHR degradation, enhances TCDD-induced *CYP1A1* transcription and AHR occupancy of the *CYP1A1* promoter, with effects dependent on cell cycle phase (Elliott et al., 2012). In the same cell model, TCDD and inhibitors of epidermal growth factor receptor kinase induce CYP1A1 and 1A2 synergistically, and CYP1A1 mRNA and protein levels display notable discordance (Joiakim et al., 2016). Two studies employed a human lymphoblastoid cell line model to characterize so-called distant SNP effects: first, a SNP located hundreds of base-pairs from a DRE creates variability in MC-stimulated AHR binding and CYP1A1 inducibility (Liu et al., 2018); second, additional SNPs at a distance from DRE sequences were identified that function as "pharmacogenomic-expression quantitative trait loci" that are dependent on AHR activation by a ligand

(Neavin et al., 2019). The AHR-regulated CYP2S1 is induced by retinoids and UV radiation in the human keratinocyte HaCaT cell line (McNeilly et al., 2012). The antibacterial triclocarban is activated by recombinant human CYP1A1 and by TCDD-treated spontaneously immortalized human epidermal keratinocytes to produce glutathione adducts (Schebb et al., 2014). In human monocyte/macrophage-derived U937 and THP-1 cells, activation of the vitamin D receptor enhances induction of CYP1A1 by B[*a*]P, B[*a*]P metabolism, and DNA adduct formation (Matsunawa et al., 2012). LS180 colorectal adenocarcinoma cells display basal AHR mRNA expression and selective induction of SULT1C3, as opposed to SULT1C2, by TCDD (Rondini et al., 2014).

Novel AHR ligands continued to be a focus for reports appearing in DMD. AHR activation was demonstrated for several interesting compounds: uncharacterized omeprazole metabolites generated by cecal bacteria (Shiizaki et al., 2014), the immunomodulator leflunomide (Patel et al., 2015), and bioactive alkaloids from *Euodia rutaecarpa* (Zhang et al., 2018). A "Special Section on Drug Metabolism and the Microbiome" from October 2015 included a characterization of several tryptophan microbiota metabolites (indole, indole-3-acetate, indole-3-aldehyde, and tryptamine) as selective AHR modulators with complex patterns of ligand- and target gene-selectivity (Cheng et al., 2015).

Several systematic transcriptomic studies of AHR relevance from the Klaassen group used branched DNA signal amplification technology, multiplex suspension arrays, RT-PCR, and RNA sequencing. Mouse hepatic AHR mRNA levels remain relatively constant with aging, with higher levels in females versus males throughout the lifespan (Fu et al., 2012); AHR levels are decreased by energy restriction only in aged mice (Zhang et al., 2010). PCB congeners with high AHR affinity decrease rat serum thyroxine levels mainly by inducing hepatic UGT activity toward thyroxine and increasing biliary excretion of the glucuronide (Martin et al., 2012). *Ahr*-null mice were used to demonstrate that suppression of hepatic arylacetamide deacetylase and carboxylesterase-3a by TCDD requires AHR (Zhang et al., 2012), the absence of AHR alters the constitutive hepatic expression of multiple phase I and II drug-metabolizing enzymes and transporters, and the induction of several target genes by TCDD is AHR-dependent (Aleksunes and Klaassen, 2012). TCDD induces mouse hepatic aldo-keto reductase AKR1B7 and 1C18 mRNA levels while suppressing AKR1C22 (Pratt-Hyatt et al., 2013). A "Special Section on Drug Metabolism and the Microbiome" from October 2015 featured the demonstration that the liver of germ-free mice shows increased AHR and CYP1A2 mRNA levels compared with conventional mice (Selwyn et al., 2015). Male mice show basal expression of AHR mRNA in liver, duodenum, jejunum, ileum, and large intestine with little divergence among these tissues (Fu et al., 2016). A "Special Section on Pediatric Drug Disposition and Pharmacokinetics" from July 2016 contained a paper reporting that mouse hepatic AHR, CAR, and pregnane X receptor (PXR) mRNA levels can be modulated by their own activators and activators of the other receptors; as well, AHR target genes show developmental age selectivity in their TCDD inducibility (Li et al., 2016). Finally, the intestine of germ-free mice shows decreased CYP1A1 mRNA levels versus conventional mice, with no difference in CYP1A2 or AHR levels (Fu et al., 2017).

Our laboratory showed that decreased hepatic AHR protein and POR activity in adrenalectomized rats are important determinants of altered AHR-mediated responses to MC (Mullen Grey and Riddick, 2011). In vivo studies of DEX dose-response, glucocorticoid receptor (GR)- and PXR-selective agonists, GR antagonism, and *PXR*-knockout rats showed important roles for GR in induction of rat liver ARNT by DEX and PXR in induction of rat liver POR by DEX (Hunter et al., 2017). Using mice with conditional hepatic POR deletion, we showed that MC alters GH signaling components and target genes via mechanisms that are both dependent and independent of hepatic microsomal P450 activities (Lee et al., 2013b), and MC suppresses hepatic CYP3A11 expression by a pretranslational mechanism independent of hepatic microsomal P450 activities (Lee et al., 2013a). Lastly, MC down-regulates CYP3A4 expression in the liver of female humanized PXR-CAR-CYP3A4/3A7 mice and a similar, but more subtle, response was seen in males since the basal hepatic CYP3A4 levels are much higher in females versus males (Crosby and Riddick, 2019).

The 2020s

A highly significant landmark discovery in the AHR field was reported very recently. The cryo-EM structure of the indirubin-bound AHR-hsp90- hepatitis B virus X-associated protein 2 complex ushers in a new era in the structure-based analysis of the AHR ligand-binding pocket (Gruszczyk et al., 2022).

DMD has published several mini-reviews and a commentary with AHR relevance in the early part of the new decade. Mini-reviews considered the ability of TCDD to modulate the alternative splicing patterns of AHR target genes such as *CYP1A1* and the existence of constitutively active AHR splice variants (Annalora et al., 2020), as well as circadian fluctuations in AHR and ARNT levels and diurnal expression and inducibility of CYP1A1 (Lu et al., 2020). Mini-reviews also covered the involvement of AHR in the transcriptional induction of MDR1 and BCRP by histone deacetylase inhibitors (You et al., 2020) and the overexpression of the AHR target gene *CYP1B1* in prostate cancer driven by hypomethylation of its promoter/enhancer region and not by altered AHR and ARNT levels (Wang et al., 2020). A "Special Section on Natural Products: Experimental Approaches to Elucidate Disposition Mechanisms and Predict Pharmacokinetic Drug Interactions" from October 2020 featured a mini-review addressing the important roles of intestinal AHR in the regulation of drug-metabolizing enzymes and its immunomodulatory activity in maintaining the intestinal barrier (Li, 2020). A "Special Section on Bile Acids, Drug Metabolism, and Toxicity" from April 2022 offered four highly pertinent minireviews. First, there was discussion of sex-dependent effects of AHR agonists in mice on serum and liver bile acids and intestinal mRNA levels for fibroblast growth factor-15 (Choudhuri and Klaassen, 2022). Second, AHR-dependent effects of TCDD and TCDF on multiple aspects of bile acid homeostasis in rats and mice were covered (Taylor et al., 2022). Third, there was consideration of the interactions between nuclear factor erythroid-derived 2-like 2 and AHR in which each xenosensor induces expression of the other (Rockwell et al., 2022). Fourth, the lowering of systemic thyroid hormone levels by AHR agonists was discussed in relation to impacts on thyroxine glucuronidation and other aspects of thyroid hormone homeostasis (Vansell, 2022). Down-regulation of AHR expression and attenuated CYP1A induction by TCDD caused by adenosine-to-inosine RNA editing in the 3′-untranslated region of AHR creating a recognition site for miR-378 was covered in a mini-review (Nakano and Nakajima, 2022). A "Special Section on Drug Metabolism in Liver Injury and Repair" from May 2022 included a mini-review describing improved liver regeneration in *Ahr*-null mice after acute toxic injury (Zhao et al., 2022). A "Special Section on Drug Metabolism and Regulation" from July 2022 featured a commentary by Tsuneo Omura offering historical perspectives on receptor-mediated induction of P450s by PAHs and barbiturates and potential roles not related to drug metabolism for AHR counterparts in invertebrates (Omura, 2022). Lastly, a "Special Section on New Era of Transporter Science: Unraveling the Functional Role of Orphan Transporters" from September 2022 contained a mini-review highlighting the regulation of multiple rodent and human organic anion transporters and OATPs by AHR activators (Zhou and Shu, 2022).

A few DMD research papers from the 2020s have reported studies conducted with rat and mouse models. A *CYP1A2*-knockout rat model generated via a CRISPR-Cas9 approach shows no change in hepatic AHR mRNA levels but a strong compensatory increase in CYP1A1 expression (Sun et al., 2021). The induction of intestinal CYP1A1 by cadmium in *UGT1*-humanized mice is lost in this mouse model lacking nuclear factor erythroid-derived 2-like 2 (Paszek and Tukey, 2020). Hepatic AHR mRNA levels and expression of AHR target genes are induced in a peroxisome proliferator-activated receptor-α-dependent fashion by the *Olea europaea* constituent oleuropein (Malliou et al., 2021). In humanized apolipoprotein E4 knock-in mice, cadmium down-regulates hepatic CYP1A2, an AHR target, only in males (Wang et al., 2022).

Studies published in DMD during the current decade continued to emphasize the importance of the human AHR system. Transcriptomic analysis of 226 human livers showed lower AHR and CYP1A2 mRNA levels in females versus males but no effect of age or race/ethnicity (Liu et al., 2021). Omeprazole induces CYP1A1, but not CYP1A2, mRNA in tissue stem cell-derived human ileal, and colon organoids (Stresser et al., 2021). Stabilization of hypoxia-inducible factor-α by treatment of primary human hepatocytes with prolyl hydroxylase domain 2 inhibitors causes CYP1A2 down-regulation, a response accompanied by decreased ARNT mRNA levels and no change in AHR mRNA levels (Takano et al., 2021). Overexpression of the hepatocyte nuclear factor-4α antisense RNA 1 in Huh7 cells causes decreased basal expression of AHR and CYP1A2 mRNA (Wang et al., 2021). The following four studies were conducted with HepaRG cells. Knockdown of the histone methyltransferase G9a increases AHR mRNA levels but has no effect on AHR expression in a steatotic condition (Pande et al., 2020). AHR-dependent induction of CYP1A2 by omeprazole is enhanced by knockout of CAR or PXR but not in the CAR/PXR double knockout (Preiss et al., 2021). CYP1A2 expression and activity are enhanced under the lower perivenous oxygen tension versus the periportal state and further enhanced by Wnt/β-catenin signaling, although these manipulations do not impact AHR mRNA levels (DiProspero et al., 2022). A "Special Section on Mechanistic and Translational Research on Transporters in Toxicology" from October 2022 contained a paper showing that perfluorinated carboxylic acids modulate expression of amino acid and xenobiotic transporters, with AHR predicted to be an important upstream factor involved in this regulation (Lim et al., 2022).

With respect to novel AHR ligands recently reported in DMD publications, a monohydroxylated metabolite of 3,3′-diindolylmethane detected in humans, 3-((1H-indole-3-yl)methyl)indolin-2-one, was found to be an AHR agonist in a DRE-driven luciferase assay in mouse Hepa-1 cells (Vermillion Maier et al., 2021). Finally, the investigational anti-inflammatory compound JNJ-2482272 is a potent activator of rat and human AHR (Coe et al., 2022).

Conclusions

With the launch of DMD in 1973 and the discovery of the AHR in 1976, the journal and the receptor have led parallel and often intersecting lives. Tracing the history of a particular scientific field can help us to appreciate the major landmark discoveries and the key players and contributors and also deepen our understanding of how knowledge in the field has evolved to the present. It may be helpful to recall Winston Churchill's paraphrasing of the Spanish philosopher George Santayana: "Those that fail to learn from history are doomed to repeat it." By reflecting on the strong history of AHR-related publications in DMD over the years, it is my hope that this mini-review will inspire current and future AHR scientists to pursue provocative questions and contribute their most important findings to the pages of DMD.

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Participated in research design: Riddick.
Performed data analysis: Riddick.
Wrote or contributed to the writing of the manuscript: Riddick.

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