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REVIEW

Role of the Aryl Hydrocarbon Receptor in Carcinogenesis and Potential as a Drug Target

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The aryl hydrocarbon receptor (AHR) is highly expressed in multiple organs and tissues, and there is increasing evidence that the AHR plays an important role in cellular homeostasis and disease. The AHR is expressed in multiple tumor types, in cancer cell lines, and in tumors from animal models, and the function of the AHR has been determined by RNA interference, overexpression, and inhibition studies. With few exceptions, knockdown of the *AHR* resulted in decreased proliferation and/or invasion and migration of cancer cell lines, and *in vivo* studies in mice overexpressing the constitutively active AHR exhibited enhanced stomach and liver cancers, suggesting a pro-oncogenic role for the AHR. In contrast, loss of the AHR in transgenic mice that spontaneously develop colonic tumors and in carcinogen-induced liver tumors resulted in increased carcinogenesis, suggesting that the receptor may exhibit antitumorigenic activity prior to tumor formation. AHR ligands also either enhanced or inhibited tumorigenesis, and these effects were highly tumor specific, demonstrating that selective AHR modulators that exhibit agonist or antagonist activities represent an important new class of anticancer agents that can be directed against multiple tumors.

Key Words: **Ah receptor; agonist activity; antagonist activity; drug target.**

Background

Poland first hypothesized that an intracellular binding protein or receptor may be the initial target for the highly toxic 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and related halogenated aromatics (HAs), and his laboratory was the first to purify and characterize the mouse hepatic aryl hydrocarbon receptor (AHR) protein (Poland and Glover, 1973; Poland *et al*., 1976). Studies in several laboratories confirmed the role for the receptor in mediating the toxicities of HAs and polynuclear aromatic hydrocarbons (PAHs), and thus, the AHR became inextricably linked to two of the most prominent classes of environmental toxicants (Goldstein *et al*., 1989; Nebert *et al*., 1975; Poland and Knutson, 1982; Safe, 1986). The AHR is a ligand-activated transcription factor that forms a nuclear heterodimer with the AHR nuclear translocator (ARNT) protein to activate gene expression through interactions with cognate dioxin responsive elements (DREs) located on Ah-responsive gene promoters (reviewed in Gu *et al*., 2000; Whitlock, 1999). AHR ligands such as TCDD induce expression of a gene battery that catalyzes the metabolism and conjugation of xenobiotics (Köhle and Bock, 2007; Nebert *et al*., 2004), and early studies on the mechanism of AHR-mediated gene expression extensively used the *CYP1A1* gene as a model (Whitlock, 1999). It is generally assumed that the classical mechanism of action derived from studies on the *CYP1A1* gene is required for inducing the prototypical toxic effects of TCDD and structurally related HAs, even though the molecular mechanisms and genes associated with toxicities such as chloracne, wasting syndrome, tumor promotion, and others are not well defined (Poland and Knutson, 1982; Whitlock, 1999).

Receptor for TCDD and Related HAs

The linkage between the AHR and the toxicity of TCDD and related compounds was also confirmed by the cloning of the receptor (Burbach *et al*., 1992; Dolwick *et al*., 1993; Ema *et al*., 1992; Schmidt *et al*., 1993) and the subsequent generation of *Ahr* knockout ($Ahr^{-/-}$) mice (Fernandez-Salguero *et al*., 1995; Mimura *et al*., 1997; Schmidt *et al*., 1996). Although there were some phenotypic differences in $Ahr^{-/-}$ mice generated in different laboratories, there was general agreement that most of the toxicities observed in wild-type mice treated with TCDD were not observed in $Ahr^{-/-}$ mice, thus confirming that this receptor was necessary for mediating the toxicity of TCDD and related HAs (Barouki *et al*., 2007; Fernandez-Salguero *et al*.,

1995, 1996, 1997; Mimura *et al*., 1997; Schmidt *et al*., 1996). These results consolidated the strong association between the AHR and toxic HAs, even though several endogenous ligands and phytochemicals have subsequently been identified as AHR ligands (Pohjanvirta, 2012). Studies in *Ahr*$^{-/-}$ mice have unraveled many endogenous functions of the AHR (see below); however, unlike the nuclear hormone receptors such as the estrogen receptor (ER) (Jordan, 2009), the development and applications of specific drugs that target the AHR have been delayed due to its association with toxic HAs.

Endogenous Function of the AHR

The development of *Ahr*$^{-/-}$ mice has demonstrated that the function of this receptor is not just the mediation of the effects of HAs and PAHs (Barouki *et al*., 2007; McMillan and Bradfield, 2007). *Ahr*$^{-/-}$ mice exhibit decreased fertility, decreased liver size, and structural and functional deficits in several tissues, and these include failure of developmental closure of the ductus venosus in liver (Lahvis *et al*., 2000, 2005), vascular abnormalities in several organs including the cardiovascular system (Lund *et al*., 2003, 2006; Sauzeau *et al*., 2011), reproductive tract problems that include decreased levels of mature follicles (Abbott *et al*., 1999; Baba *et al*., 2005; Benedict *et al*., 2000, 2003), portal duct fibrosis (Fernandez-Salguero *et al*., 1997; Schmidt *et al*., 1996), oculomotor deficits (Chevallier *et al*., 2013), and formation of uric acid stones in the urinary bladder (Butler *et al*., 2012). *Ahr*$^{-/-}$ mice also exhibit abnormalities in stem cells and their function (Singh *et al*., 2011a; Wang *et al*., 2010). One of the hallmarks of TCDD toxicity is linked to its species-/tissue-specific immunomodulatory effects (Kerkvliet, 1995; Vos, 1977), and several recent studies have demonstrated critical roles for the AHR in the immune system and autoimmunity (Aguilera-Montilla *et al*., 2013; Apetoh *et al*., 2010; DiNatale *et al*., 2010; Esser, 2012; Esser *et al*., 2009; Funatake *et al*., 2004, 2005, 2008; Gandhi *et al*., 2010; Jin *et al*., 2010; Kadow *et al*., 2011; Kerkvliet, 1995; Kiss *et al*., 2011; Lee *et al*., 2012; Li *et al*., 2011; Marshall and Kerkvliet, 2010; Marshall *et al*., 2008; Mezrich *et al*., 2010; Nguyen *et al*., 2010; Quintana *et al*., 2008; Singh *et al*., 2011b; Stevens *et al*., 2009; Veldhoen *et al*., 2008; Vos, 1977; Wu *et al*., 2011a, b). For example, regulatory T cells (Treg) that express FoxP3 control immune autoreactivity, and the inverse relationship between Treg cells and proinflammatory T cells producing interleukin 17 (T_H17) is a critical element in developing autoimmune diseases. The AHR and its ligands play a key role in controlling Treg cells and T_H17 cell differentiation. In a mouse model for experimental autoimmune encephalomyelitis (EAE), the potent AHR agonist TCDD decreased, whereas the "endogenous" AHR agonist 6-formylindolo[3,2-b]carbazole (FICZ) increased, the severity of EAE in mice (Veldhoen *et al*., 2008). It was also reported that kynurenine, a tryptophan metabolite and AHR agonist (Opitz *et al*., 2011), but not TCDD or FICZ, induced FoxP3 Tregs in $CD4^+CD25^-$ T cells from *Ahr*$^{+/+}$ B6 mice but not in *Ahr*$^{-/-}$ mice (Kadow *et al*., 2011). Moreover, the AHR and its ligands may influence tumorigenesis not only by direct effects on the cancer cell but also by modulation of the immune system (Opitz *et al*., 2011). Results showing tissue-specific AHR agonist or antagonist activities of various AHR ligands in immune systems are consistent with observations for other ligand-activated intracellular receptors, and this is the basis for development of selective receptor modulators for treatment of multiple diseases including cancer in which a receptor such as the AHR plays a key role (Jordan, 2007; Jordan and O'Malley, 2007).

SELECTIVE AHR MODULATORS

Initial skepticism regarding the AHR as a drug target was primarily due to the extensive literature demonstrating that most ligands for the receptor were toxic HAs and genotoxic PAHs such as TCDD and benzo[a]pyrene (BaP). However, the universe of AHR ligands has now greatly expanded and includes many other industrial compounds and byproducts, widely used pharmaceuticals, endogenous biochemicals including bilirubin, indigoids, FICZ and kynurenine, and several classes of chemoprotective phytochemicals such as the flavonoids, indole-3-carbinol, and related compounds (reviewed in Denison *et al*., 2011; Safe *et al*., 2012) (Fig. 1). The dramatic expansion of the number and classes of compounds that bind the AHR has clearly uncoupled the AHR from its function as an intracellular receptor for only toxic compounds, and like many other nuclear receptors (e.g., ERα), the AHR has important endogenous activity and ligands and interacts with structurally diverse chemicals.

The development of drugs that target the AHR or other ligand-activated receptors is also dependent on the concept of selective AHR modulators (SahRMs) in which a receptor ligand exhibits tissue-specific AHR agonist or antagonist (Safe *et al*., 1999, 2012). This concept was observed and rationalized for drugs such as the ER ligand tamoxifen, which is an ER antagonist in breast tumors and used for treating ER-positive breast cancer but is an ER agonist in the uterus and a risk factor for uterine cancers (Jordan, 2007; Jordan and O'Malley, 2007). Tissue-specific differences in agonist or antagonist activity of a ligand are due to multiple factors that include ligand-induced conformational changes in the receptor and subsequent interactions with critical coactivators, corepressors, and other nuclear cofactors that exhibit tissue-specific expression (Katzenellenbogen *et al*., 1996). Studies in this laboratory initially characterized the SAhRM 6-methyl-1,3,8-trichlorodibenzofuran (MCDF) that was developed as an AHR antagonist and inhibited TCDD-induced CYP1A1, porphyria, immunotoxicity, and teratogenicity in mice (Astroff and Safe, 1989; Astroff *et al*., 1988; Bannister *et al*., 1989; Harris *et al*., 1989; Piskorska-Pliszczynska *et al*., 1991; Romkes *et al*., 1987; Santostefano *et al*., 1992; Yao and Safe, 1989; Zacharewski *et al*., 1992). In contrast, MCDF did not

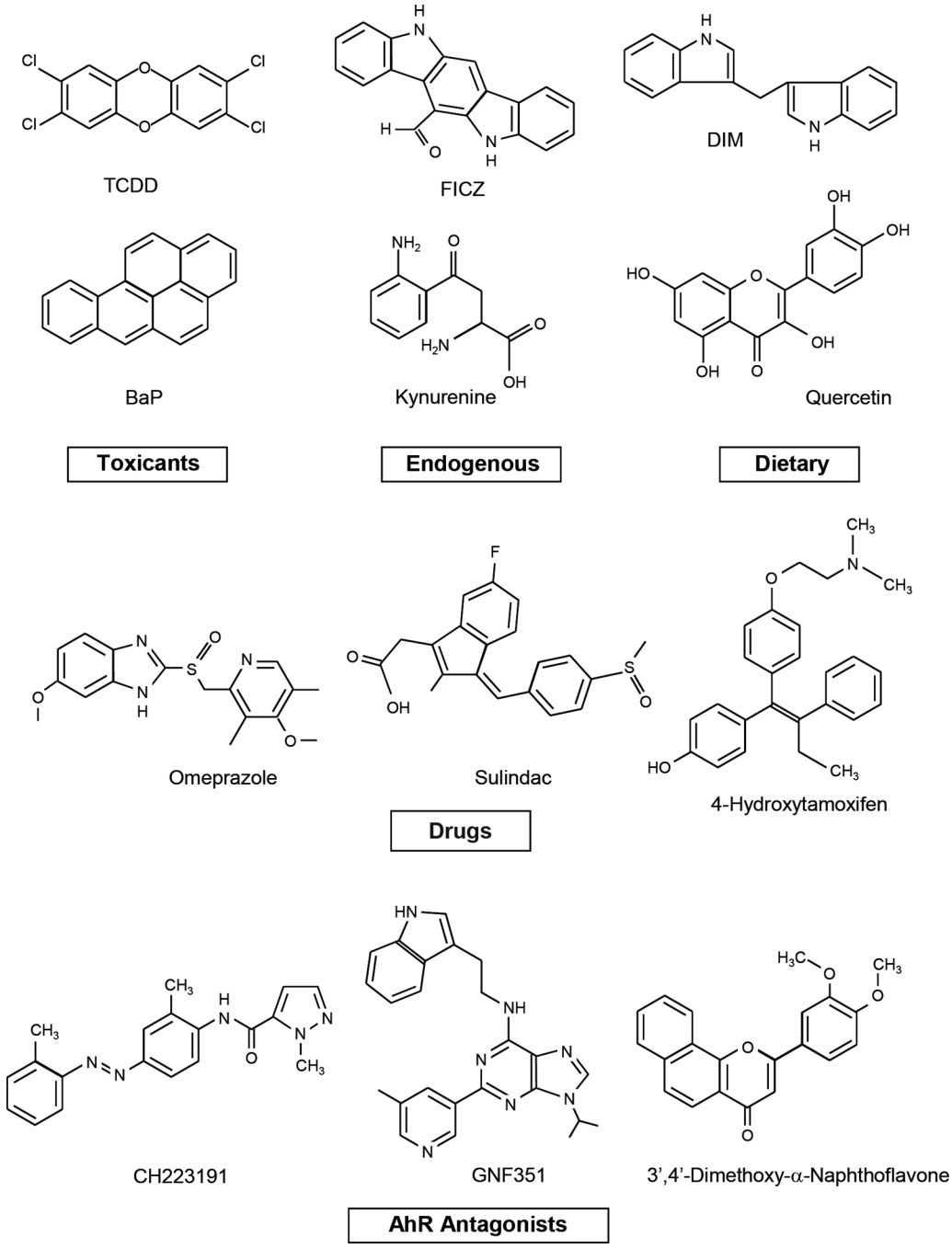

FIG. 1. Structures of different classes of AHR ligands. The AHR agonist activities have been reported for both kynurenine and kynurenic acid (DiNatale *et al*., 2010 and Opitz *et al*., 2011).

inhibit TCDD-induced antiestrogenic effects in the rodent uterus or breast cancer cells but was an AHR agonist and, like TCDD, exhibited antiestrogenic activity and inhibited mammary tumor growth in rodent models (McDougal *et al*., 1997, 2001). Other AHR ligands such as α-naphthoflavone and 3′-methoxy-4′-nitroflavone also exhibit both AHR agonist and antagonist activities (Gasiewicz and Rucci, 1991; Lu *et al*., 1996a; Santostefano *et al*., 1993; Zhou and Gasiewicz, 2003). It is also possible that the AHR agonist or antagonist activity of an AHR ligand will be dependent on tissue context but also vary with species (e.g., human vs. mouse). Recent studies have characterized new structural classes of AHR antagonists (Kim *et al*., 2006; Murray *et al*., 2011; Smith *et al*., 2011; Zhao *et al*., 2010), which may have clinical potential for treating diseases (including cancer) where AHR inhibition provides a therapeutic benefit. This has already been demonstrated in hemapoietic

stem cells where a novel AHR antagonist promotes expansion of stem cells, which is critical for future development of clinical trials with stem cells (Boitano *et al*., 2010).

ROLE OF THE AHR IN CARCINOGENESIS

AHR Expression and Function

A recent study summarized *AHR* mRNA levels from a panel of 967 cancer cell lines from the Cancer Cell Line Encyclopedia. Chondrosarcomas and esophageal, upper aerodigestive, pancreatic, and liver cancer cell lines expressed relatively high levels, whereas many subtypes of leukemia cells expressed low *AHR* mRNA levels (O'Donnell *et al*., 2012). *AHR* mRNA levels in patient data sets were higher in thyroid, colon, pancreatic, and stomach tumors compared with nontumor tissue; however, Kaplan-Meier analysis of the data indicated that *AHR* mRNA levels were not prognostic for patient survival (http://www.ncbi.nlm.nih.gov/gds). A limited number of studies on AHR protein expression in cancer patients showed higher AHR expression in pancreatic, prostate, urinary tract, lung, and esophageal tumors but not in pituitary tumors, and the location of the receptor (i.e., cytosolic and/or nuclear) was variable in most tumors (Gluschnaider *et al*., 2010; Gramatzki *et al*., 2009; Ishida *et al*., 2010; Jaffrain-Rea *et al*., 2009; Koliopanos *et al*., 2002; Lin *et al*., 2003; Portal-Nunez *et al*., 2012; Zhang *et al*., 2012a) (Table 1). In upper urinary tract tumors, there was a correlation between increasing nuclear AHR protein expression and increasing tumor grade, suggesting that at least for these tumors nuclear AHR levels predict a higher tumor grade (Portal-Nunez *et al*., 2012).

Genetic and mutagenesis studies on liver cancer cells have characterized cell lines with variable Ah responsiveness (and AHR expression), and these cells exhibit differences in cell proliferation and other responses (Ma and Whitlock, 1996; Reiners and Clift, 1999). For example, Ahr-D (defective) mouse Hepa1c1c7 cells appear less well differentiated and express low levels of albumin compared with wild-type cells, and loss of the AHR is associated with decreased rates of cell proliferation and an increased number of cells in G_0/G_1 phase of the cell cycle (Ma and Whitlock, 1996). Similar results have been reported for rat hepatoma cell lines (Weiss *et al*., 1996). In a series of elegant studies, it was shown that the AHR forms a complex with the retinoblastoma (Rb) tumor suppressor gene resulting in increased E2F-dependent gene expression and modulation of other cell cycle–related effects in liver cancer cells (Ge and Elferink, 1998; Huang and Elferink, 2005; Puga *et al*., 2000, 2009). RNA interference and knockdown of the AHR in human hepatoma HepG2 cells also resulted in growth inhibition, and this was accompanied by downregulation of several cell cycle–related genes including cyclins D1 and E, cdk2, and cdk4 (Abdelrahim *et al*., 2003). In contrast to the growth promoting effects of the AHR in liver cancer cell lines, diethylnitrosamine (DEN)–induced liver adenomas in *Ahr*$^{-/-}$ mice (male) were increased compared with wild-type mice, suggesting that the AHR exhibits tumor suppressor–like activity *in vivo* (Fan *et al*., 2010). These results contrast studies in liver cancer cell lines but may not necessarily be contradictory because the tumor suppressor–like activity of the AHR may be dominant in steps leading up to liver adenoma formation, and this function may change in adenomas and carcinomas.

The role of the AHR in modulating growth and migration of cancer cells has also been investigated in cell lines derived from other tumors, and the receptor exhibits both tumor suppressive and oncogenic activity, which is cell context dependent (Fig. 2). For example, AHR silencing decreased

TABLE 1
AHR Protein Expression in Tumors

Tissue (References)	AHR protein expression
Pancreatic (Koliopanos *et al*., 2002)	14/15 (tumors, m to h, cytosolic) 9/15 (nontumors, f)
Prostate (Gluschnaider *et al*., 2010)	Tumors (h, cytosolic and nuclear) Nontumors (w-nd, cytosolic > nuclear)
Urinary tract (Ishida *et al*., 2010)	Tumors (h, % nuclear staining increased with increasing tumor grade) Nontumor (w, cytosolic and nuclear)
Lung (Portal-Nunez *et al*., 2012)	Adenocarcinomas (h, 56%) Bronchioloalveolar carcinomas (h, 47%) Bronchiolar epithelium (h, 11%)
Lung (Lin *et al*., 2003)	Tumors (h, 59/91; l, 32/91) Nontumors (h, 7/31; l, 24/31)
Esophagus (Zhang *et al*., 2012a)	Tumors/nontumors = 2.2/1 in protein expression
Pituitary (Jaffrain-Rea *et al*., 2009)	Tumors/nontumors: Weak staining, primarily cytosolic
Gliomas (Gramatzki *et al*., 2009)	Expression in tumor and nontumor tissues (23 autopsies) WHO grade II astrocytomas > grade III anaplastic astrocytomas > grade IV glioblastomas (mean total AHR) Grade IV glioblastomas > grade III anaplastic astrocytomas ≅ grade II astrocytomas (nuclear AHR protein)

Note. m to h, medium to high; f, faint; w-nd, weak to nondetectable; w, weak.

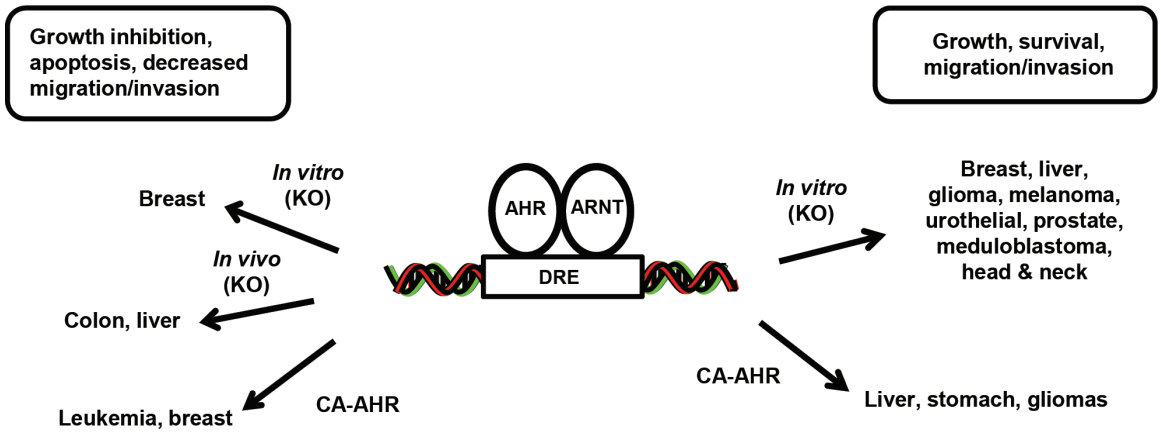

FIG. 2. AHR: endogenous functions in cancer.

growth of melanoma cancer cells overexpressing NRAS (Barretina *et al.*, 2012), decreased urothelial cancer T24 cell invasion and MMP-9 expression (Portal-Nunez *et al.*, 2012), decreased expression of fibroblast growth factor-9 and osteopontin in lung cancer cells (Chuang *et al.*, 2012; Wang *et al.*, 2009), decreased C4-2 (androgen independent) prostate cancer cell growth (Tran *et al.*, 2013), decreased DAOY medulloblastoma cell growth, and induced G_0/G_1 arrest (p27 is also induced) (Dever and Opanashuk, 2012). AHR silencing in HN30 head and neck cancer cells decreased basal and serum-stimulated cell migration, and this has been linked to downregulation of constitutive interleukin-6 (IL-6), which exhibits promigratory and growth promoting activity in many cancer cell lines (DiNatale *et al.*, 2011, 2012). Knockdown of the AHR in H508 colon cancer cells did not significantly affect growth (Xie *et al.*, 2012); and *in vivo* studies with $Ahr^{-/-}$ mice showed that loss of the AHR resulted in enhanced formation of spontaneous colonic polyps and cecal tumors (Kawajiri *et al.*, 2009). $APC^{min/+}$ mice express adenomatous poyposis coli (APC) gene mutations and spontaneously develop colonic and intestinal tumors, and loss of one *Ahr* allele ($APC^{min/+}/Ahr^{+/-}$) enhanced this response (note: $APC^{min/+}/Ahr^{-/-}$ mice were not good breeders). Thus, the constitutive Ahr exhibited tumor suppressor–like activity in a colonic tumor model, and this was similar to that observed in a mouse model for carcinogen-induced liver cancer (Fan *et al.*, 2010).

AHR silencing by RNAi in MCF-7 and BT474 cancer cells enhanced cell proliferation, and in the former cell line, the percentages of cells in G_2/M and G_0/G_1 phases of the cell cycle were increased and decreased, respectively (Zhang *et al.*, 2009). Similar results were observed in BaP-resistant T47D cells that express low AHR levels (Moore *et al.*, 1996), whereas BaP-resistant MCF-7 cells (low AHR expression) exhibited slower growth (Moore *et al.*, 1994). In contrast, knockdown of the AHR in MDA-MB-468 cells did not affect cell proliferation (Zhang *et al.*, 2009). Immortalized mammary tumor fibroblasts derived from $Ahr^{+/+}$ and $Ahr^{-/-}$ mice were used as models to show that the AHR was required for tumor growth in a sc mouse xenograft model, and AHR loss was associated with decreased migration and angiogenesis (VEGFR1) (Mulero-Navarro *et al.*, 2005). Thus, the role of AHR expression in breast cancer is variable and cell context dependent, and results of *in vivo* studies with $Ahr^{-/-}$ mice crossed with a transgenic mammary tumor model have not been reported.

AHR function has also been investigated by overexpression of a constitutively active AHR (Ca-AHR) in which amino acids 288–421 of the ligand binding domain have been deleted. Ca-AHR expressing mice rapidly developed stomach lesions and stomach cancer in both male and female mice (Andersson *et al.*, 2002). It was also reported that liver tumor prevalence and multiplicity were higher in DEN-initiated Ca-AHR versus wild-type mice, suggesting that the AHR enhanced hepatocarcinogenesis in mice (Moennikes *et al.*, 2004), whereas this contrasted to the tumor suppressor–like activity in DEN-initiated mice with or without AHR loss (Fan *et al.*, 2010). In contrast, Ca-AHR overexpression in MCF-7 breast cancer cells and Jurkat T cells inhibited growth in both cell lines and also induced apoptosis in Jurkat cells (Ito *et al.*, 2004; Köhle et al., 2002). The variable *in vitro* and *in vivo* effects of Ca-AHR are somewhat contradictory, and the utility of the Ca-AHR in predicting the role of the AHR in carcinogenesis requires further validation.

TCDD as a Carcinogen

The carcinogenicity of TCDD and its role as a tumor promoter have been extensively investigated in long-term feeding studies and in shorter term two-stage carcinogen-induced models (reviewed in Bock and Köhle, 2005; Knerr and Schrenk, 2006). The dietary studies invariably show development of hepatocellular preneoplastic nodules, adenomas or carcinomas in female and/or male rats and mice and, depending on the rodent strain/species, this may be accompanied by thyroid, thymus, skin, lung, nasal turbinate, tongue, and other oral cancers. There is also general

consensus that TCDD acts as a tumor promoter, and this has been confirmed in several animal studies; however, the mechanisms of TCDD-induced hepatocellular carcinomas are not fully understood. The International Agency for Research on Cancer (IARC) has classified TCDD as a Group I human carcinogen (IARC, 1997) based, in part, on increased overall cancer rates in exposed cohorts; however, this designation is disputed by others (Cole *et al*., 2003) and may be resolved with time.

The effects of TCDD on breast cancer were first reported in female Sprague Dawley rats administered TCDD in the diet (Kociba *et al*., 1978) for 2 years. The observed increase in hepatocellular carcinomas in female rats was accompanied by decreased rates of both age-dependent uterine and mammary tumors, which develop in these animals. The inhibition of two estrogen-dependent tumors in this rat model suggested that TCDD activation of the AHR inhibited 17β-estradiol (E2)–induced genes and responses, and the potential antiestrogenic activity of TCDD has subsequently been confirmed in the rodent uterus, breast, and endometrial cancer cells and mammary tumors (reviewed in Safe and Wormke, 2003). The effects of TCDD on mammary tumorigenesis are highly variable and dependent on the model and the timing of exposure. For example, prenatal exposure to 1 μg/kg TCDD on gestational day 15 increased mammary terminal end bud formation and enhanced susceptibility to carcinogen-induced mammary tumor formation (Brown *et al*., 1998). TCDD inhibits pregnancy-induced mammary gland development in mice; however, in parous or nulliparous mice treated with TCDD during pregnancy, there was a significant delay and decreased incidence in 7/12-dimethylbenz[a]anthracene (DMBA)-induced mammary tumor formation (Wang *et al*., 2011a). The animal models do not definitively link exposure to TCDD and other exposed populations with increased incidence of breast cancer (Safe *et al*., 2011); however, further long-term monitoring of the Seveso population accidentally exposed to TCDD will provide more definite data on the human breast cancer risks associated with exposure to TCDD.

Although the effects of different concentrations and the timing of exposure to TCDD and other relevant AHR agonists on tumor development have been reported, most studies have focused on using cancer cells as models for determining the mechanisms and pathways activated by TCDD and other AHR ligands. Results clearly demonstrate the complexity of AHR-mediated pathways and cell- and tumor-type-dependent differences in their mechanisms of action, and this is consistent with observation for other ligand-activated receptors. Furthermore, because the AHR plays a role in multiple tumor types, the identification of SAhRMs that exhibit tissue-specific AHR agonist or antagonist activities will lead to future clinical applications for AHR ligands in cancer treatment, and the therapeutic potential for these compounds will be emphasized in discussing results reported for effects of AHR ligands on various tumor types.

AHR IN CARCINOGENESIS: OPPORTUNITIES FOR CHEMOTHERAPEUTIC DRUG DEVELOPMENT

ER-Positive Breast Cancer

The antiestrogenic activity of TCDD observed in the long-term dietary feeding study in female Sprague Dawley rats (Kociba *et al*., 1978) has been extensively investigated in MCF-7 and other ER-positive breast cancer cells. Based on initial studies with TCDD, two major pathways were reported, and these included (1) induction of CYP1A1/CYP1B1 which in turn increased oxidative metabolism of E2 (Spink *et al*., 1990, 1992) and (2) activation of proteasomes by the liganded AHR and downregulation of ERα. The latter pathway showed TCDD-induced interaction of the ligand-bound AHR with ERα, which was followed by increased ubiquitination of ERα and degradation by proteasomes (Wormke *et al*., 2000b, 2003). Both pathways result in depletion of ERα and E2; however, their importance is ligand dependent because MCDF that also exhibits antiestrogenic activity in MCF-7 cells has minimal effects on induction of CYP1A1/CYP1B1 (Zacharewski *et al*., 1992). Therefore, CYP-dependent metabolism of E2 does not play a role in the antiestrogenic activity of MCDF.

The antiestrogenic activity of TCDD and other AHR ligands including MCDF and related alkyl chlorinated dibenzofurans, PAHs, and coplanar PCBs have also been reported in MCF-7 and other ER-positive breast cancer cells. For example, TCDD inhibits expression of E2-induced postconfluent focus production, cell cycle progression, plasminogen activator activities, cathepsin D, c-Fos, pS2, heat shock protein 27 (Hsp27), receptor-interacting protein 140 (RIP140), prolactin receptor, progesterone receptor, and carbamoylphosphate synthetase/aspartate transcarbamylase/dihydroorotase and BRCA-1 (Augereau *et al*., 2006; Biegel and Safe, 1990; Duan *et al*., 1999; Gierthy and Lincoln, 1988; Gierthy *et al*., 1987; Gillesby *et al*., 1997; Harper *et al*., 1994; Hockings *et al*., 2006; Khan *et al*., 2006; Krishnan and Safe, 1993; Krishnan *et al*., 1994, 1995; Lu *et al*., 1996b; Porter *et al*., 2001; Wang *et al*., 1998, 2001; Zacharewski *et al*., 1994). Several mechanisms have been described for ligand-activated inhibitory AHR-ERα cross talk, and these include direct binding of the AHR complex to inhibitory DRE (iDREs) *cis*-elements (promoters containing the core GCGTG AHR/ARNT binding motif (such as cathepsin D, pS2, Hsp27, and c-Fos); similar observations have been reported for RIP140 where a DRE and ERE overlap (Augereau *et al*., 2006). iDREs are located at various positions in the proximal gene promoters and may interfere with ERα-DNA binding or assembly of pol-ll and associated nuclear factors required for gene expression (Duan *et al*., 1999; Gillesby *et al*., 1997; Krishnan *et al*., 1995; Porter *et al*., 2001). A recent study also reported that inhibition of hormone regulation of cathepsin D expression was ARNT independent (Labrecque *et al*., 2012), and this pathway may also be important for other genes affected by inhibitory AHR-ERα cross talk. Hormonal activation of several E2-responsive genes in ER-positive breast cancer cells

also involves ERα-Sp1 bound to GC-rich promoter sequences, and TCDD inhibits ERα/Sp1-mediated transaction through competitive dissociation of the ERα/Sp1 complex because the AHR binds both proteins (Khan *et al*., 2006; Safe and Kim, 2008). Another mechanism may be due, in part, to competition (squelching) by the liganded AHR and ERα complexes for common coactivators and possibly other nuclear cofactors (Kumar and Perdew, 1999; Kumar *et al*., 1999; Nguyen *et al*., 1999). Chromatin immunoprecipitation (ChIP) assays have also provided important new insights on ERα-AHR cross talk and the corecruitment of both transcription factors to the same gene promoters (Beischlag and Perdew, 2005; Matthews *et al*., 2005). TCDD treatment recruited ERα and the AHR to the CYP1A1 promoter, and ERα contributed to estrogen-dependent regulation of Ah responsiveness. Ahmed *et al.* (2009) also showed by ChIP-seq that TCDD enhanced AHR/ARNT-ERα interactions at multiple human gene promoters, and a recent study showed novel gene-specific recruitment of both receptor complexes along with the nuclear cofactor RIP140 (Madak-Erdogan and Katzenellenbogen, 2012). This study showed that ERα-mediated gene activation is regulated, in part, through AHR-dependent modulation of RIP140 recruitment to ERα binding sites (Madak-Erdogan and Katzenellenbogen, 2012). Inhibitory AHR-ERβ cross talk has also been reported, and there is evidence that competition by the liganded AHR for ARNT decreases ERβ and to a lesser extent ERα-mediated transactivation because ARNT is a coactivator of ER (Rüegg *et al*., 2008).

Inhibitory AHR-ERα cross talk clearly plays a role in the antiestrogenic activity of TCDD and other AHR ligands; however, the liganded AHR also modulates many other genes and pathways that inhibit ER-positive breast cancer growth. For example, TCDD induces tumor growth factor β, tumor necrosis factor α, IL-1B (Vogel and Abel, 1995), IL-6 (which may be due to IL-1B induction) (Hollingshead *et al*., 2008), cyclin G2 (Ahmed *et al*., 2012), the human breast cancer resistance protein (BCRP/ABCG2) (Tan *et al*., 2010), and COX-2 (Degner *et al*., 2009). The AHR also interacts with CDK4 and RB, and TCDD causes dissociation of CDK4 from this complex, enhancing RB-dependent repression of E2F1 and inhibition of G_0/G_1 to S-phase progression (Barhoover *et al*., 2010; Huang and Elferink, 2005). It was also reported that TCDD or constitutively activated AHR enhanced phospho-JNK, decreased E-cadherin, and increased MCF-7 cell motility (EMT-like) (Diry *et al*., 2006). However, another study showed that AHR agonists or constitutively active AHR decreased mammosphere formation and inhibited Wnt/β-catenin signaling (Zhao *et al*., 2012). The rationale for these opposing observations is unclear. TCDD also decreased expression of the G-protein-coupled receptor CXCR4 and its chemokine ligand CXCL12 and also blocked E2-induced activation of CXCR4 (Hsu *et al*., 2007). This response has been linked to inhibition of MCF-7 cell migration by TCDD, and similar results have been observed for 3,3′-diindolymethane (DIM) (Hsu *et al*., 2007, 2008). TCDD also inhibited colonization of MCF-7 and ZR-75 cells in soft agar and cell invasion, and this was associated with induction of cell differentiation and differentiation markers such as K-casein (Hall *et al*., 2010).

The effects of AHR agonists on mammary tumor growth *in vivo* complement the *in vitro* data and confirm the antiestrogenic and antitumorigenic activity of these compounds. TCDD inhibits carcinogen-induced mammary tumor development and also inhibits growth of human tumors in a xenograft model, and similar results have been observed for MCDF and related compounds (Gierthy and Lincoln, 1988; Holcomb and Safe, 1994; McDougal *et al*., 1997, 2001). Moreover, 3,3′,4,4′-tetrachlorobiphenyl also inhibited carcinogen-induced mammary tumor formation (Ramamoorthy *et al*., 1999) and growth, and similar results were observed for DIM and substituted DIMs (Chen *et al*., 1998; McDougal *et al*., 2000); however, these compounds also act through other pathways.

ER-Negative Breast Cancer

Early studies with ER-negative breast cancer cells suggested that Ah responsiveness was dependent on expression of ERα (Vickers *et al*., 1989); however, it was subsequently shown that the AHR is expressed in most ER-negative breast cancer cells (Wang *et al*., 1995), although with the exception of the MDA-MB-468 cells, the fold induction of CYP1A1 (by TCDD) is decreased (Wang *et al*., 1997; Zhang *et al*., 2009). Both TCDD and MCDF inhibit growth of MDA-MB-468 cells, and this is due to induction of TGFα which is growth inhibitory in this cell line (Wang *et al*., 1997). There is evidence that the AHR may repress c-MYC in Hs578T cells (Yang *et al*., 2005). The AHR-Rb-mediated repression of E2F1 (Barhoover *et al*., 2010), induction of differentiation markers, inhibition of cell invasion (Hall *et al*., 2010), and downregulation of CXCR4 (Hsu *et al*., 2007, 2008) are observed in ER-positive MCF-7 and ER-negative MDA-MB-231 and other cell lines. MCDF and TCDD also decreased invasion of MDA-MB-231 cells, and this was due to AHR-mediated upregulation of microRNA-335 (miR-335), which in turn suppresses expression of prometastatic genes such as SOX-4 (Zhang *et al*., 2012b). MCDF also inhibits metastasis of MDA-MB-231 cells to the lung after tail vein injection, and these results are consistent with the antimetastatic effects of TCDD using metastatic 4T1.2 mouse mammary tumor cells in an orthotopic model (Wang *et al*., 2011b).

Structurally diverse chemicals that exhibit AHR agonist activity include several widely used pharmaceuticals (Hu *et al*., 2007) such as the antiallergic drug tranilast. Tranilast is an AHR agonist in MDA-MB-231 cells and inhibited cell growth migration, colony formation, mammosphere formation, and metastasis of MDA-MB-231 cells to the lung after tail vein injection (Prud'homme *et al*., 2010; Subramaniam *et al*., 2011). Several SERMs including 4-hydroxytamoxifen (4-OHT) exhibit AHR agonist activity in breast cancer cells, and it was also shown the 4-OHT blocks osteoclast differentiation (AHR dependent) and this may contribute to bone preservation associated with

use of tamoxifen for breast cancer therapy (DuSell *et al*., 2010). Recent studies in this laboratory have screened eight AHR-active pharmaceuticals as inducers of CYP1A1/CYP1B1 and inhibitors of BT474 and MDA-MB-468 breast cancer cell migration (Jin *et al*., 2012). The effects of these compounds were structure, cell context, and response dependent; mexiletine is an AHR agonist in liver cancer cells (Hu *et al*., 2007) and in BT474 cells but was an AHR antagonist in MDA-MB-468 cells. Among the eight AHR-active pharmaceuticals, flutamide, leflunomide, nimodipine, omeprazole, sulindac, and tranilast, but not 4-OHT or mexiletine, inhibited MDA-MB-468 cell migration (Jin *et al*., 2012), and current studies are further investigating these pharmaceuticals for their applications in ER-negative breast cancer chemotherapy. It is evident from the extensive research on both ER-positive and ER-negative breast cancer cells that the AHR is a highly relevant drug target. At present, at least one compound ("aminoflavone") that binds the AHR is in phase II clinical trials for breast cancer (Loaiza-Perez *et al*., 2004). This compound is a prodrug and AHR agonist that induces AHR-dependent CYP1A1/1B1, which in turn activates the drug through oxidative metabolism.

Endometrial and Ovarian Cancer

The role of the AHR and AHR agonists have not been extensively investigated in endometrial and ovarian cancer cell lines; however, there is evidence that comparable AHR-ERα cross talk and growth inhibitory pathways are operative (Castro-Rivera *et al*., 1999; Rogers and Denison, 2002; Rowlands *et al*., 1993; Wormke *et al*., 2000a) and require further investigation.

Liver Cancer

Treatment of rat and mouse liver cancer cell lines with TCDD results in the inhibition of G_0/G_1 to S-phase progression and accumulation of cells in G_0/G_1 (Elferink *et al*., 2001; Ge and Elferink, 1998; Huang and Elferink, 2005; Marlowe *et al*., 2004; Puga *et al*., 2000, 2009). These effects are accompanied by the induction of the cyclin-dependent kinase inhibitor p27 (Kolluri *et al*., 1999; Levine-Fridman *et al*., 2004) and inhibition of E2F1-regulated gene expression, which is due, in part, to interactions with RB. Some of the responses are similar in liver and breast cancer cell lines, and ligand activation of the AHR enhances interactions with RB, resulting in decreased E2F1-dependent gene expression, and this may also result in displacement of p300 (Marlowe *et al*., 2004). Detailed mechanism studies are contradictory because one report showed that the DNA binding and transactivation domains of the AHR and ARNT were not required for repression of E2F1-regulated transaction in mouse hepatoma Hep1c1 cells (Marlowe *et al*., 2004). In contrast, ARNT was required for E2F repression in rat hepatoma BP8 cells (Ah nonresponsive) transfected with an AHR expression plasmid (Huang and Elferink, 2005). It has been suggested that these cell context–dependent differences may be due to the requirement for ARNT in dissociating HSP90 from the AHR (Puga *et al*., 2002). In HepG2 cells, TCDD induces plasminogen activator inhibitor type 2 (PAI-2) mRNA (Gohl *et al*., 1996) and the anterior gradient 2 (AGR2) metastasis marker (Gohl *et al*., 1996) and enhances cellular migration via an AHR-dependent nongenomic focal adhesion kinase/Src pathway (Ambolet-Camoit *et al*., 2010). In contrast to human HepG cells, TCDD induces cancer cell growth in rat and mouse hepatoma cells, and therefore, potential application of SAhRMs for liver cancer therapy must be further investigated.

Colon, Gastric, and Pancreatic Tumors

TCDD and other AHR agonists induce proliferation of several colon cancer cell lines, and this involves extranuclear AHR-mediated activation of Src and the EGFR pathway (Tomkiewicz *et al*., 2013). AHR agonists not only enhance growth but also induce proinflammatory IL-1β and MMP-9, calcium ion flux, and the ABCG2 drug transporter in colon cancer cells (Le Ferrec *et al*., 2002; Tompkins *et al*., 2010; Villard *et al*., 2007). TCDD also induces gastric cancer cell growth and invasion and MMP-9 expression (Peng *et al*., 2009), and a report showing that DIM inhibits gastric cancer cell growth (Yin *et al*., 2012) is probably due to AHR-independent pathways. Thus, AHR agonists enhance colon and gastric cancer cell growth, suggesting a possible therapeutic role for SAhRMs that exhibit antagonist activities. In contrast, the AHR is expressed in most pancreatic tumors (14/15), and TCDD, MCDF, and related SAhRMs induce p21 and inhibit pancreatic cancer cell proliferation and anchorage-independent growth (Koliopanos *et al*., 2002), suggesting that SAhRM agonists may have clinical applications for pancreatic cancer therapy.

Prostate and Urothelial Cancers

Initial studies investigated AHR-androgen receptor (AR) cross talk in prostate cancer cells and showed that TCDD inhibited basal and androgen-induced growth and cell cycle progression (G_0/G_1 to S-phase arrest) (Barnes-Ellerbe *et al*., 2004; Jana *et al*., 1999, 2000; Morrow *et al*., 2004). β-TrCP is an E3-ligase, and depletion of this gene results in AHR upregulation and growth inhibition; TCDD did not enhance growth inhibition (Gluschnaider *et al*., 2010) nor did TCDD affect Wnt/β-catenin-AHR interactions in prostate cancer cells (Chesire *et al*., 2004). AHR agonists induced MMP-9 in androgen-insensitive PC3 and DU145 cells (Haque *et al*., 2005), suggesting that the chemotherapeutic activity of AHR agonists may primarily be associated with androgen-sensitive prostate cancer. In T24 urothelial cancer cells, TCDD induced MMP-1 and MMP-9 and enhanced cell invasion, suggesting that SAhRM antagonists may have some therapeutic activity, and this is supported by AHR silencing in these cells, which resulted in decreased invasion and MMP expression (Ishida *et al*., 2010).

Head and Neck and Lung Cancers

The AHR regulates IL-6 expression in head and neck cancers, and TCDD alone or in combination with IL-β enhances proinflammatory IL-6 expression in head and neck cancer cell

lines (DiNatale *et al*., 2011, 2012). However, treatment of these cells with the AHR antagonists 6,2′,4′-trimethoxyflavone or [*N*-(2-(1*H*-indol-3-yl)ethyl)-9-isopropyl-2-(5-methylpyridin-3-yl)-9*H*-purin-6-amine] inhibited head and neck cancer cell migration. AHR antagonists also inhibited BaP induction of the drug transporter ABCG2, demonstrating a potential clinical application for SAhRM antagonists in treatment of head and neck cancers (DiNatale *et al*., 2012).

The AHR is highly expressed in lung cancer patients (Lin *et al*., 2003; Portal-Nunez *et al*., 2012), and several reports show that various AHR agonists including tobacco smoke extracts (rich in PAHs), β-naphthoflavone, PAHs, TCDD, and related AHR agonists induce lung cancer cell growth through activation of multiple pathways (Chuang *et al*., 2012; Lin *et al*., 2003; Shimba *et al*., 2002; Wang *et al*., 2009). For example, AHR agonists induce fibroblast growth factor-9 (Wang *et al*., 2009) and growth promoting genes including PCNA and DP2 (Shimba *et al*., 2002), osteopontin (Chuang *et al*., 2012), and adrenomedullin (Portal-Nunez *et al*., 2012), which contribute to lung cancer cell growth/migration and tumor progression, respectively. Moreover, both adrenomedullin and osteopontin expression in tumors correlated with expression of AHR or AHR-regulated genes. Thus, the AHR and AHR agonists play a role in lung and head and neck cancer growth/progression, and as demonstrated for head and neck cancers, AHR antagonists may have therapeutic benefits for treating both cancers.

Melanoma, Esophageal, and Pituitary tumors

TCDD and other AHR agonists induced several MMPs and also increased invasion/migration in melanoma A2058 cells (Villano *et al*., 2006). The anti-inflammatory drug leflunomide was characterized as an AHR agonist, and inhibition of A375 melanoma cell growth and induction of p21 by leflunomide were AHR dependent (O'Donnell *et al*., 2012). In contrast, TCDD did not inhibit growth of this cell line, and further studies on the differences between TCDD versus leflunomide in these cells require further investigation.

The AHR protein is highly expressed in esophageal tumors and cancer cell lines (e.g., Eca 109 and TE-13), and the AHR agonist β-naphthoflavone inhibits invasion of esophageal cancer cells (Zhang *et al*., 2012a). Another report shows that BaP induced and AHR antagonists (salicylamide and kaempferol) inhibited expression of the ABCG2 drug transporter in cisplatin-resistant cell lines, suggesting that the use of SAhRM agonists/antagonists may be cell context dependent. Expression of the AHR and AHR interacting protein has been reported in pituitary adenomas; however, effects of SAhRMs have not been determined (Jaffrain-Rea *et al*., 2009).

Lymphomas and Leukemia

Exposure to HAs has been associated with increased lymphomas, and studies with lymphoma cancer cell lines showed that TCDD decreased apoptosis, and this was accompanied by induction of COX-2, C/EBPβ, and bcl-xl (Vogel *et al*., 2007). Moreover, AHR antagonists reversed the prosurvival effects of TCDD, suggesting that SAhRM antagonists may be useful for treating lymphoma. Retinoic acid–induced differentiation of HL-60 promyelocytic leukemia cells was due, in part, to AHR-mediated downregulation of the stem cell transcription factor Oct4 (Bunaciu and Yen, 2011). The effects of SAhRM agonists/antagonists were not determined; however, it is likely that an AHR ligand may have clinical application for some leukemias.

Neuronal Cancers

The AHR promotes proliferation of human DAOY medulloblastoma cells (Dever and Opanashuk, 2012), and TCDD induces CYP1A1 in these cells; however, the functional effects of TCDD or other AHR ligands in this cell line have not been investigated (Dever and Opanashuk, 2012). The AHR is expressed in human gliomas and glioblastoma cell lines, and treatment with 3-MC enhanced G_0/G_1 to S-phase progression in LN-308 but not LNT-229 cells (Gramatzki *et al*., 2009). The AHR antagonist CH-223191 did not affect cell cycle progression, but this compound or AHR silencing decreased the clonogenicity of these cells. CH-223191 also decreased invasiveness of the glioblastoma cell lines, demonstrating potential clinical application for SAhRM antagonists. Subsequent studies have linked tryptophan-2,3-dioxygenase-2-mediated metabolism of tryptophan to the AHR agonist kynurenine as a critical event in promoting the progression and survival of brain tumors (Adams *et al*., 2012; Opitz *et al*., 2011). Kynurenine activation of the AHR not only promotes tumor cell survival and motility but also inhibits protective immune response pathways, and it was suggested that the TDO-2-kynurenine-AHR pathway may play a role in formation of multiple tumors (Adams *et al*., 2012). These results also confirm the previous report (Gramatzki *et al*., 2009), which suggested a role for SAhRM antagonists for brain tumor chemotherapy. Interestingly, it has also been reported that indirubins (AHR ligands) decrease glioma invasion (Williams *et al*., 2011) by inhibition of GSK3, and the activity of indirubins as SAhRM antagonists in gliomas needs to be reinvestigated.

SUMMARY

There is increasing evidence that the AHR and its ligands play an important role in carcinogenesis (Figs. 2 and 3), confirming the potential for the AHR as a drug target. Many tumors express the AHR (mRNA and/or protein) and, although there may be some inconsistencies regarding the tumor suppressor or pro-oncogenic functions of the AHR (Fig. 2), it is clear that the endogenous receptor influences tumor growth, survival, migration, and invasion. There is also tumor-specific variability with respect to the effects of AHR ligands (agonists vs. antagonists) on carcinogenesis; however, in most tumors, it is clear that these ligands affect tumor growth, survival, migration, and invasion (Fig. 3). In tumors where an AHR agonist or

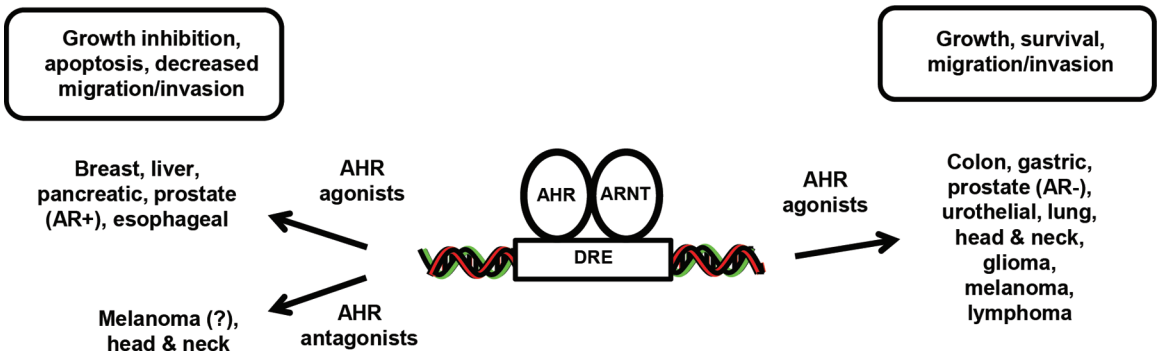

FIG. 3. Activities of AHR ligands in cancer.

antagonist exhibits pro-oncogenic activity, it should be feasible to develop a SAhRM with the reverse activity that will inhibit tumorigenesis. It has already been shown that SAhRM agonists inhibit mammary carcinogenesis (McDougal *et al*., 2001; Zhang *et al*., 2012b) and SAhRM antagonists inhibit head and neck cancer and glioblastomas (DiNatale *et al*., 2011, 2012; Gramatzki *et al*., 2009), and a similar approach can be used for treating other AHR-dependent diseases. Thus, the AHR is like many other receptors (e.g., ERα) that mediate ligand-dependent toxic and therapeutic responses, indicating the importance for continued development of new SAhRMs for clinical applications including cancer chemotherapy.

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