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Role of the Aryl Hydrocarbon Receptor in Carcinogenesis and Potential as an Anti-Cancer Drug Target

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Abstract

The aryl hydrocarbon receptor (AhR) was initially identified as the receptor that binds and mediates the toxic effects induced by 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and structurally-related halogenated aromatics. Other toxic compounds including some polynuclear aromatic hydrocarbons (PAHs) act through the AhR; however, during the last 25 years, it has become apparent that the AhR plays an essential role in maintaining cellular homeostasis. Moreover, the scope of ligands that bind the AhR includes endogenous compounds including multiple tryptophan metabolites, other endogenous biochemicals, pharmaceuticals and health promoting phytochemicals including flavonoids, indole-3-carbinol and its metabolites. It has also been shown that like other receptors, the AhR is a drug target for multiple diseases including cancer where both AhR agonists and antagonists effectively block many of the critical hallmarks of cancer in multiple tumor types. This review describes the anticancer activities of AhR ligands and demonstrates that it is time to separate the AhR from TCDD and exploit the potential of the AhR as a novel target for cancer chemotherapy.

Cancer Statistics and Background

Regulatory and cancer research agencies carefully monitor changes in cancer statistics each year and determine both incidence and death rates for all tumor types (Miller et al. 2016; Siegel et al. 2015; Torre et al. 2016). Despite scientific and medical advances in detection, treatment and understanding the unique features of each tumor type, the overall progress in terms of decreased incidence and mortality has been limited (Miller et al. 2016). For example, cancer is still the leading cause of death worldwide and the total number of cancer cases and deaths are increasing along with population growth (Torre et al. 2016). The statistics in the United States are more encouraging and from 2007–2011, cancer incidence rates decreased 1.8% in men but were unchanged in women; cancer death rates decreased by 1.8 and 1.4% in men and women, respectively (Siegel et al. 2015). Improvements in cancer incidence were not only tumor specific but also dependent on age, sex, race, socioeconomic

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status and region. Some of the most dramatic changes in cancer incidence have been correlated with lifestyle changes such as decreased smoking in males from the 1990s, leading to a significant decline in this disease (Siegel et al. 2015). The success of cancer therapies in contributing to improved survival of cancer patients is due, in part, to the extensive use of combination drug therapy regimens and the limited but impressive effects of targeted mechanism-based therapies for treatment of some tumors. For example, the use of BCR-ABL tyrosine kinase inhibitors such as imatinib has increased the 5-year survival of chronic myeloid leukemia patients from 31% to 60% (Ferdinand et al. 2012; Miller et al. 2016). Unfortunately, “wonder” drugs for most other cancers have not been developed.

The basic science of cancer initiation, promotion, progression and metastasis has been extensively studied and the progress made at the organismal, cellular and genomic levels have been remarkable and will form the future basis for successful development of new targeted therapies. Hanahan and Weinberg (Hanahan and Weinberg 2000) organized thinking about cancer based on their initial proposal of 6 hallmarks of cancer including “sustained proliferative signaling, evading growth suppressors, resisting cell death, enabling reproductive mortality, inducing angiogenesis, activating invasion and metastasis”. Two additional hallmarks, reprogramming of energy metabolism and evading immune destruction, have been added (Hanahan and Weinberg 2011), and these hallmarks now serve not only to define critical features of cancer cells but also as a framework for development of new targeted therapies. The complexity of cancer cells and tumors is apparent from the continuing efforts by pathologists and oncologists to divide tumors from each site into various subclasses based on their unique pathologies and stages (early to late) and their biochemical/molecular characteristics since these classifications are not only related to outcomes (e.g. survival times) but to specific treatment regimens. Not surprisingly, tumor classifications are continually changing based on the acquisition of new information on various cellular and molecular characteristics of each tumor type. Breast cancer classifications initially relied on expression of the estrogen receptor (ERα) in the presence or absence of the progesterone receptor (PR); this was subsequently expanded to include expression of the oncogenic epidermal growth factor receptor 2 (HER2, ErbB2) which could be targeted by antibodies such as Herceptin (trastuzumab), an antibody that binds HER2 and blocks its function. Breast cancer classifications continue to evolve and include molecular characteristics, staging, pathology and other factors (Perou et al. 2000; Sinn and Kreipe 2013; Viale 2012). Thus, tumors from the same site are highly heterogenous and provide enormous problems for designing stage-specific therapies and for overcoming subsequent drug resistance problems associated with activation of alternative pro-oncogenic pathway.

The AhR and Its Physiological Role

The AhR was initially identified as the receptor that bound the environmental toxicant 2,3,7,8-tetrachlorodibenzo-*p*-dioxin (TCDD) and structurally related toxic halogenated aromatic industrial compounds and by-products (Poland et al. 1976; Poland and Knutson 1982) (Fig. 1). Development of AhR knockout mice confirmed that this receptor was necessary to mediate the toxic effects of TCDD and other dioxin-like compounds (DLCs) (Fernandez-Salguero et al. 1996; Mimura et al. 1997). Unfortunately, this has been and continues to be a major problem in exploiting the AhR as a drug target, whereas other

receptors such as the ER that plays a role in breast cancer and other hormone-dependent diseases is a major target for selective ER modulators that are extensively used for clinical applications (Jordan 2007; Jordan 2009). Over the past 25 years, it has been well established that multiple different classes of compounds including biochemicals that are possible endogenous AhR ligands, health promoting phytochemicals, and AhR-active pharmaceuticals bind the AhR (Denison and Nagy 2003; Denison et al. 2011; Hu et al. 2007; Safe et al. 2012; Soshilov and Denison 2014) (Fig. 1). Moreover, there is increasing evidence that the AhR plays a prominent role in physiology and pathophysiology including important roles in the immune function, autoimmunity, gastrointestinal function, inflammation and cancer (Benson and Shepherd 2011; Boitano et al. 2010; Ehrlich et al. 2016; Esser 2012; Kerkvliet et al. 2009; Marshall and Kerkvliet 2010; Murray et al. 2010; Punj et al. 2014; Quintana et al. 2008; Veldhoen et al. 2008) and development of selective AhR modulators is a promising new area of pharmacological research, particularly for cancer chemotherapy (Murray et al. 2014; Safe et al. 2013).

Cancer Chemotherapies and A Role for the AhR

The standard first-line chemotherapies for most cancers include a range of cytotoxic drugs that target critical functions more highly expressed in tumor vs. non-tumor tissues/cells (Masui et al. 2013). Some of the genes/pathways that are targeted in cancer cells include membrane receptors (tyrosine kinases) and their ligands, oncogenes such as *Ras* and other pro-oncogenic factors, transcription factors and nuclear receptors. Members of the nuclear receptor superfamily are ligand activated nuclear transcription factors that include the estrogen receptor and androgen receptor which are targeted by selective receptor modulators (SRMs) for treatment of early stage receptor-positive breast and prostate cancer (Aesoy et al. 2015; Baek and Kim 2014; Burris et al. 2013; Tice and Zheng 2016). Over 80 drugs targeting 18 different nuclear receptors have been approved for various uses (Tice and Zheng 2016). In contrast, compounds targeting the aryl hydrocarbon receptor (AhR) which is also a ligand-activated nuclear transcription factor and a member of the basic helix-loop-helix (bHLH) family has not been approved for any pharmacologic applications. There are only a few AhR ligands including aminoflavone and laquinomod that have been in clinical trials for treatment of breast cancer and multiple sclerosis, respectively (Haggiag et al. 2013; Loaiza-Perez et al. 2004).

The AhR and Its Ligand in Tumorigenesis and Cancer Chemotherapy

Most initial studies on the AhR and its ligands focused on the effects of TCDD on tumor formation after long term rodent feeding studies, and there was general consensus that TCDD was hepatocarcinogen in most studies [reviewed in (Bock and Kohle 2005; Knerr and Schrenk 2006)]. TCDD-induced tumors were also observed in multiple sites, however, in a lifetime feeding study in Sprague-Dawley rats, there was a decrease in spontaneous mammary and uterine tumors (Kociba et al. 1978). The AhR has been characterized in multiple cell lines and human tumors (Safe et al. 2013) and, with the development of selective AhR modulators (SAhRMs) (Safe et al. 1999) including AhR-active pharmaceuticals, the AhR has emerged as a drug target for cancer and other diseases. In this review, we will outline the role of the AhR in cancer cell and mouse models and also the

opportunities for novel approaches of using SAhRMs as cancer therapeutics. It is also apparent that the AhR and its ligands can act as agonists or antagonists to block many of the hallmarks of cancer (Fig. 2) and these results will be apparent in the following summaries.

Genitourinary cancers.

Table 1 summarizes the effects of several AhR ligands on various genitourinary derived tumors and also the endogenous role of the AhR in prostate cancer using the TRAMP mouse model (Fritz et al. 2009). TCDD and related compounds and also omeprazole and tranilast inhibit pancreatic cancer cell invasion; however, there is evidence for different mechanisms of action dependent on the cell classification (Jin et al. 2015; Koliopanus et al. 2002). For example, in Panc1 cells which are highly invasive, the mechanism of omeprazole-mediated inhibition of invasion is due to a non-genomic AhR pathway (Jin et al. 2015). The role of the AhR and its ligands in prostate cancer cells are dependent on androgen receptor (AR) expression. There is evidence that AhR ligands are antiandrogenic in AR-expressing prostate cancer cells, and the AhR itself is growth inhibitory (Gluschnaider et al. 2010). In contrast, knockdown of the AhR in AR-negative prostate cancer cells decreases proliferation (Tran et al. 2013), multiple AhR ligands induce pro-invasion MMP9 (Haque et al. 2005), and the AhR antagonist CH223191 inhibits growth (Richmond et al. 2014). In TRAMP mice which are AR-positive, the evidence suggests that the AhR and its ligands are tumor growth inhibitory, although some mixed results were observed for TCDD (Fritz et al. 2007; Fritz et al. 2009; Moore et al. 2016). Results of limited studies in urinary tract tumors suggest that the AhR and its ligands increase invasion (Ishida et al. 2010), whereas in kidney cancer cell lines the results are contradictory and may be cell context-dependent (Callero et al. 2012; Ishida et al. 2015).

Neurological cancers.

Glioblastoma is a highly lethal tumor in which survival times are low and treatment options are limited and not very effective. Initial studies showed that the AhR was expressed in human tumors and glioblastoma cell lines, and the pro-oncogenic activity of the AhR was linked to regulation of TGFβ signaling (Gramatzki et al. 2009). Moreover, this study showed that AhR knockdown or the AhR antagonist CH223191 inhibited clonal survival and migration of glioblastoma cells. A subsequent study by this group demonstrated that tryptophan-2,3-dioxygenase-mediated metabolism of tryptophan to give kynurenine was a key pro-carcinogenic event since kynurenine promotes AhR-dependent tumor cell survival and motility (Opitz et al. 2011). A recent report indicates that AhR-integrin-TGFβ crosstalk is also involved in glioblastoma (Silginer et al. 2016). It is clear that these studies demonstrate a potential clinical role for AhR antagonists in the treatment of glioblastoma. Other neurological cancers including medulloblastoma and pituitary adenomas also express an AhR that is pro-oncogenic (Dever and Opanashuk 2012; Jaffrain-Rea et al. 2009), whereas the AhR enhances differentiation in neuroblastoma cells (Huang et al. 2011) and TCDD induces apoptosis in PC12 cells (Sanchez-Martin et al. 2010). These studies suggest different roles for the AhR and its ligand in brain cancers (Table 2).

Lung, head and neck, esophageal, melanoma, leukemia and lymphoma.

In lung cancer cells, there is evidence from most studies that PAHs and other ligands are growth promoters and induce growth promoting genes, and the constitutive AhR is also involved in lung cancer cell growth (Chuang et al. 2012; Shimba et al. 2002; Wang et al. 2009) (Table 3). The major exception to these results was observed in CL1–5 cells which express low AhR levels; however, in an AhR-inducible cell line overexpression of the AhR protected against sidestream smoke-induced ROS (Cheng et al. 2012). This “protective” effect may be significant; however, AhR overexpression was also associated with increased anchorage-independent growth and cell proliferation and this is consistent with other studies in lung cancer cells. The AhR is also pro-oncogenic in head and neck and oral cancers and AhR agonists enhance cell growth and survival, whereas AhR antagonists exhibit anticancer activity, demonstrating a possible role for these compounds in clinical applications (DiNatale et al. 2011; DiNatale et al. 2012; Stanford et al. 2016a). The AhR is expressed in esophageal cancer and leukemia/lymphomas; however, the function of the AhR and its ligands are not well defined, although one study showed that β-naphthoflavone significantly inhibited invasion of esophageal cancer cells. Contradictory data have also been reported for melanoma. Loss of the AhR enhanced tumorigenicity *in vivo* and leflunomide inhibited melanoma cell proliferation (Contador-Troca et al. 2013; O’Donnell et al. 2012); however, it was also reported that AhR knockdown decreased growth (Barretina et al. 2012) and TCDD increased invasion and expression of MMPs (Villano et al. 2006). Differences in these data may be cell context-dependent and mouse model-specific and need further investigation.

Colon and gastric cancer.

The functions of AhR ligands in colon cancer cells are cell context- and ligand-dependent. Several different ligands, including 3-methylcholanthrene (MC) (Caco-2, LS174T) and TCDD (H508, SN7-C4), exhibit pro-oncogenic responses including induction of cell growth and genes associated with migration (MMP9) and drug transport (ABCG2) (Tompkins et al. 2010; Villard et al. 2007; Xie et al. 2012). However, in several other colon cancer cell lines, the AhR ligands FICZ (LoVo) and chrysin (HCT116, DLD-1 and SW837) inhibited cell growth (Ronnekleiv-Kelly et al. 2016; Yin et al. 2016). In contrast, several reports demonstrate that the loss of the AhR in wild-type and $APC^{min/+}$ mice enhances colon/cecum carcinogenesis and in $APC^{min/+}$ and wild-type mice I3C/DIM inhibit carcinogenesis (Diaz-Diaz et al. 2016; Ikuta et al. 2013; Kawajiri et al. 2009). Thus, the *in vivo* mouse model clearly demonstrates tumor suppressor-like activity for the AhR in colon/cecum cancer and specific AhR ligands can inhibit tumorigenesis. In MNK5 gastric cancer cells ± AhR, *in vitro* and *in vivo* (xenograft-AhR) studies indicate that the AhR promotes growth, migration and apoptosis (Lai et al. 2014; Yin et al. 2013). TCDD induced proliferation and invasion of AGS cells (Peng et al. 2009), whereas DIM decreased SGC-7901 cell growth (Yin et al. 2012); however, it is not clear if the growth inhibitory effects of DIM are AhR-dependent. Expression of constitutively active AhR (CA-AhR) in mice results in gastric tumor formation, suggesting pro-oncogenic function of the receptor (Andersson et al. 2002; Kuznetsov et al. 2005). Future studies are needed to determine whether AhR agonists or antagonists will be effective for treatment for gastric cancer.

Liver cancer.

Liver cancer is a leading cause of cancer-related mortality worldwide, accounting for more than 600,000 deaths each year. Although liver cancer is much more common in Southeast Asia liver cancer cases worldwide including in the United Sates have been on the rise. The prognosis of liver cancer is quite poor, with a five-year survival rate of approximately 15% (American Cancer Society 2016). This poor outcome is explained in large part by the ability of hepatocellular carcinoma (HCC), which accounts for 90% of liver cancers, to become resistant to chemotherapy, and lack of existing targeted therapies. The only targeted therapy for liver cancer is Sorafenib, a kinase inhibitor that extends patient survival, on average, by only three months (Bruera et al. 2014). Thus, there is a dire need to make bold moves and identify effective treatment options for liver cancer patients. Based on the recent evidence summarized below, we propose that the AhR is a viable molecular target for liver cancer. The function of the AhR in liver cancer is somewhat contradictory and the role of AhR and its ligands in both *in vitro* and *in vivo* model systems is summarized in Table 5.

AhR plays a significant role in development presumably due to its ability to regulate cell growth and differentiation. AhR null mice have much smaller livers and display defects in development of vasculature (Fernandez-Salguero et al. 1996; Lahvis and Bradfield 1998; Mimura et al. 1997). Genes required for proper growth and development often play significant roles in cancer, functioning as *oncogenes* or *tumor suppressors* and sometimes both as *tumor suppressor* and *oncogene* depending on the context and stimuli. The genetic background or the expression of other coregulatory proteins play a role in the function of a gene. AhR null mice do not develop spontaneous tumors in liver suggesting that the AhR is not a classical tumor suppressor gene. Tumorigenesis is still a rare event and it is often kept under control by checks and balances in the system regulated by multiple genes that eliminate abnormal cells. The endogenous AhR functions as a tumor modifier gene in liver cancer in the absence of any exogenous ligand stimulation. The identification of a tumor modifier role for the AhR was investigated by crossing the AhR knockout mice with mice that express oncogenes or by exposure to chemical carcinogens that predispose mice to cancer. Puga and colleagues utilized genotoxic carcinogen diethylnitrosamine (DEN) to induce liver tumors in wild-type mice expressing the AhR and knockout mice lacking the AhR (Fan et al. 2010). In this study, the absence of the AhR expression was associated with increased BrdU incorporation, a marker used to identify proliferating cells. In addition, decreased expression of known tumor suppressor genes in this study strongly demonstrated a tumor suppressive modifier role for the AhR.

The AhR is highly expressed in liver cancer cells (O'Donnell et al. 2012) and several AhR ligands inhibit cancer cell proliferation and/or induce liver cancer cell death. Some of these effects have been shown to be dependent on AhR expression. Recent evidence including from our laboratories supports the possibility that the AhR can also be transformed to yield biological responses that can be exploited for the treatment of cancer (Jin et al. 2015; Jin et al. 2014; Koch et al. 2015; O'Donnell et al. 2014; O'Donnell et al. 2012; Safe et al. 2013). Chemical libraries were screened to identify AhR ligands that have anti-cancer effects. The specificity and selectivity of the identified small molecules for the AhR was validated in well-characterized cell systems. Furthermore, these compounds were tested for AhR-

dependent growth inhibitory effects in cancer cells. This resulted in identification of promising AhR ligands with potential anti-cancer effects, one of which was raloxifene. Raloxifene is a selective estrogen receptor modulator used in the clinic for prevention of osteoporosis. Raloxifene directly bound the AhR, promoted cytosol to nuclear translocation of the AhR, strongly activated AhR-driven reporter gene activity, and endogenous AhR target genes (Bisson et al. 2009; O'Donnell et al. 2014). AhR-dependent programmed cell death in breast and liver cancer cells that do not express estrogen receptor contributed to raloxifene-induced growth inhibition. Despite the ability of TCDD to strongly activate AhR signaling, TCDD did not induce apoptosis suggesting the unique activity of certain AhR ligands such as raloxifene (O'Donnell et al. 2014). Unlike TCDD, raloxifene is not a high affinity ligand and it is important to understand ligand-selective AhR signaling that drive AhR-dependent anti-cancer actions. Raloxifene is well tolerated in humans and this compound or new raloxifene-based molecules with improved AhR binding affinity need to be identified for future clinical applications.

Humans exposed to high levels of TCDD did not exhibit higher incidences of cancer (Collins et al. 2009; McBride et al. 2009). Analysis of TOXcast chemicals and their activation of nuclear receptors including AhR revealed that there is no association between AhR activation and progression of hepatic lesions (Shah et al. 2011). Human HCCLM3 hepatoma cells were inhibited both *in vitro* and *in vivo* (xenograft) by the AhR ligand ITE (Zhao et al. 2015). The FDA approved drug and anti-androgen, flutamide is also an AhR ligand, and the growth suppressive effects of flutamide are due to AhR-dependent induction of TGFβ1 in human HCC cells (Koch et al. 2015). AhR-mediated activation of TGFβ1 signaling resulted in activation of cell cycle inhibitory proteins p15 and p27, and knockdown of AhR or TGFβ1 abrogated the anti-proliferative effects of flutamide. This is an example of an AhR-active approved pharmaceutical that could be repurposed for treatment of hepatocellular carcinomas.

Breast cancer.

Breast cancer is the most common cancer among women worldwide and metastasis is responsible for most of the deaths associated with breast cancer. Breast cancer is composed of multiple subtypes with distinct molecular markers. The three major classes of breast cancers are (i) hormone receptor positive cancers that express estrogen receptor (ER) and progesterone receptor (PR), (ii) human epidermal growth factor receptor 2 (HER2) positive cancers meaning cancers with overexpression of Her2 and (iii) triple negative breast cancers (TNBC) that do not express ER, PR with normal or no expression of Her2 (American Cancer Society 2016; Santagata et al. 2014). Approximately, 20% of breast cancers are classified as TNBC, which is composed of at least six subclasses (Lehmann et al. 2011). TNBCs are the most difficult to treat with very limited options and poor prognosis.

The AhR is expressed in both hormone receptor positive and negative breast cancers including in TNBC (O'Donnell et al. 2010). Higher expression of AhR correlates with better prognosis including increased overall survival and distant metastasis-free survival in different forms of breast cancer (O'Donnell et al. 2014). Targeting AhR expressing breast cancer patient subsets with AhR-based therapeutics is an exciting possibility for patients

with limited treatment options and recent research elucidating the role of AhR in breast cancer is summarized in Table 6. Many studies presented in this Table strongly support the role of AhR as an anti-cancer target in breast cancer.

TCDD pretreatment inhibited chemical carcinogen, 7,12-dimethylbenz[a]anthracene-induced mammary tumors in CB6F1 mice (Wang et al. 2011a). Diindolylmethane (DIM), a dietary AhR ligand also inhibited DMBA-induced mammary tumors in Sprague-Dawley rats (Chen et al. 1998). TCDD exposure reduced breast tumor metastasis to the lung and to other mammary glands in a syngeneic mouse model of breast cancer metastasis (Wang et al. 2011b). Interestingly, TCDD treatment did not influence the primary tumor growth in these mice or affect proliferation in *in vitro* assays. The data from these studies support testing of AhR targeting anti-cancer compounds independently both in vitro and in vivo studies. Most of the breast cancer deaths are due to complications in distant organ metastasis and systematic testing of different classes of AhR modulators will likely identify those that effectively inhibit metastasis.

The proton pump inhibitor omeprazole activates AhR transcription and also decreases metastasis of triple negative breast cancer cells (Jin et al. 2014). Activation of the AhR by certain agonists including omeprazole down regulated G-protein coupled receptor CXCR4, which is implicated in promotion of metastasis of breast tumors (Hall et al. 2010; Hsu et al. 2008; Hsu et al. 2007; Jin et al. 2014; Wang et al. 2011b). AhR–regulated microRNAs also have roles in breast cancer metastasis. TCDD and MCDF induced expression of miR-335 in BT474 and MDA-MD-231 cells (Zhang et al. 2012a) resulting in the inhibition of the prometastatic SOX4 gene and inhibition of lung metastasis *in vivo*. The antiestrogen raloxifene induced apoptosis in TNBC cells indicating that this compound or its analogs also have potential as AhR-targeted therapeutics for breast cancer therapy (O'Donnell et al. 2014). Focused virtual ligand screening utilizing AhR ligand binding pocket models may help to identify such compounds (Bisson et al. 2009; Perkins et al. 2014).

Cancer Stem Cells

There is also evidence that the AhR plays a role in stem cell functions and this includes an early study showing that AhR antagonists promoted the expansion of hematopoietic stem cells (Bock 2017; Boitano et al. 2010; Casado et al. 2011; Hou et al. 2013; Rentas et al. 2016; Singh et al. 2009). Cancer stem cells are often drug-resistant and are important for maintaining and expanding individual tumor types. There is also evidence that the AhR can be targeted in cancer stem cells; for example, the AhR-active pharmaceutical tranilast significantly inhibits breast cancer stem cell growth and metastasis *in vivo* using MDA-MB-231 drug-surviving cancer stem cells (Prud'homme et al. 2010). Another study characterized the Ah-responsiveness of triple negative Hs578T breast cancer-derived stem cells and showed that AhR ligands induce AhR interactions with Sox2, a regulator of self-renewal and this study clearly demonstrated a role for the AhR and its agonists as enhancers of cancer stem cells (Stanford et al. 2016b). These results differ from those observed using tranilast suggesting some cell context-dependent differences in AhR function in breast cancer stem cells, and this may be related to differential expression of the AhR, Arnt, HIF-1α and other cofactors. Cheng and coworkers (2015) investigated the effects of several

tryptophan-derived AhR ligands including 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE) and demonstrated that these compounds suppressed transcription of Oct4 in stem-like cancer cells. ITE induced an AhR-dependent decrease in Oct4, a stem cell marker, and also decreased the tumorigenicity of stem-like leukemia (U87) cancer cells. In contrast, AhR antagonists enhanced leukemia stem cell activity (Pabst et al. 2014) and this corresponded to their effects reported in hematopoietic stem cells (Boitano et al. 2010). These results and other studies (Kim et al. 2016; Tsai et al. 2015) demonstrate that the AhR and AhR-regulated genes such as Oct4 are important in cancer stem cells indicating that AhR ligands (agonists or antagonists) are a unique set of agents for targeting cancer stem cells.

Concluding Remarks:

The endogenous function of the AhR as a tumor modifier and the anti-cancer effects stimulated by distinct classes of AhR ligands with diverse pharmacology offers an opportunity to pursue AhR signaling holistically beyond TCDD-induced responses. The effects of TCDD and AhR functions have been interlinked for a long time resulting in decreased support by both major funding agencies and biotech companies for developing AhR-based cancer therapeutics. The reason for the cautionary approach to target AhR in cancers is understandable, when there are other treatment options or clearly targetable molecular pathways. However, for difficult to treat cancers and for cancers where the treatment options are very limited or non-existent, such as pancreatic, liver and hormone-independent breast and prostate cancers, the time is ripe to exploit the potential of AhR signaling to develop a new class of anti-cancer therapeutics. It is important to define the modes of AhR function that contributes to its anti-cancer actions and some common themes have emerged including regulation of cell cycle genes (Hall et al. 2010; Huang and Elferink 2005; Jin et al. 2014; Kolluri et al. 1999; Levine-Fridman et al. 2004; Zhang et al. 2009), interaction with distinct co-regulatory molecules (Barhoover et al. 2010; Huang and Elferink 2005; Kang et al. 2006; Safe et al. 2013), and non-genomic pathways that contribute to the anti-cancer activities of the AhR (Jin et al. 2015) (see summary; Fig. 3). Design and selection of AhR ligands based on a given anti-cancer mechanism of action will allow discovery of molecules with therapeutic value. There are numerous successful examples from the nuclear receptor field where therapeutics targeting the retinoid X receptor (bexarotene), ER (tamoxifen and raloxifene), AR (flutamide, enzalutamide) and glucocorticoid receptor (fluticasone) (Bambury and Scher 2015; Helsen et al. 2014; le Maire et al. 2012; McDonnell and Wardell 2010; Su et al. 2016) have been identified and used in clinical applications. It will be fascinating to see FDA approved AhR-targeted compounds added to this list and this is strongly supported by the increasing number of studies showing that ligands for this receptor target many of the hallmarks of cancer (Fig. 2) through activating/inactivating various genes and pathways (Fig. 3).

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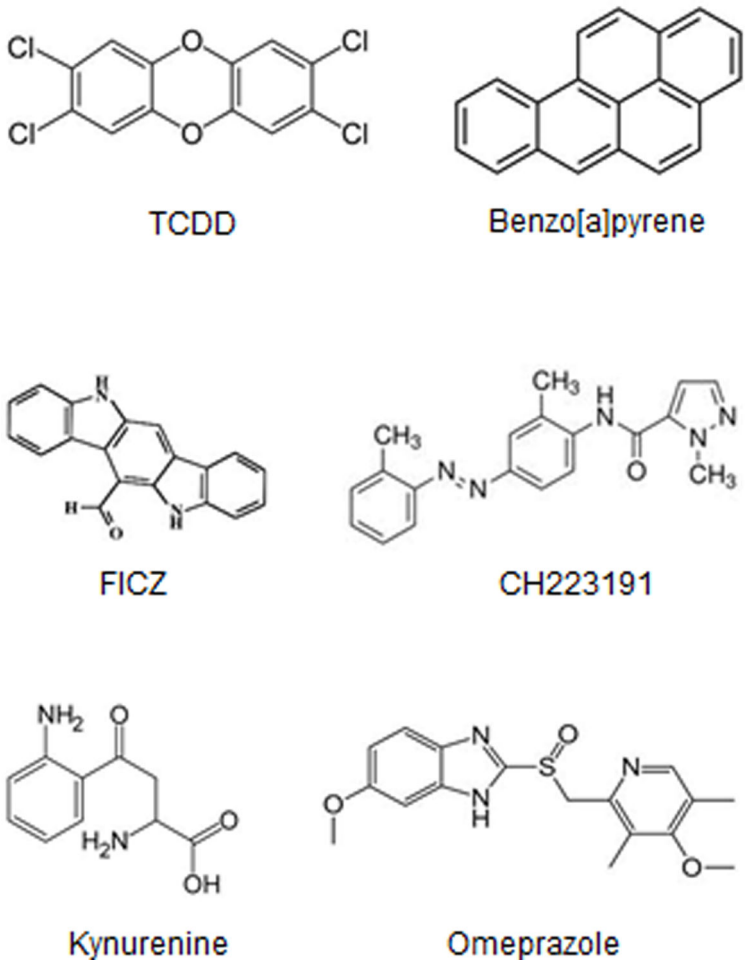

Figure 1.

AhR ligands. 2,3,7,8-TCDD and benzo[a]pyrene are classified as “toxic” AhR ligands. FICZ and kynurenine are endogenous ligands. CH223191 is an AhR antagonist and omeprazole is an AhR-active pharmaceutical.

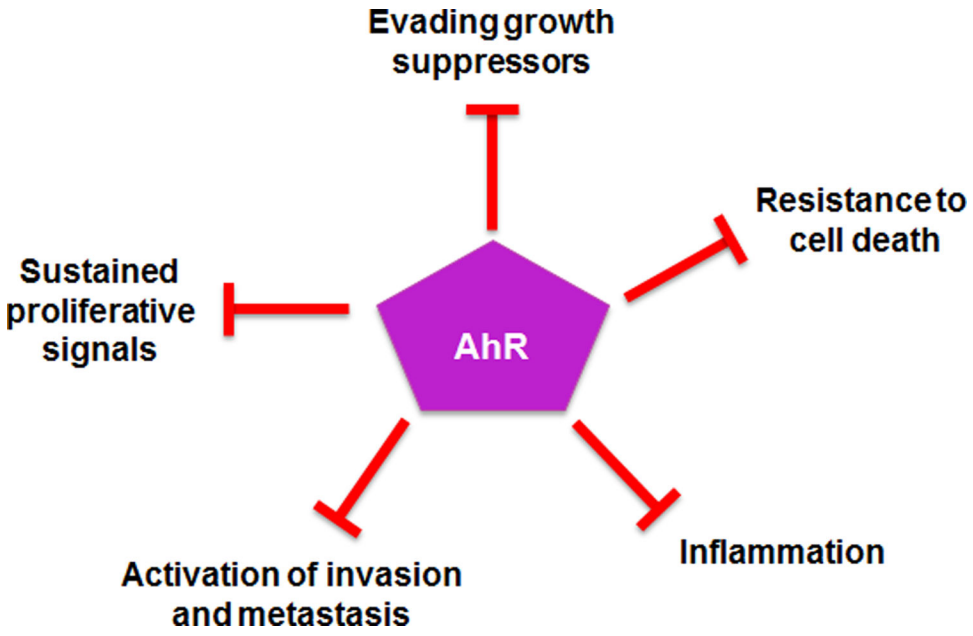

Figure 2.
Targeting the hallmarks of cancer via the AhR.

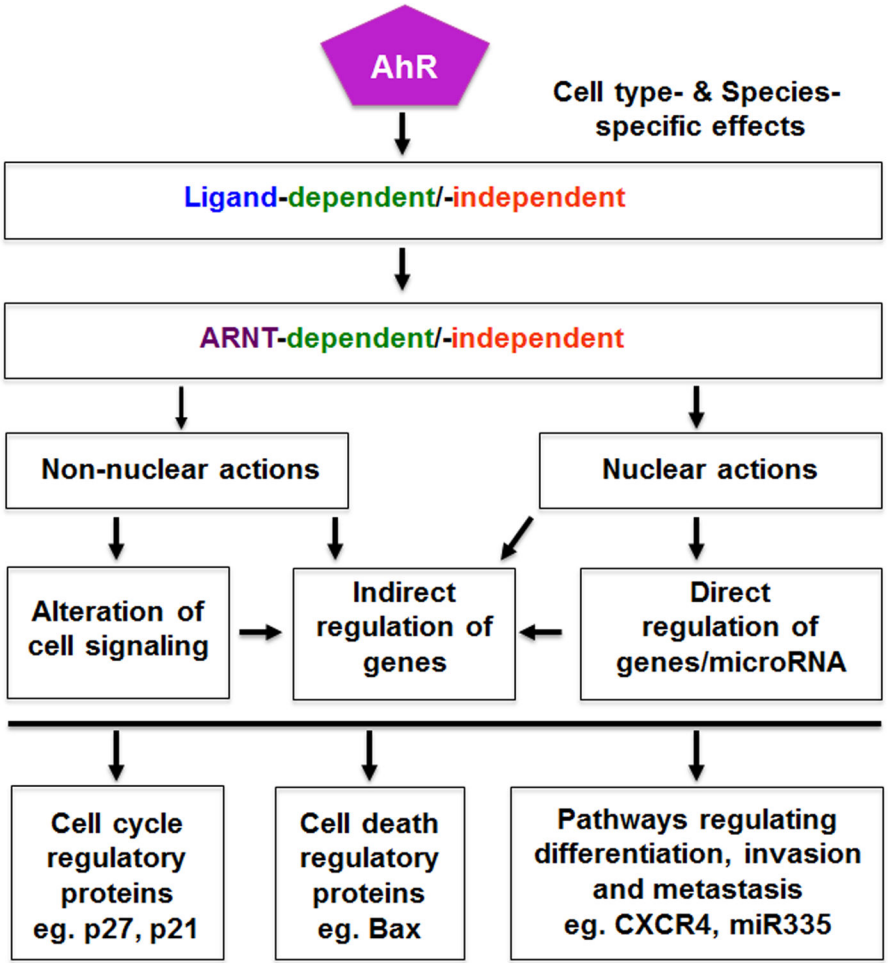

Figure 3.

A summary of the role of the AhR and its ligands (agonists or antagonists) as inhibitors of carcinogenesis.

Table 1.

Role of AhR ligands on genitourinary tumors.

Cell Line/Animal Model	Ligands/Treatment	Responses (AhR-dep)	Reference
Pancreatic			
Multiple cell lines	TCDD and alkylated PCDFs (sAhRMs)	Growth inhibition	(Koliopanus et al. 2002)
Panc1, MiaPaCa2	Omeprazole and tranilast	Inhibition of invasion	(Jin et al. 2015)
Prostate			
LNCaP	TCDD	Inhibition of DHT-induced cell proliferation/enzymes	(Barnes-Ellerbe et al. 2004)
PC3, DU145	TCDD, BaP, Soot	Enhanced MP9	(Haque et al. 2005)
LNCaP	TCDD, MCDF	Antiandrogen (transaction)	(Morrow et al. 2004)
LNCaP	TCDD	Antiandrogenic (transactivation)	(Jana et al. 1999)
	TCDD	Antiandrogenic (cell growth)	
C-42 (AR^-)	siAhR	Decreased proliferation	(Tran et al. 2013)
LNCaP	AhR expression	Decreased proliferation via β-TrCP	(Gluschnaider et al. 2010)
DU145, PC3 and PC3M (AR^-)	Caritin (flavonoid AhR ligand)	Inhibits growth *in vitro*/*in vivo*; induces apoptosis; decreases AR	(Sun et al. 2015)
LNCaP	TCDD, BaP	Gene expression changes	(Hruba et al. 2011)
TRAMP mice	$AhR^{-/-}$ cross	Decreased prostate cancer	(Fritz et al. 2007)
TRAMP mice	MCDF (SAhRM)	Decreased tumor metastasis	(Fritz et al. 2009)
TRAMP mice	TCDD	Pro- and anticarcinogenic responses	(Moore et al. 2016)
Bladder and urinary tract and kidney			
$AhR^{-/-}$ mice	AhR loss	Decreased Ugt1a1 in bladder	(Iida et al. 2010)
T27	TCDD	Increased invasion and MMPs	(Ishida et al. 2010)
	siAhR	Decreased invasion	
786-O, ACHN and 769-P renal cancer cells	Indirubin, TCDD	Increased invasion/MMPs	(Ishida et al. 2015)
	siAhR	Decreased invasion	
TK-10, Caki-1, SN12-C renal cancer	Aminoflavone	Decreased cell growth	(Callero et al. 2012)

Table 2.

Role of the AhR in neurological cancers.

Cell Line/Animal Model	Ligands/Treatment	Responses	Reference
Neurological			
Glioma cells	MC, Ch223191, siAhR/overexpression	AhR regulates growth and invasion; inhibition by antagonist/siAhR	(Gramatzki et al. 2009)
Glioma cells	Kynurenine, TCDD, siAhR/overexpression	AhR pro-oncogenic, Kyn activates growth, immune suppression	(Opitz et al. 2011)
Glioma cells, astrocytes	siAhR	AhR regulates integrin and TGFβ-induced malignancy	(Silginer et al. 2016)
Glioma patients	AhR polymorphisms	AhR polymorphisms correlate with glioma risk	(Gu et al. 2012)
Pituitary adenomas	AhR/AIP	AhR/AIP decrease correlates with increased aggressiveness	(Jaffrain-Rea et al. 2009)
Neuroblastoma SK-N-SH	AhR	AhR enhances differentiation	(Huang et al. 2011)
Medulloblastoma	siAhR/overexpression	Loss of AhR decreases proliferation	(Dever and Opanashuk 2012)
Pheochromocytoma (PC12) cells	TCDD	Induces apoptosis	(Sanchez-Martin et al. 2010)

Table 3.

Role of AhR and AhR ligands in lung, head and neck, and esophageal tumors, melanoma, and leukemia and lymphoma.

Cell Line/Animal Model	Ligands/Treatment	Responses	Reference
Lung			
A549	βNF	Induces growth	(Shimba et al. 2002)
	AhR expression	Induces growth	
Multiple	PAHs	FGF9/growth induction	(Wang et al. 2009)
H1299	BaP	Osteopontin induction	(Chuang et al. 2012)
CL1–5	Smoke particulates	AhR protects against oxidative stress	(Cheng et al. 2012)
Multiple cells	Cigarette smoke extracts	Induction of adrenomedulin	(Portal-Nunez et al. 2012)
H1355 and others	TCDD, BaP, siAhR	Decreased anchorage-independent growth (siAhR) and ROS levels (siAhR)	(Chang et al. 2007)
Head and Neck/Oral			
Multiple	TCDD, TMF	TCDD induces TMF; inhibits IL-6	(DiNatale et al. 2011)
Multiple	TMF, GNF351	AhR antagonists inhibit growth and migration/ invasion	(DiNatale et al. 2012)
Multiple	Agonist/antagonist; siAhR	Antagonists inhibit growth, invasion/migration	(Stanford et al. 2016a)
Leukemia/Lymphoma			
U937	TCDD	Cox2 induction; increased survival genes	(Vogel et al. 2007)
HL60	None	AhR downregulated Oct4	(Bunaciu and Yen 2011)
T-cell leukemia	–	AhR is expressed	(Hayashibara et al. 2003)
Multiple	–	Low AhR expression in acute lymphoblastic leukemia	(Mulero-Navarro et al. 2006)
Esophageal			
Multiple	Flavonoids	Induces ABCG2 drug resistant gene	(To et al. 2012)
Tissues/cell lines	βNF, siAhR	Suppression of invasion	(Zhang et al. 2012a)
Melanoma			
Multiple cell lines and *in vivo*	siAhR, AhR-CA	Loss of AhR enhances tumorigenicity	(Contador-Troca et al. 2013)
A375	Leflunomide	Inhibits cell proliferation	(O'Donnell et al. 2012)
A205A	TCDD	Increases MMPs and invasion	(Villano et al. 2006)
IPC-398/SK-MEL2	siAhR	Loss of AhR decreases growth	(Barretina et al. 2012)

Table 4.

Role of the Ah receptor in colon and gastric cancer.

Cell Line/Animal Model	Ligands/Treatment	Responses	Reference
Caco-2	MC	IL-1β and MMP9 induction	(Villard et al. 2007)
H508, SNU-C4	TCDD, I3C	Cell proliferation	(Xie et al. 2012)
LS174T	MC	ABCG2 induction	(Tompkins et al. 2010)
LoVo	FICZ	Cell growth inhibition	(Yin et al. 2016)
HCT116, DLD-1, SW837	Chrysin	Cell growth inhibition and apoptosis	(Ronnekleiv-Kelly et al. 2016)
$AhR^{-/-}$	–	Colonic/cecum tumors	(Kawajiri et al. 2009)
$APC^{min/+}/AhR^{-/-}$	–	Decreased time to tumors	(Kawajiri et al. 2009)
$APC^{min/+}$	I3C/DIM	Inhibition of tumorigenesis	(Kawajiri et al. 2009)
AhR^{mut}	–	Increased tumorigenesis in colitis associated tumor	(Diaz-Diaz et al. 2016)
$AhR^{+/+}$	I3C	Decreased colitis-associated tumors	(Diaz-Diaz et al. 2016)
HCT-116, DLD-1, SW837	Chrysin	Induction of apoptosis	(Ronnekleiv-Kelly et al. 2016)
$AhR^{-/-}$	–	Enhanced cecal tumors	(Ikuta et al. 2013)
$AhR^{-/-}/ASC^{-/-}$	–	Enhanced tumorigenesis	(Ikuta et al. 2013)
AGS cells	TCDD	Enhanced MMP9/invasion	(Peng et al. 2009)
SGC-7901, MKN45	siAhR	Decreased growth and MMP9, induction of apoptosis	(Yin et al. 2013)
SGC-7901	DIM	Decreased cell growth	(Yin et al. 2012)
MNK45 (xenograft)	siAhR cells	Decreased tumor weight	(Lai et al. 2014)
MNK45 (xenograft)	Biseugenol	Inhibition of EMT and AhR downregulation	(Lai et al. 2014)
CA-AhR mice	–	Increased tumorigenesis, decreased osteopontin	(Andersson et al. 2005; Kuznetsov et al. 2005)

Table 5.

Role of Ah receptor in liver cancer.

Cell Line/Animal Model	Ligands/Treatment	Response (AhR-dependent)	Reference
Humans	Exposed to high levels of TCDD	No increase in hepatic tumors	(Becker et al. 2015)
HCCLM3 human HCC cells/	ITE	Inhibition of tumor growth	(Zhao et al. 2015)
Mouse xenograft tumors/ HCCLM3 cells orthotopically transplanted into the livers of nude mice.	80 mg/kg IP 15 days of daily ip injections	AhR-dependency unknown	(Zhao et al. 2015)
HepG2	Hexachlorobenzene-induced proliferation is reversed by AhR antagonist – 4,7-o-phenantroline	AhR-dependent growth	(de Tomaso Portaz et al. 2015)
HepG2 human HCC cells; rat hepatoma cells	Flutamide	AhR-dependent growth inhibition	(Koch et al. 2015)
Multiple cell lines	Raloxifene	AhR-dependent growth inhibition	(O'Donnell et al. 2014)
HepG2 cells; Mouse and rat hepatoma cells	Raloxifene	AhR-dependent apoptosis	(O'Donnell et al. 2014)
Mouse hepatoma (Hepa-1) cells	Alternaria mycotoxins Alternariol (AMA) and alternariol methyl ether (AME) 20 – 40 μM	Inhibition of proliferation, independent of AhR Induction of apoptosis dependent on AhR	(Schreck et al. 2012)
Mice and rats	Number of ToxCast Chemicals	No clear correlation to AhR activation and hepatic lesions after treatment	(Shah et al. 2011)
WT and AhR knockout mice	Diethylnitrosamine-induced liver tumors	AhR-dependent tumor suppression	(Fan et al. 2010)
Rat hepatoma cells	TCDD	AhR-dependent cell cycle arrest	(Koch et al. 2015; Kolluri et al. 1999; Levine-Fridman et al. 2004; O'Donnell et al. 2014; Weiss et al. 1996)
Hepatoma cells	TCDD	AhR-dependent activation of p38-mitogen-activated protein kinase and induction of c-Jun	(Weiss et al. 2005)
Human HCC Huh7 cells	Curcumin	Reduction of bis(2-ethylhexyl) phthalate (DEHP) enhanced tumor growth; AhR-dependent	(Tsai et al. 2015)
Rat hepatic stem cells (rHpSCs)	TCDD (1 nM), DIM (1 and 10 μM) FICZ (10 nM)	Stimulation of colony growth	(Harrill et al. 2015)
Rat hepatoblasts (rHBs)	TCDD, DIM FICZ (1 – 100 nM)	Reduced viability No effect	(Harrill et al. 2015)
Mice Ahr$^{b1/b1}$	TCDD (10 μg/kg)	Promotion of DEN (0.1 μmol/g)-induced tumors	(Kennedy et al. 2014)
Tumor necrosis factors α and β and IL-1α and IL-1β deficient mice	TCDD (10 μg/kg)	Resistant to DEN-induced tumor promotion; Role of AhR?	(Kennedy et al. 2014)
C3H/N mice Den (90 μg/g)	PCB126 (523 μg/kg)	No significant increase in liver neoplastic lesions despite strong activation of AhR target genes	(Rignall et al. 2013)
Hepatoma 27 cells	Polycyclic aromatic hydrocarbon (PAH) and β-naphthoflavone	AhR-independent stimulation of proliferation	(Volkov et al. 2012)
Mice	TCDD (100 μg/kg); IP injection	Hepatomegaly is dependent on Arnt expression in hepatocytes	(Nukaya et al. 2010)

Cell Line/Animal Model	Ligands/Treatment	Response (AhR-dependent)	Reference
Male F344 rats	*N*-diethylnitrosamine treatment, followed by two-thirds partial hepatectomy. β-Naphthoflavone (BNF) over a period of 28 weeks	BNF increased the incidence and multiplicity of altered foci (1.7-fold and 3.3-fold) and hepatocellular adenomas (HCAs)	(Dewa et al. 2009)
B6C3F1-mice expressing constitutively active ligand binding domain deleted AhR mutant (CA-AhR)	*N*-nitrosodiethylamine (90 μg/g) at 6 weeks. Analysis after 35 weeks.	Promotion of liver cancers; Ligand-independent constitutively active AhR	(Moennikes et al. 2004)
Hepatoma cells and mice	TCDD	Increased protein myristoylation; Induction of N-myristoyltransferase 2	(Kolluri et al. 2001)

Table 6.

Role of Ah receptor in breast cancer.

Cell Line/Animal Model	Ligands/Treatment	Response (AhR-dependent)	Reference
Humans	Exposed to high levels of TCDD	No excess of breast and other gynecologic cancers	(Pesatori et al. 2009)
MDA-MB-231 cells	Raloxifene	Induction of apoptosis	(O'Donnell et al. 2014)
MCF-7 and SK-BR-3	NK150460	Induction of AhR-dependent apoptosis	(Fukasawa et al. 2015)
ZR-75-1 ER +ve breast cancer cells	20 mg/kg or 100 mg/kg oral everyday for 24 days	Inhibits AhR and Arnt-dependent growth inhibition Inhibits xenograft tumors in rats	(Fukasawa et al. 2015)
MDA-MB-468 and T47D human breast cancer/TNBC cells	2-(4-amino-3-methylphenyl)-5-fluorobenzothiazole (5F 203)	Activation of AhR and DNA damage in cancer cells, but not in nontumorigenic MCF-10A breast epithelial cells.	(McLean et al. 2015)
MDA-MB-231 and T47D cells	TCDD (10 nM; 25 μg/kg/d for 10 days) and 3,3′-diindolylmethane (DIM; 25 μM; 50 mg/kg/d for 10 days)	Induction of miR-212/132 involved in inhibition of cell migration and invasion.	(Hanieh 2015)
TNBC cells	shRNA	Suppression of AhR led to increased cellular sensitivity to anoikis, and reduced proliferation, migration, and invasion	(D'Amato et al. 2015)
Breast cancer patient tissues		AhR expression is detectable in ductal carcinoma in situ, invasive ductal carcinoma and invasive lobular carcinoma	(Li et al. 2014)
MDA-MB-468 and Cal51 human breast cancer cells	Aminoflavone	Activates AhR transcription, but growth inhibitory effects are independent of AhR	(Brinkman et al. 2014)
MCF-7, MDA-MB-231	Omeprazole 200 μM	Inhibited cell invasion in vitro	(Jin et al. 2014)
MDA-MB-231 cells in nude mice	Omeprazole 100 mg/kg/day for four weeks	Inhibited lung metastasis in vivo	(Jin et al. 2014)
TNBC BP1	CB7993113	AhR antagonist; decrease in *in vitro* invasion	(Parks et al. 2014)
MCF-7	Insulin like growth factor-2	IGF-2-induced proliferation was AhR-dependent	(Tomblin and Salisbury 2014)
MDA-MB-231	A stable clone expressing AhR ShRNA	Suppression of AhR reduced tumorigenicity	(Goode et al. 2013)
MDA-MB-231 and BT474	TCDD (10 nM) and MCDF (5 μM)	Induction of anti-metastatic miR-335	(Zhang et al. 2012b)
MDA-MB-231	MCDF (40 mg/kg/d)	Inhibition of lung metastasis	(Zhang et al. 2012b)
CB6F1 mice (Balb/c × C57Bl/6)	Administration of TCDD 10 μg/kg for three weeks prior to treatment with DMBA 1 mg/mouse/wk for six weeks	Inhibition of tumor growth in mice	(Wang et al. 2011a)
	Weekly doses of TCDD 10 μg/kg	Prior AhR activation decreases susceptibility to DMBA-induced mammary tumorigenesis	(Wang et al. 2011a)
Balb/c mice injected with syngeneic 4T1.2 mammary tumor cells into mammary gland	Gavaged weekly with TCDD (5 μg/kg)	No effect on primary tumor growth. TCDD treatment significantly suppressed lung metastasis and spread to other mammary glands. TCDD had no effect on proliferation, migration,	(Wang et al. 2011b)

Cell Line/Animal Model	Ligands/Treatment	Response (AhR-dependent)	Reference
		or colony formation in vitro on 4T1.2 cells	
Human TNBC cells (MDA-MB-453, HCC-38, MDA-MB-157, BT-474, MDA-MB-435)	TCDD, PCDD, PCDF, TCDF, PCB	AhR-dependent growth inhibition	(Zhang et al. 2009)
SKBR3, MCF-7, MDA-MB-231	TCDD, TCBDF, DIM	Inhibition of invasiveness *in vitro* Inhibition of soft-agar colony formation	(Hall et al. 2010)
SUM149 human inflammatory breast cancer cell line	Kynurenine (100 μM) xanthurenic acid (50, 100 μM)	Increased migration	(Stanford et al. 2016b)