



HAL
open science

Environmental exposure and the role of AhR in the tumor microenvironment of breast cancer

Colleen Sweeney, Gwendal Lazennec, Christoph Vogel

► **To cite this version:**

Colleen Sweeney, Gwendal Lazennec, Christoph Vogel. Environmental exposure and the role of AhR in the tumor microenvironment of breast cancer. *Frontiers in Pharmacology*, 2022, 13, pp.1095289. 10.3389/fphar.2022.1095289 . hal-03918758

HAL Id: hal-03918758

<https://hal.science/hal-03918758v1>

Submitted on 18 Oct 2023

HAL is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

1 Environmental exposure and the role of AhR in the tumor microenvironment of breast cancer

2 Colleen Sweeney¹, Gwendal Lazennec^{2*}, Christoph F.A. Vogel^{3,4*}

3 ¹Department of Biochemistry & Molecular Medicine, University of California Davis, School of
4 Medicine, Sacramento, CA, 95817, USA

5 ² CNRS, SYS2DIAG-ALCEN, Cap delta, 1682 rue de la Valsière, Montpellier, France

6 ³ Center for Health and the Environment, University of California Davis, One Shields Avenue, Davis,
7 CA 95616, USA

8 ⁴ Department of Environmental Toxicology, University of California Davis, One Shields Avenue,
9 Davis, CA 95616, USA

10 * Correspondence:

11 Corresponding Author: Christoph F.A. Vogel
12 cfvogel@ucdavis.edu

13 **Keywords: AhR₁, Breast Cancer₂, Air Pollution₃, Particulate Matter₄, Health Disparities₅,**
14 **Environmental Injustice₆**

15 Abstract

16 Activation of the aryl hydrocarbon receptor (AhR) through environmental exposure to chemicals
17 including polycyclic aromatic hydrocarbons (PAHs) and polychlorinated dibenzo-p-dioxins (PCDDs)
18 can lead to severe adverse health effects and increase the risk of breast cancer. This review considers
19 several mechanisms which link the tumor promoting effects of environmental pollutants with the AhR
20 signaling pathway, contributing to the development and progression of breast cancer. We explore
21 AhR's function in shaping the tumor microenvironment, modifying immune tolerance, and regulating
22 cancer stemness, driving breast cancer chemoresistance and metastasis. The complexity of AhR, with
23 evidence for both oncogenic and tumor suppressor roles is discussed. We propose that AhR functions
24 as a “molecular bridge”, linking disproportionate toxin exposure and policies which underlie
25 environmental injustice with tumor cell behaviors which drive poor patient outcomes.

26 1 Introduction – *Environmental Exposure and Breast Cancer*

27 Air pollution and occupational exposure studies have reported positive associations with the risk of
28 developing breast cancer (Amadou et al., 2021). Air pollution and ambient particulate matter (PM)
29 contain a complex mixture of compounds, including polycyclic aromatic hydrocarbons (PAHs) and
30 various metals (e.g. iron, nickel, copper), which may induce reactive oxygen species (ROS) and
31 inflammation (Rückerl et al., 2007, Grunig et al., 2014) and stimulate the progression of breast
32 cancer (Romaniuk et al. 2017). PAHs are generated during combustion processes and derive from
33 various sources such as indoor fireplaces, wildfires, industrial activities, and vehicular traffic and the
34 exposure to PAHs has been identified as a risk factor for breast cancer (Lichtiger et al., 2021,
35 Gamboa-Loira et al., 2022). Importantly, a stronger association of breast cancer risk was found with
36 traffic related air pollution (TRAP) and higher PAH exposure intensity and duration of exposure (Lee
37 et al. 2019, Large and Wei 2017, Mordukhovich et al. 2016, Nie et al. 2007, Shen et al. 2017, Brody
38 et al. 2007). Vehicular traffic is a major ambient source of PAH exposure and the PAH
39 benzo[a]pyrene (BaP) is classified as a human carcinogen by the International Agency for Research

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

40 on Cancer (IARC, 2010). Furthermore, BaP and other PAHs have been identified as ligands of the
41 aryl hydrocarbon receptor (AhR), a ligand-activated transcription factor, belonging to the bHLH-PAS
42 family, which regulates multiple target genes and is best known for its role as a xenobiotic receptor
43 (Boonen et al. 2020, Vogel et al. 2020). The activation of the AhR signaling pathway via
44 environmental pollutants including dioxins and PAHs has been associated with the development of
45 breast cancer (Narasimhan et al. 2018, Kolluri et al. 2017, Murray et al 2014, Warner et al. 2011,
46 Birnbaum and Fenton 2003, La Merrill et al. 2010, Donovan et al. 2018, Gearhart-Serna et al. 2020).
47 Reports from our team and other groups suggest an important role of AhR as an immune-modulator
48 and mediator of toxic responses triggered by particulate matter (PM) derived from TRAP (O'Driscoll
49 et al. 2013, O'Driscoll et al. 2018, Castaneda et al. 2018, Yuan et al. 2020).

50 Recent studies confirmed an increased risk of breast cancer with vehicular-specific PM exposure
51 among African American and Japanese American women living near major roads, highlighting the
52 link between environmental injustice and health disparities (Niehoof et al. 2020, Cheng et al. 2019).
53 Indeed, residential proximity to major roadways is a recognized risk factor beyond breast cancer, in
54 cardiovascular disease (Kulick et al. 2018, Kirwa et. al 2014, Kingsley et. al 2015, Hart et. al 2014)
55 and renal disease (Lue et. al 2013). Further, it disproportionately impacts racial and ethnic
56 minoritized groups and those of lower socioeconomic status, the legacy of the widespread practice of
57 redlining in the United States (Hwa Jung et. al 2022, Swope et. al 2022). While the Fair Housing Act
58 of 1968 prohibited racial discrimination in housing and lending, exclusionary zoning and other
59 practices such as gentrification has perpetuated residential segregation
60 ([https://www.brookings.edu/research/neighborhood-segregation-persists-for-black-latino-or-hispanic-
61 and-asian-americans/](https://www.brookings.edu/research/neighborhood-segregation-persists-for-black-latino-or-hispanic-and-asian-americans/)). In a study of Hillsborough County in Florida, Stuart et al found that blacks,
62 Hispanics, and people living below the poverty line are much more likely to reside close to sources of
63 air pollution but further from air quality monitoring sites while whites were found to live closer to
64 monitoring sites but significantly further from pollution sources (Stuart et. al 2009). Wu et al found
65 that particulate matter (PM) collected near a major Los Angeles freeway (compared to an urban
66 background location) induced significantly higher production of the cytokines IL-6, IL-8, and TNF- α ,
67 (Wu et. al 2014), suggesting a link between AhR activation, AhR-driven inflammation (Vogel et. al
68 2011, Wu et. al 2021, Vacher et. al 2018) and proximity to pollution. The interaction between
69 environmental exposure, socio-economic related stress and psychosocial stress in under-resourced
70 neighborhoods has been termed the environmental “riskscape” by Morello-Frosch et al (Morello-
71 Frosch & Shenassa, 2006, Morello-Frosch & Lopez, 2006). As noted by Morello-Frosch, the
72 Institute of Medicine recognizes this as a type of “double jeopardy” in which elevated stress impairs
73 the ability of individuals living in under-resourced neighborhoods to endure the myriad health
74 consequences of chronic environmental exposures ([https://www.scientificamerican.com/article/end-
75 double-jeopardy/#](https://www.scientificamerican.com/article/end-double-jeopardy/#)).

76

77 2 Role of AhR in Breast Cancer

78 Approximately two decades ago, AhR was found to be overexpressed in mammary cancer in rats
79 (Trombino et al. 2000) sparking curiosity as to its role in breast cancer progression. Several studies
80 have since shown that chemical exposure and AhR activation affect processes of mammary gland
81 differentiation, disrupting pregnancy-related differentiation and milk production, and increasing the
82 risk of breast cancer (Warner et. al 2002, Vorderstrasse et al. 2004, Lew et al. 2011, Belton et al.
83 2018, Kay et al. 2022). Further studies have elucidated AhR’s molecular contribution to carcinogenic
84 progression and ratified the oncogenic role of AhR in breast cancer cells (Wang et al. 2017, Wang et

85 al. 2020). In support of its role as a breast cancer oncogene, AhR activation is sufficient to transform
86 human mammary epithelial cells and promote their migration, invasion and epithelial-to-
87 mesenchymal transition (EMT) (Brooks and Eltom 2011). Work from our group showed that chronic
88 exposure of MCF10AT1 and MCF-7 cells to estradiol (E2) resulted in AhR overexpression and
89 downregulation of estrogen receptor alpha (ER α) and progesterone receptor (Zou et al. 2003, Wong
90 et al. 2009) accompanied by increased proliferation, invasion, and apoptosis resistance. The
91 resistance to apoptosis was also demonstrated in human breast cancer cell lines treated with the
92 prototypical AhR ligand TCDD when apoptosis was induced by chemotherapeutics (doxorubicin,
93 lapatinib and paclitaxel) (Bekki et al. 2015). Treatment with PAH mixtures which bind to and
94 activate AhR also increased cell proliferation and expression of antiapoptotic proteins in MCF-7 cells
95 via AhR signaling (Gearhart-Serna et al. 2020).

96 Several studies have reported AhR overexpression in human breast cancer (Li et al. 2014, D'Amato
97 et al. 2015, Vacher et al. 2018). Using samples from breast cancer patients, we found that AhR is
98 frequently over-expressed in ER-negative human breast tumors, and this is closely correlated with
99 elevated expression of the NF- κ B subunit RelB and inflammatory markers such as IL-8 (CXCL1 in
100 mouse) and COX-2 (Vogel et al. 2011). This was also observed by Vacher et al. with significant
101 overexpression of cytokines, including IL-8, in AhR high expressing tumors (Vacher et al. 2018). We
102 demonstrated that C/EBP β serves as a key transactivator for AhR-mediated COX-2 gene induction
103 (Vogel et al. 2000, Vogel et al. 2004). Interestingly, COX-2, CXCL1, and IL-8 have been identified
104 as critical genes that mediate breast cancer invasion and metastasis to lung and lymph nodes (Freund
105 et. al 2003, Minn et al. 2005, Ahmed et al. 2021). A recent report suggests that inhibition of COX-2
106 expression reduces mammary tumor multiplicity and size in the polyoma middle T antigen (PyMT)
107 mouse model (Esbona et al. 2016). In our recent study we demonstrated that overexpression of AhRR
108 (Aryl Hydrocarbon Receptor Repressor) suppresses AhR-driven (TCDD-stimulated) growth of
109 syngeneic mammary tumors as well the onset, growth and metastasis of spontaneous mammary
110 tumors in PyMT mice (Vogel et al. 2021). In human breast cancer, high expression of AhRR, the
111 dedicated AhR repressor, independently predicts prolonged metastasis-free survival (Vacher et al.
112 2018), in agreement with our findings in PyMT mice (Vogel et al. 2021). Interestingly, knockdown
113 of AhRR in normal human mammary epithelial cells resulted in anchorage-independent cell growth
114 suggesting that the AhRR may function as a tumor suppressor gene (Zudaire et al. 2008).

115 In a mouse model of BRCA1-associated breast cancer, AhR was found to transcriptionally induce the
116 EGF receptor ligand, Amphiregulin, driving tumor growth and macrophage infiltration. Of note, this
117 was inhibited by the combination of an AhR inhibitor and an EGF receptor inhibitor, suggesting new
118 therapeutic possibilities for this type of breast cancer (Kubli et. al 2019). The relationship between
119 AhR activation and breast cancer-related death was recently assessed using an artificial intelligence
120 tool to analyze the scientific literature, with strong evidence that AhR activation is an adverse
121 outcome pathway in breast cancer (Benoit et al. 2022).

122 Interestingly, many studies have also provided evidence for a tumor suppressor role for AhR, with
123 evidence that AhR can inhibit tumor growth (Fritz et al. 2007, Feng et al. 2020, Jin et al. 2014) while
124 inhibition of AhR or AhR deficiency promotes tumor development (Abdelrahim et al. 2003, Safe et
125 al. 2017). For example, in the ApcS580/+; KrasG12D/+ mouse model of colon tumorigenesis,
126 intestinal epithelial specific AhR knockout promoted tumorigenesis through enhanced Wnt signaling
127 (Han et. al 2021). In p53 deficient mice, AhR knockout significantly increased incidence of thymic
128 lymphomas and sarcomas and decreased survival (Phillips et. al 2022). In a mouse model of sonic
129 hedgehog type-medulloblastoma, AhR deletion in cerebellar granule cell progenitors accelerated
130 tumorigenesis through increased TGF β -SMAD3 signaling (Sarić et. al 2020) with high AhRR

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

131 expression linked to decreased patient survival. Further, in an unbiased functional genomics screen,
132 AhR was identified as metastasis suppressor in a lung cancer model (Nothdurft et. al 2020). In in
133 vitro studies, AhR was demonstrated to cooperate with the Rb tumor suppressor to prevent S-phase
134 cell cycle entry (Puja et al. 2000) while activation of AhR by the prototypical ligand TCDD inhibited
135 the growth of MCF7 breast cancer cells (Vogel and Abel 1995). David Sherr's team investigated
136 AhR agonists and antagonists in a direct comparison and concluded that the sustained activation of
137 AhR drives the later, more lethal stages of some cancers, but that AhR agonists under some
138 circumstances can counteract tumor development and may also serve as cancer therapeutics
139 (Narasimhan et al. 2018). In this vein, O'Donnell (O'Donnell et. al 2021) and others (Rowland et. al
140 2019) have pursued SMAhRTs, Select Modulators of AhR-regulated Transcription, to specifically
141 exploit the anti-cancer functions of AhR. Notably, they identified a modulator which induced AhR-
142 dependent Fas ligand expression and breast and liver tumor cell apoptosis without increasing
143 expression of the prototypical AhR target gene, CYP1A1, suggesting that AhR transcriptional
144 activity can be fine-tuned, to specifically unlock its function as a tumor suppressor.

145 3 Cytokines and Chemokines in Breast Cancer and the Tumor Microenvironment

146 The tumor microenvironment (TME) corresponds to the fact that tumor cells are surrounded in close
147 proximity by a number of non - cancerous cells including cancer associated fibroblasts (CAFs),
148 mesenchymal stem cells (MSCs), adipocytes, myeloid derived suppressor cells (MDSCs), tumor
149 associated macrophages (TAMs), tumor associated neutrophils (TANs), tumor infiltrating
150 lymphocytes (TILs), and endothelial cells (Binnewies et al. 2018, Joyce and Pollard 2009, Lazennec
151 and Lam 2016) . In addition to direct contact with tumor cells, TME cells will interact with tumor
152 cells though a number of different soluble factors including cytokines and chemokines, which will
153 reshape TME to support cancer initiation, progression, and metastasis (Ali and Lazennec 2007,
154 Mancini et al. 2021, Lazennec and Richmond 2010) (Fig. 1).

155 In breast cancer, many chemokines and cytokines have been analyzed and identified as important
156 factors contributing to the development of breast tumors (Masih et al. 2022, Narita et al. 2016). In
157 particular the CXCR4/CXCL12 axes has been reported to control breast cancer metastasis and the
158 involvement of CAFs (Muller et al. 2001, Orimo et al. 2005). The CAF-driven CXCR4/CXCL12 axis
159 may also stimulate the accumulation of protumorigenic lipid associated macrophages which supports
160 an immunosuppressive microenvironment in breast cancer (Timperi et al. 2022).

161 CCL2 and CCL5 have also retained attention in breast cancer, as they are expressed by cancer cells
162 and promote the recruitment of TAMs and metastasis by inducing Th2 polarization of CD4+ T cells
163 (Brunner et al. 2018, Zhang et al. 2015, Soria and Ben-Baruch 2008, Chavey et al. 2007). In
164 addition, the ligands of CXCR2 (CXCL1, 2, 3, 5, 6, 7, 8) have been shown in a number of studies to
165 be involved in the aggressiveness of triple negative breast cancers (TNBC) (Chavey et al. 2007,
166 Bieche et al. 2007, Acharyya et al. 2012). The genes of these chemokines are encoded by a small
167 region of chromosome 4q21 and have been found to be coregulated in TNBC (Bieche et al. 2007).
168 Moreover, cancer cells expressing high levels of CXCL1 and CXCL2 acquire an advantage in terms
169 of survival in metastatic sites and favor the recruitment of TANs (Acharyya et al. 2012).
170 Interestingly, CXCR2 itself is also playing a major role in the aggressiveness of TNBC, in particular
171 through its expression on TANs (Boissiere-Michot et al. 2020, Boissiere-Michot et al. 2021).
172 Although the levels of CXCR2-expressing neutrophils is correlated to high grade breast cancers, its
173 role is rather to counteract tumor progression (Boissiere-Michot et al. 2021), as it is correlated with a
174 better survival of the patients and its deletion favors tumor growth and metastasis (Timaxian et al.
175 2021). There are many links between AhR and CXCR ligands in particular. For instance, we have

176 shown that the complex of AhR and NFkB RelB was able to bind to a specific binding elements of
177 chemokines including the CXCL8 promoter and to promote its activation through protein kinase A
178 (Vogel et al. 2007). RelB/AhR complex is also involved in the overexpression of CXCL8 in breast
179 cancer (Vogel et al. 2011, Bekki et al. 2015). A significant elevated level of CXCL8 mRNAs
180 expression (56-fold) has also been found in tissue samples of high stage compared to low stage
181 patients and adipose-derived stem cells (Razmkhah et al. 2010). AhR may also interact with NFkB
182 RelA causing the upregulation of c-myc and stimulation of tumorigenesis in MCF-7 cells (Kim et al.
183 2000). Further HER2 overexpression in MCF-7 cells resulted in pro-inflammatory signaling and
184 induction of IL-6 enhancing mammosphere formation in an AhR-dependent manner (Zhao et al.
185 2013). The role of AhR as a mediator of chronic inflammation in breast cancer has been recently
186 reviewed elsewhere (Guarnieri 2020). Moreover, a recent study by Kubli et al. has shown that AhR
187 was induced by reactive oxygen species (ROS) in mammary epithelial cells, which in turn enhance
188 AREG (amphiregulin) production (Kubli et al. 2019). In basal-like and BRCA1-related breast
189 cancers, ROS expression was correlated with AhR levels and the expression of the chemokines
190 CXCL1, CXCL2 and CCL5. Targeting AhR or AREG reduced the recruitment of macrophages in
191 tumors in mouse models and AREG expression was associated with the density of macrophages in
192 human tumors. Another cytokine upregulated by AhR activation is IL-22 which is an important
193 factor controlling host defense and gut immunity. However, dysregulation of IL-22 may contribute to
194 the development of TNBC and the pathology in breast cancer (Katara et al. 2020, Wang et al. 2018,
195 Kim et al. 2014, Voigt et al. 2017). IL-22 has also been described to mediate macrophage infiltration
196 in the TME and the migration of breast cancer cells (Kim et al. 2020). Results from MCF-7 cells co-
197 cultured with preadipocytes and an in vivo zebrafish model showed that prototypical AhR ligand
198 TCDD enhanced the invasive and metastatic potential of MCF-7 cells implicating the importance of
199 AhR in the TME (Koual et al. 2021).

200 **4 AhR as a Critical Player in the Tumor Microenvironment of Breast Cancer**

201 The development of metastatic disease, which accounts for greater than 90% of cancer mortality,
202 requires collaboration between tumor cells and their environment. Recent studies reveal that the TME
203 possesses remarkable cellular heterogeneity with an important role of immune cells in the
204 development and progression of breast cancer (Place et al. 2011, Ben-Baruch 2002). The TME also
205 consists of an acellular component (e.g., soluble cytokines, chemokines, and growth factors), that
206 forms part of the stromal structure as described above. TAMs and MDSCs are tumor-associated
207 myeloid cells (TAMCs) and have been identified as key players in breast cancer progression and
208 metastasis (Cha and Koo 2020). MDSCs are myeloid cells at earlier stages of differentiation and
209 serve as precursor of TAMs (Coffelt et al. 2009). Their presence and frequency have been directly
210 correlated with tumor aggressiveness and is associated with poor survival rates in breast cancer
211 (Zhang et al. 2012, Zhao et al. 2017, Mukhtar et al. 2011a, Mahmoud et al. 2012, Leek et al. 1996,
212 Qiu et al. 2018). They have been found to drive cancer progression via immune regulatory functions
213 creating a tolerogenic environment allowing the tumor to progress (Fig. 1). TAMCs inhibit tumor
214 immune responses by blocking T cell functions and proliferation, but they also directly trigger tumor
215 growth by promoting cancer stemness, angiogenesis, EMT and metastasis formation. In breast cancer
216 patients, levels of MDSCs in peripheral blood were found to be about 10-fold higher compared to
217 healthy control individuals (Safarzadeh et al. 2019). Moreover, they found a direct relationship
218 between MDSC levels and tumor stage of breast cancer patients. The study underlines the importance
219 of MDSCs in tumor progression and invasion which was supported by Diaz-Montero et al. (Diaz-
220 Montero et al. 2009) showing that MDSC levels are associated with the clinical stage and metastatic
221 disease burden in patients with breast cancer. MDSCs possess strong immunosuppressive activities
222 and interact with other immune cells to regulate their functions. The number and abundance of TAMs

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

223 and MDSCs is considered to be an important factor in the clinical success of cancer immunotherapy,
224 underlining their critical role in suppression of immunity in breast cancer patients (Gnant et al. 2011,
225 Gomez-Roca et al. 2015).

226 AhR plays a critical role in carcinogenesis and tumor immunity (Murray et al. 2014, Xue et al. 2018).
227 Activation of AhR via Kynurenine (Kyn) produced by the immunosuppressive enzyme indoleamine
228 2, 3-dioxygenase (IDO) in glioblastoma cells has been found to induce the accumulation of TAMs
229 (Takenaka et al. 2019, McKay et al. 2021). They reported that the AhR ligand Kyn is able to activate
230 AhR in TAMs, leading to an increased expression of the chemokine receptor CCR2 by TAMs, which
231 enhances the recruitment of TAMs in response to CCL2. Moreover, AhR stimulates the production of
232 the exonucleotidase CD39 by TAMs, interfering with the function of cytotoxic CD8+ T cells
233 (Takenaka et al. 2019). In melanoma patients, high levels of IDO1 are associated with high levels of
234 Kyn and immunosuppression (Campesato et al. 2020). Using a melanoma model, it was shown that
235 tumors expressing high levels of IDO1 present an enrichment of TAMs and selective inhibition of
236 AhR decreases tumor progression, by inhibiting the immunosuppression mediated by IDO1. Another
237 link of AhR with immune response in cancer is highlighted by the fact that AhR mediates the
238 induction of the poliovirus receptor CD155 by IL-4 and LPS in macrophages, as CD155 is
239 suppressing T cell function (McKay et al. 2021). In the same line, the inhibition of AhR activity in a
240 model of pancreatic cancer promotes the infiltration of CD8+ T cells and improves the response to
241 immune therapy (Hezaveh et al. 2022). This study also showed that AhR is highly expressed in
242 TAMs, involved in their polarization, and associated with a reduction of iNOS, CCL4, and TNF α
243 levels. Further, Neamah et al. (Neamah et al. 2019) found that treatment with the AhR ligand TCDD
244 induces the accumulation of MDSCs in the peritoneal cavity. Interestingly, we found an
245 accumulation of CD11b+ F4/80+ and CD11b+ F4/80- Ly6G+ cell subsets in adipose tissue
246 associated with a significant increase of the chemokine CXCL5 in TCDD-treated mice (Vogel et al.
247 2016) which indicates accumulation of TAMs and MDSCs (Ugel et al. 2015). Although TAMs and
248 MDSCs are regarded as separate populations, some markers including CD11b are shared among
249 TAMs and MDSCs (Ugel et al. 2015). There are specific markers (e.g. Ly6G and Ly6C) that can be
250 used to distinguish them. Further, MDSCs and TANs express high levels of S100A9 and the
251 immunosuppressive enzymes IDO and arginase 1 (Arg1) which are specific for their immune-
252 suppressive activity in TME of breast cancer (Fridlender et. al 2009, Ostrand-Rosenberg 2016).

253 The polarization of TAMs and MDSCs within the TME is highly dependent on the local milieu of
254 immune regulatory factors (e.g. C/EBP β and S100A9) and cytokines and chemokines which can
255 originate from stromal cells (Fig 1). Recently, we identified C/EBP β as a critical transcription factor
256 in AhR-dependent induction of S100A9 after treatment with PM rich in PAHs (Dahlem et al. 2020).
257 The S100 calcium binding protein S100A9 has been shown to play a critical role in mediating the
258 expansion of MDSCs in breast cancer models (Zhao et al. 2012). Moreover, S100A9 can act as a
259 transcriptional coactivator during breast cancer development (Song and Struhl 2021) and promotes
260 the immune-suppressive activity of MDSCs (Ostrand-Rosenberg 2016). Regardless of any direct
261 lineage link and distinction between MDSCs, TANs and TAMs, the most important criteria for their
262 role in carcinogenesis are their immune-suppressive and pro-tumoral activities. Importantly, the AhR
263 has been demonstrated to regulate the expression of immune-regulatory markers including Arg1,
264 IDO, IL-10, COX-2, C/EBP β , and S100A9 (Neamah et al. 2019, Vogel et al. 2008, Vogel et al. 2013,
265 Dahlem et al. 2020, Benson and Shepherd 2011, Simones and Shepherd 2011, Bankoti et al. 2010),
266 which are critical factors in the pathogenesis of breast cancer (Dey et al. 2021, Yu et al. 2014, Yu et
267 al. 2013). Moreover, TCDD increased the activity of the immunosuppressive enzyme IDO which
268 mediates tumor immunity in breast cancer cells (Bekki et al. 2015). Interestingly, AhR as well as
269 NF κ B RelB have been shown to induce IDO expression (Vogel et al. 2008, Yu et al. 2014), which is

270 also critically involved in the immunosuppressive mechanisms of myeloid-derived suppressor cells
271 (MDSCs) in breast cancer (Yu et al. 2013). The number and frequency of TAMs and MDSCs have
272 been directly correlated with tumor aggressiveness, and indirectly correlated with clinical outcome in
273 breast cancer (Mukhtar et al. 2011b). The literature also shows that accumulation of TAMCs is a
274 significant prognostic factor in breast cancer (Zhao et al. 2017). A significant heterogeneity of
275 TAMCs in mammary tumors has been described (Movahedi et al. 2010) and the activation of AhR
276 has been shown to activate TAMs (Takenaka et al. 2019) and induce the accumulation of MDSCs
277 (Neamah et al. 2019). The mechanisms that are driving the polarization of immune-suppressive
278 TAMCs in the TME by AhR signaling activated through the exposure to PM, PAHs, and dioxin like
279 chemicals are not clear yet. In summary, data from the literature strongly suggest AhR's critical role
280 in the microenvironment of mammary tumorigenesis promoting tumor progression and metastasis.

281 **5 The Intersection Between Environmental Exposure and Cancer Stemness**

282 Breast cancer stem cells (BCSCs), a small but highly plastic subpopulation of tumor cells, have taken
283 center stage in the interplay between chemoresistance, recurrence, and metastasis (Shan et al. 2021).
284 BCSCs, capable of both self-renewal and recapitulation of tumor heterogeneity, are multidrug-
285 resistant (MDR) and highly immune-evasive. MDR is due in part to robust expression of the ABCG2
286 efflux protein, also known as Breast Cancer Resistance Protein (BCRP) (Zhou et al. 2001, Zattoni et.
287 al. 2022), a direct transcriptional target of AhR (Tan et al. 2010). Substantial efforts have focused on
288 strategies which will lead to the effective elimination of BCSCs, however it is recognized that
289 standard endocrine and chemotherapy regimens paradoxically enrich for BCSCs with mesenchymal
290 features, driving tumor recurrence (Li et al. 2008, Creighton et al. 2009, Famta et al. 2022).

291 AhR has been implicated in cancer stemness and immune evasion in various tumor types serving as a
292 "molecular bridge" between environmental exposure and poor patient prognosis. In lung and
293 nasopharyngeal carcinoma cells, AhR was shown to drive the expression of a panel of stemness
294 genes, including ABCG2 (Yan et al. 2018). Interestingly, ABCG2 has been directly implicated in
295 expanding the stem population in osteosarcoma cells (Zhou et al. 2001). In non-small cell lung
296 carcinoma, the deubiquitinase UCHL3 promoted cancer stemness through stabilization of AhR
297 (Ouyang et al. 2020). Recently, activation of AhR by the endogenous ligand kynurenine was linked
298 to colon cancer stemness, immune evasion through PD-L1 induction and metastasis (Miyazaki et al.
299 2022). In an oral squamous cell carcinoma model, tumor cell- and immune cell-expressed AhR
300 collaborated to promote tumor immune evasion with AhR knockout in tumor cells restoring anti-
301 tumor immunity (Kenison et al. 2021).

302 In breast cancer, tranilast, a tryptophan metabolite and AhR agonist, was shown to inhibit the BCSC
303 population in MDA-MB-231 (triple negative) breast cancer cells and abrogate metastasis in a tail
304 vein injection model (Prud'homme et al. 2010), in an AhR dependent manner. In agreement with
305 these findings, several studies reported that AhR activation inhibits the BCSC population (Yamashita
306 et al. 2021, Saito et al. 2021). In MCF7 (ER+) cells expressing a constitutively active AhR or treated
307 with the AhR agonists 3-Methylcholanthrene (3MC) or β -naphthoflavone (β -NF), the BCSC
308 population was decreased (Zhao, S. et al. 2012). Most recently, camalexin, an indole phytoalexin
309 and AhR agonist was shown to decrease the BCSC population of MCF7 and T47D (ER+) breast
310 cancer cells (Yamashita et al. 2022). Conversely, AhR activation by the potent agonists TCDD and
311 DMBA was found to increase the breast cancer stem cell population and was implicated in
312 doxorubicin resistance of MCF-7 breast cancer cells (Al-Dhfyhan et al. 2017). In Tamoxifen-resistant
313 MCF7 cells, AhR antagonism inhibited the BCSC population and also inhibited tumor growth
314 (Dubrovskaya et al. 2012). In Hs578T (triple negative) and SUM149 (inflammatory) breast cancer

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

315 cells, AhR was shown to augment the BCSC population, and its inhibition decreased tumor growth
316 and sensitized cells to both adriamycin and paclitaxel (Stanford et. al 2016). This study also found a
317 significant correlation between AhR activity and “cancer stem cell- and migration/invasion-
318 associated gene sets” in an analysis of 79 human breast cancer cells lines and more than 1,850 human
319 breast cancers. In inflammatory breast cancer, AhR was linked to BCSC maintenance through the
320 Wnt5a/ β -catenin signaling pathway (Mohamed et. al 2018). AhR crosstalk with Wnt/ β -catenin
321 signaling in the regulation of CSCs has been reported in several studies (Al-Dhfyhan et. al 2017,
322 Akhtar et. al 2022).

323 The role of AhR in cancer stemness and breast cancer stemness more specifically is complex,
324 influenced by mode of AhR activation, engagement with various signaling pathways and cell context.
325 Nevertheless, the collective evidence strongly suggests that AhR activation by environmental toxins
326 and endogenous ligands (Ala 2021) aligns with chemoresistance, recurrence and metastasis, the
327 hallmarks of cancer stemness. This places AhR at the intersection between racial/ethnic and
328 socioeconomic disparities in toxin exposure in under-resourced neighborhoods, as discussed
329 previously, and cancer stemness, undermining response to cancer therapy, worsening the riskscape
330 that an individual must navigate. In a recent review by Lagunas-Rangel, the authors pose the question
331 “Can Exposure to Environmental Pollutants Be Associated with Less Effective Chemotherapy in
332 Cancer Patients?” The authors summarize evidence which strongly supports this hypothesis, which
333 includes toxins which activate AhR (Lagunas-Rangel et. al 2022). Therachiyil examines this from the
334 perspective of gynecological cancers. (Therachiyil et. al 2022).

335 Conclusion

336 Collectively, the body of literature indicates that the role of AhR in cancer is complex, with
337 ample evidence for both an oncogenic and tumor suppressor function, depending on cell and
338 tissue context and mode of AhR activation. However, exposure studies indicate that
339 environmental pollutant-mediated activation of AhR is consistently oncogenic, highlighting the
340 potential for cautious therapeutic intervention. The data from human and in vivo studies, as well
341 as in vitro experiments suggest that exposure to environmental pollutants especially PAHs and
342 dioxin-like chemicals, potent ligands for AhR, increases breast cancer risk and worsens
343 outcome through chemoresistance, immune evasion, EMT, tumor cell proliferation, and
344 metastasis, linked functional outcomes of cancer stemness (Fig. 2). Some critical questions
345 remain, including how AhR activation modulates the tumor microenvironment. This review
346 also highlights the role of AhR at the interface between historical and existing systemic
347 practices - which reinforce residential segregation and environmental injustice - and the
348 molecular drivers of aggressive tumor biology. While policies and molecules are not frequently
349 in the same conversation, greater dialogue is needed and opportunities for “upstream” disease
350 prevention through systemic change should be prioritized.

351 Author Contributions

352 Review concept: CS, GL and CV. Review design: CS and CV. Manuscript preparation: CS, GL and
353 CV. Manuscript editing: CS and CV. Manuscript review: CS, GL and CV.

354 Conflict of Interest

355 The authors declare that the research was conducted in the absence of any commercial or financial
356 relationships that could be construed as a potential conflict of interest.

357 **Funding**

358 This work was supported by pilot funding from the Molecular Oncology Program at the UC Davis
359 Comprehensive Cancer Center and R21ES030419 (CF).

360 **Acknowledgements**

361 C.S. gratefully acknowledges the dedicated mentorship of Dr. Jann Murray-Garcia.

362 **References**

363 Abdelrahim M, Smith R 3rd, Safe S. Aryl hydrocarbon receptor gene silencing with small inhibitory
364 RNA differentially modulates Ah-responsiveness in MCF-7 and HepG2 cancer cells. *Mol Pharmacol.*
365 2003 Jun;63(6):1373-81. doi: 10.1124/mol.63.6.1373. PMID: 12761348.

366 Acharyya S, T. Oskarsson, S. Vanharanta, S. Malladi, J. Kim, P. G. Morris, K. Manova-Todorova,
367 M. Leversha, N. Hogg, V. E. Seshan, L. Norton, E. Brogi and J. Massague: A CXCL1 paracrine
368 network links cancer chemoresistance and metastasis. *Cell*, 150(1), 165-78 (2012)
369 doi:10.1016/j.cell.2012.04.042
370

371 Ahmed S, Mohamed HT, El-Husseiny N, El Mahdy MM, Safwat G, Diab AA, El-Sherif AA, El-
372 Shinawi M, Mohamed MM. IL-8 secreted by tumor associated macrophages contribute to lapatinib
373 resistance in HER2-positive locally advanced breast cancer via activation of Src/STAT3/ERK1/2-
374 mediated EGFR signaling. *Biochim Biophys Acta Mol Cell Res.* 2021 May;1868(6):118995. doi:
375 10.1016/j.bbamer.2021.118995. Epub 2021 Mar 2. PMID: 33667527.

376 Akhtar S, Hourani S, Therachiyil L, Al-Dhfyan A, Agouni A, Zeidan A, Uddin S, Korashy HM.
377 Epigenetic Regulation of Cancer Stem Cells by the Aryl Hydrocarbon Receptor Pathway. *Semin*
378 *Cancer Biol.* 2022 Aug;83:177-196. doi: 10.1016/j.semcancer.2020.08.014. Epub 2020 Aug 30.
379 PMID: 32877761.

380 Ala M. The footprint of kynurenine pathway in every cancer: a new target for chemotherapy. *Eur J*
381 *Pharmacol.* 2021 Apr 5;896:173921. doi: 10.1016/j.ejphar.2021.173921. Epub 2021 Jan 30. PMID:
382 33529725.

383
384 Al-Dhfyan A, Alhoshani A, Korashy HM. Aryl hydrocarbon receptor/cytochrome P450 1A1 pathway
385 mediates breast cancer stem cells expansion through PTEN inhibition and β -Catenin and Akt
386 activation. *Mol Cancer.* 2017 Jan 19;16(1):14. doi: 10.1186/s12943-016-0570-y. Erratum in: *Mol*
387 *Cancer.* 2017 Mar 24;16(1):69. PMID: 28103884; PMCID: PMC5244521.

388
389 Ali S and G. Lazenec: Chemokines: novel targets for breast cancer metastasis. *Cancer Metastasis*
390 *Rev*, 26(3-4), 401-20 (2007)

391 Amadou A, Praud D, Coudon T, Deygas F, Grassot L, Faure E, Couvidat F, Caudeville J, Bessagnet
392 B, Salizzoni P, Gulliver J, Leffondré K, Severi G, Mancini FR, Fervers B. Risk of breast cancer
393 associated with long-term exposure to benzo[a]pyrene (BaP) air pollution: Evidence from the French
394 E3N cohort study. *Environ Int.* 2021 Apr;149:106399. doi: 10.1016/j.envint.2021.106399. Epub 2021
395 Jan 24. PMID: 33503556.

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

- 396 Bankoti J, Rase B, Simones T, Shepherd DM. Functional and phenotypic effects of AhR activation in
397 inflammatory dendritic cells. *Toxicol Appl Pharmacol.* 2010 Jul;246(1-2):18-28. doi:
398 10.1016/j.taap.2010.03.013. Epub 2010 Mar 27. PMID: 20350561; PMCID: PMC2885531.
- 399 Bekki K, Vogel H, Li W, Ito T, Sweeney C, Haarmann-Stemmann T, Matsumura F, Vogel CF. The
400 aryl hydrocarbon receptor (AhR) mediates resistance to apoptosis induced in breast cancer cells.
401 *Pestic Biochem Physiol.* 2015 May;120:5-13.
- 402 Belton KR, Tian Y, Zhang L, Anitha M, Smith PB, Perdew GH, Patterson AD. Metabolomics
403 Reveals Aryl Hydrocarbon Receptor Activation Induces Liver and Mammary Gland Metabolic
404 Dysfunction in Lactating Mice. *J Proteome Res.* 2018 Apr 6;17(4):1375-1382.
- 405
- 406 Ben-Baruch A. Host microenvironment in breast cancer development: inflammatory cells, cytokines
407 and chemokines in breast cancer progression: reciprocal tumor-microenvironment interactions.
408 *Breast Cancer Res.* 2003;5(1):31-6. doi: 10.1186/bcr554. Epub 2002 Oct 28. PMID: 12559043;
409 PMCID: PMC154133.
- 410 Benoit L, Jornod F, Zgheib E, Tomkiewicz C, Koual M, Coustillet T, Barouki R, Audouze K, Vinken
411 M, Coumoul X. Adverse outcome pathway from activation of the AhR to breast cancer-related death.
412 *Environ Int.* 2022 May 28;165:107323. doi: 10.1016/j.envint.2022.107323. Epub ahead of print.
413 PMID: 35660951.
- 414 Benson JM, Shepherd DM. Dietary ligands of the aryl hydrocarbon receptor induce anti-
415 inflammatory and immunoregulatory effects on murine dendritic cells. *Toxicol Sci.* 2011
416 Dec;124(2):327-38. doi: 10.1093/toxsci/kfr249. Epub 2011 Sep 26. PMID: 21948866; PMCID:
417 PMC3216417.
- 418 Bieche I, C. Chavey, C. Andrieu, M. Busson, S. Vacher, L. Le Corre, J. M. Guinebretiere, S.
419 Burlinon, R. Lidereau and G. Lazennec: CXC chemokines located in the 4q21 region are up-
420 regulated in breast cancer. *Endocr Relat Cancer*, 14(4), 1039-1052 (2007)
- 421
- 422 Binnewies M, E. W. Roberts, K. Kersten, V. Chan, D. F. Fearon, M. Merad, L. M. Coussens, D. I.
423 Gabrilovich, S. Ostrand-Rosenberg, C. C. Hedrick, R. H. Vonderheide, M. J. Pittet, R. K. Jain, W.
424 Zou, T. K. Howcroft, E. C. Woodhouse, R. A. Weinberg and M. F. Krummel: Understanding the
425 tumor immune microenvironment (TIME) for effective therapy. *Nat Med*, 24(5), 541-550 (2018)
426 doi:10.1038/s41591-018-0014-x
- 427 Birnbaum LS, Fenton SE. Cancer and developmental exposure to endocrine disruptors. *Environ*
428 *Health Perspect.* 2003 Apr;111(4):389-94. doi: 10.1289/ehp.5686. PMID: 12676588; PMCID:
429 PMC1241417.
- 430 Boissiere-Michot F, W. Jacot, J. Fraisse, S. Gourgou, C. Timaxian and G. Lazennec: Prognostic
431 Value of CXCR2 in Breast Cancer. *Cancers (Basel)*, 12(8) (2020) doi:10.3390/cancers12082076
- 432
- 433 Boissiere-Michot F, W. Jacot, O. Massol, C. Mollevi and G. Lazennec: CXCR2 Levels Correlate
434 with Immune Infiltration and a Better Prognosis of Triple-Negative Breast Cancers. *Cancers (Basel)*,
435 13(10) (2021) doi:10.3390/cancers13102328
- 436 Boonen I, Van Heyst A, Van Langenhove K, Van Hoeck E, Mertens B, Denison MS, Elskens M,
437 Demaegdt H. Assessing the receptor-mediated activity of PAHs using AhR-, ER α - and PPAR γ -

- 438 CALUX bioassays. *Food Chem Toxicol*. 2020 Nov;145:111602. doi: 10.1016/j.fct.2020.111602.
439 Epub 2020 Jul 29. PMID: 32738369.
- 440 Brody JG, Moysich KB, Humblet O, Attfield KR, Beehler GP, Rudel RA. Environmental pollutants
441 and breast cancer: epidemiologic studies. *Cancer*. 2007 Jun 15;109(12 Suppl):2667-711. doi:
442 10.1002/cncr.22655. PMID: 17503436.
- 443 Brooks J, Eltom SE. Malignant transformation of mammary epithelial cells by ectopic
444 overexpression of the aryl hydrocarbon receptor. *Curr Cancer Drug Targets*. 2011 Jun;11(5):654-69.
445 doi: 10.2174/156800911795655967. PMID: 21486221; PMCID: PMC4070443.
- 446 Brummer G, D. S. Acevedo, Q. Hu, M. Portsche, W. B. Fang, M. Yao, B. Zinda, M. Myers, N.
447 Alvarez, P. Fields, Y. Hong, F. Behbod and N. Cheng: Chemokine Signaling Facilitates Early-Stage
448 Breast Cancer Survival and Invasion through Fibroblast-Dependent Mechanisms. *Mol Cancer Res*,
449 16(2), 296-308 (2018) doi:10.1158/1541-7786.MCR-17-0308
450
- 451 Campesato LF, Budhu S, Tchaicha J, Weng CH, Gigoux M, Cohen IJ, Redmond D, Mangarin L,
452 Pourpe S, Liu C, Zappasodi R, Zamarin D, Cavanaugh J, Castro AC, Manfredi MG, McGovern K,
453 Merghoub T, Wolchok JD. Blockade of the AHR restricts a Treg-macrophage suppressive axis
454 induced by L-Kynurenine. *Nat Commun*. 2020 Aug 11;11(1):4011. doi: 10.1038/s41467-020-17750-
455 z. PMID: 32782249; PMCID: PMC7419300.
- 456 Cappello and C. Gorrini: AhR controls redox homeostasis and shapes the tumor microenvironment in
457 BRCA1-associated breast cancer. *Proc Natl Acad Sci U S A*, 116(9), 3604-3613 (2019)
458 doi:10.1073/pnas.1815126116
- 459 Castañeda AR, Pinkerton KE, Bein KJ, Magaña-Méndez A, Yang HT, Ashwood P, Vogel CFA.
460 Ambient particulate matter activates the aryl hydrocarbon receptor in dendritic cells and enhances
461 Th17 polarization. *Toxicol Lett*. 2018 Aug;292:85-96. doi:10.1016/j.toxlet.2018.04.020. Epub 2018
462 Apr 22. PMID: 29689377; PMCID: PMC5971007.
- 463 Cha YJ, Koo JS. Role of Tumor-Associated Myeloid Cells in Breast Cancer. *Cells*. 2020 Jul
464 27;9(8):1785. doi: 10.3390/cells9081785. PMID: 32726950; PMCID: PMC7464644.
- 465 Chavey C, F. Bibeau, S. Gourgou-Bourgade, S. Burlinon, F. Boissiere, D. Laune, S. Roques and G.
466 Lazenec: Estrogen-receptor negative breast cancers exhibit a high cytokine content. *Breast Cancer*
467 *Res*, 9(1), R15 (2007)
- 468 Cheng I, Tseng C, Wu J, Yang J, Conroy SM, Shariff-Marco S, Li L, Hertz A, Gomez SL, Le
469 Marchand L, Whittemore AS, Stram DO, Ritz B, Wu AH. Association between ambient air pollution
470 and breast cancer risk: The multiethnic cohort study. *Int J Cancer*. 2020 Feb 1;146(3):699-711. doi:
471 10.1002/ijc.32308. Epub 2019 Apr 25. PMID: 30924138; PMCID: PMC6765455.
- 472
- 473 Coffelt SB, Hughes R, Lewis CE. Tumor-associated macrophages: effectors of angiogenesis and
474 tumor progression. *Biochimica et biophysica acta*. 2009;1796:11–18.
- 475 Creighton CJ, Li X, Landis M, Dixon JM, Neumeister VM, Sjolund A, Rimm DL, Wong H,
476 Rodriguez A, Herschkowitz JI, Fan C, Zhang X, He X, Pavlick A, Gutierrez MC, Renshaw L,

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

- 477 Larionov AA, Faratian D, Hilsenbeck SG, Perou CM, Lewis MT, Rosen JM, Chang JC. Residual
478 breast cancers after conventional therapy display mesenchymal as well as tumor-initiating features.
479 Proc Natl Acad Sci U S A. 2009 Aug 18;106(33):13820-5. doi: 10.1073/pnas.0905718106. Epub
480 2009 Aug 3. PMID: 19666588; PMCID: PMC2720409.
- 481 Dahlem C, Kado SY, He Y, Bein K, Wu D, Haarmann-Stemmann T, Kado NY, Vogel CFA. AHR
482 Signaling Interacting with Nutritional Factors Regulating the Expression of Markers in Vascular
483 Inflammation and Atherogenesis. Int J Mol Sci. 2020 Nov 5;21(21):8287. doi:
484 10.3390/ijms21218287. PMID: 33167400; PMCID: PMC7663825.
- 485 D'Amato NC, Rogers TJ, Gordon MA, Greene LI, Cochrane DR, Spoelstra NS, Nemkov TG,
486 D'Alessandro A, Hansen KC, Richer JK. A TDO2-AhR signaling axis facilitates anoikis resistance
487 and metastasis in triple-negative breast cancer. Cancer Res. 2015 Nov 1;75(21):4651-64.
488
- 489 Demicco EG, Kavanagh KT, Romieu-Mourez R, Wang X, Shin SR, Landesman-Bollag E, Seldin
490 DC, Sonenshein GE. RelB/p52 NF-kappaB complexes rescue an early delay in mammary gland
491 development in transgenic mice with targeted superrepressor IkappaB-alpha expression and promote
492 carcinogenesis of the mammary gland. Mol Cell Biol. 2005;25(22):10136–10147.
493
- 494 Dey S, Mondal A, DuHadaway JB, Sutanto-Ward E, Laury-Kleintop LD, Thomas S, Prendergast
495 GC, Mandik-Nayak L, Muller AJ. IDO1 Signaling through GCN2 in a Subpopulation of Gr-1⁺ Cells
496 Shifts the IFN γ /IL6 Balance to Promote Neovascularization. Cancer Immunol Res. 2021 Feb 23. doi:
497 10.1158/2326-6066.CIR-20-0226. Epub ahead of print. PMID: 33622713.
- 498 Diaz-Montero CM, Salem ML, Nishimura MI, Garrett-Mayer E, Cole DJ, Montero AJ. Increased
499 circulating myeloid-derived suppressor cells correlate with clinical cancer stage, metastatic tumor
500 burden, and doxorubicin-cyclophosphamide chemotherapy. Cancer Immunol Immunother. 2009
501 Jan;58(1):49-59. doi: 10.1007/s00262-008-0523-4. Epub 2008 Apr 30. PMID: 18446337; PMCID:
502 PMC3401888.
- 503 Donovan MG, Selmin OI, Romagnolo DF. Aryl Hydrocarbon Receptor Diet and Breast Cancer Risk.
504 Yale J Biol Med. 2018 Jun 28;91(2):105-127. PMID: 29962921; PMCID: PMC6020732.
- 505 Dubrovskaya A, Hartung A, Bouchez LC, Walker JR, Reddy VA, Cho CY, Schultz PG. CXCR4
506 activation maintains a stem cell population in tamoxifen-resistant breast cancer cells through AhR
507 signalling. Br J Cancer. 2012 Jun 26;107(1):43-52. doi: 10.1038/bjc.2012.105. Epub 2012 May 29.
508 PMID: 22644306; PMCID: PMC3389396.
- 509 Esbona K, Inman D, Saha S, Jeffery J, Schedin P, Wilke L, Keely P. COX-2 modulates mammary
510 tumor progression in response to collagen density. Breast Cancer Res. 2016 Mar 22;18(1):35.
511
- 512 Famta P, Shah S, Jain N, Kumar KC, Bagasariya D, Khatri DK, Raghuvanshi RS, Singh SB,
513 Srivastava S. Tumor-promoting aftermath post-chemotherapy: A focus on breast cancer. Life Sci.
514 2022 Oct 25;310:121125. doi: 10.1016/j.lfs.2022.121125. Epub ahead of print. PMID: 36306868.
515

- 516 Feng J, Zheng T, Hou Z, Lv C, Xue A, Han T, Han B, Sun X, Wei Y. Luteolin, an aryl hydrocarbon
517 receptor ligand, suppresses tumor metastasis in vitro and in vivo. *Oncol Rep.* 2020 Nov;44(5):2231-
518 2240. doi: 10.3892/or.2020.7781. Epub 2020 Sep 25. PMID: 33000272.
- 519 Freund A, Chauveau C, Brouillet JP, Lucas A, Lacroix M, Licznar A, Vignon F, Lazennec G. IL-8
520 expression and its possible relationship with estrogen-receptor-negative status of breast cancer cells.
521 *Oncogene.* 2003 Jan 16;22(2):256-65. doi: 10.1038/sj.onc.1206113. PMID: 12527894; PMCID:
522 PMC2034407.
- 523 Fridlender ZG, Sun J, Kim S, Kapoor V, Cheng G, Ling L, Worthen GS, Albelda SM. Polarization of
524 tumor-associated neutrophil phenotype by TGF-beta: "N1" versus "N2" TAN. *Cancer Cell.* 2009 Sep
525 8;16(3):183-94. doi: 10.1016/j.ccr.2009.06.017. PMID: 19732719; PMCID: PMC2754404.
- 526 Fritz WA, Lin TM, Cardiff RD, Peterson RE. The aryl hydrocarbon receptor inhibits prostate
527 carcinogenesis in TRAMP mice. *Carcinogenesis.* 2007 Feb;28(2):497-505. doi:
528 10.1093/carcin/bgl179. Epub 2006 Oct 19. PMID: 17052998.
- 529 Gamboa-Loira B, López-Carrillo L, Mar-Sánchez Y, Stern D, Cebrián ME. Epidemiologic evidence
530 of exposure to polycyclic aromatic hydrocarbons and breast cancer: A systematic review and meta-
531 analysis. *Chemosphere.* 2022 Mar;290:133237. doi: 10.1016/j.chemosphere.2021.133237. Epub 2021
532 Dec 17. PMID: 34929281.
- 533 Gearhart-Serna LM, Davis JB, Jolly MK, Jayasundara N, Sauer SJ, Di Giulio RT, Devi GR. A
534 polycyclic aromatic hydrocarbon-enriched environmental chemical mixture enhances AhR,
535 antiapoptotic signaling and a proliferative phenotype in breast cancer cells. *Carcinogenesis.* 2020 Dec
536 31;41(12):1648-1659. doi: 10.1093/carcin/bgaa047. PMID: 32747956; PMCID: PMC7791619.
- 537 Gnant M, Mlineritsch B, Stoeger H, Luschin-Ebengreuth G, Heck D, Menzel C, Jakesz R, Seifert M,
538 Hubalek M, Pristauz G, Bauernhofer T, Eidtmann H, Eiermann W, Steger G, Kwasny W, Dubsy P,
539 Hochreiner G, Forsthuber EP, Fesl C, Greil R; Austrian Breast and Colorectal Cancer Study Group,
540 Vienna, Austria. Adjuvant endocrine therapy plus zoledronic acid in premenopausal women with
541 early-stage breast cancer: 62-month follow-up from the ABCSG-12 randomised trial. *Lancet Oncol.*
542 2011 Jul;12(7):631-41. doi: 10.1016/S1470-2045(11)70122-X. Epub 2011 Jun 5. PMID: 21641868.
- 543 Gomez-Roca CA, Cassier PA, Italiano A, Cannarile M, Ries C, Brillouet A, Mueller C, Jegg AM,
544 Meneses-Lorente G, Baehner M, Abiraj K, Loirat D, Toulmonde M, D'Angelo SP, Weber K,
545 Campone M, Ruettinger D, Blay JY, Delord JP, Le Tourneau C. Phase I study of RG7155, a novel
546 anti-CSF1R antibody, in patients with advanced/metastatic solid tumors. *J Clin Oncol.* 2015;33:15.
- 547 Grunig G, Marsh LM, Esmaeil N, Jackson K, Gordon T, Reibman J, Kwapiszewska G, Park SH.
548 Perspective: ambient air pollution: inflammatory response and effects on the lung's vasculature. *Pulm*
549 *Circ.* 2014 Mar;4(1):25-35.
- 550 Guarnieri T. Aryl Hydrocarbon Receptor Connects Inflammation to Breast Cancer. *Int J Mol Sci.*
551 2020 Jul 24;21(15):5264. doi: 10.3390/ijms21155264. PMID: 32722276; PMCID: PMC7432832.
- 552 Han H, Davidson LA, Hensel M, Yoon G, Landrock K, Allred C, Jayaraman A, Ivanov I, Safe SH,
553 Chapkin RS. Loss of Aryl Hydrocarbon Receptor Promotes Colon Tumorigenesis in *ApcS580/+*;
554 *KrasG12D/+* Mice. *Mol Cancer Res.* 2021 May;19(5):771-783. doi: 10.1158/1541-7786.MCR-20-
555 0789. Epub 2021 Jan 25. PMID: 33495399; PMCID: PMC8137548.

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

556

557 Hart JE, Chiueve SE, Laden F, Albert CM. Roadway proximity and risk of sudden cardiac death in
558 women. *Circulation*. 2014 Oct 21;130(17):1474-82. doi: 10.1161/CIRCULATIONAHA.114.011489.
559 Epub 2014 Oct 13. PMID: 25332277; PMCID: PMC4382912.

560 Hezaveh K, R. S. Shinde, A. Klotgen, M. J. Halaby, S. Lamorte, M. T. Ciudad, R. Quevedo, L.
561 Neufeld, Z. Q. Liu, R. Jin, B. T. Grunwald, E. G. Foerster, D. Chaharlangi, M. Guo, P. Makhijani, X.
562 Zhang, T. J. Pugh, D. M. Pinto, I. L. Co, A. P. McGuigan, G. H. Jang, R. Khokha, P. S. Ohashi, G.
563 M. O'Kane, S. Gallinger, W. W. Navarre, H. Maughan, D. J. Philpott, D. G. Brooks and T. L.
564 McGaha: Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-
565 associated macrophages to suppress anti-tumor immunity. *Immunity*, 55(2), 324-340 e8 (2022)
566 doi:10.1016/j.immuni.2022.01.006

567 Hwa Jung K, Pitkowsky Z, Argenio K, Quinn JW, Bruzzese JM, Miller RL, Chillrud SN,
568 Perzanowski M, Stingone JA, Lovinsky-Desir S. The effects of the historical practice of residential
569 redlining in the United States on recent temporal trends of air pollution near New York City schools.
570 *Environ Int*. 2022 Nov;169:107551. doi: 10.1016/j.envint.2022.107551. Epub 2022 Sep 27. PMID:
571 36183489; PMCID: PMC9616211.

572 IARC Working Group on the Evaluation of Carcinogenic Risks to Humans (2010) Some non-
573 heterocyclic polycyclic aromatic hydrocarbons and some related exposures. *IARC Monogr Eval*
574 *Carcinog Risks Hum* 92: 1–853.

575 Jin UH, Lee SO, Pfent C, Safe S. The aryl hydrocarbon receptor ligand omeprazole inhibits breast
576 cancer cell invasion and metastasis. *BMC Cancer*. 2014 Jul 9;14:498. doi: 10.1186/1471-2407-14-
577 498. PMID: 25011475; PMCID: PMC4226953.

578 Joyce JA and J. W. Pollard: Microenvironmental regulation of metastasis. *Nat Rev Cancer*, 9(4), 239-
579 52 (2009)

580 Katara GK, Kulshrestha A, Schneiderman S, Riehl V, Ibrahim S, Beaman KD. Interleukin-22
581 promotes development of malignant lesions in a mouse model of spontaneous breast cancer. *Mol*
582 *Oncol*. 2020 Jan;14(1):211-224. doi: 10.1002/1878-0261.12598. Epub 2019 Dec 4. PMID:
583 31725949; PMCID: PMC6944104.

584 Kay JE, Cardona B, Rudel RA, Vandenberg LN, Soto AM, Christiansen S, Birnbaum LS, Fenton SE.
585 Chemical Effects on Breast Development, Function, and Cancer Risk: Existing Knowledge and New
586 Opportunities. *Curr Environ Health Rep*. 2022 Aug 19. doi: 10.1007/s40572-022-00376-2. Epub
587 ahead of print. PMID: 35984634.

588 Kenison JE, Wang Z, Yang K, Snyder M, Quintana FJ, Sherr DH. The aryl hydrocarbon receptor
589 suppresses immunity to oral squamous cell carcinoma through immune checkpoint regulation. *Proc*
590 *Natl Acad Sci U S A*. 2021 May 11;118(19):e2012692118. doi: 10.1073/pnas.2012692118. PMID:
591 33941684; PMCID: PMC8126867.

592 Kim DW, Gazourian L, Quadri SA, Romieu-Mourez R, Sherr DH, Sonenshein GE. The RelA NF-
593 kappaB subunit and the aryl hydrocarbon receptor (AhR) cooperate to transactivate the c-myc
594 promoter in mammary cells. *Oncogene*. 2000 Nov 16;19(48):5498-506. doi: 10.1038/sj.onc.1203945.
595 PMID: 11114727.

596

597 Kim K, Kim G, Kim JY, Yun HJ, Lim SC, Choi HS. Interleukin-22 promotes epithelial cell
598 transformation and breast tumorigenesis via MAP3K8 activation. *Carcinogenesis*. 2014
599 Jun;35(6):1352-61. doi: 10.1093/carcin/bgu044. Epub 2014 Feb 11. PMID: 24517997.

600 Kim EY, Choi B, Kim JE, Park SO, Kim SM, Chang EJ. Interleukin-22 Mediates the Chemotactic
601 Migration of Breast Cancer Cells and Macrophage Infiltration of the Bone Microenvironment by
602 Potentiating S1P/S1PR Signaling. *Cells*. 2020 Jan 6;9(1):131. doi: 10.3390/cells9010131. PMID:
603 31935914; PMCID: PMC7017200.

604 Kingsley SL, Eliot MN, Whitsel EA, Wang Y, Coull BA, Hou L, Margolis HG, Margolis KL, Mu L,
605 Wu WC, Johnson KC, Allison MA, Manson JE, Eaton CB, Wellenius GA. Residential proximity to
606 major roadways and incident hypertension in post-menopausal women. *Environ Res*. 2015
607 Oct;142:522-8. doi: 10.1016/j.envres.2015.08.002. PMID: 26282224; PMCID: PMC4609282.

608 Kirwa K, Eliot MN, Wang Y, Adams MA, Morgan CG, Kerr J, Norman GJ, Eaton CB, Allison MA,
609 Wellenius GA. Residential proximity to major roadways and prevalent hypertension among
610 postmenopausal women: results from the Women's Health Initiative San Diego Cohort. *J Am Heart*
611 *Assoc*. 2014 Oct 1;3(5):e000727. doi: 10.1161/JAHA.113.000727. PMID: 25274494; PMCID:
612 PMC4323802.

613 Kolluri SK, Jin UH, Safe S. Role of the aryl hydrocarbon receptor in carcinogenesis and potential as
614 an anti-cancer drug target. *Arch Toxicol*. 2017 Jul;91(7):2497-2513.

615

616 Koual M, Tomkiewicz C, Guerrero IC, Sherr D, Barouki R, Coumoul X. Aggressiveness and
617 Metastatic Potential of Breast Cancer Cells Co-Cultured with Preadipocytes and Exposed to an
618 Environmental Pollutant Dioxin: An *in Vitro* and *in Vivo* Zebrafish Study. *Environ Health Perspect*.
619 2021 Mar;129(3):37002. doi: 10.1289/EHP7102. Epub 2021 Mar 8. PMID: 33683140; PMCID:
620 PMC7939125.

621 Kubli SP, C. Bassi, C. Roux, A. Wakeham, C. Göbl, W. Zhou, S. M. Jafari, B. Snow, L. Jones, L.
622 Palomero, K. L. Thu, L. Cassetta, D. Soong, T. Berger, P. Ramachandran, S. P. Baniyadi, G.
623 Duncan, M. Lindzen, Y. Yarden, C. Herranz, C. Lazaro, M. F. Chu, J. Haight, P. Tinto, J. Silvester,
624 D. W. Cescon, A. Petit, S. Pettersson, J. W. Pollard, T. W. Mak, M. A. Pujana, P. Kulick ER,
625 Wellenius GA, Boehme AK, Sacco RL, Elkind MS. Residential Proximity to Major Roadways and
626 Risk of Incident Ischemic Stroke in NOMAS (The Northern Manhattan Study). *Stroke*. 2018
627 Apr;49(4):835-841. doi: 10.1161/STROKEAHA.117.019580. Epub 2018 Mar 14. PMID: 29540609;
628 PMCID: PMC5871599.

629

630 Kubli SP, Bassi C, Roux C, Wakeham A, Göbl C, Zhou W, Jafari SM, Snow B, Jones L, Palomero L,
631 Thu KL, Cassetta L, Soong D, Berger T, Ramachandran P, Baniyadi SP, Duncan G, Lindzen M,
632 Yarden Y, Herranz C, Lazaro C, Chu MF, Haight J, Tinto P, Silvester J, Cescon DW, Petit A,
633 Pettersson S, Pollard JW, Mak TW, Pujana MA, Cappello P, Gorrini C. AhR controls redox
634 homeostasis and shapes the tumor microenvironment in BRCA1-associated breast cancer. *Proc Natl*
635 *Acad Sci U S A*. 2019 Feb 26;116(9):3604-3613. doi: 10.1073/pnas.1815126116. Epub 2019 Feb 7.
636 PMID: 30733286; PMCID: PMC6397541.

637

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

- 638 Lagunas-Rangel FA, Liu W, Schiöth HB. Can Exposure to Environmental Pollutants Be Associated
639 with Less Effective Chemotherapy in Cancer Patients? *Int J Environ Res Public Health*. 2022 Feb
640 12;19(4):2064. doi: 10.3390/ijerph19042064. PMID: 35206262; PMCID: PMC8871977.
- 641 La Merrill M, Harper R, Birnbaum LS, Cardiff RD, Threadgill DW. Maternal dioxin exposure
642 combined with a diet high in fat increases mammary cancer incidence in mice. *Environ Health*
643 *Perspect*. 2010 May;118(5):596-601. doi: 10.1289/ehp.0901047. PMID: 20435547; PMCID:
644 PMC2866672.
- 645 Large C, Wei Y. Geographic variations in female breast cancer incidence in relation to ambient air
646 emissions of polycyclic aromatic hydrocarbons. *Environ Sci Pollut Res Int*. 2017 Jul;24(21):17874-
647 17880. doi: 10.1007/s11356-017-9395-5. Epub 2017 Jun 14. PMID: 28616736.
- 648 Lazennec G and P. Y. Lam: Recent discoveries concerning the tumor - mesenchymal stem cell
649 interactions. *Biochim Biophys Acta*, 1866(2), 290-299 (2016) doi:10.1016/j.bbcan.2016.10.004
650
- 651 Lazennec G and A. Richmond: Chemokines and chemokine receptors: new insights into cancer-
652 related inflammation. *Trends Mol Med*, 16(3), 133-44 (2010)
653
- 654 Lee DG, Burstyn I, Lai AS, Grundy A, Friesen MC, Aronson KJ, Spinelli JJ. Women's occupational
655 exposure to polycyclic aromatic hydrocarbons and risk of breast cancer. *Occup Environ Med*. 2019
656 Jan;76(1):22-29. doi: 10.1136/oemed-2018-105261. PMID: 30541747.
- 657 Leek RD, Lewis CE, Whitehouse R, Greenall M, Clarke J, et al. (1996) Association of macrophage
658 infiltration with angiogenesis and prognosis in invasive breast carcinoma. *Cancer Res* 56: 4625-
659 4629.
- 660 Lew B. J.; Manickam R.; Lawrence B. P. Activation of the Aryl Hydrocarbon Receptor During
661 Pregnancy in the Mouse Alters Mammary Development Through Direct Effects on Stromal and
662 Epithelial Tissues. *Biol. Reprod*. 2011, 84, 1094-1102. doi:10.1095/biolreprod.110.087544.
663
- 664 Lichtiger L, Rivera J, Sahay D, Miller RL. Polycyclic Aromatic Hydrocarbons and Mammary Cancer
665 Risk: Does Obesity Matter too? *J Cancer Immunol (Wilmington)*. 2021;3(3):154-162. PMID:
666 34734210; PMCID: PMC8561337.
- 667 Li X, Lewis MT, Huang J, Gutierrez C, Osborne CK, Wu MF, Hilsenbeck SG, Pavlick A, Zhang X,
668 Chamness GC, Wong H, Rosen J, Chang JC. Intrinsic resistance of tumorigenic breast cancer cells to
669 chemotherapy. *J Natl Cancer Inst*. 2008 May 7;100(9):672-9. doi: 10.1093/jnci/djn123. Epub 2008
670 Apr 29. PMID: 18445819.
- 671 Li ZD, Wang K, Yang XW, Zhuang ZG, Wang JJ, Tong XW. Expression of aryl hydrocarbon
672 receptor in relation to p53 status and clinicopathological parameters in breast cancer. *Int J Clin Exp*
673 *Pathol*. 2014 Oct 15;7(11):7931-7. PMID: 25550834; PMCID: PMC4270523.
- 674 Lue SH, Wellenius GA, Wilker EH, Mostofsky E, Mittleman MA. Residential proximity to major
675 roadways and renal function. *J Epidemiol Community Health*. 2013 Aug;67(8):629-34. doi:
676 10.1136/jech-2012-202307. Epub 2013 May 13. PMID: 23669275; PMCID: PMC4167787.

- 677 Mahmoud SM, Lee AH, Paish EC, Macmillan RD, Ellis IO, et al. (2012) Tumour-infiltrating
678 macrophages and clinical outcome in breast cancer. *J Clin Pathol* 65: 159–163.
- 679 Mancini SJC, K. Balabanian, I. Corre, J. Gavard, G. Lazennec, M. C. Le Bousse-Kerdiles, F.
680 Louache, V. Maguer-Satta, N. M. Mazure, F. Mechta-Grigoriou, J. F. Peyron, V. Trichet and O.
681 Herculat: Deciphering Tumor Niches: Lessons From Solid and Hematological Malignancies. *Front*
682 *Immunol*, 12, 766275 (2021) doi:10.3389/fimmu.2021.766275
683
- 684 Masih M, Agarwal S, Kaur R, Gautam PK. Role of chemokines in breast cancer. *Cytokine*. 2022
685 Jul;155:155909. doi: 10.1016/j.cyto.2022.155909. Epub 2022 May 18. PMID: 35597171.
- 686 McKay ZP, Brown MC, Gromeier M. Aryl Hydrocarbon Receptor Signaling Controls CD155
687 Expression on Macrophages and Mediates Tumor Immunosuppression. *J Immunol*. 2021 Mar
688 15;206(6):1385-1394. doi: 10.4049/jimmunol.2000792. Epub 2021 Jan 27. PMID: 33504618;
689 PMCID: PMC7946722.
- 690 Minn AJ, Gupta GP, Siegel PM, Bos PD, Shu W, Giri DD, Viale A, Olshen AB, Gerald WL,
691 Massagué J. Genes that mediate breast cancer metastasis to lung. *Nature*. 2005 Jul 28;436(7050):518-
692 24.
- 693 Miyazaki T, Chung S, Sakai H, Ohata H, Obata Y, Shiokawa D, Mizoguchi Y, Kubo T, Ichikawa H,
694 Taniguchi H, Aoki K, Soga T, Nakagama H, Okamoto K. Stemness and immune evasion conferred
695 by the TDO2-AHR pathway are associated with liver metastasis of colon cancer. *Cancer Sci*. 2022
696 Jan;113(1):170-181. doi: 10.1111/cas.15182. Epub 2021 Dec 2. PMID: 34714577; PMCID:
697 PMC8748246.
- 698
- 699 Mohamed HT, Gadalla R, El-Husseiny N, Hassan H, Wang Z, Ibrahim SA, El-Shinawi M, Sherr DH,
700 Mohamed MM. Inflammatory breast cancer: Activation of the aryl hydrocarbon receptor and its
701 target CYP1B1 correlates closely with Wnt5a/b- β -catenin signalling, the stem cell phenotype and
702 disease progression. *J Adv Res*. 2018 Dec 8;16:75-86. doi: 10.1016/j.jare.2018.11.006. PMID:
703 30899591; PMCID: PMC6413307.
- 704 Morello-Frosch R, Lopez R. The riskscape and the color line: examining the role of segregation in
705 environmental health disparities. *Environ Res*. 2006 Oct;102(2):181-96. doi:
706 10.1016/j.envres.2006.05.007. Epub 2006 Jul 10. PMID: 16828737.
- 707 Morello-Frosch R, Shenassa ED. The environmental "riskscape" and social inequality: implications
708 for explaining maternal and child health disparities. *Environ Health Perspect*. 2006 Aug;114(8):1150-
709 3. doi: 10.1289/ehp.8930. PMID: 16882517; PMCID: PMC1551987.
- 710 Movahedi K, Laoui D, Gysemans C, Baeten M, Stangé G, Van den Bossche J, Mack M, Pipeleers D,
711 In't Veld P, De Baetselier P, Van Ginderachter JA. Different tumor microenvironments contain
712 functionally distinct subsets of macrophages derived from Ly6C(high) monocytes. *Cancer Res*. 2010
713 Jul 15;70(14):5728-39. doi: 10.1158/0008-5472.CAN-09-4672. Epub 2010 Jun 22. PMID: 20570887.
- 714 Mordukhovich I, Beyea J, Herring AH, Hatch M, Stellman SD, Teitelbaum SL, Richardson DB,
715 Millikan RC, Engel LS, Shantakumar S, Steck SE, Neugut AI, Rossner P Jr, Santella RM, Gammon
716 MD. Vehicular Traffic-Related Polycyclic Aromatic Hydrocarbon Exposure and Breast Cancer
717 Incidence: The Long Island Breast Cancer Study Project (LIBCSP). *Environ Health Perspect*. 2016

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

- 718 Jan;124(1):30-8. doi: 10.1289/ehp.1307736. Epub 2015 May 22. PMID: 26008800; PMCID:
719 PMC4710589.
- 720 Mukhtar RA, Nseyo O, Campbell MJ, Esserman LJ. Tumor-associated macrophages in breast cancer
721 as potential biomarkers for new treatments and diagnostics. *Expert Rev Mol Diagn.* 2011b;11:91–
722 100.
- 723 Mukhtar RA, Moore AP, Nseyo O, Baehner FL, Au A, Moore DH. et al. Elevated PCNA+ tumor-
724 associated macrophages in breast cancer are associated with early recurrence and non-Caucasian
725 ethnicity. *Breast Cancer Res Treat.* 2011a;130:635–44.
- 726 Muller A, B. Homey, H. Soto, N. Ge, D. Catron, M. E. Buchanan, T. McClanahan, E. Murphy, W.
727 Yuan, S. N. Wagner, J. L. Barrera, A. Mohar, E. Verastegui and A. Zlotnik: Involvement of
728 chemokine receptors in breast cancer metastasis. *Nature*, 410(6824), 50-6 (2001)
- 729 Murray IA, Patterson AD, Perdew GH. Aryl hydrocarbon receptor ligands in cancer: friend and foe.
730 *Nat Rev Cancer.* 2014 Dec;14(12):801-14.
731
- 732 Narasimhan S, Stanford Zulick E, Novikov O, Parks AJ, Schlezinger JJ, Wang Z, Laroche F, Feng H,
733 Mulas F, Monti S, Sherr DH. Towards Resolving the Pro- and Anti-Tumor Effects of the Aryl
734 Hydrocarbon Receptor. *Int J Mol Sci.* 2018 May 7;19(5):1388. doi: 10.3390/ijms19051388. PMID:
735 29735912; PMCID: PMC5983651.
- 736 Narita D, Seclaman E, Anghel A, Ilina R, Cireap N, Negru S, Sirbu IO, Ursoniu S, Marian C. Altered
737 levels of plasma chemokines in breast cancer and their association with clinical and pathological
738 characteristics. *Neoplasma.* 2016;63(1):141-9. doi: 10.4149/neo_2016_017. PMID: 26639244.
- 739 Neamah WH, Singh NP, Alghetaa H, Abdulla OA, Chatterjee S, Busbee PB, Nagarkatti M,
740 Nagarkatti P. AhR Activation Leads to Massive Mobilization of Myeloid-Derived Suppressor Cells
741 with Immunosuppressive Activity through Regulation of CXCR2 and MicroRNA miR-150-5p and
742 miR-543-3p That Target Anti-Inflammatory Genes. *J Immunol.* 2019 Oct 1;203(7):1830-1844. doi:
743 10.4049/jimmunol.1900291. Epub 2019 Sep 6. PMID: 31492743; PMCID: PMC6755129.
- 744 Nie J, Beyea J, Bonner MR, Han D, Vena JE, Rogerson P, Vito D, Muti P, Trevisan M, Edge SB,
745 Freudenheim JL. Exposure to traffic emissions throughout life and risk of breast cancer: the Western
746 New York Exposures and Breast Cancer (WEB) study. *Cancer Causes Control.* 2007 Nov;18(9):947-
747 55. doi: 10.1007/s10552-007-9036-2. Epub 2007 Jul 14. PMID: 17632764.
- 748 Niehoff NM, Keil AP, Jones RR, Fan S, Gierach GL, White AJ. Outdoor air pollution and terminal
749 duct lobular involution of the normal breast. *Breast Cancer Res.* 2020 Sep 24;22(1):100. doi:
750 10.1186/s13058-020-01339-x. PMID: 32972455; PMCID: PMC7513536.
- 751 Nothdurft S, Thumser-Henner C, Breitenbücher F, Okimoto RA, Dorsch M, Opitz CA, Sadik A,
752 Esser C, Hölzel M, Asthana S, Forster J, Beisser D, Kalmbach S, Grüner BM, Bivona TG, Schramm
753 A, Schuler M. Functional screening identifies aryl hydrocarbon receptor as suppressor of lung cancer
754 metastasis. *Oncogenesis.* 2020 Nov 19;9(11):102. doi: 10.1038/s41389-020-00286-8. PMID:
755 33214553; PMCID: PMC7677369.
- 756

- 757 O'Donnell EF 3rd, Jang HS, Liefwalker DF, Kerkvliet NI, Kolluri SK. Discovery and Mechanistic
758 Characterization of a Select Modulator of AhR-regulated Transcription (SMAhRT) with Anti-cancer
759 Effects. *Apoptosis*. 2021 Jun;26(5-6):307-322. doi: 10.1007/s10495-021-01666-0. Epub 2021 Apr
760 24. PMID: 33893898.
- 761 O'Driscoll CA, Gallo ME, Fechner JH, Schauer JJ, Mezrich JD. Real-world PM extracts
762 differentially enhance Th17 differentiation and activate the aryl hydrocarbon receptor (AHR).
763 *Toxicology*. 2019 Feb 15;414:14-26. doi: 10.1016/j.tox.2019.01.002. Epub 2019 Jan 3. PMID:
764 30611761; PMCID: PMC7065493.
- 765 O'Driscoll CA, Mezrich JD. The Aryl Hydrocarbon Receptor as an Immune-Modulator of
766 Atmospheric Particulate Matter-Mediated Autoimmunity. *Front Immunol*. 2018 Dec 6;9:2833. doi:
767 10.3389/fimmu.2018.02833. PMID: 30574142; PMCID: PMC6291477.
- 768 Orimo A, P. B. Gupta, D. C. Sgroi, F. Arenzana-Seisdedos, T. Delaunay, R. Naeem, V. J. Carey, A.
769 L. Richardson and R. A. Weinberg: Stromal fibroblasts present in invasive human breast carcinomas
770 promote tumor growth and angiogenesis through elevated SDF-1/CXCL12 secretion. *Cell*, 121(3),
771 335-48 (2005)
- 772 Ostrand-Rosenberg S. Immune Suppressive Myeloid-Derived Suppressor Cells in Cancer.
773 *Encyclopedia of Immunology Volume 4*, 2016, Pages 512-525
- 774 Ouyang L, Yan B, Liu Y, Mao C, Wang M, Liu N, Wang Z, Liu S, Shi Y, Chen L, Wang X, Cheng
775 Y, Cao Y, Xiao D, Zhang L, Liu S, Tao Y. The deubiquitylase UCHL3 maintains cancer stem-like
776 properties by stabilizing the aryl hydrocarbon receptor. *Signal Transduct Target Ther*. 2020 Jun
777 17;5(1):78. doi: 10.1038/s41392-020-0181-3. PMID: 32546741; PMCID: PMC7297794.
- 778 Phillips JL, Löhr CV, Nguyen BD, Buermeyer AB, Kolluri SK. Loss of the aryl hydrocarbon
779 receptor increases tumorigenesis in p53-deficient mice. *Toxicol Appl Pharmacol*. 2022 Nov
780 1;454:116191. doi: 10.1016/j.taap.2022.116191. Epub 2022 Aug 1. PMID: 35926564.
- 781 Place AE, Jin Huh S, Polyak K. The microenvironment in breast cancer progression: biology and
782 implications for treatment. *Breast Cancer Res*. 2011;13(6):227. doi: 10.1186/bcr2912. Epub 2011
783 Nov 1. PMID: 22078026; PMCID: PMC3326543.
- 784 Prud'homme GJ, Glinka Y, Toulina A, Ace O, Subramaniam V, Jothy S. Breast cancer stem-like
785 cells are inhibited by a non-toxic aryl hydrocarbon receptor agonist. *PLoS One*. 2010 Nov
786 3;5(11):e13831. doi: 10.1371/journal.pone.0013831. PMID: 21072210; PMCID: PMC2972222.
- 787 Puga A, Barnes SJ, Dalton TP, Chang Cy, Knudsen ES, Maier MA. Aromatic hydrocarbon receptor
788 interaction with the retinoblastoma protein potentiates repression of E2F-dependent transcription and
789 cell cycle arrest. *J Biol Chem*. 2000 Jan 28;275(4):2943-50. doi: 10.1074/jbc.275.4.2943. PMID:
790 10644764.
- 791 Qiu SQ, Waaijer S, Zwager MC, de Vries EG, van der Vegt B, Schröder CP. Tumor-associated
792 macrophages in breast cancer: innocent bystander or important player? *Cancer Treat Rev*. (2018)
793 70:178–89. doi: 10.1016/j.ctrv.2018.08.010
- 794

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

- 795 Razmkhah M, Jaberipour M, Hosseini A, Safaei A, Khalatbari B, Ghaderi A. Expression profile of
796 IL-8 and growth factors in breast cancer cells and adipose-derived stem cells (ASCs) isolated from
797 breast carcinoma. *Cell Immunol.* 2010;265(1):80-5. doi: 10.1016/j.cellimm.2010.07.006. Epub 2010
798 Jul 23. PMID: 20705284.
- 799 Romaniuk A, Lyndin M, Sikora V, Lyndina Y, Romaniuk S, Sikora K. Heavy metals effect on breast
800 cancer progression. *J Occup Med Toxicol.* 2017 Nov 28;12:32. doi: 10.1186/s12995-017-0178-1.
801 PMID: 29209407; PMCID: PMC5704424.
- 802 Rowland LK, Campbell PS, Mavingire N, Wooten JV, McLean L, Zylstra D, Thorne G, Daly D,
803 Boyle K, Whang S, Unternaehrer J, Brantley EJ. Putative tumor suppressor cytoglobin promotes aryl
804 hydrocarbon receptor ligand-mediated triple negative breast cancer cell death. *J Cell Biochem.* 2019
805 Apr;120(4):6004-6014. doi: 10.1002/jcb.27887. PMID: 30450577; PMCID: PMC6382570.
- 806
- 807 R ckerl R, Greven S, Ljungman P, Aalto P, Antoniadou C, Bellander T, Berglind N, Chrysohoou C,
808 Forastiere F, Jacquemin B, von Klot S, Koenig W, K chenhoff H, Lanki T, Pekkanen J, Perucci CA,
809 Schneider A, Sunyer J, Peters A; AIRGENE Study Group. Air pollution and inflammation
810 (interleukin-6, C-reactive protein, fibrinogen) in myocardial infarction survivors. *Environ Health*
811 *Perspect.* 2007 Jul;115(7):1072-80.
812
- 813 Safarzadeh E, Hashemzadeh S, Duijf PHG, Mansoori B, Khaze V, Mohammadi A, Kazemi T,
814 Yousefi M, Asadi M, Mohammadi H, Babaie F, Baradaran B. Circulating myeloid-derived
815 suppressor cells: An independent prognostic factor in patients with breast cancer. *J Cell Physiol.*
816 2019 Apr;234(4):3515-3525. doi: 10.1002/jcp.26896. Epub 2018 Oct 26. PMID: 30362521.
- 817 Safe S, Cheng Y, Jin UH. The Aryl Hydrocarbon Receptor (AhR) as a Drug Target for Cancer
818 Chemotherapy. *Curr Opin Toxicol.* 2017 Feb;2:24-29. doi: 10.1016/j.cotox.2017.01.012. Epub 2017
819 Feb 1. PMID: 28459113; PMCID: PMC5407490.
- 820 Saito N, Kanno Y, Yamashita N, Degawa M, Yoshinari K, Nemoto K. The Differential Selectivity of
821 Aryl Hydrocarbon Receptor (AHR) Agonists towards AHR-Dependent Suppression of
822 Mammosphere Formation and Gene Transcription in Human Breast Cancer Cells. *Biol Pharm Bull.*
823 2021;44(4):571-578. doi: 10.1248/bpb.b20-00961. PMID: 33790107.
- 824 Sari  N, Selby M, Ramaswamy V, Kool M, Stockinger B, Hogstrand C, Williamson D, Marino S,
825 Taylor MD, Clifford SC, Basson MA. The AHR pathway represses TGF -SMAD3 signalling and
826 has a potent tumour suppressive role in SHH medulloblastoma. *Sci Rep.* 2020 Jan 10;10(1):148. doi:
827 10.1038/s41598-019-56876-z. PMID: 31924815; PMCID: PMC6954114.
- 828 Shan NL, Shin Y, Yang G, Furmanski P, Suh N. Breast cancer stem cells: A review of their
829 characteristics and the agents that affect them. *Mol Carcinog.* 2021 Feb;60(2):73-100. doi:
830 10.1002/mc.23277. Epub 2021 Jan 11. PMID: 33428807; PMCID: PMC7855917.
- 831 Shen J, Liao Y, Hopper JL, Goldberg M, Santella RM, Terry MB. Dependence of cancer risk from
832 environmental exposures on underlying genetic susceptibility: an illustration with polycyclic
833 aromatic hydrocarbons and breast cancer. *Br J Cancer.* 2017 Apr 25;116(9):1229-1233. doi:
834 10.1038/bjc.2017.81. Epub 2017 Mar 28. PMID: 28350789; PMCID: PMC5418454.

835

836 Simones T, Shepherd DM. Consequences of AhR activation in steady-state dendritic cells. *Toxicol*
837 *Sci.* 2011 Feb;119(2):293-307. doi: 10.1093/toxsci/kfq354. Epub 2010 Nov 19. PMID: 21097750;
838 PMID: PMC3023567.

839 Song R and Struhl K. S100A8/S100A9 cytokine acts as a transcriptional coactivator during breast
840 cellular transformation. *Sci Adv.* 2021 Jan 1;7(1):eabe5357. doi: 10.1126/sciadv.abe5357. PMID:
841 33523865; PMID: PMC7775746.

842 Soria G and A. Ben-Baruch: The inflammatory chemokines CCL2 and CCL5 in breast cancer.
843 *Cancer Lett*, 267(2), 271-85 (2008)
844

845 Stanford EA, Wang Z, Novikov O, Mulas F, Landesman-Bollag E, Monti S, Smith BW, Seldin DC,
846 Murphy GJ, Sherr DH. The role of the aryl hydrocarbon receptor in the development of cells with the
847 molecular and functional characteristics of cancer stem-like cells. *BMC Biol.* 2016 Mar 16;14:20.
848 doi: 10.1186/s12915-016-0240-y. PMID: 26984638; PMID: PMC4794823.
849

850 Stuart AL, Mudhasakul S, Sriwatanapongse W. The social distribution of neighborhood-scale air
851 pollution and monitoring protection. *J Air Waste Manag Assoc.* 2009 May;59(5):591-602. doi:
852 10.3155/1047-3289.59.5.591. PMID: 19583159.
853

854 Swope CB, Hernández D, Cushing LJ. The Relationship of Historical Redlining with Present-Day
855 Neighborhood Environmental and Health Outcomes: A Scoping Review and Conceptual Model. *J*
856 *Urban Health.* 2022 Aug 1:1–25. doi: 10.1007/s11524-022-00665-z. Epub ahead of print. PMID:
857 35915192; PMID: PMC9342590.
858

859 Takenaka MC, Gabriely G, Rothhammer V, Mascanfroni ID, Wheeler MA, Chao CC, Gutiérrez-
860 Vázquez C, Kenison J, Tjon EC, Barroso A, Vandeventer T, de Lima KA, Rothweiler S, Mayo L,
861 Ghannam S, Zandee S, Healy L, Sherr D, Farez MF, Prat A, Antel J, Reardon DA, Zhang H, Robson
862 SC, Getz G, Weiner HL, Quintana FJ. Control of tumor-associated macrophages and T cells in
863 glioblastoma via AHR and CD39. *Nat Neurosci.* 2019 May;22(5):729-740. doi: 10.1038/s41593-019-
864 0370-y. Epub 2019 Apr 8. Erratum in: *Nat Neurosci.* 2019 Sep;22(9):1533. PMID: 30962630;
865 PMID: PMC8052632.

866 Tan KP, Wang B, Yang M, Boutros PC, Macaulay J, Xu H, Chuang AI, Kosuge K, Yamamoto M,
867 Takahashi S, Wu AM, Ross DD, Harper PA, Ito S. Aryl hydrocarbon receptor is a transcriptional
868 activator of the human breast cancer resistance protein (BCRP/ABCG2). *Mol Pharmacol.* 2010
869 Aug;78(2):175-85. doi: 10.1124/mol.110.065078. Epub 2010 May 11. PMID: 20460431.

870 Therachiyil L, Hussein OJ, Uddin S, Korashy HM. Regulation of the aryl hydrocarbon receptor in
871 cancer and cancer stem cells of gynecological malignancies: An update on signaling pathways.
872 *Semin Cancer Biol.* 2022 Oct 15;86(Pt 3):1186-1202. doi: 10.1016/j.semcancer.2022.10.003. Epub
873 ahead of print. PMID: 36252938.

874 Timaxian C, C. F. A. Vogel, C. Orcel, D. Vetter, C. Durochat, C. Chinal, N. G. P, M. L. Aknin, F.
875 Mercier-Nome, M. Davy, I. Raymond-Letron, T. N. Van, S. D. Diermeier, A. Godefroy, M. Gary-
876 Bobo, F. Molina, K. Balabanian and G. Lazennec: Pivotal Role for Cxcr2 in Regulating Tumor-

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

- 877 Associated Neutrophil in Breast Cancer. *Cancers (Basel)*, 13(11) (2021)
878 doi:10.3390/cancers13112584
- 879 Timperi E, Gueguen P, Molgora M, Magagna I, Kieffer Y, Lopez-Lastra S, Sirven P, Baudrin LG,
880 Baulande S, Nicolas A, Champenois G, Meseure D, Vincent-Salomon A, Tardivon A, Laas E,
881 Soumelis V, Colonna M, Mechta-Grigoriou F, Amigorena S, Romano E. Lipid-Associated
882 Macrophages Are Induced by Cancer-Associated Fibroblasts and Mediate Immune Suppression in
883 Breast Cancer. *Cancer Res.* 2022 Sep 16;82(18):3291-3306. doi: 10.1158/0008-5472.CAN-22-1427.
884 PMID: 35862581.
- 885 Trombino AF, Near RI, Matulka RA, Yang S, Hafer LJ, Toselli PA, Kim DW, Rogers AE,
886 Sonenshein GE, Sherr DH. Expression of the aryl hydrocarbon receptor/transcription factor (AhR)
887 and AhR-regulated CYP1 gene transcripts in a rat model of mammary tumorigenesis. *Breast Cancer*
888 *Res Treat.* 2000, 63(2):117-31.
- 889 Ugel S, De Sanctis F, Mandruzzato S, Bronte V. Tumor-induced myeloid deviation: when myeloid-
890 derived suppressor cells meet tumor-associated macrophages. *J Clin Invest.* (2015) 125:3365–76. doi:
891 10.1172/JCI80006
- 892 Vacher S, Castagnet P, Chemlali W, Lallemand F, Meseure D, Pocard M, Bieche I, Perrot-Applanat
893 M. High AHR expression in breast tumors correlates with expression of genes from several signaling
894 pathways namely inflammation and endogenous tryptophan metabolism. *PLoS One.* 2018 Jan
895 10;13(1):e0190619.
- 896 Vogel C, Abel J. Effect of 2,3,7,8-tetrachlorodibenzo-p-dioxin on growth factor expression in the
897 human breast cancer cell line MCF-7. *Arch Toxicol.* 1995;69(4):259-65. doi:
898 10.1007/s002040050168. PMID: 7755487.
- 899 Vogel C, Boerboom AM, Baechle C, El-Bahay C, Kahl R, Degen GH, Abel J. Regulation of
900 prostaglandin endoperoxide H synthase-2 induction by dioxin in rat hepatocytes: possible c-Src-
901 mediated pathway. *Carcinogenesis.* 2000 Dec;21(12):2267-74.
- 902 Vogel CF, Sciallo E, Park S, Liedtke C, Trautwein C, Matsumura F. Dioxin increases C/EBPbeta
903 transcription by activating cAMP/protein kinase A. *J Biol Chem.* 2004 Mar 5;279(10):8886-94.
904
- 905 Vogel CF, E. Sciallo, W. Li, P. Wong, G. Lazennec and F. Matsumura: RelB, a New Partner of Aryl
906 Hydrocarbon Receptor-Mediated Transcription. *Mol Endocrinol*, 21(12), 2941-55 (2007)
907
- 908 Vogel CF, Goth SR, Dong B, Pessah IN, Matsumura F. Aryl hydrocarbon receptor signaling
909 mediates expression of indoleamine 2,3-dioxygenase. *Biochem Biophys Res Commun.* 2008;
910 375(3):331-5.
- 911 Vogel CF, Li W, Wu D, Miller JK, Sweeney C, Lazennec G, Fujisawa Y, Matsumura F. Interaction
912 of aryl hydrocarbon receptor and NF- κ B subunit RelB in breast cancer is associated with interleukin-
913 8 overexpression. *Arch Biochem Biophys.* 2011 Aug 1; 512(1):78-86.
914
- 915 Vogel CF, Wu D, Goth SR, Baek J, Lollies A, Domhardt R, Grindel A, Pessah IN. Aryl hydrocarbon
916 receptor signaling regulates NF- κ B RelB activation during dendritic-cell differentiation. *Immunol*

- 917 Cell Biol. 2013 Oct;91(9):568-75. doi: 10.1038/icb.2013.43. Epub 2013 Sep 3. PMID: 23999131;
918 PMCID: PMC3806313.
- 919
- 920 Vogel CF, Khan EM, Leung PS, Gershwin ME, Chang WL, Wu D, Haarmann-Stemmann T,
921 Hoffmann A, Denison MS. Cross-talk between aryl hydrocarbon receptor and the inflammatory
922 response: a role for nuclear factor- κ B. *J Biol Chem*. 2014 Jan 17;289(3):1866-75.
923
- 924 Vogel CF, Chang WL, Kado S, McCulloh K, Vogel H, Wu D, Haarmann-Stemmann T, Yang G,
925 Leung PS, Matsumura F, Gershwin ME. Transgenic Overexpression of Aryl Hydrocarbon Receptor
926 Repressor (AhRR) and AhR-Mediated Induction of CYP1A1, Cytokines, and Acute Toxicity.
927 *Environ Health Perspect*. 2016 Jul;124(7):1071-83. doi: 10.1289/ehp.1510194. Epub 2016 Feb 5.
928 PMID: 26862745; PMCID: PMC4937866.
- 929 Vogel CFA, Van Winkle LS, Esser C, Haarmann-Stemmann T. The aryl hydrocarbon receptor as a
930 target of environmental stressors - Implications for pollution mediated stress and inflammatory
931 responses. *Redox Biol*. 2020 Jul;34:101530. doi: 10.1016/j.redox.2020.101530. Epub 2020 Apr 18.
932 PMID: 32354640; PMCID: PMC7327980.
- 933 Vogel CFA, Lazennec G, Kado SY, Dahlem C, He Y, Castaneda A, Ishihara Y, Vogeley C, Rossi A,
934 Haarmann-Stemmann T, Jugan J, Mori H, Borowsky AD, La Merrill MA, Sweeney C. Targeting the
935 Aryl Hydrocarbon Receptor Signaling Pathway in Breast Cancer Development. *Front Immunol*. 2021
936 Mar 8;12:625346. doi:10.3389/fimmu.2021.625346. PMID: 33763068; PMCID: PMC7982668.
- 937 Voigt C, May P, Gottschlich A, Markota A, Wenk D, Gerlach I, Voigt S, Stathopoulos GT, Arendt
938 KAM, Heise C, Rataj F, Janssen KP, Königshoff M, Winter H, Himsl I, Thasler WE, Schnurr M,
939 Rothenfuß S, Endres S, Kobold S. Cancer cells induce interleukin-22 production from memory
940 CD4⁺ T cells via interleukin-1 to promote tumor growth. *Proc Natl Acad Sci U S A*. 2017 Dec
941 5;114(49):12994-12999. doi: 10.1073/pnas.1705165114. Epub 2017 Nov 17. PMID: 29150554;
942 PMCID: PMC5724250.
- 943 Vorderstrasse B. A.; Fenton S. E.; Bohn A. A.; Cundiff J. A.; Lawrence B. P. A novel effect of
944 dioxin: exposure during pregnancy severely impairs mammary gland differentiation. *Toxicol. Sci*.
945 2004, 782248–25710.1093/toxsci/kfh062.
946
- 947 Wang S, Yao Y, Yao M, Fu P, Wang W. Interleukin-22 promotes triple negative breast cancer cells
948 migration and paclitaxel resistance through JAK-STAT3/MAPKs/AKT signaling pathways. *Biochem*
949 *Biophys Res Commun*. 2018 Sep 10;503(3):1605-1609. doi: 10.1016/j.bbrc.2018.07.088. Epub 2018
950 Jul 23. PMID: 30072097.
- 951 Wang Z, Monti S, and Sherr D. The diverse and important contribution of AHR to cancer and cancer
952 immunity. *Curr Opin Toxicol*. 2017 Feb;2:93-102.
- 953 Wang Z, Snyder M, Kenison JE, Yang K, Lara B, Lydell E, Bennani K, Novikov O, Federico A,
954 Monti S, Sherr DH. How the AHR Became Important in Cancer: The Role of Chronically Active
955 AHR in Cancer Aggression. *Int J Mol Sci*. 2020 Dec 31;22(1):387. doi: 10.3390/ijms22010387.
956 PMID: 33396563; PMCID: PMC7795223.

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

- 957 Warner M, Eskenazi B, Mocarelli P, Gerthoux PM, Samuels S, Needham L, Patterson D, Brambilla
958 P. Serum dioxin concentrations and breast cancer risk in the Seveso Women's Health Study. *Environ*
959 *Health Perspect.* 2002 Jul;110(7):625-8. doi: 10.1289/ehp.02110625. PMID: 12117637; PMCID:
960 PMC1240906.
- 961 Wong PS, Li W, Vogel CF, Matsumura F. Characterization of MCF mammary epithelial cells
962 overexpressing the Arylhydrocarbon receptor (AhR). *BMC Cancer.* 9: 234, 2009.
- 963
- 964 Wu W, Muller R, Berhane K, Fruin S, Liu F, Jaspers I, Diaz-Sanchez D, Peden DB, McConnell R.
965 Inflammatory response of monocytes to ambient particles varies by highway proximity. *Am J Respir*
966 *Cell Mol Biol.* 2014 Dec;51(6):802-9. doi: 10.1165/rcmb.2013-0265OC. PMID: 24895888; PMCID:
967 PMC4291543.
- 968
- 969 Wu Z, Yan L, Lin J, Ke K, Yang W. Constitutive TDO2 expression promotes liver cancer
970 progression by an autocrine IL-6 signaling pathway. *Cancer Cell Int.* 2021 Oct 17;21(1):538. doi:
971 10.1186/s12935-021-02228-9. PMID: 34657635; PMCID: PMC8522106.
- 972 Xue P, Fu J, Zhou Y. The Aryl Hydrocarbon Receptor and Tumor Immunity. *Front Immunol.* 2018
973 Feb 13;9:286. doi: 10.3389/fimmu.2018.00286. PMID: 29487603; PMCID: PMC5816799.
- 974 Yamashita N, Yoshizuka A, Kase A, Ozawa M, Taga C, Sanada N, Kanno Y, Nemoto K, Kizu R.
975 Activation of the aryl hydrocarbon receptor by 3-methylcholanthrene, but not by indirubin,
976 suppresses mammosphere formation via downregulation of CDC20 expression in breast cancer cells.
977 *Biochem Biophys Res Commun.* 2021 Sep 17;570:131-136. doi: 10.1016/j.bbrc.2021.07.047. Epub
978 2021 Jul 17. PMID: 34280616.
- 979 Yamashita N, Taga C, Ozawa M, Kanno Y, Sanada N, Kizu R. Camalexin, an indole phytoalexin,
980 inhibits cell proliferation, migration, and mammosphere formation in breast cancer cells via the aryl
981 hydrocarbon receptor. *J Nat Med.* 2022 Jan;76(1):110-118. doi: 10.1007/s11418-021-01560-8. Epub
982 2021 Aug 31. PMID: 34463909.
- 983 Yan B, Liu S, Shi Y, Liu N, Chen L, Wang X, Xiao D, Liu X, Mao C, Jiang Y, Lai W, Xin X, Tang
984 CE, Luo D, Tan T, Jia J, Liu Y, Yang R, Huang J, Zhou H, Cheng Y, Cao Y, Yu W, Muegge K, Tao
985 Y. Activation of AhR with nuclear IKK α regulates cancer stem-like properties in the occurrence of
986 radioresistance. *Cell Death Dis.* 2018 May 1;9(5):490. doi: 10.1038/s41419-018-0542-9. PMID:
987 29706625; PMCID: PMC5924755.
- 988 Yu J, Du W, Yan F, Wang Y, Li H, Cao S, Yu W, Shen C, Liu J, Ren X. Myeloid-derived suppressor
989 cells suppress antitumor immune responses through IDO expression and correlate with lymph node
990 metastasis in patients with breast cancer. *J Immunol.* 2013 Apr 1;190(7):3783-97. doi:
991 10.4049/jimmunol.1201449. Epub 2013 Feb 25. PMID: 23440412.
- 992 Yu J, Wang Y, Yan F, Zhang P, Li H, Zhao H, Yan C, Yan F, Ren X. Noncanonical NF- κ B
993 activation mediates STAT3-stimulated IDO upregulation in myeloid-derived suppressor cells in
994 breast cancer. *J Immunol.* 2014 Sep 1;193(5):2574-86.
- 995

- 996 Yuan W, Fulgar CC, Sun X, Vogel CFA, Wu CW, Zhang Q, Bein KJ, Young DE, Li W, Wei H,
997 Pinkerton KE. In vivo and in vitro inflammatory responses to fine particulate matter (PM_{2.5}) from
998 China and California. *Toxicol Lett.* 2020 Aug 1;328:52-60. doi: 10.1016/j.toxlet.2020.04.010. Epub
999 2020 Apr 19. PMID: 32320776; PMCID: PMC7641014.
- 1000
- 1001 Zattoni IF, Delabio LC, Dutra JP, Kita DH, Scheiffer G, Hembecker M, Pereira GDS, Moure VR,
1002 Valdameri G. Targeting breast cancer resistance protein (BCRP/ABCG2): Functional inhibitors and
1003 expression modulators. *Eur J Med Chem.* 2022 Jul 5;237:114346. doi:
1004 10.1016/j.ejmech.2022.114346. Epub 2022 Apr 6. PMID: 35483322.
- 1005 Zhang QW, Liu L, Gong CY, Shi HS, Zeng YH, Wang XZ, et al. . Prognostic significance of tumor-
1006 associated macrophages in solid tumor: a meta-analysis of the literature. *PLoS ONE.* (2012)
1007 7:e50946. 10.1371/journal.pone.0050946
- 1008 Zhang Q, J. Qin, L. Zhong, L. Gong, B. Zhang, Y. Zhang and W. Q. Gao: CCL5-Mediated Th2
1009 Immune Polarization Promotes Metastasis in Luminal Breast Cancer. *Cancer Res*, 75(20), 4312-21
1010 (2015) doi:10.1158/0008-5472.CAN-14-3590
- 1011 Zhao F, Hoechst B, Duffy A, Gamrekelashvili J, Fioravanti S, Manns MP, Greten TF, Korangy F.
1012 S100A9 a new marker for monocytic human myeloid-derived suppressor cells. *Immunology.* 2012
1013 Jun;136(2):176-83. doi: 10.1111/j.1365-2567.2012.03566.x. PMID: 22304731; PMCID:
1014 PMC3403264.
- 1015 Zhao S, Kanno Y, Nakayama M, Makimura M, Ohara S, Inouye Y. Activation of the aryl
1016 hydrocarbon receptor represses mammosphere formation in MCF-7 cells. *Cancer Lett.* 2012 Apr
1017 28;317(2):192-8. doi: 10.1016/j.canlet.2011.11.025. Epub 2011 Nov 26. PMID: 22123295.
- 1018 Zhao S, Ohara S, Kanno Y, Midorikawa Y, Nakayama M, Makimura M, Park Y, Inouye Y. HER2
1019 overexpression-mediated inflammatory signaling enhances mammosphere formation through up-
1020 regulation of aryl hydrocarbon receptor transcription. *Cancer Lett.* 2013 Mar 1;330(1):41-8. doi:
1021 10.1016/j.canlet.2012.11.021. Epub 2012 Nov 27. PMID: 23196063.
- 1022 Zhao X, Qu J, Sun Y, Wang J, Liu X, Wang F, et al. Prognostic significance of tumor-associated
1023 macrophages in breast cancer: a meta-analysis of the literature. *Oncotarget.* (2017) 8:30576–86. doi:
1024 10.18632/oncotarget.15736
- 1025 Zhou S, Schuetz JD, Bunting KD, Colapietro AM, Sampath J, Morris JJ, Lagutina I, Grosveld GC,
1026 Osawa M, Nakauchi H, Sorrentino BP. The ABC transporter Bcrp1/ABCG2 is expressed in a wide
1027 variety of stem cells and is a molecular determinant of the side-population phenotype. *Nat Med.* 2001
1028 Sep;7(9):1028-34. doi: 10.1038/nm0901-1028. PMID: 11533706.
- 1029 Zhou S, Schuetz JD, Bunting KD, Colapietro AM, Sampath J, Morris JJ, Lagutina I, Grosveld GC,
1030 Osawa M, Nakauchi H, Sorrentino BP. The ABC transporter Bcrp1/ABCG2 is expressed in a wide
1031 variety of stem cells and is a molecular determinant of the side-population phenotype. *Nat Med.* 2001
1032 Sep;7(9):1028-34. doi: 10.1038/nm0901-1028. PMID: 11533706.
- 1033

Running Title: AhR, the molecular bridge between environmental injustice and health disparities

1034 Zou E, Matsumura F. Long-term exposure to beta-hexachlorocyclohexane (beta-HCH) promotes
1035 transformation and invasiveness of MCF-7 human breast cancer cells. Long-term exposure to beta-
1036 hexachlorocyclohexane (beta-HCH) promotes transformation and invasiveness of MCF-7 human
1037 breast cancer cells. *Biochem Pharmacol.* 2003, 66(5):831-40. PMID: 12948864.

1038

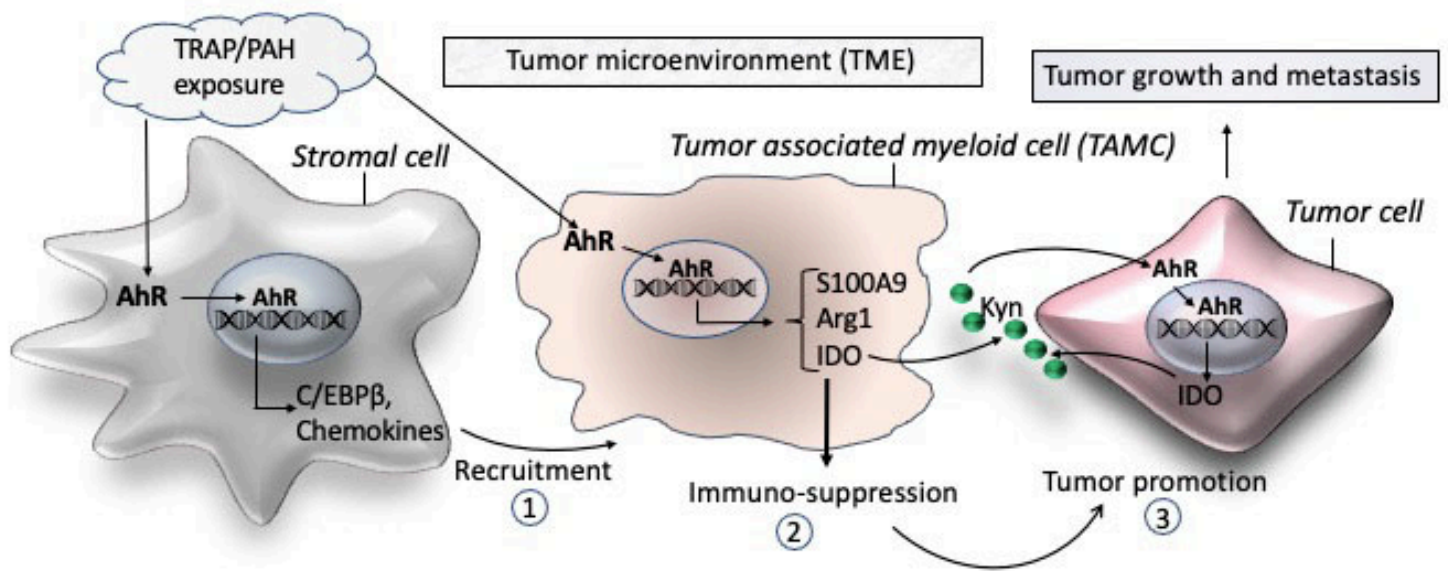
1039 Zudaire E, Cuesta N, Murty V, Woodson K, Adams L, Gonzalez N, Martínez A, Narayan G, Kirsch
1040 I, Franklin W, Hirsch F, Birrer M, Cuttitta F. The aryl hydrocarbon receptor repressor is a putative
1041 tumor suppressor gene in multiple human cancers. *J Clin Invest.* 2008 Feb;118(2):640-50. doi:
1042 10.1172/JCI30024. PMID: 18172554; PMCID: PMC2157559.

1043

1044 **Figure Legends**

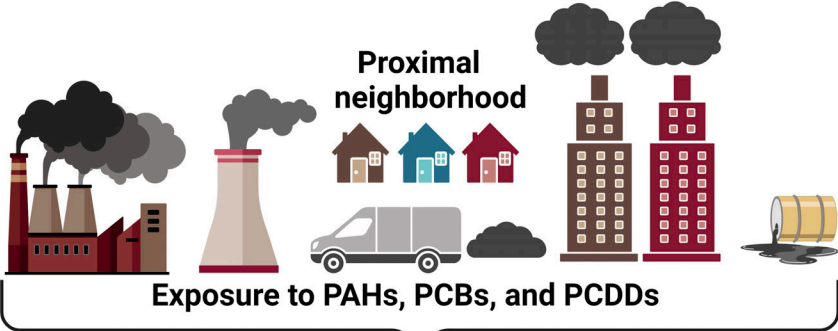
1045 **Figure 1:** Schematic of proposed mechanisms by which traffic-associated air pollution (TRAP)
1046 activates AhR to induce the accumulation of TAMCs (1) and expression of immune suppressive
1047 factors (2) leading to a tumor promoting microenvironment (3) and growth and metastasis of breast
1048 cancer.

1049 **Figure 2:** Overview of the link between systemic exclusion, environmental injustice, and AhR-driven
1050 tumor biology. Discriminatory housing and lending policies (ex: redlining) drove neighborhood
1051 racial/ethnic and socioeconomic segregation which persists today due to ongoing systemic
1052 discrimination and gentrification. Resources were and are disproportionately allocated to wealthier
1053 neighborhoods, contributing to neighborhood disinvestment. The proximal neighborhood has more
1054 traffic, pollution-generating factories and dump sites. It has less green space for stress relief and
1055 exercise, worsening the riskscape that individuals in the proximal neighborhood must navigate.
1056 Individuals living in the proximal neighborhood are chronically exposed to environmental toxins,
1057 tipping the scales of environmental justice against them. Polycyclic aromatic hydrocarbons (PAHs),
1058 Polychlorinated dibenzo-p-dioxins (PCDDs), and Polychlorinated biphenyls (PCBs) are generated by
1059 combustion processes as components of ambient particulate matter (PM) derived from urban areas
1060 and industrial activities. PAHs, PCDDs and PCBs robustly activate the AhR signaling pathway,
1061 promoting cancer stemness and interrelated functional outcomes, including plasticity,
1062 chemoresistance, EMT and immune evasion, which synergize to drive breast cancer metastasis and
1063 disparate outcomes for individuals in proximal neighborhoods.



Systemic Exclusion and Disinvestment

Gentrification and Displacement



Environmental Injustice



Distal neighborhood

