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

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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 through 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
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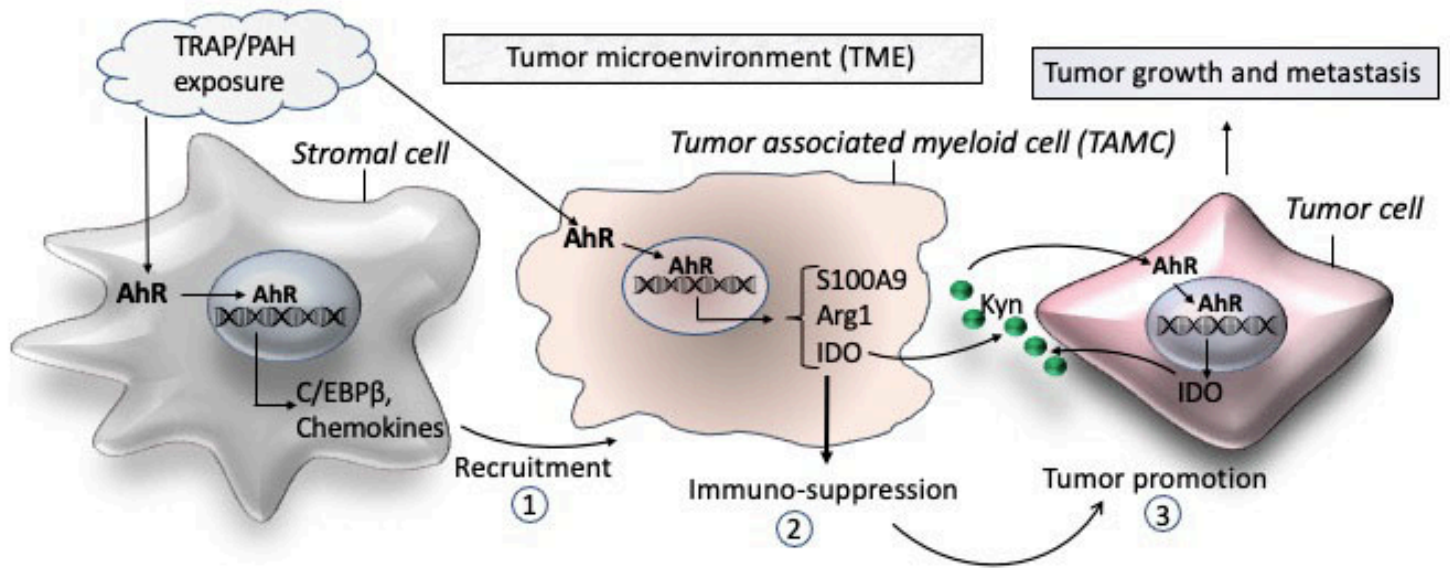
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1044 **Figure Legends**

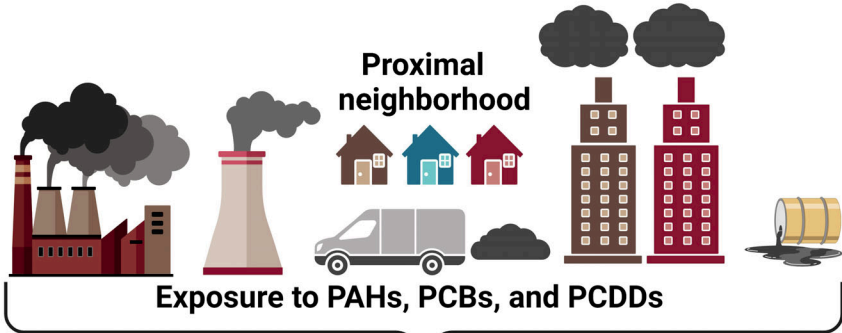
1045 **Figure 1:** Schematic of proposed mechanisms by which traffic-associated air pollution (TRAP)
1046 activates AhR to induce the accumulation of TAMCs (1) and expression of immune suppressive
1047 factors (2) leading to a tumor promoting microenvironment (3) and growth and metastasis of breast
1048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

