REVIEW

The aryl hydrocarbon receptor in environmentally induced cervical cancer: A Narrative review

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ABSTRACT

The aryl hydrocarbon receptor (AhR) plays a crucial role in cellular responses to various environmental pollutants, including several known carcinogens. As a ligand-activated transcription factor, AhR activation modulates the expression of genes involved in critical cellular processes, including detoxification pathways, cell proliferation and differentiation, and immune system regulation. The AhR exhibits pleiotropic effects under normal physiological conditions, contributing to the development and function of various organ systems. AhR activity is important in angiogenesis, cardiomyocyte differentiation, oocyte maturation, oculomotor nerve formation, and hematopoietic stem cell maintenance. Additionally, AhR plays a role in regulating immune cell differentiation and function, maintaining the integrity of the intestinal epithelium and its associated immune system, and mediating UVB-induced DNA damage repair responses in the skin. It acts as a critical environmental sensor, mediating cellular responses to various exogenous ligands. Importantly, activation or inhibition of AhR affects distinct signaling pathways depending on the specific ligand and cellular context. Ligands for the AhR are divided into exogenous or endogenous and have agonistic or antagonistic activity. Recently, the AhR role was determined in cancer development. It can exert both tumor-promoting and tumor-suppressive effects depending on factors such as the specific ligand, cell type, and tissue microenvironment. Emerging evidence suggests that AhR may represent a promising target for immunotherapy and serve as a potential biomarker for cervical cancer. AhR interacts with apoptotic pathway, immune checkpoint system, steroid hormones, and immune cell regulation process in cervical cancer. Despite its potential significance, the precise role of AhR in cervical cancer development and progression is still unknown. In this review, we describe significant roles of AhR in gynecological cancers; e.g., in cervical cancer.

Key Words: Aryl hydrocarbon receptor, Gynecological cancer, Cervical cancer, Function, Immunotherapy target, Biomarker

1. INTRODUCTION

Gynecological cancers pose a significant threat to women's health, impacting the reproductive system and overall well-being. Accumulating evidence suggests that exposure to environmental pollutants, including polycyclic aromatic hydrocarbons (PAHs), can contribute to the development and progression of gynecological malignancies. These pollutants exert their carcinogenic effects by stimulating the proliferation of precancerous and cancerous cells.[1] The aryl hydrocarbon receptor (AhR) has emerged as a critical mediator of cellular responses to environmental chemicals, including many known carcinogens. Research has highlighted the intricate involvement of AhR in various cancer-related signaling pathways, including those governing apoptosis, immune checkpoint regulation, epithelial-mesenchymal transition, and G-protein-coupled receptor signaling. Furthermore, studies have begun to unravel the dysregulation of AhR sig-

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naling in gynecological cancers, suggesting its potential role in tumorigenesis and progression.[2, 3]

Several factors beyond environmental pollutants influence the development and progression of gynecological cancers. Viral infections, alterations in the microbiome composition, and epigenetic dysregulation, including changes in non-coding RNA (ncRNA) expression, have been implicated in cellular transformation and contribute to the overall risk of these malignancies.[2, 3] Cervical cancer, like many other malignancies, is often resistant to chemotherapy. This resistance has been linked, in part, to the presence of cancer stem cells (CSCs), a subpopulation of highly tumorigenic cells characterized by their ability to evade apoptosis induced by conventional therapies.[4] The identified cervical CSCs based on a stemness-specific property (i.e., high expression of Aldehyde dehydrogenase (ALDH)) were found to be resistant to chemotherapeutic drugs.[5] Elevated ALDH expression has been observed in cervical cancer cells and linked to aggressive tumor behavior, including increased rates of cell proliferation, migration, and overall tumorigenesis.[6] Cervical CSCs exhibit a distinct molecular profile characterized by the expression of stemness-associated genes, including those encoding ABC transporters, OCT4, Nanog, SOX2, cytokeratin 17 (CK-17), and Musashi-1 (MSI1). Notably, the expression of CSC-related genes, such as MSI1 and CD49f, has been associated with poor clinical outcomes in cervical cancer patients, suggesting their potential utility as prognostic biomarkers.[7] Also, high expression of Shh gene (related to sonic hedgehog signaling pathway) was detected in cervical intraepithelial neoplasia and cervical cancer.[8] On the other hand, Notch is a significant pathway that is deregulated in cancer, leading to the metastatic potential of tumors.[9] Activation of the AhR pathway by environmental chemicals has been implicated in the expansion and maintenance of CSC populations, potentially contributing to cancer initiation and progression.[10] AhR regulates tumorigenesis by retaining the properties of CSC, resulting in chemoresistance and the proliferation of tumor cells.[11] In contrast, AhR activation was reported to inhibit the growth of liver and breast cancers.[12] Thus, it seems to study precisely the roles of AhR and its effects on the transcriptional regulation of CSCs in gynecological cancers.[1] The role of AhR in cancer is multifaceted, as it can exert both tumor-promoting and tumor-suppressive effects depending on the cellular context and specific ligand involved. This duality of function complicates the understanding of AhR signaling in cancer. Indeed, the expression level and activity of AhR can significantly vary in different tumor types. The evolutionary history of AhR in vertebrates has resulted in its ability to bind a wide range of both endogenous and exogenous ligands. For example, AhR demonstrates an affinity for endogenous ligands like kynurenine and exogenous ligands such as benzo(a)pyrene (BaP). Importantly, these ligands can exhibit tissue-specific agonist or antagonist activity, further highlighting the complexity of AhR signaling.[13, 14] In this review, we describe prominent roles of AhR and its related genes in gynecological cancers especially in cervical cancer.

2. Cervical cancer

Cervical cancer represents a significant global health concern, ranking as the fourth most frequently diagnosed cancer among women worldwide. Notably, it is the seventh most common cancer overall, underscoring its impact on women's health.[15, 16] The previous studies showed that tumor can be metastasize to lung and then liver, bone and brain in cervical cancer patients [16]. This malignancy was strongly associated to viral infections especially human papillomavirus (HPV) infection.[17–19] Surgery and chemotherapy are two standard therapies against cervical cancer.[20] However, chemoresistance was observed in the advanced stages of cancer. Tumor invasion, metastasis, and recurrence represent significant challenges in cancer treatment, often leading to poor therapeutic response and ultimately impacting patient survival.[21] Given the challenges associated with treating advanced cervical cancer, there is a pressing need to identify new therapeutic targets and predictive biomarkers. Recent research has highlighted that AhR and CYP1A1 (a member of the CYP1 gene family) may serve as prognostic biomarkers for determining prognosis and immune infiltration in cervical cancer.[22]

While AhR is increasingly recognized for its involvement in various cancers, including cervical cancer, its precise role in tumorigenesis and progression remains complex and incompletely understood. AhR overexpression has been observed in several cancer types, including cervical cancer, suggesting its potential as a therapeutic target.[23] However, further research is warranted to fully elucidate the specific mechanisms by which AhR contributes to cervical cancer development and to evaluate its suitability as a target for novel therapies.

3. AhR-mediated transcriptional control of CSC pathways in cervical cancer

Chemotherapy resistance, often driven by the presence of treatment-refractory CSCs, represents a major obstacle in achieving long-term survival for cervical cancer patients. The presence of genetic diversity in cervical cancer was related to a high prevalence of chemotherapy resistance and metastasis.[24, 25] For example, research by Vishnoi et al. revealed that the human papillomavirus (HPV) E6 oncogene could

increase the population of CSCs within cervical tumors.[26] Cervical CSCs identified based on high levels of ALDH expression were resistant to cisplatin in the treatment of cervical cancer.[27,28] As mentioned above, several stemness-related genes were determined in cervical CSCs.[29] Studies have implicated AhR in the regulation of tumorigenesis, suggesting a potential role in preserving CSC properties and promoting tumor development.[30] Exposure to environmental pollutants, such as PAHs, could activate the AhR/CYP1 pathway in gynecological cancers. This activation can lead to the upregulation of genes associated with resistance to chemotherapy and radiotherapy, including genes encoding β-catenin, ALDH1, CD133, SOX2, and IDO1, among others. These findings suggest a potential mechanism by which environmental exposures may contribute to treatment resistance in these malignancies. To et al. highlight the intricate involvement of AhR/CYP1 pathways in promoting key CSC characteristics within cervical cancer. For instance, activation of the ABCG2 transporter, a well-known CSC marker, has been linked to AhR/CYP1 signaling.[31] Furthermore, this pathway can enhance tumor proliferation through the activation of PI3K/AKT and MAPK signaling cascades. Additionally, AhR/CYP1 activation may contribute to tumor survival by tipping the balance of apoptotic regulators, favoring anti-apoptotic proteins like BCL-2, BCL-XL, and MCL-1 while suppressing pro-apoptotic proteins such as BAX and BAK.[32] Finally, evidence suggests that AhR/CYP1 signaling might facilitate immune evasion by tumor cells, potentially through interactions with the kynurenine pathway, G-protein-coupled receptors, and hormone receptors, including the follicle-stimulating hormone receptor (FSHR).[32] These findings underscore the multifaceted role of AhR/CYP1 signaling in driving cervical cancer progression and highlight its potential as a therapeutic target.

4. Definition of aryl hydrocarbon receptor

The AhR is a ligand-activated transcription factor residing in the cytoplasm. As a member of the basic Helix-Loop-Helix–Period/ARNT/Single-minded (bHLH-PAS) family, AhR plays a crucial role in regulating gene expression programs involved in diverse cellular processes, including hydrocarbon metabolism, cell proliferation and differentiation, detoxification, and immune system modulation.[33] AhR demonstrates a remarkable capacity to bind a broad range of ligands, including naturally occurring and synthetic compounds. Aromatic hydrocarbons, such as dioxins and biphenyls, are well-established ligands for AhR.[1] Additionally, AhR exhibits an affinity for various chemical carcinogens, including dioxins and polyaromatic hydrocarbons, highlighting its role in cellular responses to environmental pollutants.[33]

The AhR signaling pathway, first characterized in the early 1990s, involves a complex series of events culminating in gene expression changes.[34] In its inactive state, AhR resides in the cytoplasm as part of a multi-protein complex. This complex includes chaperone proteins such as heat shock protein 90 (HSP90) and its co-chaperone p23, as well as immunophilin-like Ah receptor-interacting protein (AIP), also known as hepatitis B virus (HBV) X-associated protein 2 (XAP2), and pp60 Src. These interacting partners ensure proper AhR folding and prevent its premature degradation while simultaneously masking its nuclear localization signal and DNA binding domain.[1,34] Upon binding to a ligand, AhR undergoes a conformational change, leading to its dissociation from the cytoplasmic complex and subsequent translocation to the nucleus. Within the nucleus, AhR forms a heterodimer with the aryl hydrocarbon receptor nuclear translocator (ARNT). This pivotal interaction, first described in 1992, is mediated by specific domains within AhR identified in 1994.[1,34] The AhR/ARNT heterodimer binds to specific DNA sequences known as xenobiotic responsive elements (XREs), characterized by the core sequence TNGCGTG. This binding event recruits transcriptional co-activators, including NCoA-2 and p/CIP, ultimately initiating the transcription of target genes. Many AhR-regulated genes are involved in xenobiotic metabolism, such as those encoding cytochrome P450 enzymes (CYPs), including CYP1A1, CYP1A2, and CYP1B1.[1,34] Following its transcriptional regulatory role, AhR is exported back to the cytoplasm, where it is targeted for degradation by the 26S proteasome, ensuring tight control of its activity.[1] Figure 1 shows the transcriptional AhR signaling pathway.

CYP1A1, a key enzyme induced downstream of AhR activation, plays a significant role in the bioactivation of certain procarcinogens. This enzymatic conversion often generates highly reactive metabolites, such as diol epoxides, which are capable of forming DNA adducts. These adducts can disrupt DNA integrity and contribute to genomic instability, potentially driving tumorigenesis. Furthermore, CYP1A1 induction has been linked to various hallmarks of cancer progression, including enhanced tumor cell proliferation, evasion of apoptosis, increased invasiveness and metastatic potential, stemness properties, and resistance to chemotherapy[35] (see Figure 2). These findings highlight the potential oncogenic implications of AhR-mediated CYP1A1 induction in the context of environmental carcinogen exposure.[35]

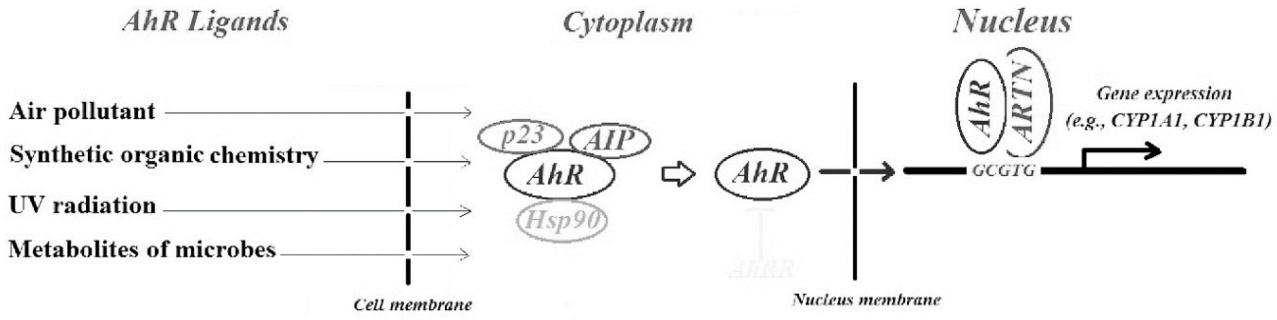

Figure 1. Schematic representation of the aryl hydrocarbon receptor (AhR) signaling pathway

Upon binding to environmental ligands, AhR dissociates from its cytoplasmic chaperone complex and translocates into the nucleus. Within the nucleus, AhR heterodimerizes with the aryl hydrocarbon receptor nuclear translocator (ARNT). The AhR/ARNT complex subsequently binds to xenobiotic responsive elements (XREs) within the promoter regions of target genes, such as CYP1A1 and CYP1B1, leading to their transcriptional activation. AhRR (AhR repressor) acts as a negative regulator of AhR signaling.

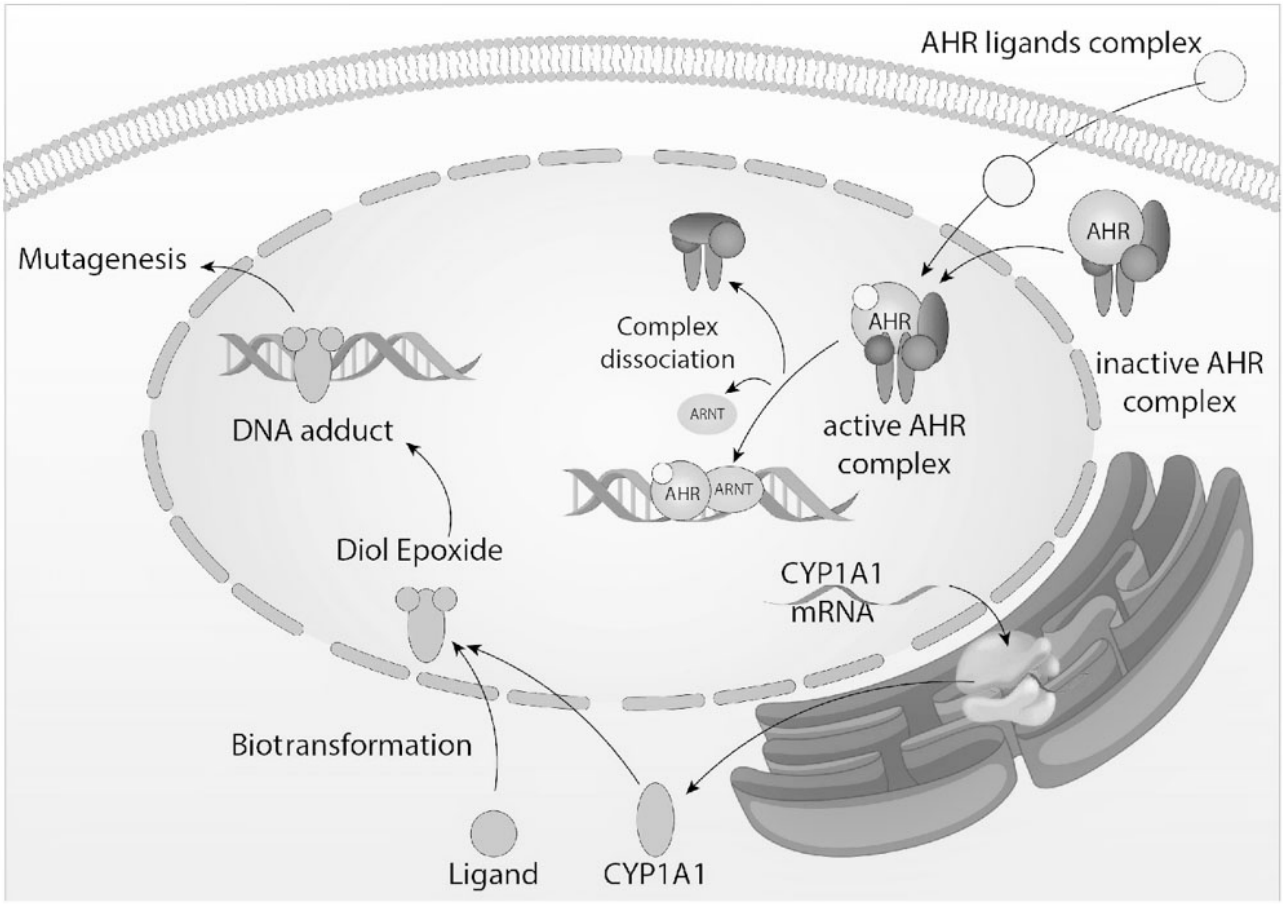

Figure 2. The role of the AhR/CYP1 pathway in cancer

Activation of the AhR signaling pathway induces the expression of cytochrome P450 1A1 (CYP1A1), an enzyme involved in the metabolism of various compounds, including procarcinogens. CYP1A1 can bioactivate certain procarcinogens into highly reactive metabolites, such as diol epoxides, which can subsequently form DNA adducts. This DNA damage, coupled with the modulation of various cellular pathways downstream of AhR activation, can contribute to several hallmarks of cancer, including enhanced tumorigenesis, proliferation, invasion, metastasis, and chemoresistance, as well as evasion of apoptosis and the acquisition of stemness properties.

Beyond its canonical role in xenobiotic metabolism, AhR signaling extends to interactions with other cellular pathways, including those mediated by steroid hormone receptors. For example, AhR has been shown to interact with the estrogen receptor, potentially influencing estrogen-responsive gene expression. Additionally, AhR can modulate cell cycle progression through interactions with key regulators like Rb and E2F1. Furthermore, AhR can cooperate with transcription factors such as c-Maf, expanding its repertoire of target genes. Importantly, AhR can also exert biological effects independent of its transcriptional activity. For instance, AhR can associate with and stabilize tissue factor (TF), a key regulator of coagulation, potentially contributing to thrombosis. AhR may also signal through its interaction with Src kinase or via E3 ubiquitin ligase activity, highlighting the diversity of its downstream effectors.[34] In some contexts, AhR overexpression has been linked to increased cell proliferation and migration. This effect is mediated, at least in part, through the upregulation of N-myc downstream-regulated gene 1 (NDRG1). For example, in breast cancer cells, AhR can directly activate NDRG1 transcription through an AhR binding site within the NDRG1 promoter, particularly under hypoxic conditions. This observation suggests a potential therapeutic avenue for targeting AhR signaling to inhibit tumor progression in hypoxic tumor microenvironments.[36]

5. The regulating roles of AhR in gynecological cancers

AhR expression has been confirmed in various female reproductive tissues, including the endometrium and myometrium, suggesting a potential role for this receptor in regulating physiological processes within these organs.[1,37] AhR is a significant regulator of some physiological functions (e.g., ovulation, fertilization, pregnancy, and fertility) in the female reproductive organs. Beyond its physiological roles, AhR has been implicated in tumorigenesis, exhibiting a complex duality in its effects. Specifically, AhR can function as either a tumor suppressor or a tumor promoter, depending on the cellular context and the nature of the ligands involved. The reports showed that the activation or overexpression of AhR induces tumorigenesis in various gynecological cancers.[22] It was observed that its expression was upregulated in endometrial cancer cells compared to normal endometrium tissues. In contrast, some studies showed that AhR ligands might inhibit the proliferation and migration of endometrial cancer likely through blocking estrogen receptor signaling by AhR leading to anti-tumorigenic effects.[32,38] The antiestrogenic effect of AhR was mainly investigated in breast cancer, but this AhR-estrogen crosstalk was slightly known in gynecological cancers such as cervical cancer. Given the intricate and context-dependent nature of AhR signaling in cancer, further research is warranted to fully elucidate the precise mechanisms by which AhR contributes to the development and progression of gynecological malignancies.[1] On the other hand, due to the importance of AhR in tumorigenesis, its role in regulating CSCs has been increasingly studied by researchers. Emerging evidence suggests a role for AhR activation in promoting stemness characteristics in various cancers, including oral squamous cell carcinoma. This effect may involve AhR binding to promoter regions of genes associated with stemness, thereby driving the growth and maintenance of CSCs.[1]

6. Functions of AhR in cervical cancer

Cervical cancer poses a significant threat to women's health globally, emphasizing the critical need to unravel the molecular mechanisms driving its development and to identify reliable biomarkers for early detection and treatment personalization.[22] The AhR and its extensive network of downstream target genes, estimated to encompass approximately 5,860 genes, have emerged as potential key players in cervical cancer biology. Among these genes, 3209 genes were positively, and 2,651 genes were negatively correlated with AhR. AhR-related ten genes such as CYP1A1, ARNT2, HSP90AA1, ARNT, AIP, PTGES3, HSP90AB1, CYP1B1, ESR1 and MAF, respectively showed prominent roles as a risk factor in cervical cancer.[22] A negative correlation has been observed between the prognosis of cervical cancer patients and the expression levels of specific genes. Elevated expression of AhR, CYP1A1, HSP90AA1, and HSP90AB1, along with reduced expression of ESR1, has been linked to poorer clinical outcomes in these patients. Furthermore, high expression and activity of AhR and its regulated genes (i.e., CYP1A1 and CYP1B1) were risk factors for prognosis in patients with cervical cancer.[22] CYP1A1 polymorphisms were also shown as a risk factor for the development of cervical cancer.[39,40] In a study by Alshammari et al., CYP1B1 expression was significantly higher in cervical cancer patients (91%) compared to healthy individuals. Furthermore, elevated CYP1B1 expression correlated positively with disease grade and lymph node metastasis, suggesting its potential utility as a prognostic marker in cervical cancer.[41] The interplay between genetic predisposition and environmental exposures is increasingly recognized as a critical factor in cervical cancer development. A study investigating the impact of functional genetic variants within four essential xenobiotic-metabolizing genes (AhR, CYP1A1-MspI, GSTM1, and GSTT1) in Tunisian women provided evidence supporting this notion. Specifically, the study revealed that

certain combinations of polymorphisms within these genes were associated with an elevated risk of cervical cancer, highlighting the importance of gene-environment interactions in this malignancy.[42]

AhR acts through cross-talk with other cell signaling pathways, as well. Up to now, various molecular targets regulated by AhR have been involved in cervical cancer apoptosis. For instance, AhR activation could upregulate the expression of pro-apoptotic proteins (e.g., Bax and p53), whereas downregulate anti-apoptotic factors (e.g., Bcl-2), leading to the induction of apoptosis in cervical cancer cells.[1] Moreover, AhR was found to interact with other signaling pathways involved in apoptosis regulation. AhR has been shown to engage in crosstalk with other signaling pathways, including the nuclear factor kappa B (NF-κB) pathway, a crucial regulator of cell survival and apoptosis. This interaction highlights the potential for AhR to influence these critical cellular processes. AhR-NF-κB interactions could modulate the expression of key apoptotic proteins that affect the fate of cervical cancer cells.[43] Immune checkpoint inhibitors have emerged as a groundbreaking advancement in cancer therapy within the past two decades, revolutionizing treatment approaches for various malignancies.[44]

Beyond its role in apoptosis regulation, AhR signaling has been implicated in modulating the expression of immune checkpoint molecules, including PD-L1. The PD-1/PD-L1 axis represents a critical immune checkpoint pathway often exploited by tumor cells to evade immune surveillance and establish an immunosuppressive tumor microenvironment.[1,22] The expression of PD-1 or PD-L1 in cervical cancer was more prevalent in patients with evident clinical traits. It was shown that PD-1 in T cells was induced through the activation of AhR in gynecological cancers. Activation of AhR could upregulate the expression of PD-L1, leading to the evasion of immune surveillance by cervical cancer cells.[1,22] Moreover, the primary pathway of tryptophan metabolism involves the indoleamine 2, 3-dioxygenase (IDO) and tryptophan 2, 3-dioxygenase (TDO) enzymes leading to the formation of the metabolite kynurenine.[45,46] Emerging evidence suggests a potential synergistic effect between AhR inhibition and IDO1 blockade in enhancing anti-tumor immunity within the cervical cancer microenvironment. This combination therapy holds promise for counteracting the immunosuppressive mechanisms often employed by tumors to evade immune destruction. Supporting this notion, research by Low et al. revealed an intriguing link between IDO1 expression and stemness in cervical cancer.[45,46] Their work demonstrated that IDO1 can regulate the expression of Notch1, a key stemness regulator, by facilitating the binding of the AhR/ARNT complex to the Notch1 promoter. This finding suggests a potential mechanism by which IDO1, potentially in concert with AhR signaling, may contribute to the maintenance of stem-like properties within cervical tumors.

On the other hand, the importance and efficiency of some widely used or potential anti-cancer drugs (e.g., alpha-naphthoflavone (ANF), betanaphthoflavone (BNF), clotrimazole (CLO), dimethoxybenzoquinone (DMB), paclitaxel (PAC), rifampicin (RIF) and RU-486) were studied as nuclear receptors (AhR or PXR (pregnane X receptors)) agonists or antagonists on HeLa cells, a cell line model for cervical cancer.[47] The results demonstrated that ANF and PAC act as agonists of the AhR-mediated transcription in a dose-dependent manner. Moreover, PAC and RIF induced PXR as a potent agonist. Among these drugs, only BNF showed an antagonistic activity toward AhR and PXR.[47] Sasaki-Kudoh et al. also demonstrated that cisplatin inhibited the AhR activation. Exposure to cisplatin, a chemotherapeutic agent, has been observed to induce the dissociation of HSP90 from AhR. Moreover, the induction of CYP1A1 was inhibited in the presence of cisplatin. Intriguingly, treatment with cisplatin led to the absence of detectable AhR in the soluble fraction of HeLa cells. This observation suggests that cisplatin may promote the dissociation of AhR from its protective HSP90 chaperone complex, potentially targeting it for degradation via the proteasome pathway.[48]

As known, cervical cancer is linked to HPV infection. The E6 and E7 proteins, encoded by the human papillomavirus (HPV) genome, are vital oncogenic drivers in cervical carcinogenesis. The E6 protein exerts its oncogenic effects, in part, by directly interacting with the tumor suppressor protein p53. This interaction promotes the degradation of p53, effectively nullifying its cell cycle regulatory functions and thereby contributing to uncontrolled cell proliferation. In contrast, the E7 protein targets retinoblastoma (Rb) tumor suppressor. Studies have shown that host cells can target the E6 and E7 viral oncoproteins for degradation through the ubiquitin-proteasome pathway. This process involves the ubiquitin-conjugating enzyme E2L3 (UBE2L3), which facilitates the attachment of ubiquitin molecules to the target proteins, marking them for proteasomal degradation.[49] AhR signaling appears to influence the expression of UBE2L3, as the UBE2L3 gene promoter harbors XREs capable of binding the AhR/ARNT complex. This finding suggests a potential mechanism by which AhR activation, potentially in response to xenobiotics, could modulate the degradation of HPV E6 and E7 oncoproteins. Further supporting a role for AhR in this process, Arellano-Gutiérrez et al. investigated the impact of indole-3-carbinol (I3C), an AhR ligand, on cervical cancer cells in vitro and in patient samples. Their study examined the effects of I3C on cell proliferation, apop-

tosis, and the expression levels of UBE2L3 and CYP1A1, providing insights into the complex interplay between AhR signaling, xenobiotic metabolism, and HPV-associated carcinogenesis. The results demonstrated that I3C induced the AhR activation, and reduced cell proliferation likely through UBE2L3 mRNA induction leading to the ubiquitination of HPV E7 protein. Thus, natural AhR ligands such as I3C showed a promising strategy for the treatment of selective and cost-effective cancer.[49]

Another main note is the progression of gynecological cancers through disruption in steroid hormones, i.e., estrogen, progesterone, and androgen) and their downstream signaling. Steroid hormones play a crucial role in the development and growth of reproductive tissues, such as the breast and cervix.[50,51] AhR has been shown to interact with estrogen receptor-α (ERα), potentially influencing the development of cervical cancer. This interaction may involve AhR altering ERα conformation, leading to the activation of ERα, downstream transcription factors, and protein complexes.[52] Elevated expression of AHR, CYP1A1, HSP90AA1, and HSP90AB1, along with reduced ESR1 expression, has been linked to poor survival outcomes in cervical cancer patients.[53] This indicates a potential role for these genes as prognostic biomarkers and warrants further investigation into their involvement in tumor immune responses.[53] Emerging evidence suggests that AhR may play a multifaceted role in modulating immune system activity within the tumor microenvironment of cervical cancer. AhR activation in immune cells within the tumor microenvironment can elicit an immunosuppressive response by inducing the IL-10 secretion, transforming growth factor-β (TGF-β) and vascular endothelial growth factor A (VEGFA), and subsequently decreasing the anti-tumor immune response.[32,54] Furthermore, AhR activation influenced the differentiation of CD4+ T cells. It can promote the differentiation of T regulatory cells (Tregs) that suppress immune responses and also the activity of cytotoxic CD8+ T cells for killing tumor cells.[55] AhR has been implicated in B-cell differentiation, potentially by suppressing the transcription of EBF1 and PAX5 genes involved in regulating metabolism within B-cell progenitors.[22,56] AhR activation in dendritic cells (DCs) can affect their function in antigen presentation and T cell activation, leading to the generation of tolerogenic DCs that fail to stimulate an effective anti-tumor immune response.[57] Emerging research suggests targeting AhR could offer a novel therapeutic avenue for modulating interleukin-6 (IL-6) levels in specific cancer types. As known, the expression and signal transduction of IL-6 in tumor cells can induce both protumor and antitumor properties.[58] Given the importance of IL-6 in tumor progression, identifying factors influencing its expression within the tumor microenvironment is crucial. Research suggests a potential role for AhR in this process. For example, AhR activity demonstrated a synergized effect with IL-1B or PMA treatment in elevating IL-6 levels in both MCF-7 breast cancer and ECC-1 endocervical cancer cell lines. This regulation of IL-6 mRNA expression appears at the chromatin level, with AhR influencing the IL-6 promoter. Notably, AhR and RELA, a member of the NF-κB family, seem to be required for this synergistic induction of IL-6, highlighting a potential mechanism by which AhR might contribute to tumor development.[58] Some AhR functions are shown in Table 1.

7. Carcinogenic and environmental ligands for AhR

The initial discovery of a hydroxylase inducer, later identified as a critical class of AhR ligands, dates back to the work of Poland and Glover in 1973.[59–61] In 1974, various sensitivities to the environmental chemical materials (e.g., tetrachlorodibenzo(p)dioxin (TCDD)) were observed in mice with genetic differences likely due to polymorphisms in unknown "induction" receptors.[62] Emerging evidence suggests mutagenesis may not be the sole driver of carcinogenicity for some environmental chemicals, highlighting the need to explore alternative mechanisms. It may be due to an inducer receptor. In this line, AhR was purified in 1988,[63] determined its sequence in 1991 with a highly conserved N-terminal sequence,[64] and cloned its gene in 1992.[65,66] Research into the effects of environmental chemicals has revealed that many can exert their influence through AhR. In some instances, this involves ligand-induced, AhR-mediated transcriptional upregulation of cytochrome P450 phase 1 hydroxylase, such as CYP1A1, CYP1A2, and CYP1B1. This upregulation can lead to the conversion of pro-carcinogens into mutagenic epoxide intermediates, highlighting a potential pathway for environmentally driven carcinogenesis.[34] Studies in mice have demonstrated the significance of these hydroxylases in PAH-induced carcinogenesis. Notably, mice lacking these enzymes exhibited a reduced incidence of malignant lymphomas and other tumors associated with PAH exposure. However, functional changes of AhR in humans led to a lower sensitivity to toxic PAHs compared to non-human primates. In contrast, sensitivity to nontoxic endogenous AhR ligands was maintained in human.[34] These findings underscore a compelling link between AhR and carcinogenesis. The proposed mechanism involves the activation of AhR by environmental compounds, leading to the induction of Phase 1 P450 hydroxylases. This, in turn, can result in generating mutagenic intermediates, either from pro-carcinogenic compounds or endogenous substrates like

estradiol or polyunsaturated fats. Ultimately, these events can culminate in DNA mutation and tumor development.[34] On the other hand, the relationship between AhR and innate/ adaptive immunity was proved. Emerging evidence suggests that AhR and its associated pathways, including its metabolites and endogenous ligands, may exert significant influence within the tumor microenvironment, potentially contributing to immune evasion and tumor progression. AhR has been implicated in various aspects of immune cell regulation, including T cell differentiation, where it influences the development of both CD4+ and CD8+ T cell lineages; B cell differentiation, where it potentially suppresses B cell development by inhibiting the transcription factors EBF1 and PAX5;[22] NK cell function, acting as a critical cofactor in IL-10 production by NK cells; and monocyte differentiation, where it modulates monocyte differentiation into dendritic cells and macrophages.[22] These immunomodulatory effects of AhR may have significant implications for the tumor immune landscape. Notably, Wang et al. highlighted the crucial role of tumor-infiltrating immune cells in cervical cancer prognosis,[67] further emphasizing the importance of understanding AhR's influence within this context.

The AhR repressor (AhRR), identified in 1999, provides a negative feedback loop for AhR signaling.[68,69] AhRR suppresses AhR activity without directly interfering with its DNA binding capacity.[70,71] Notably, several cancers, including cervical cancer, exhibit low AhRR expression, potentially due to mechanisms like DNA hypermethylation and gene silencing.[34,72] This pattern suggests a tumor suppressor role for AhRR in specific contexts. Supporting this notion, the downregulation of AhRR in a human lung cancer cell line led to increased resistance to apoptosis, enhanced motility and invasion in vitro, and more significant angiogenic potential in vivo.[72] Further research into the role of AhRR in cervical cancer development and progression is warranted.

Table 1. The possible roles of the activated AhR in cancer

Target	Mechanism	Ref.
Apoptotic pathway	a) Controlling the expression of apoptosis genes b) Regulating the T cell apoptosis through modulation of Fas and Fas ligand expression c) Crosstalk between AhR and Bcl-2 pathways d) Higher stemness in gynecological malignancies e) Potential interplay between AhR and NF-κB signaling in cervical cancer f) Upregulating the expression of pro-apoptotic proteins (*e.g.,* Bax and p53), and downregulating anti-apoptotic factors (*e.g.,* Bcl-2) in cervical cancer	[1, 32, 43, 44]
Immune checkpoint proteins (ICP: PD-1 or PD-L1)	a) Mediating PD-L1 expression and suppressing the immune response in colon cancer b) PD-L1 expression in cervical cancer c) Induction of PD-1 in T cells in gynecological cancer d) Upregulation of PD-1 expression on CD8+ T cells e) Modulation of CD4+ T cell differentiation, potentially favoring T regulatory cell development	[1, 22, 45, 46]
Steroid hormones	a) Interaction with estrogen receptor alpha leads to a change in its conformation, promoting the development of cervical cancer	[50-52]
Immune cell regulation process	a) Promotion of IL-10, TGFβ, and VEGFA production, potentially contributing to a tumor-permissive microenvironment. b) Generation of tolerogenic DCs	[53-57]

8. CONCLUSION AND FUTURE STUDIES

Various studies applied environmental and endogenous AhR ligands to determine the role of AhR in cancer. The reports indicated a complex relationship between the AhR and cancer features (e.g., an increase in malignant cell invasion, migration, metastasis, CSC formation, and survival). These studies showed some primary data such as: a) cancer prevention can be influenced by minimizing exposure to various environmental AhR ligands; b) cancer interception can be primarily considered before malignancy by identification of early markers of AhR activity; c) AhR-related cancers can be treated by utilizing specific AhR inhibitors. Generally, the role of AhR was determined in cancer development that it can act as a positive or negative regulator of carcinogenesis. Several strategies were investigated to target AhR as a first-line cancer treatment. Various antagonists were tested to reduce the level of AhR expression in tumors when it has an oncogenic function. In contrast, different agonists were used to promote activation of AhR when it acts as a tumor suppressor. Moreover, the AhR is a potential immunother-

apy target and biomarker for cervical cancer. Interaction of AhR with apoptotic pathway, immune checkpoint system, steroid hormones, and immune cell regulation process was studied in cervical cancer. However, the mechanism of AhR action in cervical cancer has not been fully elucidated to date. Thus, further studies need to find the roles and mechanisms of AhR and its metabolites in the promotion or suppression of cervical cancer.

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The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

DATA SHARING STATEMENT
No additional data are available.

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