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Regulation of the aryl hydrocarbon receptor in cancer and cancer stem cells of gynecological malignancies: An update on signaling pathways

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ABSTRACT

Gynecological malignancies are a female type of cancers that affects the reproductive system. Cancer metastasis or recurrence mediated by cellular invasiveness occurs at advanced stages of cancer progression. Cancer Stem Cells (CSCs) enrichment in tumors leads to chemoresistance, which results in cancer mortality. Exposure to environmental pollutants such as polycyclic aromatic hydrocarbons is associated with an increased the risk of CSC enrichment in gynecological cancers. One of the important pathways that mediates the metabolism and bioactivation of these environmental chemicals is the transcription factor, aryl hydrocarbon receptor (AhR). The present review explores the molecular mechanisms regulating the crosstalk and interaction of the AhR with cancer-related signaling pathways, such as apoptosis, epithelial-mesenchymal transition, immune checkpoints, and G-protein-coupled receptors in several gynecological malignancies such as ovarian, uterine, endometrial, and cervical cancers. The review also discusses the potential of targeting the AhR pathway as a novel chemotherapy for gynecological cancers.

1. Introduction

Gynecological malignancies affect the female reproductive organs, the ovary, cervix, endometrium, vagina, and vulva [1], and are a major cause of high mortality and morbidity in women worldwide [2]. As per the American Cancer Society, endometrial, cervical, and ovarian cancer rank third, fifth and seventh in terms of cancer occurrence in women in 2021. Several physiological, genetic, environmental, and lifestyle factors are associated with these cancers' occurrence and frequency. Viral infections and microbiome composition are also reported to be related to the risk of gynecological cancers [3]. In addition, epigenetic changes involving non-coding RNA (ncRNAs) contribute significantly to the cellular transformation process and subsequent stages of progression in gynecological cancers [4]. Advanced gynecological cancers have a poor prognosis, wherein the identification of adequate treatment strategies still constitutes a significant challenge. Despite the advancement in the available treatment regimens, including concurrent radio-chemotherapy, gynecological cancers present a relatively higher rate of locoregional recurrence [5]. One of the crucial reasons for this is the acquisition of chemoresistance upon cycles of drug administration.

Abbreviations: 3MC, 3-methylcholanthrene; ABC, ATP binding cassette; AhR, aryl hydrocarbon receptor; ALDH, aldehyde dehydrogenase; ARNT, AhR nuclear translocator; bHLH, basic Helix-Loop-Helix; BRCA1, breast cancer type 1 susceptibility protein; CCRT, concurrent chemoradiotherapy; CSC, cancer stem cell; CYP, cytochrome P450 proteins; CYP1A1, cytochrome P450 proteins 1A1; CYP1B1, cytochrome P450 proteins 1B1; EMT, epithelial-mesenchymal transition; EpCAM, epithelial cell adhesion molecule; FOXP3, forkhead box protein P3; GPCRs, G-protein-coupled receptors; GPER, G-protein estrogen receptor; HEC, human uterine endometrial cancer; HER2, human epidermal growth receptor 2; HPV, human papillomavirus; HSP90, heat shock protein 90; IARC, International Agency for Research on Cancer; ICP, immune checkpoint; IDO1, indolamine 2,3-dioxygenase; JAK, janus kinase; KLF4, Krüppel-like factor 4; KP, kynurenine pathway; mTOR, mammalian target of rapamycin; NF-κB, nuclear factor kappa-B; NICD, intracellular domain of notch; OCT4, octamer binding transcription factor 4; PAHs, polycyclic aromatic hydrocarbons; PAS, Period/ARNT/Single; PCBs, polychlorinated biphenyls; PI3K, phosphoinositide 3-kinase; PM, particulate matter; SCF, stem cell factor; Shh, sonic hedgehog; SNAI2, transcriptional repressor 2; SOX2, SRY-box transcription factor; SP, side population; STAT, signal transducer and activator of transcription; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TGF, transforming growth factor; TME, tumor microenvironment; XRE, xenobiotic responsive elements.

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Concurrent chemoradiotherapy is currently the standard treatment for locally advanced cervical cancer, according to the recommendations of the National Comprehensive Cancer Network. However, patients are experiencing local or metastatic relapse after therapy [6]. On the other hand, ovarian cancer is the most lethal form of gynecological malignancies, characterized by vague symptoms and a higher recurrence rate [7]. It comes with the burden of being asymptomatic in almost 65 % of cases and challenging timely diagnosis [8]. The five-year overall survival rate of ovarian cancer in its early stages is around 47 % which is even lower in advanced stages [9]. Even though the first-line therapy response rate is satisfactory, most patients presented with relapse within subsequent years [10]. Endometrial cancer, the most common type of uterine cancer, is hormone-dependent cancer attributed to endogenous/exogenous exposure to estrogen hormone. Postmenopausal women were found to have a higher risk of developing the disease [11,12]. Endometrial cancer has a high metastasis level and a lower survival rate [13]. Vaginal cancers are rare (3 % of gynecological cancers) but highly aggressive, mainly epidermal in origin, and usually metastasized from another primary site [14]. Most vaginal cancers occur in postmenopausal or older women [15], whereas vulvar cancer, that accounts for 4 % of all gynecological malignancies, is associated with delay in both presentation and diagnosis, with approximately 40 % of women presenting with advanced stages [16].

Until now, therapy management in gynecological cancers has not advanced much past cytoreductive surgery followed by platinum-based chemotherapy. Patients' lower survival rates, higher recurrence, and increased relapse rates make these cancers a global burden on female lives [17]. All these malignancies, when progressed to advanced stages, have shown chemoresistance. Reports recommend that cancer invasion, metastasis, and recurrence ultimately lead to poor treatment outcomes. More specifically, cancer-related death is mainly interceded by chemo-resistant cancer stem cells (CSCs) [18].

2. Cancer stem cells in gynecological cancer

Resistance to chemotherapy in cancer is highly correlated to the failure of these chemotherapeutic drugs to irradicate a small fraction of cancer cells termed cancer stem cells (CSCs) [8]. Primarily discovered in leukemia [19], the persistence of CSCs was later confirmed in solid malignancies like breast, colon, pancreatic, and gynecological malignancies [20]. Several theories are proposed on the emergence of CSCs, either normal stem cells mutated to be oncogenic or cancer cells attaining stemness even within individual tumors of the same origin [21]. Mounting evidence has suggested a positive correlation between higher number of CSCs and increased aggressiveness and poor outcome. CSCs are characterized by specific cell surface markers cluster of differentiation, including CD24, CD44, CD9, CD133, and epithelial cell adhesion molecule (EpCAM). They also possess high enzymatic activities of aldehyde dehydrogenase (ALDH), a CSC-specific molecular marker [22,23]. Notably, CSCs can form tumor spheroids when grown in ultra-low attachment plates [18]. Another major property of CSCs is the upregulation of the drug efflux mechanism, which can be attributed to the high expression of a specific group of transporter proteins, namely ATP binding cassette (ABC) drug transporters, ABCG2. This ability of drug effluxion against the concentration gradient leads to the occurrence of a specific side population of cells when assessed by flow cytometry assay [24,25]. CSCs can also be identified and characterized by the expression of specific transcription factors such as octamer binding transcription factor 4 (OCT4), SRY-box transcription factor 2 (SOX2), homeobox protein (Nanog), and Krüppel-like factor 4 (KLF4) [26] (Fig. 1).

Reportedly, CSCs use several pathways for their self-renewal and maintenance, namely Wnt/β-catenin [27], Sonic hedgehog (Shh) [28–30], Notch [31], and B cell-specific Moloney murine leukemia virus integration site 1 (BMI1) [32]. In addition, epithelial-mesenchymal transition (EMT) is regulated by the high activity of the Wnt/β-catenin in the nucleus, causing the arrest of the tumor cell division and retaining the self-renewal capacity of the CSCs [33–35]. In addition, several

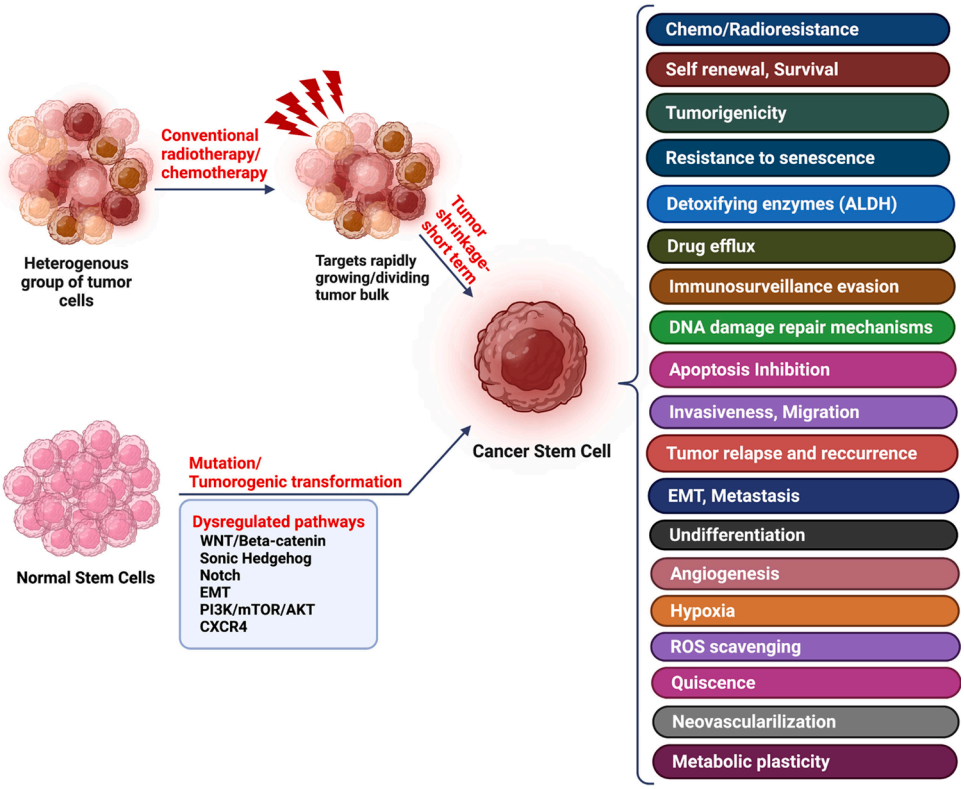

Fig. 1. CSCs development and characteristics. Emergence of CSCs has been majorly hypothesized to be either through the oncogenic transformation of the normal stem cells or through the acquisition of stemness by the tumor cells during cancer progression. CSCs are highly linked to chemoresistance, tumorigenicity, metastasis, and angiogenesis. Examples of mechanisms that mediate the effect of CSCs include self-renewal capacity, drug efflux, apoptosis inhibition, DNA damage, and EMT. (Created with Biorender.com).

signaling pathways are found to be dysregulated in CSCs, such as Janus kinase (JAK)/signal transducer and activator of transcription (STAT), phosphatase and tensin homolog (PTEN), phosphoinositide 3-kinases (PI3K), AKT, mammalian target of rapamycin (mTOR), and nuclear factor-κB (NF-κB) [36,37] that support the unregulated self-renewal and differentiation properties of CSCs [38,39].

Knowing that gynecological malignancies are majorly CSC-derived, how they are regulated at the molecular level is still unclear and warrants further investigation. In this section, we discuss the role and involvement of CSCs in several types of gynecological cancers.

2.1. CSCs in ovarian cancer

Nowadays, it has become increasingly accepted that ovarian cancer is driven by CSCs [7,40]. It is believed that the high relapse rate in ovarian cancer (70 %) is due to the survival of the CSC subpopulation that evades drug effects. Moreover, dormant ovarian CSCs are capable of repopulating again, leading to even more aggressive, drug-resistant diseases [41]. However, the exact mechanisms by which ovarian cancer cells transform into CSCs remain uninvestigated. Although little is known about ovarian CSC location and CSC progenitors, recent studies have aided in understanding CSC evolution and establishment within tumors [42]. It is reported that ovarian CSCs not only initiate peritoneal spread and relapse but also induce chemoresistance. In a study with cells derived from human ovarian tumors, it was found that the overexpression of Patched and glioma-associated oncogene homolog 1 (Gli1), CSC markers and main components of the Shh pathway, was correlated with poor survival rates and increased invasiveness and aggressiveness of cancer [43]. The proportion of $CD44^{+}/CD24^{-}$ cells corresponded to the clinical aggressiveness of each ovarian cancer cell line histologic subtype. For instance, the proportion of $CD44^{+}/CD24^{-}$ cells in the endometroid ovarian cancer cell line (TOV112D) is 0.5 % compared to 99 % in the more aggressive clear cell ovarian cancer cell line ES2 [44]. A correlation between the relative abundance of ovarian cancer cells with stem cell-like properties ($CD44^{+}/CD24^{-}$) and a higher recurrence rate was observed in patients with ovarian cancer [44] Studies suggest that ovarian carcinogenesis is associated with EMT in response to different signals from the tumor microenvironment (TME) [45]. Overexpression of CD44 was observed in metastatic and relapsed tumors and chemoresistant cancer cells. Moreover, CD133, another surface molecule frequently associated with CSC, is correlated to clinical advancement in ovarian cancer. In addition, human epithelial ovarian cancer (EOC) $CD44^{+}/CD117^{+}$ cells possess CSC properties and chemoresistance [46]. Studies have also reported that a loss of p53 function can result in chemotherapeutic drug resistance in various tumors, including ovarian [47] and endometrial [48,49] cancers. Direct evidence supporting the role of *P53* inactivating mutations in driving CSCs has recently been reported [50]. For example, Pinho et al. showed that deletion of *P53* in pancreatic acinar cells enhanced the expression of CSC markers and promoted sphere formation [51]. Similarly, breast CSCs that lack p53 expression showed higher mammosphere formation ability than p53-positive cells [52]. Yet, similar evidence in gynecological CSCs is still lacking.

2.2. CSCs in cervical cancer

The genetic heterogeneity in cervical carcinoma is associated with a high incidence of chemoresistance, metastasis, and pelvic recurrence [53]. Although human papillomavirus (HPV) infection is considered the primary causative agent [54], CSCs also play a prominent role in the disease development, metastasis, recurrence, and prognosis. In this line, numerous studies suggested a link between HPV infection and the development of CSCs in gynecological cancers [55,56]. For instance, Vishnoi et al. demonstrated that HPV gene E6 enhances hedgehog transcription factor Gli-induced self-renewal in cervical cancer and increases the CSC numbers [57]. Cervical cancer is observed to have impaired chemotherapy-induced apoptosis, which is believed to be primarily mediated by CSC subpopulation [58]. Consistently, cervical CSCs identified based on high expression of ALDH, a stemness-specific property, were found to be resistant to cisplatin, the most commonly used chemotherapeutic drug in cervical cancer [59]. ALDH expression is associated with higher cell proliferation rates, sphere formation, migration, and tumorigenesis in cervical cancer cells [60]. Moreover, studies also report that high ALDH expression correlates with poor survival [61]. Several stemness-associated genes, such as ABC transporters, OCT4, Nanog, SOX2, cytokeratin 17 (CK-17), and Musashi-1 (MSI1), have been observed in cervical CSCs [62–64]. Remarkably, the expression of CSCs-related genes, such as MSI1 and CD49f, is reported to be associated with poor prognosis in cervical cancer patients [64]. Increased expression of Shh protein has been demonstrated in cervical cancer and its precursor lesions in cervical intraepithelial neoplasia [65]. In addition, Notch is one of the significant pathways mostly deregulated in cancer and is correlated to the metastatic potential of tumors [66].

2.3. CSCs in endometrial cancer

Endometrial CSCs were first identified and established from the EMTOKA cell line in vitro [67]. Later, using immunocompromised mice, Hubbard et al. confirmed the presence of CSCs in endometrial cancer and suggested that this population may be responsible for producing endometrial tumor cells [68]. Several endometrial CSC-specific markers have been studied and identified till now alongside other tumors [69]. CD117 is a cell-surface receptor tyrosine kinase that, when stimulated by stem cell factor (SCF), imparts stemness properties to cells [70,71]. Reports suggest that $CD117^{+}$ endometrial cancer cells showed an enhanced proliferative and colony-forming ability in a SCF-dependent manner which was abrogated by an anti-SCF antibody in vitro [72]. CD55, a cell surface complement inhibitor, was reported to be highly expressed in endometrial cancer cells and CSCs. $CD55^{+}$ cells were characterized by higher self-renewal and chemoresistance properties compared to $CD55^{-}$ cells [73]. Analysis of 113 endometrial cancer samples by Rutella et al. identified $CD133^{+}$ cells with higher proliferative and colony-forming ability compared to $CD133^{-}$ cells, which upon transplantation into immunocompromised mice, differentiated to the original tumor phenotype [74]. Various other studies also reported the enhanced tumorigenic ability of $CD133^{+}$ cells [75–78]. Side population (SP) refers to a subpopulation of cells with the ability to exclude fluorescent dye Hoechst 33342 from the cytoplasm [79]. It is seen as a dim tail in the flow cytometric plot [80]. This is due to the enhanced expression of ABC transporters that assist with the efflux of molecules, including chemotherapeutic drugs, thereby imparting drug resistance [81,82]. Remarkably, Liu et al. revealed that SP isolated from different endometrial cancer cell lines possessed more vital clone formation ability and higher resistance to paclitaxel and radiotherapy than non-SP [82]. In addition, it has been reported that cells with higher ALDH1 levels are more tumorigenic, invasive, and resistant to cisplatin than low-expression ALDH1 cells, which correlates with a poor prognosis in endometrial cancer patients [83].

3. Gynecological cancers and environmental pollutants

Exposure to air pollutants has been associated with an increased risk to women's health. A recent study has assessed the association between air pollution and gynecological cancer risk. Their findings suggest a positive correlation between the risk of gynecological cancers and higher concentrations of air pollutants [84]. Exposure to air pollutants such as polycyclic aromatic hydrocarbons (PAHs) plays a role in activating environmental carcinogens [85] and promoting the proliferation of cancer cells [86]. Mounting evidence suggests a link between CSC development and PAH exposure [87]. One of the major pathways that mediate the metabolism and bioactivation of these environmental

chemicals is the aryl hydrocarbon receptor (AhR) pathway, whose role in cancer development and profileration of CSCs is recently demonstrated [18,88].

AhR is a cytoplasmic ligand-activated transcriptional factor that belongs to the family basic Helix-Loop-Helix–Period/ARNT/Single-minded (bHLH-PAS), which is involved in the regulation of genes involved in hydrocarbon metabolism [89,90]. Several ligands have been identified for AhR, most of them being aromatic hydrocarbons such as dioxins and biphenyls [91]. The International Agency for Research on Cancer (IARC) has classified 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD) as carcinogenic to humans, whereas polychlorinated biphenyls (PCBs) are probably carcinogenic to humans [92]. AhR is found in the cytoplasm as an inactive protein complexed with two molecular chaperons Heat Shock Protein 90 (HSP90), a co-chaperone p23, and hepatitis B Virus X-associated protein 2 (XAP2) (Fig. 2). Complexing with these proteins ensures appropriate folding and helps proper ligand recognition [93]. Ligand binding facilitates the nuclear translocation of AhR to the nucleus, where it gets dissociated from its complex and forms a heterodimer with the AhR nuclear translocator (ARNT). The formed heterodimer then binds to a specific nucleotide sequence (TNGCGTG) known as xenobiotic responsive element (XRE) [94] to initiate the transcriptional regulation of genes that code for proteins involved in the xenobiotic metabolism, such as the cytochrome P450 proteins (CYPs), specifically CYP1A1, CYP1A2, and CYP1B1 [95]. After transcriptional regulation, AhR gets transported to the cytoplasm, where it gets degraded by the 26S proteasome [96].

AhR is reported to have a role in regulating and expanding several cancers, including breast, oral, pharyngeal, colorectal, colon, and choriocarcinoma [18,97,98]. Controversially, AhR activation has been reported to suppress the growth of breast and liver cancers [99,100]. AhR regulates tumorigenesis by maintaining CSC characteristics, thus directing chemoresistance and cancer cell proliferation [98,101]. Though the role and involvement of AhR in mediating the CSCs has been extensively reviewed by our group and others, how AhR affects the CSCs of gynecological cancers is still not yet reviewed. This article explores the role and involvement of AhR in the transcriptional regulation of CSCs in gynecological cancers.

4. Regulation of CSCs by AhR in gynecological cancers

Several studies have shown that AhR protein and transcripts are expressed in various female reproductive organs, including ovaries [102], endometrium [103], and myometrium [104]. It has been demonstrated that both inhibition and activation of AhR gene expression induce adverse outcomes in the female reproductive system and impair its function, indicating that AhR plays a significant role in the gynecologic organs [104]. While AhR is thought to be an essential regulator of several physiological functions in the female reproductive system, including ovulation, fertilization [105], pregnancy [106], and fertility [104,107], evidence showed that AhR also plays a crucial role in tumorigenesis. However, the AhR's role in cancer is complex since both pro- and antitumorigenic effects have been reported [108]. It is well-documnted that AhR activation or overexpression promotes tumorigenesis in various gynecological cancers [98,109–113]. For example, Deuster et al. showed that low expression of AhR in ovarian cancer patients is associated with a better prognosis [114] Fig. 3.

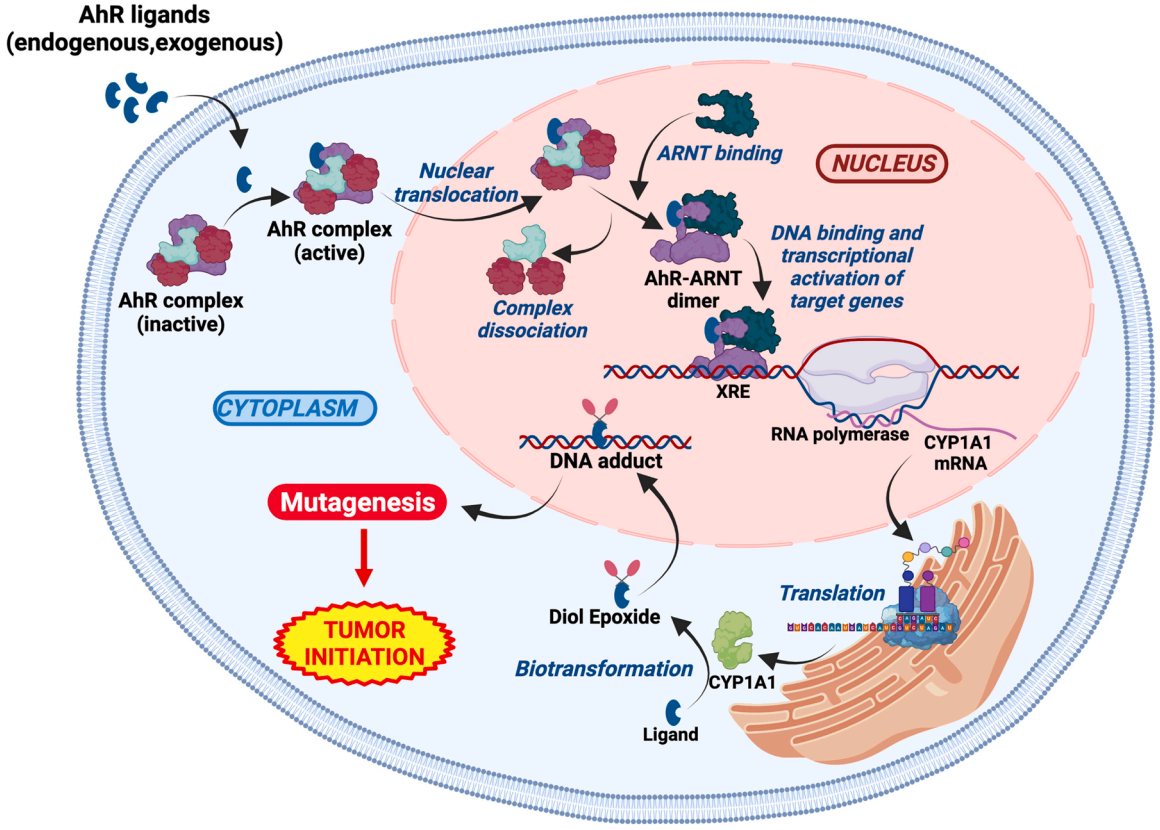

Fig. 2. Model of transcriptional regulation of AhR/CYP1 pathway and its effects in gynecological cancers. Activation of cytosolic AhR upon exposure to environmental toxicants (AhR ligands) leads to the translocation of the receptor to the nucleus, where it gets dissociated from its complex to heterodimerize with ARNT. AhR-ARNT dimer then binds to specific xenobiotic responsive elements (XRE) to initiate the transcriptional regulation of genes such as CYP1A1. Induction of CYP1A1 bioactivates these procarcinogens to highly diol epoxide reactive molecules which attach DNA causing DNA adduct and modulation of numerous cellular pathways. This in turn enhances tumorigenesis, tumor proliferation, apoptosis evasion, tumor invasion, metastasis, stemness and chemoresistance in these cancer cells. (Created with Biorender.com).

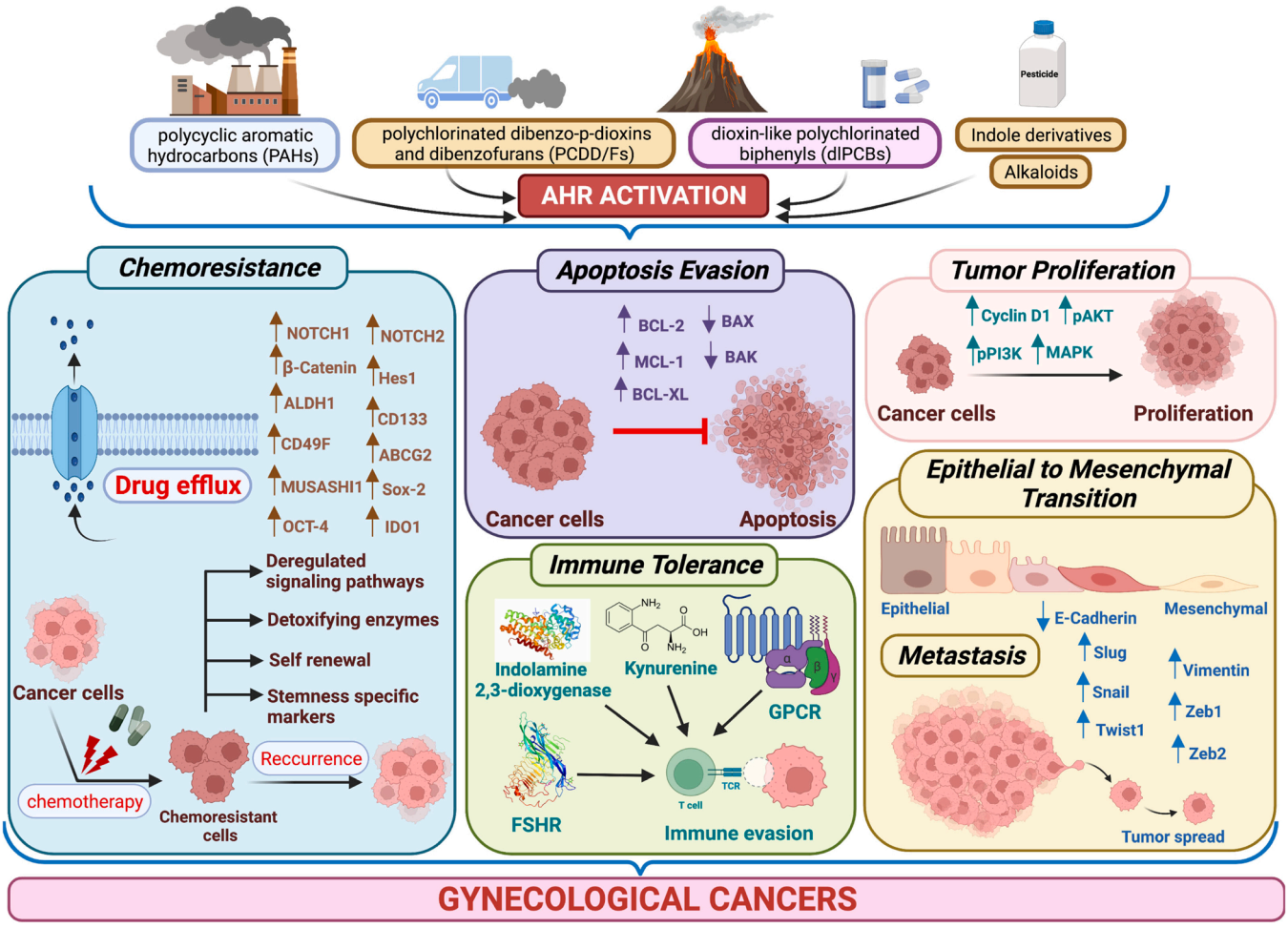

Fig. 3. Mechanisms of transcriptional regulation of CSC-related pathways by AhR/CYP1 pathway. Exposure to environmental chemicals such as PAHs of various sources such as factory waste, volcano eruption, pharmaceutical/medicinal/drug derivatives, pesticides, etc. results in activation of the AhR/CYP1 pathway in gynecological cancers. The activation of the AhR/CYP1A1 pathway in turn results in the activation of several genes such as NOTCH1, NOTCH2, β-Catenin, Hes1, ALDH1, CD49F, CD133, ABCG2, SOX2, IDO1, and OCT4 involved in imparting chemo- and radio-resistance to cancer cells. In addition, increased tumor proliferation by activating pathways such as PI3K/AKT and MAPK, and apoptosis inhibition by upregulating anti-apoptotic proteins such as BCL-2, BCL-XL, MCL-1, and down-regulating BAX, BAK is also observed. Moreover, immune evasion of cancer cells via cross-talking with G-protein coupled receptors, Kynurenine pathway, IDOI, and hormone receptors such as follicle stimulating hormonal receptor (FSHR) is also detected in many gynecological cancers. Induction of EMT by AhR upon activation by its ligands enabling cancer cells to attain mesenchymal characteristics and metastasize to other body parts is a crucial incidence observed in gynecological cancers. (Created with Biorender.com).

Similarly, AhR expression was upregulated in endometrial cancer cells compared to normal endometrium tissues [115]. However, some studies reported that AhR ligands might suppress endometrial or ovarian cancer proliferation and migration [115–117]. This anti-tumorigenic effect might be mediated through AhR-estrogen crosstalk. It has been reported that AhR blocks estrogen receptor signaling [118]. While the anti-estrogenic effect of AhR has been extensively studied in breast cancer, little is known about this crosstalk in gynecological cancers. Therefore, more studies are needed to fully dissect the mechanisms and impact of AhR signaling on gynecological cancers and their different histological subtypes. Due to its importance in mediating tumorigenesis, the role of AhR in regulating CSCs is increasingly being investigated. To date, available evidence shows that AhR activation might promote stemness in multiple types of cancers, including breast cancer [18], oral squamous cell carcinoma [119], choriocarcinoma [98], and ovarian cancer [110]. Nevertheless, the exact molecular mechanisms and transcriptional regulation of CSCs mediated by AhR are not fully understood and have not been reviewed before. Therefore, in the coming sections, we will summarize the mechanisms by which AhR regulates CSCs in gynecological cancers.

4.1. Ovarian cancer

AhR is expressed in several ovarian cells, including the follicles in all species, and thus AhR ligands are known as potent ovo-toxicants [120]. AhR expression has been observed in several histotypes of ovarian cancers with varying stages and tumor grading [116]. In addition, overexpression of CYP1B1 protein has been demonstrated in primary and metastatic ovarian cancer, while no expression was observed in normal ovaries [121]. Despite the long-established role of AhR in ovarian physiological function, its impact on ovarian tumorigenesis is not fully understood, especially in the highly aggressive subpopulations of ovarian CSCs. Conflicting results have been reported about the effect of AhR in ovarian cancer, encompassing both promotion and inhibition of tumor cell growth and proliferation. The potential role of AhR in suppressing the development of ovarian cancer was described by Li et al., in which treatment of the ovarian adenocarcinoma cell line (OVCAR-3) cell line with TCDD resulted in suppression of tumor cell proliferation [117]. Nevertheless, these findings could not be reproduced in other ovarian cancer cell lines [110,117].

On the other hand, several studies reported increased proliferation and stemness in ovarian cancer cells upon exposure to AhR activators

[109–111]. Clinically, it has been reported that high cytoplasmic AhR expression is significantly associated with shorter overall survival (85.07 months vs. 183.46 months) [114]. In the same study, an association of AhR with histology, tumor grading, and tumor size upon immunohistochemistry analysis has also been reported [114]. In the following section, we will dissect various potential mechanisms involved in AhR-mediated transcriptional regulation in ovarian cancer, especially epithelial ovarian cancer (EOC) and the CSC subpopulation. A summary of the studies that describe the mechanisms of AhR/CYP1 in gyencological cancers and CSCsis presented in Table 1.

In serous (EOC), AhR and androgen receptor (AR) are found to coregulate the expression of ABCG2. This study analyzed the AR-AhR interactions using a co-immunoprecipitation assay in three serous EOC cell lines and found that both AhR and AR were physically interacting. Moreover, they reported that TCDD induced AhR translocation to the nucleus and interaction with the alternative AREs within the proximal ABCG2 promoter region, thereby imparting resistance to paclitaxel and therapy failure in serous EOC [122]. Another study showed that CYP1B1 enhanced the resistance of EOC to paclitaxel in vivo and in vitro. They found that CYP1B1 was overexpressed in more than 92% of EOC samples (49 out of the 53) and that was associated with drug resistance. In metastatic EOC tissues, there was a similar pattern of CYP1B1 expression (13 out of 14 samples, 92.8 %). However, this effect of increased resistance to paclitaxel was abrogated by α-naphthoflavone (α-NF), a specific inhibitor of AhR, both in vitro and in vivo [123]. On the other hand, it has been reported that CYP1A1 gene polymorphism could mediate the incidence and development of EOC. The study analyzed CYP1A1*3 polymorphisms in 117 patients with EOC and 202 control subjects which showed that the frequency of individuals carrying the Ile/Val allele was significantly higher in EOC than in the control group with a 5.7-fold higher risk for ovarian epithelial neoplasm [124].

PAX8 is a member of the paired box family of transcription factors, which is frequently expressed in primary EOC and is believed to be involved in tumorigenesis. It is seen that PAX8 binding sites mainly exist next to the motifs of the AhR/ARNT. Chip-seq data analysis explored non-promoter PAX8 binding sites of the PAX8 gene, indicating a co-regulation between AhR/ARNT motif in IGROV-1 cell line, a well-established model for drug-resistant ovarian carcinoma [125]. Min Su et al. showed an essential correlation between AhR and EMT and the degree of malignancy using gene ontology-based integrative analysis. In this study, AhR was found to enhance tumor initiation in serous ovarian tumors. They also identified multiple differentially expressed genes in several aspects, comparing databases of serous borderline ovarian tumors and serous ovarian carcinomas [126].

Although most studies on the chemical carcinogenesis of gynecological cancers have addressed the role of exposure to exogenous AhR ligands, minimal information is known about the impact of endogenous AhR activators. Some examples of these endogenous molecules are 2-(1'H-indole-3'-carbonyl)-thiazole-4-carboxylic acid methyl ester (ITE), tryptophan metabolites such as tryptamine (TA) and indole acetic acid (IAA), heme metabolites such as bilirubin, dietary compounds such as Indole-3-carbinol derivatives, and others [127]. Contrary to exposure to environmental pollutants, endogenous AhR ligands showed a differential effect, probably due to their physiological role. Wang et al. have shown that ITE decreased human ovarian cancer OVCAR-3 and SKOV-3 cell proliferation and migration in vitro and ovarian cancer growth in mice through an AhR-dependent mechanism [116]. In EOC, a recent study has shown that administration of kynurenine, an endogenous AhR ligand, to ovarian cancer cells induced the immune checkpoints on $CD8^+$ T cells in the tumor microenvironment [128]. Another link supporting the role of endogenous AhR ligands on ovarian cancer was recently reported by Xi et al., who showed elevated levels of bilirubin, an endogenous AhR ligand, to be a positive prognostic marker in ovarian cancer [129].

Table 1
Summary of studies that describe the regulatory mechanisms of AhR/CYP in gynecological cancer and CSCs.

Species	AhR/CYP pathway	Effect on Cancer and CSCs	Ref.
Cancer patients	Low expression of AhR	Better prognosis	[114]
	Higher expression of CYP1B1 protein	↑ primary and metastatic cancer ↔ no expression in normal ovaries	[121]
Human A2780 cells	Overexpression of AhR	poor prognosis through interaction with Era	[112]
	High cytoplasmic AhR expression	shorter survival from to 85 months compared to 183.5 in control	
Human metastatic EOC	Overexpression of CYP1B1	↑ Resistance to paclitaxel	[123]
	Treatment with AhR inhibitor (α-NF)	↑Sensitivity to paclitaxel	
IGROV-1 cells	AhR/ARNT coregulates PAX8	↑ Tumorigenesis	[125]
EOC patient samples	CYP1A1 gene Polymorphism	↑ Tumor incidence risk and development	[124]
Serous ovarian carcinoma	Synergistic AhR binding pathway with EMT	Tumor initiation	[126]
Human EOC OVCAR-3 cells	Treatment with TCDD, AhR activator	↑ AR-AhR complex coupled with ABCG2 lead to resistance to paclitaxel	[122]
		↑ Proliferation	[225]
Human EOC OVCAR-3 (WT ER), SKOV-3 (mutated ER)	Treatment with exogenous AhR ligand (TCDD) or endogenous AhR ligand (ITE)	↓ Proliferation of OVCAR-3 ↔ no effect on SKOV-3 proliferation	[116, 117]
Human EC Ishikawa	Treatment with AhR agonist (CB126)	↑ Proliferation at low doses and ↓ proliferation at higher doses	[260]
	Treatment with AhR agonists (TCDD, BaP)	↓ E2-induced cell growth in cells transfected with E2 responsive constructs	[272]
Human EC RL95–2 cells & tissues	Treatment with AhR agonist (BaP)	↓ Cell adhesion	[271]
Rats	Treatment with AhR agonist (TCDD) for two years	↑ incidence of uterine cancer	[252]
	Treatment with AhR activator (3-MC)	↑ stemness Notch2, Hes1, Cyclin D, and Akt.	[109] [140]
	Treatment with AhR inhibitor (a-NF)	↑ CSC marker Slug expression ↓ stemness markers	
Mice	Treatment with AhR agonist (TCDD)	↓ Estrogen-induced uterine growth and proliferation	[273]
	Exposure of ovaries to AhR activation PAHs	↑ oocytes death and apoptosis	[102]

4.1.1. Expression of cancer stemness markers

Experimental evidence for ovarian CSCs was first reported in 2005 [130]. Since then, accumulating evidence has revealed that ovarian CSCs are a crucial mediator in ovarian cancer growth, metastasis, relapse, and chemoresistance [131]. The effect of AhR activation on ovarian cancer and its relation to stemness markers and associated pathways have recently been evaluated by our group. Treatment of A2780 ovarian cancer cell line with TCDD significantly increased expression of the stemness marker ALDH1 and anti-apoptotic proteins (BCL-2, BCL-XL, and MCL-1) known to be upregulated in CSCs [110]. Consistently, it has been shown that daily administration of 3-methylcholanthrene (3-MC), a potent AhR activator, to immature rats enhances AhR binding to promoter regions of cancer stemness-associated genes such as Notch2, Hes1, Jag1, and Akt [109]. This effect was

blocked by α-NF, an AhR antagonist, suggesting that AhR might be involved in mediating the growth and maintenance of ovarian CSCs [109]. Besides, although not directly studied in ovarian CSCs, AhR activation enhanced the expression of the multidrug resistance transporter ABCG1, a well-established CSC marker.

ALDH1A1 has been described as a candidate ovarian CSC marker and is associated with chemoresistance, first identified by Landen et al. [132]. Reports show that ALDH expression was highly associated with a poor survival rate in ovarian cancer patients. Knockdown of ALDH1 sensitized cancer cells to taxanes and platinum drugs. A higher viability and recurrence capability were identified in $ALDH^+$ SKOV-3 cells after cisplatin treatment, indicating their higher resistance capacity. This group further identified and isolated both $ALDH^+$ and $CD133^+$ cells that could quickly induce tumors in xenograft models, and these cells were presented with worse outcomes in ovarian cancer patients [133]. Studies in various breast cancer cell lines demonstrate that AhR expression is elevated in $ALDH^+$ cells [18]. Moreover, the knockdown of AhR diminishes ALDH1 activity, whereas activation of AhR enhances ALDH1 activity and the expression of stem cell- and invasion-related genes [18]. Our recent study validated these findings in ovarian cancer, where AhR induction by TCDD induced ALDH1A1 expression in an ovarian cancer cell line, A2780 [110].

4.1.2. Epithelial-mesenchymal transition (EMT)

It is estimated that 80 % of patients with ovarian cancer will develop resistance and subsequently metastasis within five years of treatment initiation, despite initial response. Accumulating evidence has shown that EMT is crucial in driving chemotherapeutic resistance, stemness, and metastasis in various tumors. EMT is a reversible process wherein the epithelial cells lose their adhesive properties, leading to the acquisition of mesenchymal properties and migratory capabilities [134]. Ovarian CSCs have been observed to show mesenchymal characteristics and be involved in tumor initiation and metastasis [135]. At the molecular level, it has been reported that EMT is an essential mediator in driving ovarian cancer metastasis and thereby cancer progression and chemoresistance, stemness, and recurrence by modulating transcription factors that activate EMT in cancer like zinc finger e-box binding homeobox 1 and 2 (Zeb1, Zeb2), and Snail, Slug, and twist family bHLH transcription factor 1 (Twist1) [136–141]. A recent study from our laboratory has shown that activation of AhR by TCDD induced EMT in ovarian cancer cell lines A2780 [110]. Notably, we observed a reduction in the epithelial marker (E-cadherin) along with a concomitant increase in the expression of mesenchymal markers (vimentin and snail).

Interestingly, several previous studies have reported a tight correlation between AhR and EMT in ovarian cancer [110,142]. For instance, Su et al. revealed that the expression of the EMT transcription factor Slug, also known as snail family transcriptional repressor 2 (SNAI2), in serous ovarian cancer was associated with poor survival and increased histological malignancy from borderline ovarian tumor to early- and late-stage- serous ovarian cancer [126]. It has been reported that Slug transcription is activated by AhR; and that AhR silencing leads to the abolishment of Slug induction by AhR ligand, 3-MC [143]. Since elevated expression of EMT transcription factor, Snail, was accompanied by increased expression of AhR-related biomarkers such as SRC proto-oncogene, non-receptor tyrosine kinase, ARNT, and TATA-Box Binding Protein (TBP) in ovarian cancer tissues, Su et al. suggested a synergistic AhR binding with EMT effect on serous ovarian cancer [126]. Even though our group and others have reported that AhR activation could induce EMT, the molecular mechanisms of their interactions leading to chemotherapy resistance warrant further investigation.

4.1.3. Tumor suppressor genes

Breast cancer type 1 susceptibility protein (BRCA1) is a tumor suppressor gene that plays a significant role in repairing DNA damage, mainly, double-stranded DNA breaks via homologous recombination [144–146]. Germline mutations in the BRCA1 gene have been widely associated with an increased risk of developing breast and ovarian cancers [146]. In addition to its involvement in tumor initiation, BRCA1 mutations were also linked to aggressive tumor behaviors, including the migratory potential of tumor cells and its associated signaling pathway EMT [144]. For instance, high-grade serous ovarian cancer with BRCA1 mutations is found to be highly aggressive and is accompanied by a poor prognosis [147]. Other studies reported that the reduced expression of BRCA1 rather than its mutation is primarily involved in tumorigenesis [148]. AhR-instigated hypermethylation is an important epigenetic alteration of the BRCA1 gene, which has been extensively reported in breast cancer [148], wherein studies have reported that activation and recruitment of the AhR to the BRCA1 promoter hamper 17 β-estradiol (E2)-dependent stimulation of BRCA1 transcription and protein levels [149]. Even though this has not been identified in ovarian cancer, a similar effect could be anticipated due to higher BRCA1 mutations being a predisposing factor for high-grade serous ovarian cancer.

4.1.4. Apoptosis and chemoresistance

Apoptosis is a natural mechanism involved in programmed cell death and acts to maintain tissue homeostasis by eliminating aged or defective cells [150]. Besides, apoptosis plays an essential physiological role in ovaries, mainly contributing to follicular atresia and corpus luteum regression which are necessary for maintaining a healthy reproductive system in females [151,152]. The inability to control granulosa cell apoptosis and initiate follicular atresia has been associated with an increased risk of hormone-related cancers, including ovarian cancer, and chemotherapeutic resistance [153]. Alteration in the apoptotic pathway is a well-recognized hallmark of cancer wherein the cells are characterized by overexpression of anti-apoptotic proteins such as BCL-2, BCL-XL, or MCL-1 and downregulation of pro-apoptotic proteins such as BAX or BAK [154]. Consequently, targeting apoptosis machinery represent one of the most effective nonsurgical treatments for cancer [155]. In ovarian cancer, dysregulation of apoptosis machinery was correlated with resistance to chemotherapy [156,157]. For instance, BCL-XL expression is associated with poor chemotherapy response in ovarian cancer patients, and its inhibition via navitoclax increased chemosensitivity to platinum-based drugs in various ovarian cancer cell lines [158]. However, CSCs are featured with increased innate resistance to apoptosis and chemotherapy, compared to more differentiated cells [159,160]. Several factors have been linked to apoptosis evasion in CSCs, including the upregulation of multidrug resistance transporters (e.g., ABCG2, MRP, BCRP) [161,162]. On the other hand, the expression of death receptors (e.g., Fas and TRAIL) was found to be lower in CSCs, decreasing their sensitivity to Fas-induced apoptosis and as a result their response to chemotherapy [158,159]. Moreover, since the majority of anti-cancer therapies preferentially target replicating cancer cells, the ability of CSCs to maintain a quiescent nondividing state protects them from chemotherapy-induced apoptosis as well as immune surveillance [163–165].

Several studies showed that AhR could influence apoptosis by regulating the expression of genes involved in the apoptotic pathway [113,166]. Notably, exposure of ovaries to PAHs, known AhR activators, leads to the destruction of oocytes, implying the involvement of AhR in mediating cell death signaling and potentially explaining the infertility issues observed in women who smoke [102,167]. This observation is further supported by Robles et al. findings which showed that AhR knockout attenuated oocyte apoptosis in fetal ovaries leading to a two-fold higher number of primordial follicles than AhR-wile-type female germ cells [102]. On the other hand, AhR was repeatedly shown to exert the opposite effect in cancer cells, where it mediates anti-apoptotic responses in various types of cancers, including lymphoma, breast, lung, ovarian, and pancreatic cancer [168–171]. Recently, our group demonstrated that AhR activation by TCDD in an ovarian cancer cell line (A2780) significantly upregulated the anti-apoptotic proteins BCL-2, BCL-XL, and MCL-1 which was accompanied by a reduction in early/late apoptosis [110]. Remarkably, the same study found that

inhibition of apoptotic pathway by AhR activation was associated with higher stemness, as evident by induction of ALDH expression, EMT, and upregulation of Wnt/β-catenin [110].

Moreover, chemoresistance is directly influenced by AhR in both CSC and non-stem-cell populations [18,87,98,119]. Stanford et al. revealed that inhibition of AhR by CH223191 significantly enhanced response to adriamycin and paclitaxel in both $ALDH^{low}$ and $ALDH^{high}$ triple-negative breast cancer cells (Hs578T) [18]. Additionally, AhR was induced in ovarian cancer cells (A2780) in response to paclitaxel treatment. Its activity was more upregulated in paclitaxel-resistance ovarian cancer cells than wild-type cells [172]. These findings are consistent with previous studies demonstrating AhR involvement in evasion of chemotherapeutic-induced apoptosis.

Among the suggested mechanisms for AhR-mediated chemotherapeutic resistance is the induction of the multidrug efflux transporter ABCG2 [173,174]. Tan et al. demonstrated that AhR is a direct transcriptional regulator of ABCG2 [175]. Later, it was suggested that the androgen receptor (AR), which is known to play a role in the growth and progression of EOC, is involved in AhR-mediated ABCG2 expression [122,176,177]. In this study, Chung et al. reported that treating serous EOC cells with paclitaxel or TCDD caused activation of AR-AhR complex coupled with the ABCG2 regulatory axis imparting resistance to the EOC cells [122]. At first, through manipulating the expression of AR using AR-cDNA or AR-shRNA in HeyA8, OVCAR-3, and SKOV3ip1 cells, they found that ABCG2 efflux ability was positively regulated by AR expression in EOC cells. Next, using a co-immunoprecipitation assay , the authors have identified AR-AhR interactions [122]. Since high expression of ABCG2 is a well-recognized CSC marker and is strongly associated with therapeutic resistance [161,162,178], it is suggested that AhR might be involved in mediating resistance in ovarian CSCs through induction of ABCG2. Hence, inhibiting AhR may represent a potentially effective therapeutic strategy for targeting ovarian CSCs when used in combination with other chemotherapies. Nonetheless, studies directly evaluating the role of AhR in regulating apoptosis, specifically in the CSC subpopulation of gynecological cancers, are limited. Thus, more studies are needed to unravel the therapeutic potential of AhR modulation in overcoming therapeutic resistance induced by CSCs in gynecological malignancies.

4.1.5. Immune checkpoint system

Immune checkpoint (ICP) proteins or regulators are an essential part of the immune system playing an important role in preventing tissue damage caused by uncontrolled immune responses [179]. ICPs act in ligand-receptor pairs to control the interaction between cells of the innate and adaptive immune system, primarily T cells, antigen-presenting cells, and tumor cells. When an inhibitory checkpoint and partner proteins bind, they switch off signals sent to trigger immune responses. It has been found that inhibitory ICPs are usually upregulated in cancer cells [180]. This can prevent the immune system from destroying cancer cells. Although ICPs are primarily involved in controlling immune responses, it has been observed that they might also be involved in promoting self-renewal, metastasis, and therapeutic resistance [181–185].

Immune checkpoint inhibitors (ICPIs) are molecules that block the immune checkpoint proteins from their binding to the partner proteins, thereby preventing the 'switch off' process and allowing the T cells to kill tumor cells. Over the past decade, ICPIs have shown profound success in multiple types of tumors and have become an essential pillar in cancer therapy. Nevertheless, many cancer patients showed primary or quired resistance and failed to respond to these treatments [186]. Remarkably, it has been recently suggested that the CSCs subpopulation may protect cancer cells from immune destruction and thus limit their response to immunotherapy [186,187]. Several studies have shown that CSCs can mediate immune evasion through multiple mechanisms, including differential expression of ICPs, the release of immunosuppressive pro-inflammatory factors, suboptimal expression of human leukocyte antigen (HLA) molecules, and tumor-associated antigens. These features render CSCs invisible to immune surveillance, preventing cytotoxic immune cells from recognizing and killing CSCs [188–190].

The most extensively studied ICPs are programmed death 1 (PD-1) and its ligand (PD-L1). The PD-1/PD-L1 is an ICP pathway and adaptive immune resistance mechanism of the tumor cells in response to endogenous immune anti-tumor activity. Numerous studies on multiple types of cancer have shown that PD-L1 is commonly upregulated in CSC subpopulations, and its expression is linked to immune evasion and unfavorable prognosis [191–193]. Notably, Miyazaki et al. reported that AhR mediates PD-L1 expression and dampens the immune response in colon cancer cells [194]. Similarly, it was found that AhR activity is necessary for PD-L1 expression and maintenance of CSC features in patient-derived cancer spheroids [194]. While a similar effect on PD-L1 has not yet been evaluated in gynecological CSCs, it has been recently revealed that PD-1 in T cells is induced via activation of AhR in ovarian cancer [128]. In this study, McCloud et al. assessed the effect of indoleamine 2,3-dioxygenase (IDO1), an immunoregulatory enzyme, on PD-1 expression [128]. Activation of IDO1 generates Kynurenine, an endogenous AhR ligand, that was found to promote immune evasion through driving the differentiation of $CD4^+$ T cells into immunosuppressive T regulatory cells in an AhR-dependent mechanism [195,196]. Besides, Kynurenine was found to upregulate the co-inhibitory receptor, PD-1, on $CD8^+$ T cells. Remarkably, this effect was abrogated upon administration of AhR antagonist, CH223191, indicating that AhR is necessary for Kynurenine-mediated PD-1 expression [128]. Additional investigations by McCloud et al. identified AhR-XRE binding sites in the promoter region of several human checkpoint receptors (e.g., PD-1, Lag3, Tim3, Klrg1, Ctla4, Btla, 2B4, CD160, and TIGIT) through computational analysis [128]. A chromatin immunoprecipitation study further supported kynurenine-mediated AhR binding to XRE motifs on PD-1 promoter [128]. In this line, McCloud et al. suggested that Kynurenine modulates chromatin accessibility in regulatory regions of T cell inhibitory receptors, facilitating AhR binding to XRE motifs on the promoter region of the inhibitory receptors, particularly PD-1 gene promoter [128]. These findings indicate that combining AhR inhibition with IDO1 blockade may enhance anti-tumor immunity and overcome immune suppression in ovarian cancer and other tumors. Taken together, using AhR antagonist alone or in combination with IDO1 inhibitor may aid in reversing the immunomodulatory signature in CSCs through downregulation of ICPs that are known to be altered in this population. Yet, more studies are needed to validate the potential utility of AhR modulators in targeting CSCs of gynecological cancers.

4.1.6. G-protein-coupled receptors (GPCRs)

G-protein-coupled receptors (GPCRs) are integral transmembrane proteins representing the human genome's largest family. GPCRs sense a large spectrum of extracellular signals, including ions, peptides, amino acids, or proteins such as neurotransmitters and growth factors [197,198]. The role and involvement of GPCRs in several cancers have been reported, wherein they contribute to tumor progression, migration, and metastasis [199]. More importantly, recent studies suggested an essential role for GPCR in regulating CSCs-related signaling and markers such as the Wnt pathway and Lgr proteins [200–203]. The critical impact of endocrine hormones on the development of gynecological cancers makes endocrine GPCR of particular interest in ovarian cancer [204,205]. Recent evidence suggests that endocrine GPCR is involved in the progression and metastasis of ovarian cancer [205–210]. For instance, activation of the G protein estrogen receptor (GPER) in ovarian cancer cells promoted cell proliferation, migration, and invasion [206,207,210]. Notably, GPER-induced signaling was essential for the maintenance of CSCs in breast cancer [211,212]. Chan et al. reported that GPER silencing leads to a reduction in stemness characteristics. In contrast, activation of GPER by tamoxifen enhanced stem cell features as detected by tumor sphere formation ability in vitro and tumor growth in vivo [211].

A functional correlation between AhR and GPER, triggered by AhR ligand 3-MC, has been reported to lead to the stimulation of SKBR3 breast cancer cell lines, as analyzed by co-immunoprecipitation studies [213]. These findings suggest a potential involvement of AhR in GPER-mediated regulation of CSCs. However, contradictory results showing that GPER expression in ovarian cancer is correlated with favorable outcomes have also been reported [205,208,214]. Thus, more studies are needed to fully understand the role of GPER in ovarian cancer and its crosstalk with AhR, especially in the CSCs subpopulation. Follicle-stimulating hormone receptor (FSHR) is another endocrine GPCR associated with enhanced proliferation, survival, and metastasis in ovarian cancer [205,215,216]. Additionally, it has been found that activation of FSHR increases the expression of OCT4 and promotes EMT in ovarian cancer, indicating that FSHR may act as a mediator in promoting ovarian CSCs [217,218]. Knockout of AhR in mice resulted in lower mRNA expression of FSHR than wild-type mice [219]. Although these findings suggest a potential role for AhR in regulating FSHR transcription, the experiments were assessed in normal ovaries; hence, data still need to be validated in an ovarian cancer model. The effect of GPCR signaling on ovarian CSCs and its regulation by AhR remains unknown.

4.1.7. Crosstalk with steroid hormones

Steroid hormones (i.e., estrogen, progesterone, and androgen) regulate the growth and development of human tissues, especially breasts and reproductive organs. Accordingly, disruption in steroid hormones and their downstream signaling have been linked to the progression of gynecological cancer [220,221]. Epidemiological studies have shown that estrogen is involved in promoting ovarian carcinogenesis; and that the risk of ovarian cancer increases by increasing the duration of estrogen exposure [220,222]. Notably, recent studies suggested that steroid hormones also regulate the proliferation, differentiation, and metastasis of CSCs [220]. For instance, estrogen was found to reduce the proliferation and self-renewal of CSCs by inhibiting the translation of the embryonic stem cell genes Nanog, Oct-4, and Sox2 in breast cancer cells [220,223]. On the other hand, Cheng et al. showed that induction of the transcription factor E2F6 by estrogen upregulates ovarian CSC markers (CD44 and c-KIT) [224,225]. Similarly, Chung et al. reported that overexpression of AR in EOC cells enhances the expression of the CSC marker, ABCG2 [122]. The same study showed that AR-mediated ABCG2 expression could be induced by AhR agonist TCDD [122]. Mechanistically, AR was found to be physically interacting with AhR forming a complex that could be activated by TCDD [122,226].

The crosstalk between ER and AhR and their effect on carcinogenesis is more complicated, with both anti-estrogenic and estrogenic activities being reported. For instance, Rogers et al. showed that TCDD reduces the level of ER in BG-1 ovarian cancer cells when cultured in a standard medium but not in an estrogen-stripped medium [226]. Besides, TCDD was found to suppress the growth of the ER^+ ovarian cancer cell line (OVCAR-3) while it did not affect the proliferation of the SKOV-3 cell line, which has a defective ERα [117]. Consistently, Wang et al. reported a reduction in proliferation of OVCAR-3 cell line but not ER mutated ovarian cancer cell line (SKOV-3) upon treatment with ITE, an endogenous AhR ligand [116]. Nevertheless, Takahashi et al. showed that TCDD increases the proliferation of the ovarian cancer CAOV-3 cell line, which was accompanied by an increase in AhR and ERα mRNA expressions when cultured in a low FBS medium [227]. The impact of AhR on estrogen and other steroid hormones signal transduction in ovarian cancer and CSCs is complex; hence, more studies are needed to fully understand the crosstalk between AhR and steroid hormones on CSCs.

4.2. Cervical cancer

Cervical cancer, which originates in the tissues of the cervix, is the fifth most commonly occurring cancer in women globally, with a significantly lower survival rate at metastatic stages [228,229]. Cervical cancer is caused by the human papillomavirus (HPV). The cervical CSCs population is frequently resistant to chemotherapy due to the high expression of efflux transporters [228]. Other potential cervical epithelial stem cell markers include MSI1, ALDH1, SOX2, and CD49f [63,64]. AhR and its regulatory genes were found to correlate with the biological regulation of cervical cancer and development. Meta-analysis studies on a large sample size have shown that polymorphism in *Msp*I and Ile462Val of the CYP1A1 is a risk factor for cervical cancer development in several ethnicities [230–232]. In addition, a recent study by Alshammari et al. has demonstrated a higher CYP1B1 expression in 91 % of cervical cancer patients than in normal healthy subjects. The increase in CYP1B1 expression was positively correlated with the grades of the diseases and metastasis to the lymph node [233]. Furthermore, increased activities and expressions of AhR and its regulated genes CYP1A1 and CYP1B1 were associated with poor prognosis [112], in which analysis of the Linked Omics database demonstrated a positive correlation between AhR and 3209 genes, whereas 2651 genes showed a negative correlation with AhR. Importantly, by investigating the relationship between AhR and its related genes and the prognosis of cervical cancer patients, the authors concluded that overexpression of AhR was associated with poor prognosis [112].

One of the hypothesized mechanisms is that AhR interacts with ERα, causing conformational changes leading to the activation of several transcription factors and multiple protein complexes to mediate the development and progression of cervical cancer [234]. IDO1 mediates tryptophan metabolism and T cell suppression in human cells, whose expression was found to be increased in cervical CSCs [235]. Kynurenine, the first breakdown product of the IDO1-mediated tryptophan metabolism, is an endogenous ligand for the AhR. Low et al. studied the interaction between IDO1 and stemness in cervical cancer and reported that IDO1 regulates Notch1 expression by binding AhR/ARNT to the Notch1 promoter. Furthermore, they found that Notch1 activation contributes to the increased IDO1 expression in cervical CSCs. In addition, it has been shown that shRNA knockdown of Notch1 decreased the expression of IDO1 in cervical CSCs. Importantly, the administration of Ro-4929097, a γ-secretase inhibitor and anti-cancer drug, inhibited the binding of the intracellular domain of Notch (NICD) to the IDO1 promoter. Moreover, the knockdown of IDO1 also decreased NICD expression in cervical CSCs, correlated with the reduced binding of ARNT to the Notch1 promoter [236].

A correlation between higher expression of ALDH1 and poor survival rate is observed in cervical squamous cell cancer patients that received post-operative adjuvant chemotherapy before radical hysterectomy [237]. ALDH1 may also be a useful prognostic biomarker in cervical cancer [61]. The role of ALDH1 in cellular migration and its link to tumorigenicity and aggressiveness is also reported [238]. The induction of AhR by 3-MC was associated with increased $ALDH^+$ cell population in tamoxifen-resistant cells but not in chemosensitive human breast cancer MCF7 cells [239]. SOX2 expression is higher in cervical cancer cells when compared to normal cervical cells; its expression, along with OCT4 was observed to be highly correlated to poor survival in cervical cancer patients [62,240,241]. The CSC marker, ABCG2, is transcriptionally activated by the AhR/CYP1 pathways through the binding of AhR to the XRE sequence on the ABCG2 promoter region [173–175]. There are limited studies on the effect of AhR on cervical CSCs. Thus, further studies are highly warranted to understand the impact of AhR/CYP activation on cervical CSC development and features.

4.3. Uterine and endometrial cancer

Endometrial cancer is mainly divided into two types; estrogen-dependent type I, which is the most common and less aggressive, and type II estrogen-independent [242,243]. Endometrial CSCs were established earlier [68], where the expression of stemness markers, such as SOX2, Nanog, and OCT4, has been reported in endometrial CSCs isolated

from endometrial cancer with higher expansion potentials and colony-forming capabilities [244]. These cells are also found to express several CSC markers and self-renewal genes [68]. It was also reported that chemoresistance of uterine cancer to platinum- and taxane-based chemotherapy is mediated through DNA repair mechanisms, efflux pumps, and survival pathways such as PI3K/AKT pathway and mitogen-activated protein kinase (MAPK) pathway [245]. In addition, several CSC-related signaling pathways were found to be expressed in endometrial CSCs, including, Wnt/β-Catenin [246–248], Notch, and PI3K/AKT [249–252].

In endometrial cancer cells, it has been reported that administration of ITE, an endogenous AhR ligand, inhibited cell proliferation and migration in vitro in AN3CA and HEC-1B cell lines and in xenograft growth in mice, where this effect was associated with a significant increase in CYP1A1 and CYP1B1 mRNA and protein levels [115]. For instance, activation of AhR using TCDD enhanced spheroid formation ability, whereas AhR inhibition by shRNA significantly reduced stem cell-like characteristics in choriocarcinoma, a type of gestational malignancy that develops in the uterus [98]. Mechanistically, Wu et al. showed that the AhR-mediated effect on the uterine CSCs might be at least partially mediated through the Wnt/β-catenin pathway and ABCG2 transporter [98]. In this context, previous studies have reported higher levels of AhR mRNA in early events of uterine endometrial cancer cells than in normal endometrium. Notably, the differential expressions of AhR in early and advanced stages are mediated through an estrogen-related mechanism. In that, it has been reported that AhR expression was higher in estrogen-independent responsive grade 3 endometrioid adenocarcinoma than in estrogen-dependent responsive grade 1 and 3 endometrioid adenocarcinoma [253]. Another supporting evidence is the observations of Yoshizawa and his team, who reported that long-term exposure of female rats to TCDD significantly increased uterine squamous cell carcinoma [254]. This effect could be attributed to an increase in the expression of CYP1A1 since human endometrium epithelial cells (RL95–2) exposed to benzo[*a*]pyrene (BaP), an AhR inducer, exhibited higher expression levels of CYP1A1, with no changes in CYP1A2 or CYP1B1 levels [255]. In addition to its crosstalk with estrogen, it has been observed that AhR interacts with AR, leading to the progression of endometrial cancer upon activation with TCDD [256].

On the contrary, other studies have reported a protective role for AhR activation against endometrial cancer due to its anti-estrogenic activity. This hypothesis was supported by the association between cigarette smoke, which contains many AhR activators, and the lower risk of endometrial cancer [257]. Consistently, several AhR agonists, TCDD and BaP, and selective modulators, 3',4'-dimethoxy-αNF (DiMNF), repressed estrogen-dependent gene transcription in endometrial cancer cells [258–260]. Labrecque et al. showed that knockdown of AhR with siRNA diminished TCDD-induced repression of estrogen signaling, indicating that AhR is involved in mediating its anti-estrogenic activity [258]. Several mechanisms have been proposed for the observed anti-estrogenic activity, including direct inhibition of ER signaling by binding to inhibitory XRE and indirectly by decreasing circulatory E2 through induction of CYP metabolizing enzymes [116,118,261]. While AhR agonists induced anti-estrogenic activity was associated with protective effects in some studies, others report reverse or no association with tumorigenesis in endometrial cancer.

The initiation of chemical carcinogenesis depends on the magnitude (dose or concentration) and the duration of exposure to environmental pollutants. In this context, an epidemiological study involving 3538 workers with occupational exposure to TCDD was conducted to examine the association of TCDD exposure dose and duration and the risk of tumor development. The study revealed that workers with chronic high-level exposure to TCDD are more likely to be at higher risk of cancer development than those with recent low-dose exposure [262]. These results are consistent with the theoretical and experimental knowledge that promoters usually require a longer period to accelerate tumor progression. For instance, Chen et al. showed that treatment of Ishikawa endometrial cancer cells with low doses of CB126, an AhR agonist, induced cancer cell proliferation, whereas treating the same cell line with higher doses resulted in an opposite effect [263]. In this line, a dose-response study using 3-MC, an AhR activator that also stimulates ERα activity, revealed that the half-maximum effective concentration (EC_{50}) required to activate ER was 100 fold higher than that required for AhR in Ishikawa cells [264]. Unlike 3-MC, other AhR agonists (i.e., BZ126 or TCDD) evaluated in the same study did not stimulate ERα-dependent reporter activity [264]. These findings indicate that both types of AhR ligands and their doses are among the factors that control the direction and magnitude of AhR effect on estrogen signaling.

Moreover, the anti-estrogenic effect of AhR is different among species. For example, while TCDD produced an anti-estrogenic effect in vivo Holtzman rat model [265], it did not cause an anti-estrogenic effect in Sprague-Dawley rat endometrial epithelial cells [221]. The crosstalk between AhR and estrogen and their effect on carcinogenesis is complex and is affected by numerous mediators. Despite being evaluated in several studies, currently, there is no consensus on the effect of AhR on estrogen signaling since both anti-estrogenic and estrogenic activity has been reported. However, it is well accepted that AhR is an essential mediator in controlling estrogen signaling and carcinogenesis in endometrial cancer. Therefore, more studies are needed to fully understand AhR downstream signaling and the potential therapeutic utility of its modulators.

Human epidermal growth receptor 2 (HER2) mediated PI3K/AKT activation increases paclitaxel resistance in endometrial cancer cells [266]. For instance, HER2 signaling promotes AhR-mediated Memo-1 expression and migration in colorectal cancer. The group found that established a close link between extracellular HER2 activation and AhR/ARNT transcriptional activity in colorectal cancer [267]. In addition, increased tumorigenicity is associated with upregulated expression of EMT-associated genes like TWIST1 and SNAI1 in endometrial CSCs. In addition, treatment with salinomycin, an EMT blocker, inhibited the tumorigenicity of these cells [268]. Moreover, expression of ALDH high cells showed elevated expression of SOX2, Nanog, OCT4, and Myc [269]. In this instance, both PI3K/AKT pathway and MAPK pathway are found to be regulated by AhR in several cancers, such as breast cancer [270]. On the contrary, a report suggests that AhR activation gives rise to anti-estrogenic actions and may consequently reduce the development of endometrial cancer [221]. Studies from several groups have established that AhR could be a potential therapeutic target for endometrial cancer and several other cancers like prostate, ER-positive breast cancer, and pancreatic cancer [259,271–273]. Specimens from human uterine endometrial cancer (HEC) exhibited an increased level of the AhR with a decreased expression of tumor suppressor genes known as nuclear factor 1 C (NF1C), whereas overexpression of NF1C suppressed AhR activation [253]. This deregulation of AhR by NF1C could be a novel potential targeted therapy for endometrial cancer.

5. Conclusions and future directions

Gynecological cancers are a huge burden to female lives globally. A major and highly challenging factor that prevents an efficient treatment regime is chemoresistance owing to the presence of CSCs. The existence of CSCs has challenged the efficiency of treatments and clinical outcomes of many cancers, including both hematological and solid cancers. As there are studies that suggest the occurrence of several gynecological cancers like ovarian cancer in highly polluted areas, is likely to be due to exposure to chemical carcinogens. In this context, AhR has an inevitable role in regulation of gynecological malignancies as the regulator of proteins involved in the metabolism of these polycyclic aromatic hydrocarbons. AhR activation is also reported to upregulate many CSC maintenance pathways. The current review presents an update on the molecular mechanisms involved in the regulation of AhR and CSC-mediated pathways such as Wnt/β-Catenin, Notch, apoptosis, EMT, ICP, and GPCRs. AhR/CYP pathway exhibited a differential effect

subjected to the type of gynecological cancer involved (Fig. 3). Though many studies have been done on investigating the possible role of AhR in regulating CSCs, this field is still in its infancy and needs deep mining.

Conflict of Interest

There are no financial or other interests in this manuscript that might be construed as a conflict of interest.

Data availability

No data was used for the research described in the article.

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