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Writing Issues

67

Issues left

17

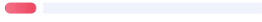
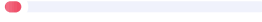



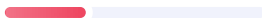
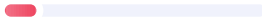
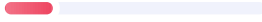
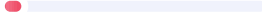







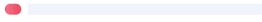

Critical

50Advanced

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Writing Issues

29	Correctness	
2	Text inconsistencies	
1	Faulty subject-verb agreement	
1	Determiner use (a/an/the/this, etc.)	
2	Incorrect verb forms	
7	Punctuation in compound/complex sentences	
5	Ungrammatical sentence	
2	Comma misuse within clauses	
3	Incorrect phrasing	
1	Confused words	
2	Misspelled words	
1	Unknown words	
2	Wrong or missing prepositions	
12	Engagement	
12	Word choice	
24	Clarity	
16	Wordy sentences	
3	Paragraph can be perfected	
5	Unclear sentences	
2	Delivery	
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Aryl Hydrocarbon Receptor dynamics in ESCC: From immune modulation to therapeutic opportunities

ABSTRACT

Esophageal squamous cell carcinoma (ESCC) is a substantial global health burden. Immune¹ escape mechanisms are important² in ESCC progression, enabling cancer cells to escape the surveillance of the host immune system. One¹ key player in this process is the Aryl Hydrocarbon Receptor (AhR), which influences multiple cellular processes, including proliferation, differentiation, metabolism, and immune regulation. Dysregulated¹ AhR signaling participates in ESCC development by stimulating carcinogenesis, epithelial-mesenchymal transition (EMT), and immune escape. Targeting¹ AhR signaling is a potential therapeutic approach for ESCC, with AhR ligands showing efficacy in preclinical studies. Additionally¹, modification of AhR ligands and combination therapies present new opportunities for therapeutic intervention. This¹ review aims to address the knowledge gap related to the role of AhR signaling in ESCC pathogenesis and immune escape.

Key Words: Esophageal squamous cell carcinoma (ESCC); Aryl hydrocarbon receptor (AhR); Immune escape; Tumor microenvironment; Immunosuppression; Therapeutic targeting

Core Tip: Esophageal squamous cell carcinoma (ESCC) utilizes immune escape mechanisms, including major histocompatibility complex (MHC) downregulation and immune checkpoint manipulation, which enhances tumor

progression. The Aryl Hydrocarbon Receptor (AhR), which is crucial in health and disease, significantly influences ESCC development and immune evasion through carcinogenic pathways. AhR activation triggers proliferation, inhibits apoptosis, and induces epithelial-mesenchymal transition (EMT). Moreover, AhR suppresses effector T cells and enrolls immunosuppressive myeloid cells. Therapeutic AhR targeting with AhR ligands showed promise in inhibiting tumor growth, controlling the immune microenvironment, and enhancing treatment efficacy. Combining AhR-targeted therapies with conventional treatments or dietary interventions has the potential to improve ESCC patient outcomes.

INTRODUCTION

Esophageal squamous cell carcinoma (ESCC), a severe malignancy of the esophagus, shows a significant global health burden (ESCC is the eighth most common cancer globally)[1]. It shows a notable geographical variation, with particularly high incidence rates in East Asia, Central Asia, and certain regions of Africa[2].

ESCC emerges through a multistep process involving progressive genetic and molecular alterations within the esophageal epithelium[3]. Chronic exposure to established carcinogens, such as tobacco smoke and excessive alcohol consumption, triggers cellular damage and initiates a cascade of events leading to uncontrolled proliferation and malignant transformation[4]. These factors can lead to point mutations in tumor suppressor genes such as p53, which regulate cell cycle progression and DNA repair[5]. Moreover, amplification of oncogenes, such as cyclin D1, promote cell cycle dysregulation and uncontrolled growth[6]. Furthermore, epigenetic modifications, such as DNA methylation and histone acetylation configurations, can inhibit tumor suppressor genes and provide a pro-tumorigenic microenvironment[7]. These genetic and molecular aberrations interfere with normal cellular processes,

leading to the development of pre-cancerous lesions characterized by squamous epithelial hyperplasia and dysplasia. If left unchecked, these pre-cancerous lesions may progress to invasive ESCC.

Despite advancements in treatment procedures, ESCC prognosis is still poor, emphasizing the need for a better understanding of the main processes that stimulate tumorigenesis and immune escape.

IMMUNE ESCAPE: A CANCEROUS DEFENSE MECHANISM

ESCC development is counterbalanced by the host immune system, which employs a two-edged plan for immune surveillance, including innate and adaptive immunity[8]. The ability of cancer cells to evade the detection of immune system and elimination is a hallmark of tumor progression[9]. In ESCC, the immune escape demonstrates through a sophisticated connection of various mechanisms utilized by tumor cells to create a microenvironment that protects them from immune attack[10].

To escape the strong immune surveillance system, ESCC cells organize a multi-dimensional immune escape program (Figure 1). One of the key mechanisms includes downregulation of Major Histocompatibility Complex (MHC) molecules on the cell surface[11]. MHC molecules function as antigen presentation platforms, allowing T cells to recognize and eliminate foreign or abnormal cells. By reducing MHC expression, ESCC cells become undetectable to the immune system, making them resistant to T cell-mediated cytotoxicity[12].

Furthermore, ESCC cells actively modulate the tumor microenvironment (TME) to create an immunosuppressive state[13]. They achieve this by secreting chemokines and cytokines that recruit and activate regulatory T cells (Tregs) and myeloid-derived suppressor cells (MDSCs)[10]. The suppressive cell populations directly inhibit the T lymphocytes (CTLs) and suppress the immune response[8].

Immune escape in ESCC also involves utilization of¹³ immune checkpoint pathways. These¹ pathways, mediated by molecules such as PD-L1 and CTLA-4, act as regulatory brake on the immune system to prevent excessive immune activation and autoimmunity[13, 14]. ESCC¹ cells can upregulate the expression of these checkpoint ligands, allowing them to bind to their corresponding receptors on T cells and effectively deactivate the anti-tumor T cell response[15].

In addition to the previously mentioned mechanisms, ESCC cells show a flexible immune escape repertoire. They¹ can express ligands that bind to inhibitory receptors on T cells, leading to T cell exhaustion and dysfunction[13]. ESCC¹ cells can also reprogram their metabolism to escape immune recognition and resist immune-mediated cytotoxicity[10]. Furthermore¹, they can produce immunosuppressive enzymes, such as indoleamine 2,3-dioxygenase (IDO), which reduces essential amino acids required for T cell activation and function, disabling¹⁴ the anti-tumor immune response[16].

By using these diverse immune escape methods, ESCC cells create a microenvironment that protects them from immune attack and promotes tumor progression. Understanding¹ these mechanisms is crucial for developing novel therapeutic strategies that can¹⁵ enhance the anti-tumor immune response and improve patient outcomes.

ARYL HYDROCARBON RECEPTOR (AHR) SIGNALING: A MASTER REGULATOR WITH DIVERSE FUNCTIONS IN HEALTH AND DISEASE

AhR is a ubiquitous and complicated ligand-activated transcription factor that has significant influences on¹⁶ various physiological processes[17]. AhR¹, which is¹ primarily found in the cytoplasm with chaperone proteins, goes through significant¹⁸ changes upon binding to ligands [18]. These¹ ligands are categorized into two main groups: exogenous, which includes environmental pollutants

such as polycyclic aromatic hydrocarbons (PAHs), and endogenous, which comprises metabolites from tryptophan breakdown, such as tryptophan and kynurenine[19]. When a ligand binds, AhR alters its shape, releases from its chaperone complex, and moves to the nucleus[20]. It pairs with ARNT and attaches to specific DNA sequences called xenobiotic response elements (XREs) in the regulatory regions of the target genes. This interaction initiates the transcription of various genes, influencing several cellular processes via AhR signaling[21]. Beyond its well-recognized role in xenobiotic metabolism, AhR signaling applies an excessive influence on numerous biological processes, including cellular proliferation and differentiation[22], angiogenesis[23], cellular metabolism[24], oxidative stress response[25], immune regulation[26], and inflammation[27].

Studies have demonstrated that AhR signaling affects the proliferation and differentiation of epithelial cells, lymphocytes, and hematopoietic progenitor cells[22]. Moreover, AhR may influence the expression of pro-angiogenic factors such as vascular endothelial growth factor (VEGF)¹⁹, and impact both physiological and pathological angiogenesis[23]. AhR activation also influences insulin sensitivity, glucose uptake, and lipogenesis. Dysregulation of these pathways may contribute to the development of metabolic disorders, such as obesity and type 2 diabetes (T2DM)[24]. AhR signalling can influence cellular metabolism and, promote the Warburg effect. This metabolic shift not only enhances tumor cell proliferation, but can also create an immunosuppressive microenvironment by changing the levels of metabolites and signaling molecules that modulate immune cells[28]. The cellular environment is consistently influenced by the²² reactive oxygen species (ROS) produced during normal metabolic processes. AhR¹ can modulate the antioxidant defense system by targeting the expression of enzymes such as heme oxygenase-1 (HO-

1), NAD(PH), and quinone oxidoreductase 1 (NQO1), which are important²³ in protecting cells from oxidative damage[25].

AhR signaling exerts a detailed and context-specific influence on the immune system. It¹ modulates the function of several immune cell populations, including T cells, B cells, and antigen-presenting cells (APCs)[26]. AhR¹ activation can promote the differentiation of regulatory T cells (Tregs) with immunosuppressive properties²⁴, while simultaneously²⁵ inhibiting the proliferation and function of effector T cells[29]. AhR¹ can influence the expression of MHC²⁶, and co-stimulatory molecules on APCs²⁶, and impact the efficiency of antigen presentation and T cell²⁶ activation[30]. The tumor microenvironment²⁷ is often characterized by chronic inflammation, which can promote tumorigenesis. AhR¹ signaling can influence the expression of inflammatory mediators, such as cytokines and chemokines, forming an inflammatory milieu within the tumor microenvironment. While¹ some inflammatory responses can promote anti-tumor immunity, chronic inflammation initiated by aberrant AhR activation can create a pro-tumorigenic microenvironment[27]. The¹ multi-dimensional nature of the AhR highlights its potential as a double-edged sword. While¹ it contributes to essential physiological processes, including xenobiotic metabolism, immune homeostasis, and tissue development, its dysregulation can be involved in various disease pathologies, including cancer. Understanding the important²⁸ role of AhR signaling in ESCC, especially its influence on the tumor immune microenvironment and immune escape mechanisms, could be beneficial in the development of novel therapeutic strategies²⁹.

AHR AND ESCC DEVELOPMENT

Exposure to environmental carcinogens, such as polycyclic aromatic hydrocarbons (PAHs) found in cigarette smoke and certain dietary components³⁰

is a well-established risk factor for ESCC development[31]. These carcinogens can activate AhR signaling via direct ligand binding[32]. The activated AhR pathway influences multiple cellular processes that contribute to ESCC tumorigenesis. Studies have demonstrated that AhR activation can promote the proliferation of esophageal epithelial cells by modulating cell cycle regulatory proteins such as cyclin D1 and p21[33]. Moreover, AhR signaling can inhibit apoptosis and, the programmed cell death pathway, by influencing the expression of anti-apoptotic factors such as Bcl-2[34]. These effects create conditions favorable for deregulated cell proliferation, which is a characteristic of cancer. Chronic exposure to carcinogens can induce DNA damage in esophageal epithelial cells[35]. However, AhR activation can further exacerbate this issue by downregulating the expression of key DNA repair enzymes[36]. This impaired repair system increases the accumulation of mutations and, eventually increases the risk of malignant transformation. Cancer cells exhibit a distinct metabolic profile compared to healthy cells. ESCC development and progression may be initiated by a subpopulation of cancer stem cells (CSCs) with self-renewal and differentiation capabilities[37, 38]. AhR activation has been studied in promoting the stemness properties of ESCC cells[39]. Epithelial-Mesenchymal Transition (EMT) is a critical process by which epithelial cells lose their polarized phenotype and acquire mesenchymal characteristics, gaining migratory and invasive potential[40]. AhR activation has been shown to induce EMT in various cell types, including esophageal epithelial cells[41]. Studies have demonstrated that AhR ligands can upregulate the expression of EMT-inducing transcription factors such as Twist1 and Snail, promoting the acquisition of an invasive phenotype by cancer cells[42]. The EMT process is crucial for ESCC progression and metastasis, by enabling cancer cells to detach from the primary tumor, migrate through the basement

membrane, and invade the surrounding tissues and lymphatic vessels. EMT can also enhance the resistance of ESCC cells to anoikis, a type of cell death triggered by detachment from the extracellular matrix[43]. This combined effect of increased motility and resistance to anoikis promotes the dissemination of ESCC cells to other organs, resulting in the formation of metastases.

AHR AND IMMUNE ESCAPE IN ESCC

While certain studies have indicated that activating AhR might enhance anti-cancer immune responses, other studies suggest its possible involvement in immune evasion mechanisms in ESCC. AhR activation can suppress effector T cells, the main attacking cells of the adaptive immune response[44]. Studies have shown that some AhR ligands can inhibit the proliferation and cytokine production of CD8+ cytotoxic T lymphocytes (CTLs) and weaken the immune response against ESCC cells[45]. Additionally, AhR activation can promote the differentiation of Tregs, a population of immunosuppressive T cells that dampens the anti-tumor immune response[46]. The tumor microenvironment in ESCC is often infiltrated by immunosuppressive myeloid cells, including myeloid-derived suppressor cells (MDSCs)[13]. AhR activation promotes the recruitment and expansion of MDSCs, which contributes to the suppression of anti-tumor immunity[47]. Immune checkpoint molecules, such as PD-L1 and CTLA-4, act as inhibitory agents in the immune system to prevent autoimmunity. However, ESCC cells can use these checkpoints to escape immune response[48]. Some studies suggested that AhR activation upregulates the expression of PD-L1 on ESCC cells, potentially participating in immune escape by inhibiting T cell function[49]. Table 1 summarizes the influence of AhR signaling on ESCC development, progression, and immune escape.

THE THERAPEUTIC POTENTIAL OF TARGETING AHR SIGNALING IN ESCC

The complex influence of AhR signaling on ESCC development, progression, and immune escape presents an interesting opportunity for the development of novel therapeutic strategies. While the aberrant AhR activation can promote tumorigenesis and create an immunosuppressive microenvironment, its proper modulation could be beneficial for disrupting these processes and boosting the anti-tumor immune response.

Preclinical studies investigating AhR ligands in ESCC models have yielded interesting results[49]. Several antagonists could competitively bind to the ligand-binding domain, and block the activation of AhR signaling pathways and their downstream effects on ESCC cells[49]. Studies have demonstrated that AhR antagonists can suppress ESCC cell proliferation, migration, and invasion, potentially inhibiting tumor progression and metastasis[50]. AhR antagonists exhibit immunomodulatory effects within the tumor microenvironment, by inhibiting AhR signaling. These antagonists may reduce the population of immunosuppressive MDSCs and Tregs, and simultaneously enhancing the function and proliferation of effector T cells, leading to a more powerful anti-tumor immune response[51, 52]. Several AhR antagonists are currently under investigation for their therapeutic potential in ESCC, including CH-223191, NH3 (Ammonia), and specific small molecules[53]. Not only AhR antagonists but also some naturally derived AhR agonists, such as curcumin[54] and quercetin[55] have been shown to exhibit regulatory properties on immune response in cancer. This controversy could be due to the structural and metabolic differences of different AhR ligands. Furthermore, synthetic AhR antagonists are being actively developed, with some demonstrating promising preclinical results[51]. Table 2 has summarized some of the most promising candidates, their mechanisms of action, and potential effects on malignancies.

Beyond directly targeting the AhR itself, manipulating the endogenous ligands that activate this pathway offers another potential therapeutic avenue. The gut microbiota plays an important role in metabolizing dietary components into ligands that can activate AhR signaling[56]. Strategies aimed at modulating the gut microbiota composition, potentially through prebiotics or probiotics, could be studied to influence the production of these ligands and their subsequent impact on AhR signaling in ESCC[57]. Moreover, dietary factors can also influence AhR ligand production. Identifying and employing natural AhR modulators, such as indole-3-carbinol found in cruciferous vegetables, into the diet could be a preventive or complementary therapeutic approach for ESCC patients[58, 59]. Some AhR agonists such as TCDD bind tightly to the AhR, leading to long-lasting activation that disrupts normal cellular processes and promotes cancer development. However, I3C, and its metabolites transiently activate the AHR. This controlled activation helps in detoxifying carcinogens, inhibiting abnormal cell growth, and promoting cancer cell death, highlighting their potential anticancer effects [58, 59]. However, the effectiveness of dietary AhR modulators is not well-established by the lack of comprehensive studies on the metabolic kinetics, permeability, and transport of dietary compounds. Future research should focus on these aspects to better understand and optimize the role of these compounds on ESCC treatment.

The therapeutic potential of AhR-targeted strategies may be further intensified when combined with existing treatment approaches for ESCC. For instance, combining selected AhR ligands (agonist or antagonist) with conventional therapies such as surgery, radiation, or chemotherapy could offer synergistic effects. These traditional therapies can induce DNA damage and cell death in ESCC cells, while AhR ligands may suppress tumor growth and metastasis by inhibiting proliferation and invasion[60]. Additionally, AhR ligands could be

particularly effective when combined with immune checkpoint inhibitors[61].
Clinical trials investigating the combination of AhR-targeted therapies with other treatment strategies are suggested to determine their efficacy and safety in ESCC patients.

CONCLUSION

Immune escape mechanisms play a crucial role in ESCC progression, allowing cancer cells to evade the surveillance of the host immune system. The AhR activation, triggered by environmental carcinogens such as PAHs, promotes various hallmarks of cancer, including proliferation, apoptosis inhibition, and metabolic reprogramming. Moreover, AhR signaling contributes to immune escape by suppressing T cell function, recruiting immunosuppressive myeloid cells, and upregulating immune checkpoint molecules like PD-L1. Targeting AhR signaling presents a promising therapeutic approach for ESCC. AhR ligands (agonist or antagonist), both natural and synthetic, have shown potential in preclinical studies by inhibiting tumor growth and modulating the immune microenvironment. Modulating AhR ligands through dietary interventions may offer new therapeutic approaches. Furthermore, combining AhR-targeted therapies with conventional treatments or immune checkpoint inhibitors may result in synergistic effects, enhancing overall therapeutic efficacy.

1.	<i>. Immune; . One; . Dysregulated; . Targeting; . Additionally; . This; . The; . AhR; . Moreover; . Therapeutic; . Combining; . It; . Chronic; . These; . Furthermore; . If; . In; . MHC; . By; . They; . ESCC; . Understanding; . When; . Beyond; . Dysregulation; . While; . Studies; . However; . Cancer; ...</i>	Text inconsistencies	Correctness
2.	important → essential	Word choice	Engagement
3.	which is	Wordy sentences	Clarity
4.	can potentially	Wordy sentences	Clarity
5.	particularly → exceptionally	Word choice	Engagement
6.	promote → promotes	Faulty subject-verb agreement	Correctness
7.	the development of	Wordy sentences	Clarity
8.	<i>Despite advancements in treatment procedures, ESCC prognosis is still poor, emphasizing the need for a better understanding of the main processes that stimulate tumorigenesis and immune escape.</i>	Paragraph can be perfected	Clarity
9.	the immune	Determiner use (a/an/the/this, etc.)	Correctness
10.	demonstrates → is demonstrated	Incorrect verb forms	Correctness
11.	tumor cells utilize	Wordy sentences	Clarity
12.	<i>To escape the strong immune surveillance system, ESCC cells organize a multi-dimensional immune escape program (Figure 1). One of the key mechanisms includes downregulation of Major Histocompatibility Complex (MHC) molecules on the cell surface[11].</i>	Paragraph can be perfected	Clarity

13.	<i>Immune escape in ESCC also involves utilization of immune checkpoint pathways. These pathways, mediated by molecules such as PD-L1 and CTLA-4, act as regulatory brake on the immune system to prevent excessive immune activation and autoimmunity[13, 14].</i>	Paragraph can be perfected	Clarity
14.	disabling → turning off	Potentially sensitive language	Delivery
15.	that can → to	Wordy sentences	Clarity
16.	significantly influences	Wordy sentences	Clarity
17.	which is	Wordy sentences	Clarity
18.	significant → substantial	Word choice	Engagement
19.),	Punctuation in compound/complex sentences	Correctness
20.	<i>AhR signalling can influence cellular metabolism and, promote the Warburg effect.</i>	Ungrammatical sentence	Correctness
21.	proliferation,	Comma misuse within clauses	Correctness
22.	<i>The cellular environment is consistently influenced by the reactive oxygen species (ROS) produced during normal metabolic processes.</i>	Unclear sentences	Clarity
23.	important → essential	Word choice	Engagement
24.	properties,	Punctuation in compound/complex sentences	Correctness
25.	simultaneously	Wordy sentences	Clarity

26.	<i>AhR can influence the expression of MHC, and co-stimulatory molecules on APCs, and impact the efficiency of antigen presentation and T cell activation[30].</i>	Ungrammatical sentence	Correctness
27.	<i>The tumor microenvironment is often characterized by chronic inflammation, which can promote tumorigenesis.</i>	Unclear sentences	Clarity
28.	important → critical, vital	Word choice	Engagement
29.	the development of → developing	Wordy sentences	Clarity
30.	certain → specific	Word choice	Engagement
31.	components	Punctuation in compound/complex sentences	Correctness
32.	<i>Moreover, AhR signaling can inhibit apoptosis and, the programmed cell death pathway, by influencing the expression of anti-apoptotic factors such as Bcl-2[34].</i>	Ungrammatical sentence	Correctness
33.	which is	Wordy sentences	Clarity
34.	carcinogenic exposure	Wordy sentences	Clarity
35.	eventually	Punctuation in compound/complex sentences	Correctness
36.	<i>This impaired repair system increases the accumulation of mutations and, eventually increases the risk of malignant transformation.</i>	Unclear sentences	Clarity
37.	<i>AhR activation has been studied in promoting the stemness properties of ESCC cells[39].</i>	Incorrect phrasing	Correctness

38.	<i>AhR activation has been studied in promoting the stemness properties of ESCC cells[39].</i>	Unclear sentences	Clarity
39.	Epithelial-mesenchymal transition	Confused words	Correctness
40.	by	Wordy sentences	Clarity
41.	by enabling → as it enables	Incorrect phrasing	Correctness
42.	<i>This combined effect of increased motility and resistance to anoikis promotes the dissemination of ESCC cells to other organs, resulting in the formation of metastases.</i>	Unclear sentences	Clarity
43.	ESCC → EACH	Misspelled words	Correctness
44.	certain → specific	Word choice	Engagement
45.	anti-cancer; anticancer	Text inconsistencies	Correctness
46.	main → central, primary	Word choice	Engagement
47.	ESCC → EACH	Misspelled words	Correctness
48.	interesting → exciting	Word choice	Engagement
49.	to develop	Wordy sentences	Clarity
50.	in	Wordy sentences	Clarity
51.	interesting → exciting	Word choice	Engagement
52.	domain,	Punctuation in compound/complex sentences	Correctness
53.	microenvironment,	Punctuation in compound/complex sentences	Correctness

54.	<i>These antagonists may reduce the population of immunosuppressive MDSCs and Tregs, and simultaneously enhancing the function and proliferation of effector T cells, leading to a more powerful anti-tumor immune response[51, 52].</i>	Ungrammatical sentence	Correctness
55.	and	Wordy sentences	Clarity
56.	!	Punctuation in compound/complex sentences	Correctness
57.	has summarized → summarizes	Incorrect verb forms	Correctness
58.	an important → a vital, an essential	Word choice	Engagement
59.	is important	Wordy sentences	Clarity
60.	<i>indole-3-carbinol</i>	Unknown words	Correctness
61.	<i>Some AhR agonists such as TCDD bind tightly to the AhR, leading to long-lasting activation that disrupts normal cellular processes and promotes cancer development.</i>	Ungrammatical sentence	Correctness
62.	I3C,	Comma misuse within clauses	Correctness
63.	<i>This controlled activation helps in detoxifying carcinogens, inhibiting abnormal cell growth, and promoting cancer cell death, highlighting their potential anticancer effects [58, 59].</i>	Incorrect phrasing	Correctness
64.	by → due to	Wrong or missing prepositions	Correctness
65.	dietary → nutritional	Word choice	Engagement
66.		Tone suggestions	Delivery
67.	on → in	Wrong or missing prepositions	Correctness