ImmunoTargets and Therapy

Dovepress
Taylor & Francis Group

Open Access Full Text Article

REVIEW

A Review of Aryl Hydrocarbon Receptor–Mediated Immune Regulation in Cutaneous Squamous Cell Carcinoma Progression

Huiyan Han[1], Qinyi Dong[2], Zijian Zhang[2], Siying Li[1], Han Zhang[1], Xinman Wang[1], Jiahao Bai[1], Lei Shi[1], Xiaoyi Fu[2], Kaili Zheng[1], Lili Liang[1]

[1]The Cosmetic and Plastic Surgery Department of Shanxi Provincial People's Hospital, Shanxi Medical University, Taiyuan, 030012, People's Republic of China; [2]The Third Clinical College, Shanxi University of Chinese Medicine, Taiyuan, People's Republic of China

Correspondence: Lili Liang, Email amyliangli@163.com

Abstract: The aryl hydrocarbon receptor (AhR) is a ligand-activated transcription factor that was initially discovered for its role in mediating the toxicity of environmental pollutants such as dioxins. Recent studies have demonstrated that AhR plays significant roles in various physiological and pathological processes, including immune regulation and tumor development. Cutaneous squamous cell carcinoma (cSCC), the second most common skin malignancy, is closely associated with the immune microenvironment. This review systematically outlines the structure, function, and signaling pathways of AhR, as well as its role in the immune system, with a focus on how AhR influences the progression of cSCC by regulating the functions of various immune cells, including T cells, dendritic cells, macrophages, and myeloid-derived suppressor cells. In particular, this review highlights the central role of the "tryptophan–kynurenine–AhR" axis, along with AhR-mediated regulation of immune checkpoints (such as PD-1/PD-L1, CTLA-4, and TIM-3), its crosstalk with inflammatory signaling pathways (including NF-κB, STAT3, and TGF-β), and the impact of AhR on antigen presentation and immunoediting. Furthermore, it discusses the role of AhR ligands in cSCC and the potential of targeting AhR for therapy, providing a novel theoretical foundation and strategic insights for the immunotherapy of cSCC. This review systematically summarizes the immunomodulatory mechanisms of AhR, integrating findings from studies specific to cSCC and those from other tumor types. It should be noted that some mechanistic evidence is derived from non-cSCC research models, and its applicability to cSCC requires further validation.

Keywords: aryl hydrocarbon receptor, cutaneous squamous cell carcinoma, immune system, tumor microenvironment, AhR ligands

Introduction

The skin is the largest organ of the human body, serving as the primary barrier against physical, chemical, and biological damage. However, prolonged external stimuli, especially ultraviolet (UV) radiation, can induce malignant transformation of skin cells, leading to the development of skin cancer. Cutaneous squamous cell carcinoma (cSCC) is the second most common non-melanoma skin cancer, with its global incidence rising annually.[1] In China, the age-standardized incidence rate of cSCC has more than doubled from 1990 to 2021, with a sustained upward trend projected through 2030.[2] Although most localized cSCC cases have a favorable prognosis after surgical excision, patients with advanced, metastatic, or unresectable cSCC often face a poor prognosis, limited therapeutic options, and insensitivity to traditional radiotherapy and chemotherapy.[3]

In recent years, immune checkpoint inhibitors (ICIs), such as anti-programmed cell death protein 1 (anti-PD-1) antibodies, have shown significant efficacy in treating advanced cSCC. This underscores the central role of the immune system in controlling cSCC progression,[4] even demonstrating favorable safety in elderly and immunocompromised populations.[5] The tumor immune microenvironment (TME) of cSCC is a complex ecosystem composed of tumor cells, immune cells, stromal cells, cytokines, and chemokines. The dynamic balance within this microenvironment—

https://doi.org/10.2147/ITT.S601152
Received: 4 February 2026
Accepted: 30 April 2026
Published: 16 May 2026

specifically the interplay between immunosuppressive and immune-activating states—directly determines tumor growth, invasion, and metastasis.[6] Therefore, a deep understanding and targeted modulation of key molecules within the cSCC immune microenvironment is fundamental for developing novel immunotherapeutic strategies.

It is in this context that the aryl hydrocarbon receptor (AhR) has emerged as a molecule of significant interest. AhR is an evolutionarily conserved, ligand-activated transcription factor belonging to the Per-Arnt-Sim (PAS) protein family. Initially identified as a receptor for environmental toxins such as 2,3,7,8-tetrachlorodibenzo-p-dioxin (TCDD),[7] subsequent research has broadened the understanding of its physiological functions. AhR can be activated by various endogenous ligands derived from tryptophan metabolism and microbial products, positioning it as a "molecular sentinel" sensing both internal and external environmental changes.[8] Substantial evidence indicates that AhR plays a pleiotropic role in regulating the differentiation, function, and homeostasis of immune cells, profoundly influencing both innate and adaptive immune responses.[9]

In oncology, AhR can act as either a tumor suppressor or a promoter, depending on the cancer type, the specific ligands present in the microenvironment, their concentration, and the cell types involved.[10] Within the skin, AhR is abundantly expressed in keratinocytes, melanocytes, and resident immune cells. AhR signaling regulates skin barrier function, pigmentation, wound healing, and responses to UV damage.[11] Recent studies have increasingly focused on the role of AhR in cSCC development, particularly its mechanisms of influencing tumor progression via the tumor immune microenvironment. For instance, kynurenine—an endogenous AhR ligand produced by tumor or immune cell metabolism—can activate AhR in immune cells, inducing immunosuppression and facilitating tumor immune evasion.[12]

This review aims to systematically summarize the molecular characteristics of AhR and its regulatory network within the immune system, with a focus on its role in the pathological context of cSCC. We will discuss in detail how AhR signaling influences the immune microenvironment and disease progression of cSCC by modulating the functions of key immune cells (T cell subsets, antigen-presenting cells, and myeloid-derived suppressor cells), thereby shaping the balance between anti-tumor immunity and immune escape. Distinct from previous studies, this review specifically emphasizes the role of AhR as a central node connecting the environment, metabolism, and immune responses in cSCC. It systematically outlines the mechanisms by which AhR participates in immune checkpoint regulation, crosstalk with inflammatory signaling pathways, and modulation of antigen presentation. By integrating evidence from cSCC-specific studies and findings from other tumor types, this review provides new perspectives for the development of more effective immunotherapies for cSCC.

Search Strategy

This review strictly followed the PRISMA 2020 guidelines to ensure rigorous and transparent literature screening and analysis. Relevant literatures were retrieved from PubMed, Web of Science, Embase and CNKI from their inception to March 2026. The search focused on innovative studies from 2011 to 2026 for timeliness and academic traceability, with early landmark basic studies also included. Search terms combined MeSH and free words, including "aryl hydrocarbon receptor", "AhR", "cutaneous squamous cell carcinoma", "cSCC", "immune system", "tumor immune microenvironment", "immune regulation", "immunotherapy target" and "AhR ligands". A search strategy was built with Boolean operators (AND, OR, NOT) based on the research topic. Literature screening followed the PRISMA 2020 flow chart: duplicate literatures were removed via EndNote 2025 by title, author, journal and publication year; two independent researchers excluded irrelevant studies by title and abstract; full-text evaluation was performed on potentially eligible literatures; disputes were resolved through joint discussion with a third independent researcher. A structured quality assessment was adopted for all included studies, ensuring only medium and high-quality literatures were used for the final summary and analysis.

Overview of the Pathophysiology of Cutaneous Squamous Cell Carcinoma (cSCC)

As a malignant tumor originating from epidermal keratinocytes, the pathophysiological process of cSCC is a complex cascade driven by environmental factors, genetic alterations, and the immune microenvironment.

The primary causative factor of cSCC is chronic exposure to ultraviolet (UV) radiation, particularly UVB. UV radiation can directly damage DNA, inducing characteristic C>T or CC>TT mutations, known as "UV fingerprint mutations." These mutations accumulate in critical tumor suppressor genes (such as TP53, which is mutated in over 80% of cSCC cases) and proto-oncogenes, disrupting cell cycle control, apoptosis, and DNA repair mechanisms, thereby conferring uncontrolled proliferative capacity to keratinocytes.[13] UV radiation also induces local and systemic immunosuppression, weakening the immune surveillance of early cancerous cells.[14]

Due to the large number of UV-induced gene mutations, cSCC typically exhibits a high tumor mutational burden (TMB). Theoretically, a high TMB can generate a large number of tumor neoantigens, making cSCC an immunologically "hot" tumor with high immunogenicity.[15] Indeed, histological observations confirm that dense T-cell infiltration is often present within cSCC lesions, yet the tumors continue to progress. This suggests the existence of a dominant immunosuppressive network in the tumor immune microenvironment (TME). This network drives immune escape by exhausting or paralyzing effector T cells through mechanisms involving regulatory T cells (Tregs), myeloid-derived suppressor cells (MDSCs), M2-like tumor-associated macrophages (TAMs), immune checkpoint molecules (eg, PD-L1), and inhibitory metabolites (eg, kynurenine).[16] Therefore, the progression of cSCC can be viewed as the synergistic outcome of the intrinsic malignant proliferative properties of tumor cells and the immunosuppressive effects mediated by the microenvironment.

AhR Structure, Ligands, and Signaling Pathway

To understand the complex role of AhR in the immune microenvironment of cSCC, it is essential to first gain a clear understanding of its basic molecular biological characteristics, including its protein structure, diverse ligands, and the signal transduction pathways activated thereafter.

Molecular Structure of AhR

The N-terminal bHLH domain is responsible for DNA binding and dimerization with the Aryl Hydrocarbon Receptor Nuclear Translocator (ARNT).[17] The PAS (Per-Arnt-Sim) domain is divided into two subdomains: PAS-A and PAS-B. The PAS-A domain stabilizes the dimer structure through protein-protein interactions, while the PAS-B domain contains the ligand-binding pocket, which recognizes and binds both endogenous and exogenous ligands (such as environmental pollutants and physiological active substances).[18] The C-terminal region contains the transcriptional activation domain (TAD) (Table 1), which recruits coactivators to initiate the transcription of downstream genes.[19] Table 1

In the resting state, that is, in the absence of ligand binding, AhR resides in the cytoplasm and associates with a chaperone complex composed of heat shock protein 90 (Hsp90), AhR-interacting protein (AIP, also known as XAP2), and p23. The function of this chaperone complex is to maintain the conformational stability of AhR, keeping it in an inactive yet readily activatable state, and to prevent its translocation into the nucleus before activation.[20]

Diverse Ligands of AhR

The exogenous ligands of AhR primarily include environmental pollutants and industrial by-products, such as dioxins (eg, TCDD), polycyclic aromatic hydrocarbons (PAHs, eg, benzo[a]pyrene), and polychlorinated biphenyls (PCBs). These ligands exhibit high affinity and long half-lives. Their persistent activation of AhR constitutes the molecular basis for adverse effects such as immunotoxicity, teratogenicity, and carcinogenicity.[8]

Table 1 Main Domains and Functions of the AHR Protein

Domain	Location	Core Function
Basic helix-loop-helix (bHLH)	Amino terminus (N-terminus)	Mediates DNA binding and protein dimerization
PAS-A	Downstream of bHLH domain, upstream of PAS-B	Stabilizes heterodimer structure
PAS-B	Downstream of PAS-A	Specifically binds ligands
Transactivation domain (TAD)	Carboxyl terminus (C-terminus)	Activates target gene transcription
Linker region	Between PAS-A and PAS-B	Adapts ligand-induced conformational changes

https://doi.org/10.2147/ITT.S601152

Endogenous ligands are produced by the body's own metabolism and are essential for the physiological functions of AhR. They mainly originate from the tryptophan metabolic pathway, where tryptophan is metabolized via the kynurenine (Kyn) pathway to generate AhR ligands such as Kyn and kynurenic acid. In the tumor microenvironment, the high expression of indoleamine 2,3-dioxygenase (IDO1) or tryptophan 2,3-dioxygenase (TDO2) leads to extensive breakdown of tryptophan into Kyn, thereby activating AhR.[12] Recent studies indicate that L-amino acid oxidase (IL4I1), a key tryptophan-metabolizing enzyme, can produce metabolites such as indole-3-pyruvate (I3P). These metabolites act as AhR ligands and play a widespread role in driving tumor immune escape.[21] Furthermore, 6-formylindolo[3,2-b]carbazole (FICZ), a photoproduct generated from tryptophan under ultraviolet (UV) light, is one of the strongest known endogenous AhR agonists and is closely involved in the skin's response to UV radiation.[22] Other endogenous ligands also include bilirubin and eicosanoids.[23]

In addition to environmental and endogenous ligands, dietary and symbiotic microbial ligands are also critical sources of AhR activation. Indole-3-carbinol (I3C), abundant in cruciferous vegetables such as broccoli, can be converted into potent AhR agonists like indolo[3,2-b] carbazole (ICZ) under gastric acid conditions (Table 2). Meanwhile, molecules such as indole and indole-3-acetic acid, produced by gut microbiota from tryptophan metabolism, are essential for maintaining intestinal barrier integrity and local immune homeostasis.[24] Recent studies further emphasize that microbial-derived AhR ligands not only regulate intestinal immunity but also remotely influence skin barrier function and neuroinflammation via the "gut-skin axis".[9] This provides a new perspective for intervening in cSCC progression by modulating microbial metabolism. Table 2

The Signaling Pathway of AhR

The canonical signaling pathway of AhR is a ligand-induced transcriptional regulatory process (As shown in Figure 1). Upon ligand binding to the PAS-B domain of the cytoplasmic AhR complex, AhR undergoes a conformational change, exposing its nuclear localization signal. This leads to the dissociation of chaperone proteins such as Hsp90 and subsequent nuclear translocation of AhR. Inside the nucleus, AhR forms a heterodimer with ARNT.[25] This dimer recognizes and binds to xenobiotic response elements (XREs) in the promoter or enhancer regions of target genes. Following XRE binding, coactivators such as p300/CBP and SRC-1, along with RNA polymerase II, are recruited to initiate the transcription of downstream target genes.[26] Typical AhR target genes encode cytochrome P450 family enzymes, including CYP1A1, CYP1A2, and CYP1B1, which are involved in the metabolism of various exogenous and endogenous substances.[27] Furthermore, AhR induces the expression of the AhR repressor (AhRR), which competitively binds to ARNT, thereby establishing a negative feedback regulation of the AhR signaling pathway.[28]

In addition to the classical DRE-dependent transcriptional regulatory pathway, AhR also exerts significant biological functions through various non-canonical mechanisms. Recent studies have revealed that ligand-activated AhR itself can function as an E3 ubiquitin ligase, directly catalyzing the ubiquitination and degradation of target proteins (such as estrogen receptor α and androgen receptor), thereby regulating protein stability and function in a transcription-independent manner.[29] Meanwhile, AhR can indirectly inhibit STAT3 activation by inducing the expression of suppressor of cytokine signaling 2 (SOCS2), a negative regulator of the JAK/STAT signaling pathway that targets STAT3 and associated kinases for degradation. Additionally, AhR can directly interact with phosphorylated STAT proteins to regulate their transcriptional activity, influencing processes such as Th17 cell differentiation.[30] AhR can also regulate key signaling pathways through protein-protein interactions. For example, AhR exhibits complex bidirectional crosstalk with the NF-κB pathway: it can inhibit the expression of pro-inflammatory genes by binding to RelA/RelB or competing

Table 2 Major Ligand Categories and Representative Substances of AHR

Ligand Category	Representative Substances
Exogenous Synthetic Ligands	Dioxins (TCDD), Polycyclic Aromatic Hydrocarbons (Benzopyrene, Anthracene), Polychlorinated Biphenyls (PCBs), DDT
Endogenous Ligands	Tryptophan Metabolites (Kynurenine, Kynurenic Acid, I3P, FICZ), Bilirubin, Eicosanoids
Dietary/Microbiota-Derived Ligands	Indolo[3,2-b]carbazole (ICZ), Indole, Indole-3-Acetic Acid

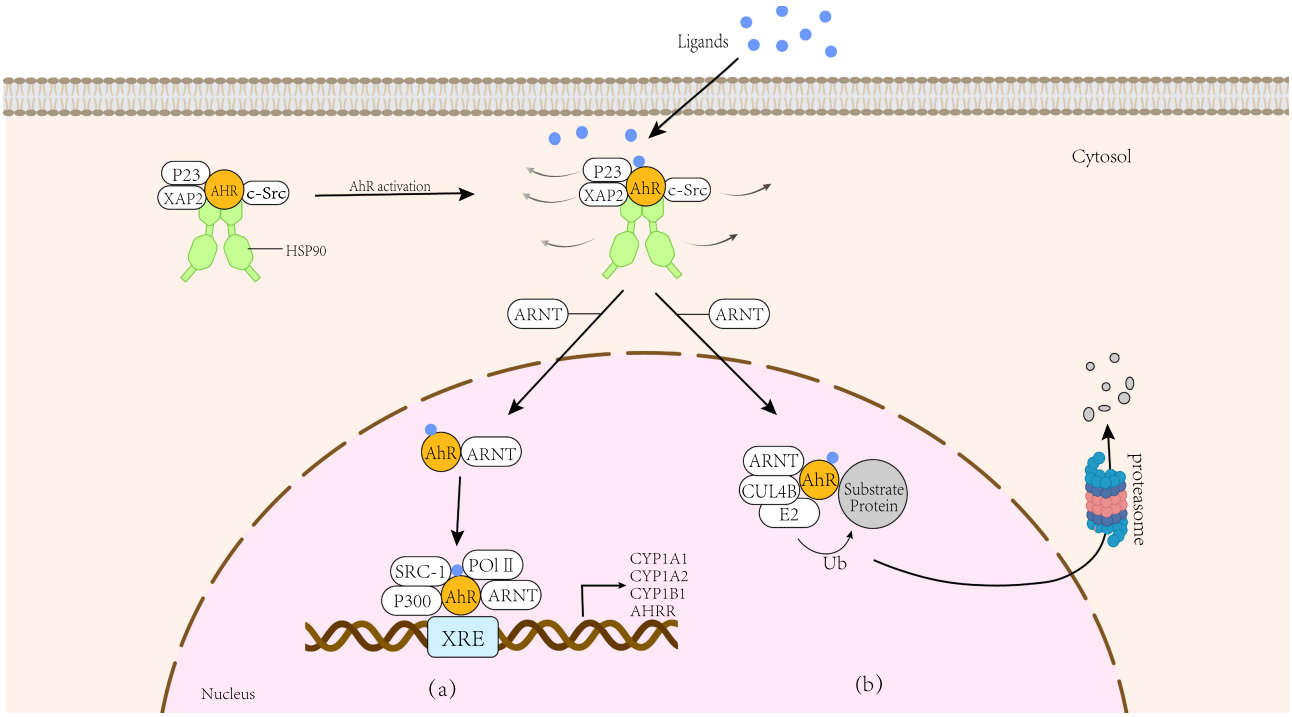

Figure 1 Canonical and Non-Canonical AhR Signaling Pathways.
Notes: (**a**) illustrates the canonical AhR signaling pathway: In the cytoplasm, unactivated AhR forms a complex with chaperone proteins like Hsp90 and AIP. Upon binding of exogenous ligands (eg, TCDD, PAHs) or endogenous ligands (eg, Kyn, FICZ), AhR undergoes a conformational change, the chaperone proteins dissociate, and AhR translocates into the nucleus. Inside the nucleus, AhR forms a heterodimer with ARNT, which binds to xenobiotic response elements (XREs) in the promoter regions of target genes, recruits co-activators, and initiates transcription of target genes like CYP1A1, CYP1B1, and AhRR. (**b**) illustrates one of the non-canonical AhR signaling pathways: Ligand-bound AhR assembles an atypical E3 ubiquitin ligase complex based on CUL4B to mediate the ubiquitination of target proteins. The ubiquitinated target proteins are subsequently degraded via the proteasome pathway. This process enables rapid cellular responses to ligand signals by directly mediating protein degradation, thereby regulating cellular processes.

for co-activators, and it can also cooperate with RelB to promote the transcription of genes such as IL-22, participating in the maintenance of mucosal barrier homeostasis.[29]

The Pleiotropic Regulatory Role of AhR in the Immune System

AhR acts as an integrator of environmental, metabolic, and immune signals, playing a critical regulatory role across all levels of the immune system. It not only influences the development and differentiation of immune cells but also finely tunes their effector functions, thereby maintaining immune homeostasis or, under pathological conditions such as cancer, driving immune dysregulation.[31] AhR's regulation of immune cells is highly cell-type-specific and ligand-dependent. Understanding these complex regulatory networks is essential for elucidating its role in cSCC.

Regulation of T Cells by AhR

AhR Shapes the Immune Microenvironment by Regulating CD4+ T Cell Subsets

AhR is a core transcription factor regulating the differentiation of $CD4^+$ helper T cells, and its specific effects exhibit strong ligand- and context-dependency. On one hand, upon activation by specific ligands such as UV-derived FICZ in the skin, AhR cooperates with STAT3 to directly promote the differentiation of pro-inflammatory Th17 cells.[32] This process plays a critical role in shaping the skin inflammatory microenvironment and provides a potential mechanism for the establishment of cSCC-associated inflammation.[33] On the other hand, in the tumor microenvironment, Kyn, a tryptophan metabolite generated by excessive IDO1/TDO2 activity, serves as the primary ligand driving the immunosuppressive functions of AhR.[12] The Kyn-AhR signaling axis potently induces the differentiation of highly suppressive regulatory T cells (Tregs) and enhances their immunosuppressive function by directly upregulating molecules such as CTLA-4 and LAG-3.[34] This dual and opposing nature of pro-inflammatory and anti-inflammatory functions reveals the complexity of

https://doi.org/10.2147/ITT.S601152

AhR in immune regulation. A key debate in the field centers on what determines whether AhR ultimately promotes inflammation or suppresses it in a given context, which likely involves the integrated effects of multiple factors including ligand type, ligand concentration, cell type, and co-stimulatory signals.[9,30]

Impairing $CD8^+$ Cytotoxic T Lymphocyte (CTL) Function

$CD8^+$ cytotoxic T lymphocytes are the central effector cells that directly kill tumor cells. In the tumor microenvironment, AhR signaling pathway, persistently activated by the Kyn, is a key factor leading to functional exhaustion and dysfunction of $CD8^+$ T cells.

AhR hyperactivation impairs the antitumor function of $CD8^+$ T cells through three interrelated mechanisms: First, it directly induces CTL apoptosis or promotes their entry into a state of functional anergy, leading to impaired proliferation and reduced secretion of effector molecules such as IFN-γ and granzyme B.[35] Second, it upregulates the expression of immune checkpoint molecules including PD-1, TIM-3, and LAG-3, thereby driving CTL exhaustion. Treatment with AhR antagonists can reverse this exhausted phenotype, restore IFN-γ production, and synergize with anti-PD-1 therapy.[36,37] Third, it inhibits the aerobic glycolysis pathway upon which activated effector T cells rely, forcing CTLs into an inefficient metabolic state and restricting their anti-tumor activity.[38]

In addition to these direct effects on CTLs, AhR also indirectly impairs CTL function by reshaping the differentiation landscape of $CD4^+$ T cells. Within the cSCC microenvironment, Kyn-AhR signaling preferentially drives the differentiation of immunosuppressive regulatory T cells (Tregs) rather than that of Th1-type helper T cells.[12,34] Consequently, this not only diminishes Th1-mediated positive help for CTLs but also enhances Treg-mediated immunosuppression. In summary, AhR exerts a pivotal regulatory role within the cSCC immune escape network through a dual mechanism: directly exhausting CTL effector functions and indirectly reshaping the differentiation balance of $CD4^+$ T cells.

AhR Regulation of Dendritic Cells (DCs)

Dendritic cells (DCs) serve as a critical bridge linking innate and adaptive immunity, responsible for antigen presentation and initiating T cell immune responses. Activation of AhR signaling can significantly disrupt DC function, promoting their shift from an immunostimulatory state toward a tolerogenic phenotype. Under normal conditions, mature DCs highly express MHC class II molecules, co-stimulatory molecules (CD80, CD86), and secrete pro-inflammatory cytokines such as IL-12, thereby effectively activating T cells. However, AhR ligands (eg, TCDD or Kyn in the tumor microenvironment) can inhibit DC maturation induced by stimuli such as lipopolysaccharide (LPS), leading to down-regulation of co-stimulatory molecules and reduced IL-12 secretion. This impairs their ability to activate effector T cells, particularly Th1 cells.[39] More importantly, AhR activation can actively induce DCs to express immunosuppressive molecules. AhR directly binds to the promoter of the "IDO1" gene, upregulating IDO1 expression. This further depletes tryptophan and generates Kyn, forming a "Kyn–AhR–IDO1" positive feedback loop that amplifies immunosuppression.[40] Concurrently, AhR-activated DCs increase the secretion of inhibitory cytokines such as IL-10 and TGF-β, directly inducing Treg differentiation. Therefore, in the tumor microenvironment, sustained AhR signaling transforms DCs, which should initiate antitumor immunity, into key participants in establishing and maintaining immune tolerance, thereby facilitating tumor immune escape.

AhR Regulation of Tumor-Associated Macrophages (TAMs) and Myeloid-Derived Suppressor Cells (MDSCs)

Myeloid cells, primarily including tumor-associated macrophages (TAMs) and myeloid-derived suppressor cells (MDSCs), play a critical role in the tumor microenvironment. TAMs often exhibit an M2-like phenotype, which supports tumor growth, angiogenesis, and immunosuppression. The AhR signaling pathway is an important driver of macrophage polarization toward this phenotype.[41] After activation, AhR significantly upregulates key markers of M2 macrophages, such as arginase-1 (Arg1), CD206, and the immunosuppressive cytokine IL-10, while suppressing M1 macrophages that possess anti-tumor functions.[42] Targeted knockout of AhR in macrophages can reverse their M2 phenotype and restore their anti-tumor function.[43]

On the other hand, MDSCs are a heterogeneous group of immature myeloid cells that strongly inhibit T cell function through mechanisms such as expressing arginase-1 (Arg1), producing reactive oxygen species (ROS), and generating nitric oxide (NO).[44] Kyn-mediated AhR signaling in the tumor microenvironment not only promotes the expansion and differentiation of MDSC precursors in the bone marrow, but also directly enhances the immunosuppressive capacity of MDSCs by upregulating the expression of Arg-1 and inducible nitric oxide synthase (iNOS).[45]

Notably, AhR-mediated regulation of TAMs and MDSCs is not an isolated event, but forms a synergistic myeloid immunosuppressive network. On one hand, AhR-driven M2-like TAMs promote the recruitment and expansion of MDSCs through the secretion of cytokines such as IL-10 and TGF-β.[43] On the other hand, MDSCs further reinforce M2 polarization of TAMs by producing factors such as IL-1β.[45] This positive feedback loop renders myeloid immunosuppression a self-sustaining mechanism of immune evasion in the cSCC microenvironment. The relative contribution of TAMs and MDSCs to immunosuppression in cSCC, as well as their causal relationship with T cell exhaustion, remains to be clarified. Detailed analyses using single-cell sequencing and lineage-tracing approaches in animal models and clinical samples will help elucidate the dynamic regulation of the myeloid immunosuppressive network and its role in tumor immune escape.

AhR Regulation of Other Immune Cells

In addition to the key immune cells mentioned above, AhR also regulates other immune cells such as innate lymphoid cells (ILCs) (Table 3). For instance, among ILCs—particularly group 3 innate lymphoid cells (ILC3s)—AhR is essential for their development and function. AhR activation can induce ILC3s to produce significant amounts of IL-22, which is crucial for maintaining the integrity of mucosal barriers such as those in the intestine.[46] In the skin, IL-22 is also involved in tissue repair and defense against certain pathogens. However, in certain cancer contexts, IL-22 has been shown to promote tumor cell proliferation and survival. Its specific role in cSCC requires further investigation.[33]

In summary, AhR profoundly influences multiple aspects of the immune system through a complex and interconnected regulatory network. Within the tumor microenvironment, AhR signaling predominantly driven by endogenous ligands, mainly Kyn, tends to suppress antitumor immunity and promote immune evasion. By impairing CTL cytotoxicity, promoting the expansion and function of immunosuppressive cells such as Tregs and MDSCs, and reshaping DCs and macrophages into a "pro-tumor" phenotype, AhR collectively facilitates tumor growth and progression.Table 3

Mechanisms by Which AhR Influences cSCC Progression via the Immune System

Research on the mechanisms by which AhR regulates cSCC progression through the immune system is still advancing, and the current evidence remains incomplete. In this section, when elaborating on the specific immune mechanisms through which AhR regulates cSCC progression, we prioritize direct evidence from cSCC-related basic and clinical

Table 3 Interaction Between Immune Cells and AhR Signaling

Immune Cell Type	Effects of AhR Signaling Activation
T Cells (CD4+ T Cells)	Promotes Treg differentiation and enhances immunosuppression; Facilitates Th17 cell differentiation and involvement in inflammatory responses; Induces CD4+ T cell exhaustion and upregulates PD-1 expression
Regulatory T Cells (Tregs)	Promotes Treg differentiation and functional maintenance, strengthens the immunosuppressive microenvironment, and inhibits effector T cell activation
T Cells (CD8+ T Cells)	Induces CD8+ T cell exhaustion; Suppresses cytotoxicity and upregulates exhaustion markers such as PD-1 and TIM-3
Dendritic Cells (DCs)	Affects DC differentiation, maturation, and antigen-presenting function, leading to a shift toward an immunotolerant phenotype
Macrophages	Regulates macrophage polarization, promoting M2-type (immunosuppressive) polarization while inhibiting M1-type (pro-inflammatory, anti-tumor) polarization
Myeloid-Derived Suppressor Cells (MDSCs)	Promotes MDSC expansion and function, enhances their inhibitory effect on T cells, and maintains the immunosuppressive microenvironment

https://doi.org/10.2147/ITT.S601152

studies. We also appropriately draw upon established findings from other tumor types, including glioblastoma, melanoma, breast cancer, and lung cancer,[10,12,37,43] to more systematically elucidate the immunomodulatory role of AhR in cSCC. It should be noted that some mechanistic conclusions in this section are derived from non-cSCC models, and their direct applicability and regulatory patterns in cSCC require further validation through targeted studies.

AhR Regulation of Tumor Microenvironment Immune Cells

The development of cSCC is a multi-step process, in which the interaction between tumor cells and the immune microenvironment is crucial. AhR activation can increase the infiltration of immunosuppressive cells in the cSCC microenvironment. Research by Piper et al showed that AhR-activated cSCC secretes chemokines such as CCL2 and CCL22, which recruit Tregs and MDSCs into the tumor tissue.[46] These immunosuppressive cells secrete factors like IL-10 and TGF-β to suppress effector T cell function, thereby promoting tumor immune escape.[47] In mouse models, treatment with AhR antagonists has been shown to reduce Treg infiltration and enhance anti-tumor immunity.[48]

cSCC cells highly express IDO1 and produce abundant Kyn, which directly suppresses $CD8^+$ T-cell function by activating AhR, resulting in inhibited proliferation, reduced effector function, and increased apoptosis.[49] Meanwhile, AhR activation upregulates PD-1 expression in T cells and enhances their sensitivity to PD-L1-mediated inhibitory signals.[50] In addition, Kyn in the cSCC microenvironment inhibits NK-cell activation and cytotoxicity by activating AhR, reducing the expression of perforin and granzyme.[51,52] In TAMs, AhR activation promotes macrophage polarization toward the M2 phenotype, characterized by elevated expression of M2 markers including CD206 and Arg1, and the production of immunosuppressive and tumor-promoting factors.[53] M2-type TAMs support cSCC progression by facilitating angiogenesis, matrix remodeling, and immune suppression,[54] whereas AhR blockade reverses M2 polarization of TAMs and remodels the tumor microenvironment.[55]

Emerging evidence from multiple preclinical models converges on a central paradigm: AhR activation regulates immunosuppression in cSCC via three interrelated mechanisms. First, tumor-derived Kyn establishes an autocrine positive feedback loop by upregulating IDO1 in dendritic cells, forming a self-sustaining immunosuppressive microenvironment.[40] Second, AhR signaling cooperates with the STAT3 and NF-κB pathways to suppress cytotoxic T-cell function and promote Treg expansion.[56] Third, AhR activation induces metabolic reprogramming by inhibiting glycolysis, linking AhR signaling to T-cell exhaustion.[38] However, translating these mechanistic insights into clinical applications remains hindered by several critical knowledge gaps. Most studies rely on transplantable tumor models, which may not fully recapitulate the unique UV-driven mutagenic features of human cSCC.[13,15] The relative contributions of tumor cell-intrinsic AhR signaling and immune cell-specific AhR signaling to immune evasion remain to be defined.[43] Whether AhR antagonism can reverse established immune tolerance, rather than merely preventing its induction, requires further validation.[37]

AhR-Mediated Regulation of Immune Checkpoints

AhR is not only a key regulator of immune cell function but also plays a central role in establishing the immunosuppressive tumor microenvironment by directly or indirectly modulating multiple immune checkpoint molecules and pathways. Distinct from the regulation of single checkpoint molecules, AhR exerts a unique multitarget effect by simultaneously upregulating the expression or activity of multiple immune checkpoint molecules.[56] This enables the AhR-activated tumor microenvironment to evade therapeutic pressure from single checkpoint blockade through multiple mechanisms.

AhR contributes significantly to the regulation of the PD-1/PD-L1 axis. Multiple studies have shown that Kyn-activated AhR in cSCC cells can upregulate PD-L1 expression, a process involving the cooperation of several transcription factors such as STAT3 and NF-κB.[56] Simultaneously, AhR activation upregulates PD-1 expression on T cells, making them more susceptible to PD-L1-mediated inhibition.[54] This bidirectional regulation reinforces the immunosuppression mediated by the PD-1/PD-L1 pathway. Clinical studies have found a positive correlation between AhR activity and PD-L1 expression in tumor tissues from cSCC patients.[57] The tryptophan-catabolizing enzymes IDO1 and TDO2 are key for Kyn production. Research indicates that approximately 50–70% of cSCC cases highly express IDO1, which is associated with higher tumor grade, lymph node metastasis, and poor prognosis.[58] TDO2 expression is also upregulated in a subset of cSCC cases.[59] The high expression of these enzymes leads to tryptophan depletion and

Kyn accumulation in the tumor microenvironment. By activating AhR, Kyn further promotes Treg differentiation and stability,[60] inhibits effector T-cell function,[61] induces T-cell apoptosis,[62] suppresses dendritic cell maturation,[63] and promotes MDSC expansion.[64,65] In addition, tryptophan depletion itself can lead to T cell anergy and apoptosis through activation of GCN2 kinase.[66]

Beyond the PD-1/PD-L1 axis, AhR is also involved in regulating other immune checkpoints. Studies have shown that AhR activation can upregulate the expression of inhibitory receptors such as CTLA-4, TIM-3, and LAG-3.[67] In cSCC, AhR can also modulate the CD47-SIRPα "don't eat me" signal, thereby inhibiting macrophage phagocytosis of tumor cells.[68] This multi-target regulatory feature has important therapeutic implications. Although PD-1/PD-L1 inhibitors have achieved significant efficacy in advanced cSCC, some patients still develop primary or acquired resistance. Given that AhR can simultaneously drive multiple resistance mechanisms, the combination of AhR antagonists and immune checkpoint inhibitors represents a promising strategy to overcome resistance, with the advantage of simultaneously blocking multiple compensatory inhibitory pathways.[37] Currently, inhibitors targeting the Trp-Kyn-AhR axis, including IDO1 inhibitors (eg, epacadostat, navoximod), TDO2 inhibitors, and AhR antagonists, are under development.[69] Preclinical studies have shown that these inhibitors can reverse immunosuppression and exhibit synergistic anti-tumor effects when combined with immune checkpoint blockade.[70]

AhR Regulation of Inflammation-Related Signaling Pathways

In cSCC, the synergistic interaction between AhR and NF-κB plays an important role in driving inflammation. NF-κB activation can be triggered by pathways such as TWEAK/Fn14. For instance, TWEAK promotes cIAP1 upregulation and activates NF-κB through RIP1, directly driving cSCC cell proliferation.[71] Activated AhR can directly interact with NF-κB (eg, the p65 subunit), forming a transcriptional complex that cooperatively upregulates the expression of protumor inflammatory factors such as IL-6, IL-8, and COX-2. This promotes tumor progression and remodels the immune microenvironment.[72]

STAT3 is a commonly activated pathway in cSCC, promoting proliferation, survival, and immune escape. Studies indicate that AhR can activate STAT3 phosphorylation by upregulating cytokines such as IL-6 or through interactions with tyrosine kinases. The two pathways cooperate to upregulate the expression of immunosuppressive factors (eg, IL-10, TGF-β) and pro-angiogenic factors (eg, VEGF).[73] Moreover, STAT3 directly transcriptionally upregulates the rate-limiting tryptophan-metabolizing enzyme IDO1. Its catalytic product, Kyn, serves as an endogenous ligand for AhR, forming an "AhR→STAT3→IDO1→Kyn→AhR" positive feedback loop (As shown in Figure 2). This persistently depletes tryptophan and accumulates immunosuppressive metabolites, fundamentally reinforcing tumor immune escape.[74]

Furthermore, a reciprocal regulatory relationship exists between AhR and TGF-β signaling in cSCC. TGF-β exerts tumor-suppressive effects in early stages but promotes invasion and immunosuppression in later stages. AhR can modulate both TGF-β expression and receptor sensitivity, while TGF-β can also induce AhR expression.[75] During advanced tumor progression, these two pathways functionally cooperate: they jointly induce Treg differentiation, suppress effector T cell function, and promote epithelial-mesenchymal transition (EMT). This enhances both immunosuppression and invasive capacity, synergistically driving cSCC progression.[76]

The Impact of AhR on Antigen Presentation and Immunoediting in cSCC

Effective antigen presentation is a prerequisite for initiating anti-tumor immune responses. AhR disrupts this process at multiple levels: it downregulates MHC-I expression on tumor cells to limit antigen presentation;[77] it inhibits dendritic cell maturation and the expression of co-stimulatory molecules, thereby impairing their antigen-presenting capacity;[78] and it interferes with antigen processing machinery, such as the proteasome and TAP transporter.[64] Collectively, these effects impede the priming and activation of anti-tumor T cells.

According to the immunoediting theory, tumor development progresses through three successive phases: elimination, equilibrium, and escape.[79] Current evidence suggests that AhR expression and activity exhibit dynamic changes throughout these three phases. In the elimination phase, transformed cells with low AhR expression are more readily recognized and eliminated by the immune system. In the equilibrium phase, some cells acquire mild immunosuppressive capacity by upregulating AhR activity, establishing a dynamic balance with the immune system. In the escape phase,

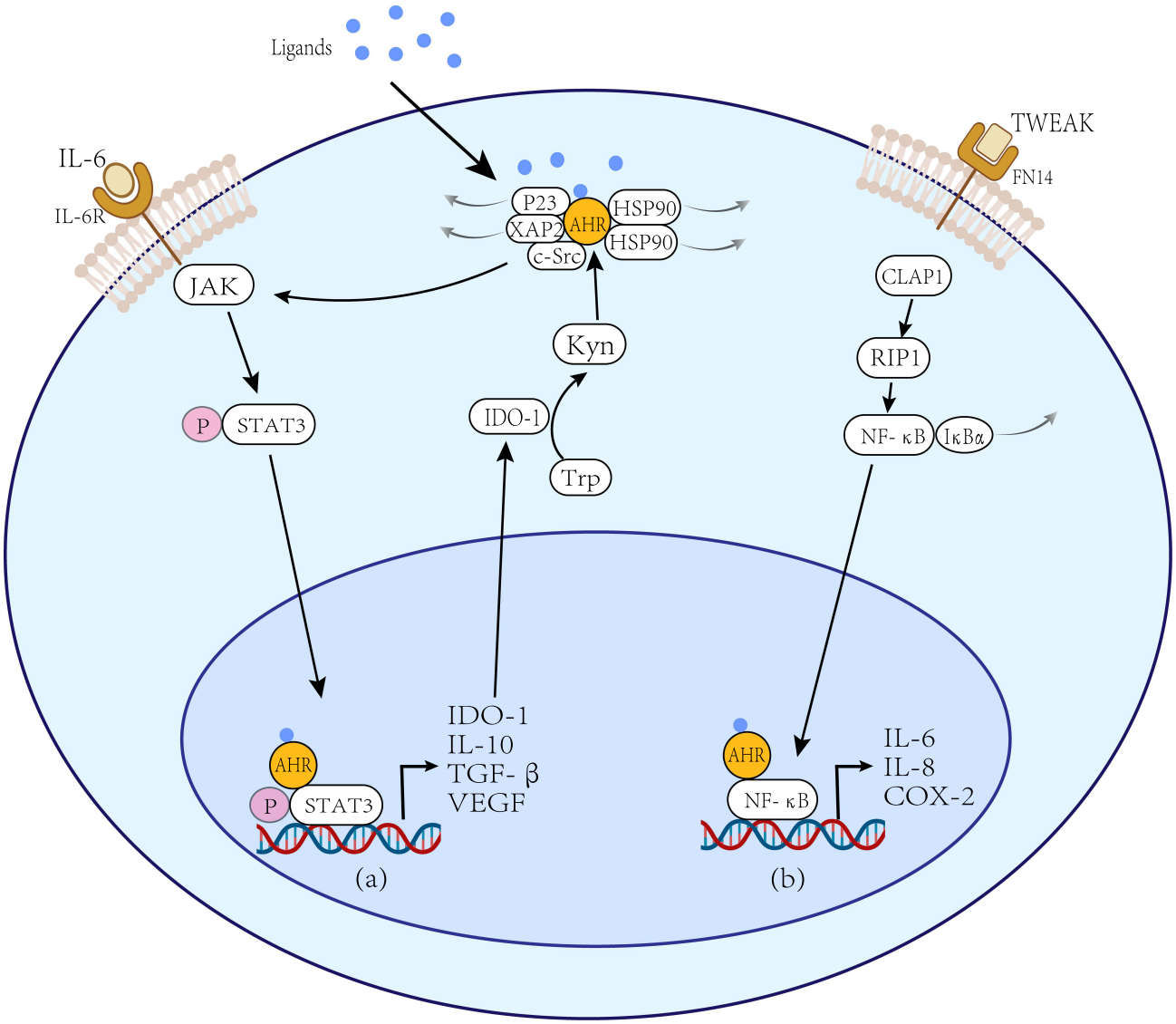

Figure 2 The AhR-NF-κB Synergistic Pathway and AhR-STAT3 Positive Feedback Loop in cSCC.
Notes: (**a**) The AhR-STAT3 signaling axis: Binding of IL-6 to its receptor or AhR ligand-induced release of c-Src from the cytoplasmic multiprotein complex can both activate JAK, leading to STAT3 phosphorylation. Phosphorylated STAT3 translocates into the nucleus, where it forms a complex with AhR and binds to SRE (Serum Response Element) regulatory sequences. This complex cooperatively upregulates the transcription of factors such as IL-10, TGF-β, and VEGF. Concurrently, STAT3 directly transcriptionally upregulates IDO1. The catalytic product of IDO1, kynurenine (Kyn), acts as an endogenous ligand for AhR, further activating AhR and establishing a positive feedback loop: "AhR → STAT3 → IDO1 → Kyn → AhR". (**b**)The AhR-NF-κB synergistic pathway: Following TWEAK binding to Fn14, cIAP1 undergoes ubiquitination and its activity is enhanced. A signaling complex involving RIP1 facilitates the release of the NF-κB dimer (primarily p65/p50) from its inhibited state bound to IκBα. The released dimer translocates into the nucleus, forms a functional complex with AhR, and binds to the κB sites on target genes. This complex cooperatively upregulates the expression of pro-inflammatory and pro-tumorigenic factors such as IL-6, IL-8, and COX-2, thereby promoting the initiation and progression of cSCC.

tumor cells with high AhR expression establish a robust immunosuppressive network, achieving complete immune evasion.[80] Under the dual selective pressures of diminished immunogenicity and enhanced immunosuppression, this process drives the formation of highly immunoevasive cSCC.[81]

However, the upstream signals driving this dynamic evolution remain poorly understood. The reasons for the gradual increase in AhR expression and activity during cSCC progression have yet to be elucidated, which may involve cumulative UV-induced gene mutations, persistent accumulation of kynurenine in the microenvironment, and epigenetic alterations.[12] Clarifying this issue is of great significance for early intervention in immune evasion of cSCC.

Potential and Strategies of AhR as a Therapeutic Target for cSCC

AhR plays a central pro-tumorigenic role within the immune microenvironment of cSCC, participating in nearly all key aspects of immune evasion. These include the suppression of T-cell function, induction of Tregs and MDSCs, and the shaping of tolerogenic APCs, while it may also directly promote tumor cell proliferation. Therefore, targeting the AhR signaling pathway represents a highly promising novel immunotherapeutic strategy that may reprogram the immunosuppressive microenvironment and restore antitumor immunity. This section will discuss the main strategies of targeting AhR.

Direct AhR Antagonism

Directly blocking AhR activation with small-molecule antagonists represents the most straightforward strategy. These compounds competitively bind to the ligand-binding pocket of AhR, preventing endogenous ligands such as Kyn from binding, thereby inhibiting its nuclear translocation and transcriptional activation and cutting off the immunosuppressive signaling at its source. Within the cSCC microenvironment, AhR antagonists can confer multiple benefits: blocking AhR signaling in T cells prevents their exhaustion, downregulates the expression of checkpoint molecules such as PD-1 and TIM-3, and restores T-cell proliferation as well as effector functions including IFN-γ and perforin production, thereby "reactivating" suppressed tumor-infiltrating lymphocytes (TILs).[37] A recent study further demonstrated that AhR inhibitors not only reverse T-cell exhaustion but also significantly enhance tumor sensitivity to immunotherapy by remodeling the interferon (IFN) signaling pathway.[80] Inhibiting Kyn-induced Treg differentiation and attenuating their function can relieve the suppression of effector T cells. Blocking AhR signaling in DCs, macrophages, and MDSCs can reverse their immunosuppressive phenotypes. For example, it can prevent DCs from acquiring a tolerogenic phenotype, inhibit their production of IDO1, and restore antigen-presenting capacity,[40] while also preventing macrophage polarization toward the M2 phenotype and the expansion of MDSCs.[41,43] At present, several highly selective AhR antagonists have entered preclinical and early clinical studies. Among them, IK-175 and BAY2416964 are oral small-molecule inhibitors specifically designed to block Kyn-mediated AhR activation. In preclinical models, these agents have demonstrated antitumor activity as monotherapies and have been shown to enhance the efficacy of immune checkpoint inhibitors,[82–84] providing support for targeting AhR in the treatment of solid tumors such as cSCC.

Combination Therapeutic Strategies

Although PD-1/PD-L1 inhibitors have achieved success in advanced cSCC, some patients still experience primary or acquired resistance. Activation of the AhR pathway is one of the key mechanisms underlying resistance to immune checkpoint inhibitors (ICIs). Therefore, combining AhR antagonists with ICIs is considered a promising synergistic strategy. The mechanisms of synergy include the following: AhR antagonists can dismantle immunosuppressive cells and pathways such as Tregs, MDSCs, and AhR pathway–driven exhaustion, thereby converting the immunosuppressive "cold" microenvironment into an immune-activated "hot" microenvironment, which facilitates the efficacy of PD-1 antibodies.[37] During ICI therapy, tumors may develop resistance by upregulating alternative immunosuppressive pathways, including the IDO1–Kyn–AhR axis. The combined use of AhR antagonists can disrupt this mechanism and restore tumor sensitivity to ICIs.[83] Moreover, AhR signaling can directly upregulate PD-1 expression on the surface of T cells. Thus, the application of AhR antagonists not only enhances T-cell function through multiple mechanisms but also downregulates PD-1 expression levels. The combination of AhR antagonists with PD-1 antibodies can simultaneously block the AhR pathway and PD-1 signaling….and the PD-1/PD-L1 pathway, two immunosuppressive mechanisms that are both independent and interrelated, thereby maximally relieving T-cell functional inhibition and restoring their proliferative capacity and cytotoxic activity.[36] In addition, recent single-cell sequencing studies have revealed that the heterogeneity of AhR activity is highly correlated with the exhaustion status of specific intratumoral CD8+ T-cell subsets. Combined blockade can selectively expand effector T-cell populations with stem-like characteristics, leading to sustained tumor regression.[85] At the level of microbial regulation, antimicrobial peptides (such as lantibiotics) or metabolites (such as 6-HAP) secreted by commensal bacteria like Staphylococcus epidermidis can inhibit the colonization and oncogenic activity of cSCC-associated pathogens including Staphylococcus aureus and HPV. Their combination with AhR antagonists can ameliorate microbial dysbiosis and the immunosuppressive microenvironment.[71] Moreover, cIAP1 inhibitors (such as MV1) can suppress cSCC proliferation mediated by the TWEAK/Fn14 axis. When used in combination with

AhR antagonists and PD-1 inhibitors, they may produce a triple synergistic effect characterized by "release of immune suppression, inhibition of tumor proliferation, and enhancement of immune effector function." Preclinical models have demonstrated inhibitory effects on TWEAK-overexpressing cSCC.[86] These strategies offer new avenues for overcoming resistance to existing immune checkpoint inhibitors (ICIs) and for expanding the population of patients who may benefit from such therapies.

However, it should be noted that the direct regulatory relationship between AhR and PD-L1 in cSCC has not yet been fully elucidated. In visceral cancer models such as lung cancer, studies have demonstrated that AhR can directly regulate PD-L1 expression. In contrast, AhR in the skin may exert a more complex dual role due to its interactions with ultraviolet radiation and tumor-derived metabolites. The mechanism by which these multiple signals are integrated still requires further validation and investigation in cSCC. Future research should focus on the context-dependent functions of AhR in skin tumors, as well as its crosstalk with UV radiation and the PD-1/PD-L1 pathway.

Targeting the Upstream Pathway: Reconsideration of IDO1/TDO2 Inhibitors

Another strategy involves inhibiting the synthesis of the key upstream ligand Kyn, that is, using IDO1 or TDO2 inhibitors. By blocking the conversion of tryptophan to Kyn, this approach not only restores tryptophan levels and alleviates T-cell "nutrient deprivation" but also reduces Kyn accumulation to prevent AhR activation.[34] However, the Phase III clinical trial (ECHO-301/KEYNOTE-252) evaluating the combination of the IDO1 inhibitor Epacadostat with Pembrolizumab (an anti–PD-1 antibody) in advanced melanoma ended in failure.[87] Possible reasons include tumor compensation through alternative pathways such as TDO2, inadequate patient selection, and insufficient drug potency or pharmacokinetic properties. Nevertheless, this strategy has not been completely abandoned. Current research directions focus on developing more potent and selective IDO1 inhibitors, dual IDO1/TDO2 inhibitors, or combination regimens with chemotherapy, radiation therapy, or targeted therapy, and validating these approaches in precisely stratified patient populations.[30,45] In addition, for cSCC with high IDO1 expression, reassessing the combined application of next-generation metabolic enzyme inhibitors with radiotherapy or nanodrug delivery systems, in conjunction with the latest biomarker-based screening strategies, remains of significant translational relevance.[88]

Conclusion

This review systematically elucidates how AhR influences the progression of cSCC by modulating the immune system and discusses its potential as a therapeutic target. AhR primarily shapes a highly immunosuppressive tumor microenvironment in cSCC through the "tryptophan–kynurenine–AhR" axis and related signaling cascades. This process promotes the functions of suppressive cells such as Tregs and MDSCs, inhibits the antitumor activities of $CD8^+$ T cells and NK cells, and cooperates with immune checkpoint pathways such as PD-1/PD-L1 to drive immune evasion. In addition, this review highlights the pivotal role of AhR as a core molecule linking external environmental stimuli, metabolism, and immune responses. It underscores the potential of AhR as a therapeutic target for cSCC immunotherapy, including the development of AhR antagonists and their rational combination with immune checkpoint inhibitors. Further elucidation of the underlying mechanisms and optimization of such targeting strategies will open new avenues for precision immunotherapy of cSCC, providing novel theoretical foundations and directions with great scientific value and clinical promise.

However, this review also has certain limitations. First, AhR signaling exhibits strong ligand- and cell-context dependency, and its specific roles in different cSCC subtypes or disease stages require further clarification. cSCC encompasses a heterogeneous group of lesions, including conventional cutaneous squamous cell carcinoma, follicular-derived squamous cell carcinoma, basaloid squamous cell carcinoma, and squamous cell carcinoma in situ (including actinic keratosis and Bowen's disease subtypes). Although keratoacanthoma is separated from squamous cell carcinoma in the current WHO classification, it may serve as an important comparative model for understanding the spectrum of AhR-mediated immune regulation. Whether the immunomodulatory functions of AhR vary across these distinct lesion types or tumor differentiation states remains to be systematically investigated. Second, most current mechanistic evidence is derived from preclinical models, which may not fully recapitulate the complex, multi-stage process of UV-driven cSCC development in humans. Third, the translational potential of AhR-targeted therapy is complicated by the

pleiotropic physiological functions of AhR in maintaining barrier integrity, xenobiotic metabolism, and immune homeostasis, raising concerns about off-target toxicity with systemic administration.

Future research may focus on the following directions: developing tissue-selective or microenvironment-responsive AhR modulators, such as topical formulations, tumor microenvironment-responsive prodrugs, or nanoparticle delivery systems, to enhance efficacy while reducing systemic toxicity; investigating the crosstalk between AhR signaling and other immunometabolic or epigenetic pathways to construct a more comprehensive network of cSCC immune evasion; conducting stratified studies across different cSCC subtypes, stages, and differentiation states, which is crucial for better defining the context-specific roles of AhR signaling; and performing biomarker-based stratified clinical studies to identify patient populations most likely to benefit from AhR-targeted therapies and to determine optimal combination regimens. On this basis, well-designed clinical trials are urgently needed to evaluate the safety, tolerability, and efficacy of AhR-targeted drugs in cSCC patients.

Abbreviations

AhR, aryl hydrocarbon receptor; AhRR, AhR repressor; AIP, ARNT-interacting protein; APCs, antigen-presenting cells; Arg1, arginase-1; ARNT, Aryl Hydrocarbon Receptor Nuclear Translocator; bHLH, basic helix-loop-helix; CCL2, chemokine (C-C motif) ligand 2; CCL22, chemokine (C-C motif) ligand 22; CD206, cluster of differentiation 206; cIAP1, cellular inhibitor of apoptosis protein 1; COX-2, cyclooxygenase-2; cSCC, cutaneous squamous cell carcinoma; CTL, cytotoxic T lymphocyte; CTLA-4, cytotoxic T-lymphocyte-associated protein 4; CYP1A1, cytochrome P450 family 1 subfamily A member 1; CYP1A2, cytochrome P450 family 1 subfamily A member 2; CYP1B1, cytochrome P450 family 1 subfamily B member 1; DCs, dendritic cells; EMT, epithelial-mesenchymal transition; FICZ, 6-formylindolo[3,2-b]carbazole; Hsp90, heat shock protein 90; I3C, indole-3-carbinol; ICIs, immune checkpoint inhibitors; ICZ, indolo[3,2-b]carbazole; IDO1, indoleamine 2,3-dioxygenase 1; IL-10, interleukin-10; IL-22, interleukin-22; IL-6, interleukin-6; IL-8, interleukin-8; ILCs, innate lymphoid cells; ILC3s, group 3 innate lymphoid cells; iNOS, inducible nitric oxide synthase; IFN-γ, interferon-gamma; Kyn, kynurenine; LAG-3, lymphocyte-activation gene 3; LPS, lipopolysaccharide; MDSCs, myeloid-derived suppressor cells; MHC, major histocompatibility complex; NF-κB, nuclear factor kappa-B; NK, natural killer; NO, nitric oxide; PAS, Per-Arnt-Sim; PAHs, polycyclic aromatic hydrocarbons; PCBs, polychlorinated biphenyls; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; RIP1, receptor-interacting protein 1; ROS, reactive oxygen species; SOCS2, suppressor of cytokine signaling 2; STAT3, signal transducer and activator of transcription 3; TAD, transcriptional activation domain; TAMs, tumor-associated macrophages; TAP, transporter associated with antigen processing; TCDD, 2,3,7,8-tetrachlorodibenzo-p-dioxin; TDO2, tryptophan 2,3-dioxygenase; TGF-β, transforming growth factor-beta; TIM-3, T-cell immunoglobulin and mucin-domain-containing protein 3; TILs, tumor-infiltrating lymphocytes; TME, tumor microenvironment; Tregs, regulatory T cells; UV, ultraviolet; VEGF, vascular endothelial growth factor; XREs, xenobiotic response elements.

Funding

This work was supported by Supported by Fundamental Research Program Shanxi Province [grant numbers: 202303021211236].

Disclosure

The authors report no conflicts of interest in this work.

References

1. Waldman A, Schmults C. Cutaneous squamous cell carcinoma. *Hematol Oncol Clin North Am*. 2019;33(1):1–12. doi:10.1016/j.hoc.2018.08.001
2. Huang S, Jiang J, Wong HS, Zhu P, Ji X, Wang D. Global burden and prediction study of cutaneous squamous cell carcinoma from 1990 to 2030: a systematic analysis and comparison with China. *J Glob Health*. 2024;14:04093. doi:10.7189/jogh.14.04093
3. Que SKT, Zwald FO, Schmults CD. Cutaneous squamous cell carcinoma: incidence, risk factors, diagnosis, and staging. *J Am Acad Dermatol*. 2018;78(2):237–247. doi:10.1016/j.jaad.2017.08.059
4. Migden MR, Rischin D, Schmults CD, et al. PD-1 blockade with cemiplimab in advanced cutaneous squamous-cell carcinoma. *N Engl J Med*. 2018;379(4):341–351. doi:10.1056/NEJMoa1805131
5. Migden MR, Khushalani NI, Chang ALS, et al. Cemiplimab in locally advanced cutaneous squamous cell carcinoma: results from an open-label, Phase 2, single-arm trial. *Lancet Oncol*. 2020;21(2):294–305. doi:10.1016/S1470-2045(19)30728-4

6. Gajewski TF, Schreiber H, Fu YX. Innate and adaptive immune cells in the tumor microenvironment. *Nat Immunol*. 2013;14(10):1014–1022. doi:10.1038/ni.2703
7. Kronenberg S, Esser C, Carlberg C. An aryl hydrocarbon receptor conformation acts as the functional core of nuclear dioxin signaling. *Nucleic Acids Res*. 2000;28(12):2286–2291. doi:10.1093/nar/28.12.2286
8. Uberoi A, Bartow-McKenney C, Zheng Q, et al. Commensal microbiota regulates skin barrier function and repair via signaling through the aryl hydrocarbon receptor. *Cell Host Microbe*. 2021;29(8):1235–1248.e8. doi:10.1016/j.chom.2021.05.011
9. Gutiérrez-Vázquez C, Quintana FJ. Regulation of the Immune Response by the Aryl Hydrocarbon Receptor. *Immunity*. 2018;48(1):19–33. doi:10.1016/j.immuni.2017.12.012
10. Murray IA, Patterson AD, Perdew GH. Aryl hydrocarbon receptor ligands in cancer: friend and foe. *Nat Rev Cancer*. 2014;14(12):801–814. doi:10.1038/nrc3846
11. Vogeley C, Esser C, Tüting T, Krutmann J, Haarmann-Stemmann T. Role of the aryl hydrocarbon receptor in environmentally induced skin aging and skin carcinogenesis. *Int J Mol Sci*. 2019;20(23):6005. doi:10.3390/ijms20236005
12. Opitz CA, Litzenburger UM, Sahm F, et al. An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature*. 2011;478 (7368):197–203. doi:10.1038/nature10491
13. Di Nardo L, Pellegrini C, Di Stefani A, et al. Molecular genetics of cutaneous squamous cell carcinoma: perspective for treatment strategies. *J Eur Acad Dermatol Venereol*. 2020;34(5):932–941. doi:10.1111/jdv.16098
14. Fania L, Didona D, Di Pietro FR, et al. Approaches. *Biomedicines*. 2021;9(2):171. doi:10.3390/biomedicines9020171
15. Chitsazzadeh V, Coarfa C, Drummond JA, et al. Cross-species identification of genomic drivers of squamous cell carcinoma development across preneoplastic intermediates. *Nat Commun*. 2016;7:12601. doi:10.1038/ncomms12601
16. Zhou T, Feng Y, Che D, et al. MRGPRX2-mediated mast cell activation promotes malignant progression of cutaneous squamous cell carcinoma through IL-17A release. *J Invest Dermatol*. 2025. doi:10.1016/j.jid.2025.10.595
17. Fukunaga BN, Hankinson O. Identification of a novel domain in the aryl hydrocarbon receptor required for DNA binding. *J Biol Chem*. 1996;271 (7):3743–3749. doi:10.1074/jbc.271.7.3743
18. Denison MS, Soshilov AA, He G, DeGroot DE, Zhao B. Exactly the same but different: promiscuity and diversity in the molecular mechanisms of action of the aryl hydrocarbon (dioxin) receptor. *Toxicol Sci*. 2011;124(1):1–22. doi:10.1093/toxsci/kfr218
19. Sondermann NC, Faßbender S, Hartung F, et al. Functions of the aryl hydrocarbon receptor (AHR) beyond the canonical AHR/ARNT signaling pathway. *Biochem Pharmacol*. 2023;208:115371. doi:10.1016/j.bcp.2022.115371
20. Bahman F, Choudhry K, Al-Rashed F, Al-Mulla F, Sindhu S, Ahmad R. Aryl hydrocarbon receptor: current perspectives on key signaling partners and immunoregulatory role in inflammatory diseases. *Front Immunol*. 2024;15:1421346. doi:10.3389/fimmu.2024.1421346
21. Sadik A, Somarribas Patterson LF, Öztürk S, et al. IL4I1 is a metabolic immune checkpoint that activates the AHR and promotes tumor progression. *Cell*. 2020;182(5):1252–1270.e34. doi:10.1016/j.cell.2020.07.038
22. Guarnieri T. Light sensing beyond vision: focusing on a possible role for the FICZ/ahr complex in skin optotransduction. *Cells*. 2024;13(13):1082. doi:10.3390/cells13131082
23. Phelan D, Winter GM, Rogers WJ, Lam JC, Denison MS. Activation of the Ah receptor signal transduction pathway by bilirubin and biliverdin. *Arch Biochem Biophys*. 1998;357(1):155–163. doi:10.1006/abbi.1998.0814
24. Zelante T, Iannitti RG, Cunha C, et al. Tryptophan catabolites from microbiota engage aryl hydrocarbon receptor and balance mucosal reactivity via interleukin-22. *Immunity*. 2013;39(2):372–385. doi:10.1016/j.immuni.2013.08.003
25. Diao X, Shang Q, Guo M, et al. Structural basis for the ligand-dependent activation of heterodimeric AHR-ARNT complex. *Nat Commun*. 2025;16 (1):1282. doi:10.1038/s41467-025-56574-7
26. Wójtowicz AK, Honkisz E, Zięba-Przybylska D, Milewicz T, Kajta M. Effects of two isomers of DDT and their metabolite DDE on CYP1A1 and AhR function in human placental cells. *Pharmacol Rep*. 2011;63(6):1460–1468. doi:10.1016/s1734-1140(11)70710-1
27. Tian J, Feng Y, Fu H, Xie HQ, Jiang JX, Zhao B. The aryl hydrocarbon receptor: a key bridging molecule of external and internal chemical signals. *Environ Sci Technol*. 2015;49(16):9518–9531. doi:10.1021/acs.est.5b00385
28. Nebert DW, Dalton TP, Okey AB, Gonzalez FJ. Role of aryl hydrocarbon receptor-mediated induction of the CYP1 enzymes in environmental toxicity and cancer. *J Biol Chem*. 2004;279(23):23847–23850. doi:10.1074/jbc.R400004200
29. Ohtake F, Fujii-Kuriyama Y, Kato S. AhR acts as anE3ubiquitin ligase to modulate steroid receptor functions. *Biochem Pharmacol*. 2009;77 (4):474–484. doi:10.1016/j.bcp.2008.08.034
30. Quintana FJ, Basso AS, Iglesias AH, et al. Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature*. 2008;453 (7191):65–71. doi:10.1038/nature06880
31. Rothhammer V, Quintana FJ. The aryl hydrocarbon receptor: an environmental sensor integrating immune responses in health and disease. *Nat Rev Immunol*. 2019;19(3):184–197. doi:10.1038/s41577-019-0125-8
32. Veldhoen M, Hirota K, Westendorf AM, et al. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. *Nature*. 2008;453(7191):106–109. doi:10.1038/nature06881
33. Kimura A, Naka T, Nohara K, Fujii-Kuriyama Y, Kishimoto T. Aryl hydrocarbon receptor regulates Stat1 activation and participates in the development of Th17 cells. *Proc Natl Acad Sci U S A*. 2008;105(28):9721–9726. doi:10.1073/pnas.0804231105
34. Mezrich JD, Fechner JH, Zhang X, Johnson BP, Burlingham WJ, Bradfield CA. An interaction between kynurenine and the aryl hydrocarbon receptor can generate regulatory T cells. *J Immunol*. 2010;185(6):3190–3198. doi:10.4049/jimmunol.0903670
35. Liu Y, Liang X, Dong W, et al. Tumor-repopulating cells induce PD-1 expression in CD8+ T cells by transferring kynurenine and AhR activation. *Cancer Cell*. 2018;33(3):480–494.e7. doi:10.1016/j.ccell.2018.02.005
36. Liu Y, Zhou N, Zhou L, et al. IL-2 regulates tumor-reactive CD8+ T cell exhaustion by activating the aryl hydrocarbon receptor. *Nat Immunol*. 2021;22(3):358–369. doi:10.1038/s41590-020-00850-9
37. Takenaka MC, Gabriely G, Rothhammer V, et al. Control of tumor-associated macrophages and T cells in glioblastoma via AHR and CD39. *Nat Neurosci*. 2019;22(5):729–740. Erratum in: Nat Neurosci. 2019 Sep;22(9):1533. doi:10.1038/s41593-019-0370-y
38. Mascanfroni ID, Takenaka MC, Yeste A, et al. Metabolic control of type 1 regulatory T cell differentiation by AHR and HIF1-α. *Nat Med*. 2015;21 (6):638–646. doi:10.1038/nm.3868

39. Wang Y, Jin TH, Farhana A, et al. Exposure to cigarette smoke impacts myeloid-derived regulatory cell function and exacerbates airway hyper-responsiveness. *Lab Invest*. 2014;94(12):1312–1325. doi:10.1038/labinvest.2014.126
40. Campesato LF, Budhu S, Tchaicha J, et al. Blockade of the AHR restricts a Treg-macrophage suppressive axis induced by L-Kynurenine. *Nat Commun*. 2020;11(1):4011. doi:10.1038/s41467-020-17750-z
41. Li J, Wang L, Wang M, Zhang H. Activation of aryl hydrocarbon receptor attenuates intestinal inflammation by enhancing IRF4-mediated macrophage M2 polarization. *Biochim Biophys Acta Mol Basis Dis*. 2025;1871(4):167735. doi:10.1016/j.bbadis.2025.167735
42. Yang X, Liu H, Ye T, et al. AhR activation attenuates calcium oxalate nephrocalcinosis by diminishing M1 macrophage polarization and promoting M2 macrophage polarization. *Theranostics*. 2020;10(26):12011–12025. doi:10.7150/thno.51144
43. Hezaveh K, Shinde RS, Klötgen A, et al. Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity. *Immunity*. 2022;55(2):324–340.e8. doi:10.1016/j.immuni.2022.01.006
44. Chen Y, Xu Y, Zhao H, et al. Myeloid-derived suppressor cells deficient in cholesterol biosynthesis promote tumor immune evasion. *Cancer Lett*. 2023;564:216208. doi:10.1016/j.canlet.2023.216208
45. Wei Y, Peng N, Deng C, et al. Aryl hydrocarbon receptor activation drives polymorphonuclear myeloid-derived suppressor cell response and efficiently attenuates experimental Sjögren's syndrome. *Cell Mol Immunol*. 2022;19(12):1361–1372. doi:10.1038/s41423-022-00943-5
46. Piper CJM, Rosser EC, Oleinika K, et al. Aryl hydrocarbon receptor contributes to the transcriptional program of IL-10-producing regulatory B cells. *Cell Rep*. 2019;29(7):1878–1892.e7. doi:10.1016/j.celrep.2019.10.018
47. Munn DH, Mellor AL. IDO in the tumor microenvironment: inflammation, counter-regulation, and tolerance. *Trends Immunol*. 2016;37(3):193–207. doi:10.1016/j.it.2016.01.002
48. D'Amato NC, Rogers TJ, Gordon MA, et al. A TDO2-AhR signaling axis facilitates anoikis resistance and metastasis in triple-negative breast cancer. *Cancer Res*. 2015;75(21):4651–4664. doi:10.1158/0008-5472.CAN-15-2011
49. Sinclair LV, Neyens D, Ramsay G, Taylor PM, Cantrell DA. Single cell analysis of kynurenine and System L amino acid transport in T cells. *Nat Commun*. 2018;9(1):1981. doi:10.1038/s41467-018-04366-7
50. Hoffmann A, Baltimore D. Circuitry of nuclear factor kappaB signaling. *Immunol Rev*. 2006;210:171–186. doi:10.1111/j.0105-2896.2006.00375.x
51. Shin JH, Zhang L, Murillo-Sauca O, et al. Modulation of natural killer cell antitumor activity by the aryl hydrocarbon receptor. *Proc Natl Acad Sci U S A*. 2013;110(30):12391–12396. doi:10.1073/pnas.1302856110
52. Wagage S, John B, Krock BL, et al. The aryl hydrocarbon receptor promotes IL-10 production by NK cells. *J Immunol*. 2014;192(4):1661–1670. doi:10.4049/jimmunol.1300497
53. Abdrabou AM, Ahmed SU, Fan MJ, et al. Identification of Vista regulators in macrophages mediating cancer cell survival. *Sci Adv*. 2024;10(48):eadq8122. doi:10.1126/sciadv.adq8122
54. Qian BZ, Pollard JW. Macrophage diversity enhances tumor progression and metastasis. *Cell*. 2010;141(1):39–51. doi:10.1016/j.cell.2010.03.014
55. Zhao B, Degroot DE, Hayashi A, He G, Denison MS. CH223191 is a ligand-selective antagonist of the Ah (Dioxin) receptor. *Toxicol Sci*. 2010;117(2):393–403. doi:10.1093/toxsci/kfq217
56. Cooks T, Pateras IS, Jenkins LM, et al. Mutant p53 cancers reprogram macrophages to tumor supporting macrophages via exosomal miR-1246. *Nat Commun*. 2018;9(1):771. doi:10.1038/s41467-018-03224-w
57. Zhai L, Spranger S, Binder DC, et al. Molecular pathways: targeting IDO1 and other tryptophan dioxygenases for cancer immunotherapy. *Clin Cancer Res*. 2015;21(24):5427–5433. doi:10.1158/1078-0432.CCR-15-0420
58. Liu X, Shin N, Koblish HK, et al. Selective inhibition of IDO1 effectively regulates mediators of antitumor immunity. *Blood*. 2010;115(17):3520–3530. doi:10.1182/blood-2009-09-246124
59. Moretti S, Menicali E, Voce P, et al. Indoleamine 2,3-dioxygenase 1 (IDO1) is up-regulated in thyroid carcinoma and drives the development of an immunosuppressant tumor microenvironment. *J Clin Endocrinol Metab*. 2014;99(5):E832–E840. doi:10.1210/jc.2013-3351
60. Wu C, Spector SA, Theodoropoulos G, et al. Dual inhibition of IDO1/TDO2 enhances anti-tumor immunity in platinum-resistant non-small cell lung cancer. *Cancer Metab*. 2023;11(1):7. doi:10.1186/s40170-023-00307-1
61. Liu X, Yang M, Xu P, et al. Kynurenine-AhR reduces T-cell infiltration and induces a delayed T-cell immune response by suppressing the STAT1-CXCL9/CXCL10 axis in tuberculosis. *Cell Mol Immunol*. 2024;21(12):1426–1440. doi:10.1038/s41423-024-01230-1
62. Munn DH, Sharma MD, Baban B, et al. GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. *Immunity*. 2005;22(5):633–642. doi:10.1016/j.immuni.2005.03.013
63. Lee GK, Park HJ, Macleod M, Chandler P, Munn DH, Mellor AL. Tryptophan deprivation sensitizes activated T cells to apoptosis prior to cell division. *Immunology*. 2002;107(4):452–460. doi:10.1046/j.1365-2567.2002.01526.x
64. Nguyen NT, Kimura A, Nakahama T, et al. Aryl hydrocarbon receptor negatively regulates dendritic cell immunogenicity via a kynurenine-dependent mechanism. *Proc Natl Acad Sci U S A*. 2010;107(46):19961–19966. doi:10.1073/pnas.1014465107
65. Holmgaard RB, Zamarin D, Li Y, et al. Tumor-expressed IDO recruits and activates MDSCs in a treg-dependent manner. *Cell Rep*. 2015;13(2):412–424. doi:10.1016/j.celrep.2015.08.077
66. Van de Velde LA, Guo XJ, Barbaric L, et al. Stress kinase GCN2 controls the proliferative fitness and trafficking of cytotoxic T cells independent of environmental amino acid sensing. *Cell Rep*. 2016;17(9):2247–2258. doi:10.1016/j.celrep.2016.10.079
67. Litzenburger UM, Opitz CA, Sahm F, et al. Constitutive IDO expression in human cancer is sustained by an autocrine signaling loop involving IL-6, STAT3 and the AHR. *Oncotarget*. 2014;5(4):1038–1051. doi:10.18632/oncotarget.1637
68. Tripathi C, Tewari BN, Kanchan RK, et al. Macrophages are recruited to hypoxic tumor areas and acquire a pro-angiogenic M2-polarized phenotype via hypoxic cancer cell derived cytokines Oncostatin M and Eotaxin. *Oncotarget*. 2014;5(14):5350–5368. doi:10.18632/oncotarget.2110
69. Munn DH, Sharma MD, Hou D, et al. Expression of indoleamine 2,3-dioxygenase by plasmacytoid dendritic cells in tumor-draining lymph nodes. *J Clin Invest*. 2004;114(2):280–290. doi:10.1172/JCI21583
70. Prendergast GC, Metz R, Muller AJ, Merlo LM, Mandik-Nayak L. IDO2 in immunomodulation and autoimmune disease. *Front Immunol*. 2014;5:585. doi:10.3389/fimmu.2014.00585
71. Liang L, Cheng C, Hu G, et al. TWEAK promotes the proliferation of squamous cell carcinoma cells through activating cIAP1 signals. *Front Oncol*. 2020;10:439. doi:10.3389/fonc.2020.00439
72. Kimura A, Naka T, Nakahama T, et al. Aryl hydrocarbon receptor in combination with Stat1 regulates LPS-induced inflammatory responses. *J Exp Med*. 2009;206(9):2027–2035. doi:10.1084/jem.20090560

73. Vogel CF, Sciullo E, Li W, Wong P, Lazennec G, Matsumura F. RelB, a new partner of aryl hydrocarbon receptor-mediated transcription. *Mol Endocrinol*. 2007;21(12):2941–2955. doi:10.1210/me.2007-0211
74. Grishanova AY, Perepechaeva ML. Kynurenic Acid/AhR signaling at the junction of inflammation and cardiovascular diseases. *Int J Mol Sci*. 2024;25(13):6933. doi:10.3390/ijms25136933
75. Koch DC, Jang HS, O'Donnell EF, et al. Anti-androgen flutamide suppresses hepatocellular carcinoma cell proliferation via the aryl hydrocarbon receptor mediated induction of transforming growth factor-β1. *Oncogene*. 2015;34(50):6092–6104. doi:10.1038/onc.2015.55
76. Quintana FJ, Murugaiyan G, Farez MF, et al. An endogenous aryl hydrocarbon receptor ligand acts on dendritic cells and T cells to suppress experimental autoimmune encephalomyelitis. *Proc Natl Acad Sci U S A*. 2010;107(48):20768–20773. doi:10.1073/pnas.1009201107
77. Busbee PB, Rouse M, Nagarkatti M, Nagarkatti PS. Use of natural AhR ligands as potential therapeutic modalities against inflammatory disorders. *Nutr Rev*. 2013;71(6):353–369. doi:10.1111/nure.12024
78. Novikov O, Wang Z, Stanford EA, et al. An aryl hydrocarbon receptor-mediated amplification loop that enforces cell migration in ER-/PR-/Her2-human breast cancer cells. *Mol Pharmacol*. 2016;90(5):674–688. doi:10.1124/mol.116.105361
79. Chmill S, Kadow S, Winter M, Weighardt H, Esser C. 2,3,7,8-Tetrachlorodibenzo-p-dioxin impairs stable establishment of oral tolerance in mice. *Toxicol Sci*. 2010;118(1):98–107. doi:10.1093/toxsci/kfq232
80. Schreiber RD, Old LJ, Smyth MJ. Cancer immunoediting: integrating immunity's roles in cancer suppression and promotion. *Science*. 2011;331 (6024):1565–1570. doi:10.1126/science.1203486
81. Vogeley C, Rolfes KM, Krutmann J, Haarmann-Stemmann T. The aryl hydrocarbon receptor in the pathogenesis of environmentally-induced squamous cell carcinomas of the skin. *Front Oncol*. 2022;12:841721. doi:10.3389/fonc.2022.841721
82. Aggen DH, McKean M, Hoffman-Censits JH, et al. IK-175, an oral aryl hydrocarbon receptor inhibitor, alone and with nivolumab in patients with advanced solid tumors and urothelial carcinoma. *Clin Cancer Res*. 2025. doi:10.1158/1078-0432
83. Kober C, Roewe J, Schmees N, et al. Targeting the aryl hydrocarbon receptor (AhR) with BAY 2416964: a selective small molecule inhibitor for cancer immunotherapy. *J Immunother Cancer*. 2023;11(11):e007495. doi:10.1136/jitc-2023-007495
84. McGovern K, Castro AC, Cavanaugh J, et al. Discovery and characterization of a novel aryl hydrocarbon receptor inhibitor, IK-175, and its inhibitory activity on tumor immune suppression. *Mol Cancer Ther*. 2022;21(8):1261–1272. doi:10.1158/1535-7163.MCT-21-0984
85. Dean JW, Helm EY, Fu Z, et al. The aryl hydrocarbon receptor cell intrinsically promotes resident memory CD8+ T cell differentiation and function. *Cell Rep*. 2023;42(1):111963. doi:10.1016/j.celrep.2022.111963
86. Zhang Z, Liang L, Jiang X, et al. Skin microbiome influences the progression of cutaneous squamous cell carcinoma through the immune system. *World J Surg Oncol*. 2025;23(1):129. doi:10.1186/s12957-025-03791-5
87. Long GV, Dummer R, Hamid O, et al. Epacadostat plus pembrolizumab versus placebo plus pembrolizumab in patients with unresectable or metastatic melanoma (ECHO-301/KEYNOTE-252): a Phase 3, randomised, double-blind study. *Lancet Oncol*. 2019;20(8):1083–1097. doi:10.1016/S1470-2045(19)30274-8
88. Prendergast GC, Malachowski WP, DuHadaway JB, Muller AJ. Discovery of IDO1 inhibitors: from bench to bedside. *Cancer Res*. 2017;77 (24):6795–6811. doi:10.1158/0008-5472.CAN-17-2285