

Tryptophan metabolism: From physiological functions to key roles and therapeutic targets in cancer (Review)

JIAWEI ZHAO^{1,2*}, XIAOHUI BAI^{1,2*}, JINGJING DU^{2*}, YUJING CHEN^{2,3}, XIAOTONG GUO^{2,3},
JUZHENG ZHANG^{2,3}, JINFENG GAN^{2,3}, PEITAO WU^{2,3}, SIQI CHEN^{2,4},
XINWEN ZHANG^{2,3}, JINFENG YANG^{2**}, JIAMIN JIN^{1-3**} and LI GAO^{1-3**}

¹Department of Urology, The Second Affiliated Hospital of Guilin Medical University, Guilin, Guangxi 541199, P.R. China; ²Key Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, Guilin, Guangxi 541199, P.R. China; ³Guangxi Health Commission Key Laboratory of Tumor Immunology and Receptor-Targeted Drug Basic Research, Guilin Medical University, Guilin, Guangxi 541199, P.R. China; ⁴Department of Oral Bioscience, Tokushima University Graduate School of Biomedical Sciences, Tokushima 780-8501, Japan

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Abstract. Tryptophan (Trp) metabolism is a complex and important biochemical process in humans. It is vital in protein synthesis and is a precursor of various bioactive molecules. Trp is metabolized through the kynurenine, serotonin and indole pathways, mediating diverse physiological functions, including neurotransmitter synthesis, immune regulation, antioxidant effects, and biosynthesis of niacin and melatonin. These metabolic pathways maintain essential functions under normal physiological conditions. However, they are significantly affected by various types of cancers. Trp metabolites regulate tumor angiogenesis, affect the self-renewal of cancer stem cells, and participate in immune evasion and cell death through complex mechanisms. As the mechanisms underlying Trp metabolism in diseases are increasingly being elucidated, targeting Trp metabolic pathways has emerged as a promising therapeutic strategy. Further investigation of the molecular mechanisms underlying Trp metabolism and its role in diseases may provide new perspectives and approaches for diagnosing and treating diseases.

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1. Introduction

Tryptophan (Trp) is an essential aromatic amino acid in the human body that performs various key physiological functions (1-3). Trp metabolism primarily involves three pathways: the kynurenine (Kyn) pathway, catalyzed by indoleamine 2,3-dioxygenase (IDO) or Trp 2,3-dioxygenase (TDO); the serotonin [or 5-hydroxytryptamine (5-HT)] pathway, mediated by the gut microbiota; and the indole pathway, which is largely dependent on the gut microbiota. A total of ~95% of Trp is metabolized through the Kyn pathway, catalyzed by TDO in the liver and IDO in immune cells such as macrophages and dendritic cells (DCs). The products of this pathway include Kyn, nicotinic acid, and nicotinamide, which ultimately enter the nicotinamide adenine dinucleotide (NAD⁺) synthesis pathway to produce essential redox-regulating molecules for cells (4). The 5-HT pathway consumes ~1% Trp to produce 5-HT, which is an important neurotransmitter and vasoactive substance. The gut microbiota metabolizes Trp to indole derivatives via the indole pathway. These metabolites activate the host aryl hydrocarbon receptor (AhR), thereby regulating gut barrier function and immune responses (5). Dysregulated Trp metabolism is associated with cancer stem cell (CSC) self-renewal, tumor angiogenesis, and immune evasion. For example, tumors can use the Trp-Kyn pathway to suppress local immune responses and promote the formation of an immunosuppressive tumor microenvironment (TME) that facilitates cancer progression (6). IDO is overexpressed in

Correspondence to: Dr Jiamin Jin, Key Laboratory of Tumor Immunology and Microenvironmental Regulation, Guilin Medical University, 1 Zhiyuan Road, Guilin, Guangxi 541199, P.R. China
E-mail: jinjiamin@glmc.edu.cn

*,** Contributed equally

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various cancers and associated with poor prognosis (7). Therefore, targeting the Trp metabolism has emerged as a promising therapeutic strategy in oncology. Previous studies have focused on the therapeutic potential of inhibiting key enzymes in the Trp metabolic pathway, such as IDO and TDO, to enhance antitumor immune responses and improve the efficacy of cancer immunotherapy (8). New compounds targeting Trp metabolism are being investigated to assess their ability to modulate immune responses and inhibit tumor growth, highlighting significant opportunities and challenges (9). Given the central role of Trp metabolism in cancer biology, recent advances have highlighted the potential of multi-targeted approaches, such as combining Trp pathway modulators with immune checkpoint inhibitors (ICIs), to overcome drug resistance and enhance antitumor efficacy. Additionally, emerging insights into the crosstalk between Trp metabolism and the gut microbiome have opened new avenues for drug discovery with the development of novel compounds aimed at modulating these interactions. The aim of the present review was to provide a comprehensive overview of Trp metabolism and its dysregulation in cancer, focusing on its therapeutic implications. Herein, the key metabolic pathways of Trp, their roles in cancer development and progression, and the latest advances in targeting these pathways for cancer therapy are discussed. By understanding the complex mechanisms underlying Trp metabolism, effective therapeutic strategies can be developed to treat cancer and improve patient outcomes.

2. Trp metabolism pathways and their clinical biomarker implications

Trp metabolism involves three key amino acid pathways (Fig. 1). These metabolites reflect the metabolic status of the body and can serve as potential disease biomarkers with significant clinical importance.

Kynurenine pathway. Trp is an essential substrate for protein synthesis and is involved in various biological processes. In the human body, the Kyn pathway is the predominant metabolic route accounting for the majority of Trp metabolism, in which Trp is oxidized to N-formyl-L-Kyn by TDO or IDO. Subsequently, N-formyl-L-kyn is converted to L-kyn using formylase. L-Kyn is further metabolized to 3-hydroxy-L-Kyn in a reaction catalyzed by Kyn 3-monooxygenase (KMO). 3-Hydroxy-L-Kyn is then transformed into 3-hydroxyanthranilic (3-HAA) acid via oxidation by 3-HAA oxidase, which generates anthranilic acid. Kyn can be converted into kynurenic acid (KYNA) by Kyn aminotransferases. KYNA exerts neuroprotective effects by inhibiting glutamate receptors and reducing neuroexcitatory toxicity (10-12). The Kyn pathway is the predominant pathway for Trp metabolism, accounting for over 95% of Trp catabolism. Various metabolites generated in this metabolic pathway are closely associated with immune regulation, inflammation and neurodegenerative diseases. For instance, an elevated Kyn/Trp ratio often correlates with disease progression and poor prognosis in patients with cancer (such as lung cancer) (13-15). Studies have shown that Trp metabolism is altered in the early adenoma stage and persists throughout colorectal cancer (CRC) progression in patients with CRC. Moreover, compared with the control group, the

activities of IDO1 and Trp hydroxylase (TPH) enzymes were significantly increased in patients with CRC, suggesting that the Kyn and serotonin pathways may play important roles in immune regulation. Further analysis revealed that patients with colon cancer are more prone to Trp catabolism than patients with rectal cancer. These findings indicated that early abnormalities in Trp metabolism may help colon cancer evade immune surveillance and resist immunosuppression (16). Abnormalities in Trp metabolism are significant in non-cancer-related diseases. For example, elevated Kyn levels are considered to be closely related to neuroinflammation and neurotoxicity in patients with depression (17), and increased quinolinic acid (QA) levels in the cerebrospinal fluid are significantly associated with cognitive decline in patients with neurodegenerative diseases (18). These studies reveal the potential pathological mechanisms of Trp metabolic abnormalities in various diseases and their importance as biomarkers.

5-HT pathway. The 5-HT pathway is another important pathway involved in Trp metabolism. This pathway converts Trp to the neurotransmitter 5-HT, also known as serotonin, where Trp is hydroxylated to form 5-hydroxyTrp (5-HTP) by TPH (19). The conversion of Trp to 5-HTP by TPH is followed by decarboxylation of 5-HTP to 5-HT by aromatic L-amino acid decarboxylase (AADC). TPH, the rate-limiting enzyme in this pathway, has two isoforms: TPH1, which is predominantly expressed in peripheral tissues, and TPH2, which is primarily expressed in the central nervous system (CNS) (20). The decarboxylation of 5-HTP to 5-HT by AADC occurs in the neuronal cytoplasm, and 5-HT is subsequently stored in synaptic vesicles and released into the synaptic cleft to exert its neurotransmitter effects (21). 5-HT binds various receptors in the synaptic cleft to mediate its physiological effects. After the action of 5-HT is terminated, primarily through reuptake by the 5-HT transporter (SERT), it is restored, metabolized, or degraded (22). Within neurons, it is mainly metabolized by monoamine oxidase to form 5-hydroxyindoleacetaldehyde, which is then converted to 5-hydroxyindoleacetic acid (5-HIAA) by aldehyde dehydrogenase and ultimately excreted as a metabolic product (23). 5-HT is acetylated by N-acetyltransferase to form N-acetyl-5-HT (NAc-5-HT), which is then converted into melatonin via O-methylation by hydroxy-indole-O-methyltransferase (24). The 5-HT pathway of Trp metabolism and its metabolites have garnered widespread attention in clinical studies as potential cancer biomarkers. Studies have demonstrated that 5-HT plays a crucial role in the susceptibility to esophageal cancer (EC) and may serve as a potential EC biomarker (25). Moreover, 5-HT metabolism is implicated in the development and progression of various tumors, and relevant research has revealed the therapeutic potential of targeting key enzymes, metabolites and receptors within the 5-HT metabolic pathway (26). Specifically, Trp and its metabolites interact with 5-HT receptors (5-HT_{1A}, 1B, 2A and 2B) to regulate cancer cell proliferation and metastasis (27). Under normal physiological conditions, Trp metabolism occurs through both 5-HT and indole pathways, with these enzymes and their metabolites widely distributed in various cells and tissues (28). In addition, the metabolic pathway of the end product of Trp metabolism,

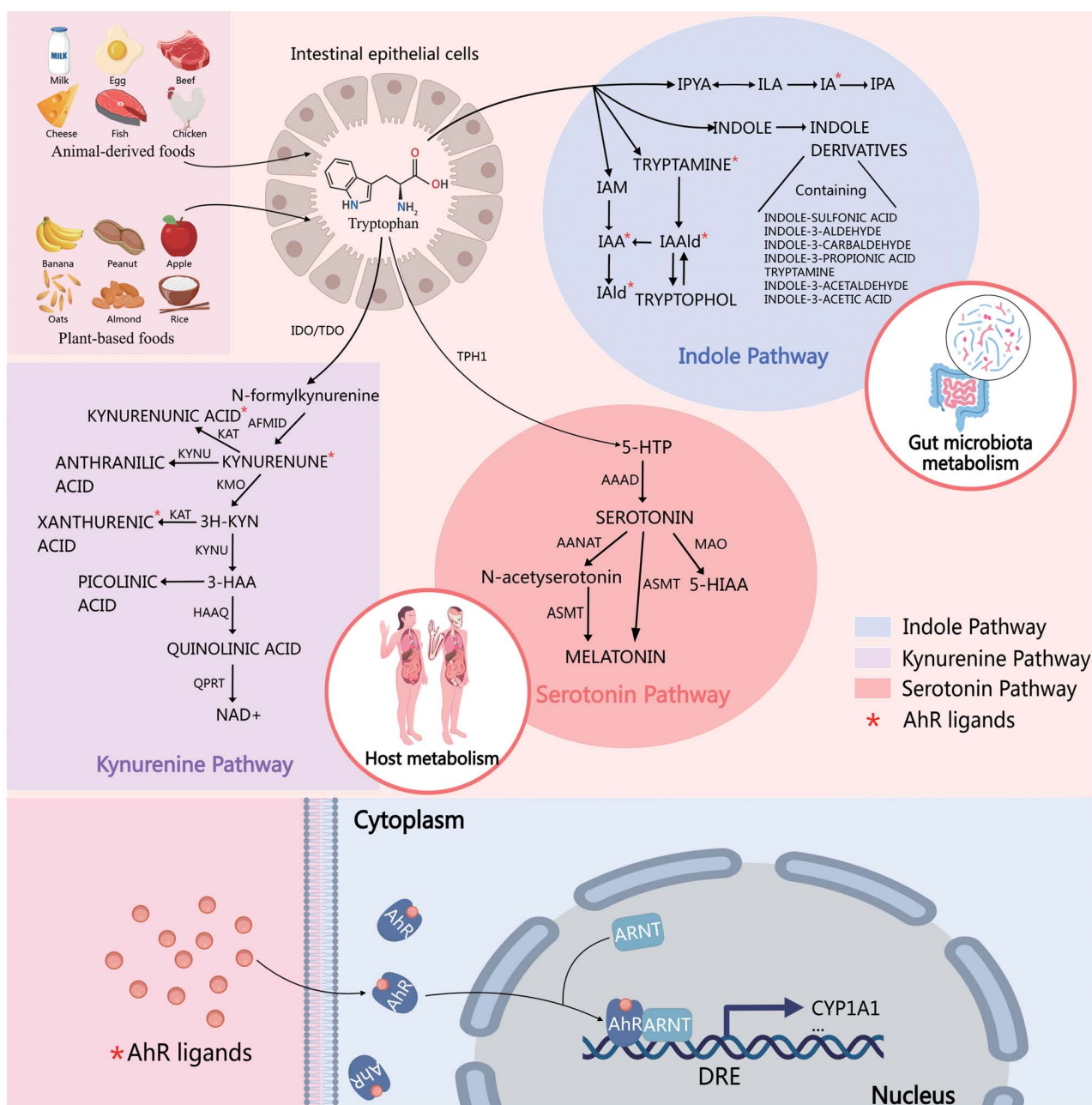


Figure 1. Pathways of tryptophan metabolism through the 5-HT, Kyn, and indole pathways.

5-HIAA, in malignant melanoma is an important direction for future studies (29).

Indole pathway. The indole-synthesis pathway is an essential metabolic process. This pathway occurs primarily in the gut microbiota, where Trp is converted into various bioactive molecules via enzymatic reactions. These molecules play crucial roles in host physiological and pathological processes (30). In the indole pathway, Trp is catalytically degraded by tryptophanase (Trpase) secreted by gut bacteria to produce tryptamine. Subsequently, in the presence of gut bacteria, tryptamine undergoes a series of complex enzymatic reactions to generate indoles. Tryptamine transaminase plays a key role in this process by efficiently converting tryptamine into indole (31,32). Indoles can be further oxidized to indoxyl

sulfate, an important intermediate in the indole pathway. Additionally, indole can be metabolized into other derivatives, such as indole-3-acetaldehyde and indole-3-pyruvic acid, via alternative pathways (33,34). Indole-3-acetic acid (IAA) is an auxin essential for plant growth regulation (35). Indole and its derivatives have various biological functions in the cells that produce them, primarily in gut health and immune regulation. Indole compounds (for example, indole-3-propionic acid) activate AhR, modulate gut barrier function, reduce the production of inflammatory cytokines, and enhance the gut immune balance (30). Regarding the gut microbiota, indole metabolites protect gut health by influencing gut barrier function and inflammatory responses (31). Trp metabolism plays a significant role in the interaction between the host and pathogens and involves multiple metabolic pathways. Indole

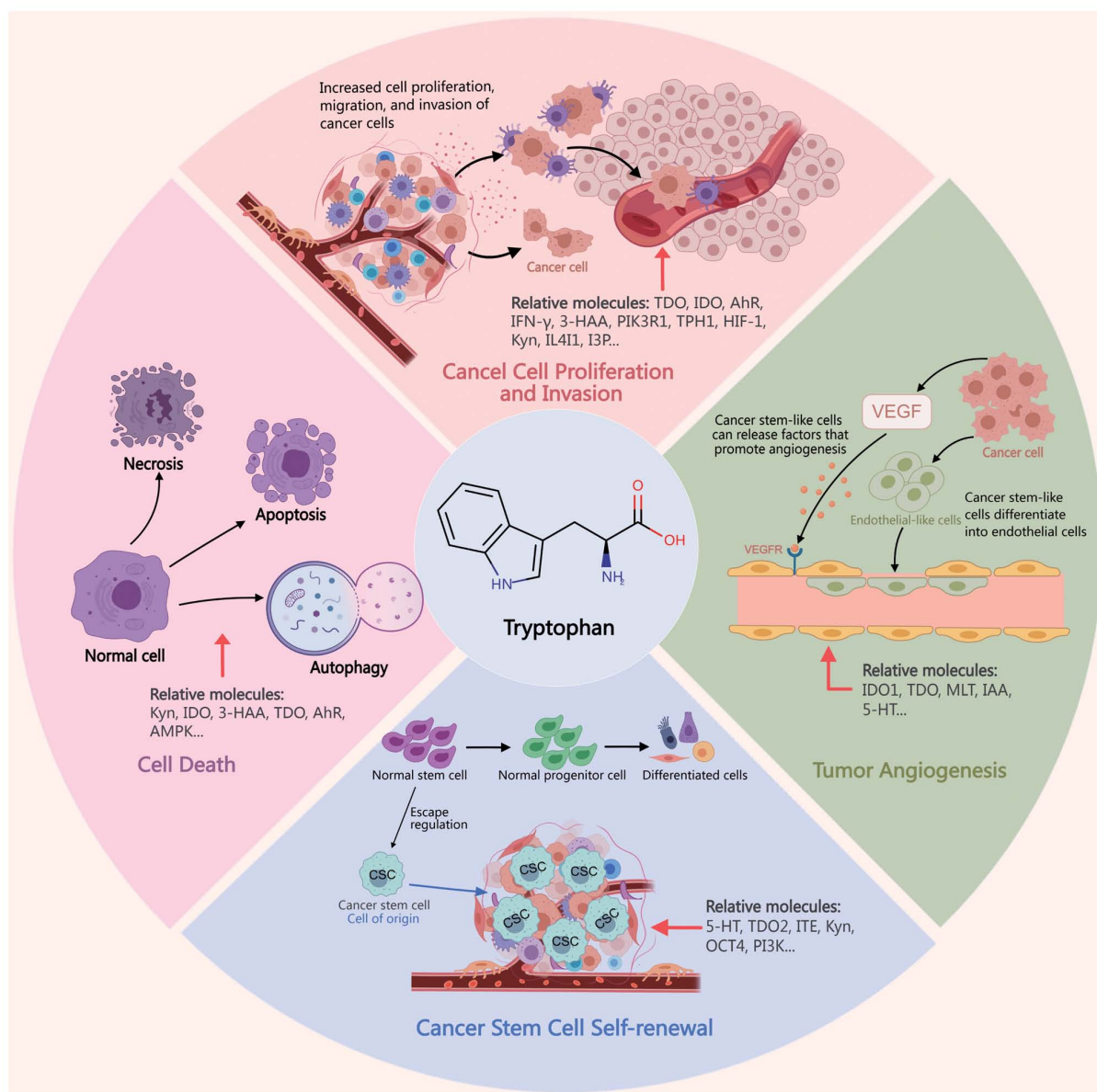


Figure 2. Role of tryptophan metabolism and related molecules in cancer-related processes such as cancer cell proliferation and invasion, tumor angiogenesis, self-renewal of cancer stem cells, and cell death. IDO, 2,3-dioxygenase; TDO, Trp 2,3-dioxygenase; 3-HAA, 3-hydroxyanthranilic acid; Kyn, kynurenine; AhR, aryl hydrocarbon receptor; 5-HT, 5-hydroxytryptamine; HIF-1, hypoxia-inducible factor 1.

and its derivatives are unique metabolites produced by human gut microbiota. Trp metabolism undergoes significant changes in CRC, and studies have shown that this is related to alterations in the populations of indole-producing bacteria. Indole exhibits anti-inflammatory effects and demonstrates potential therapeutic value through specific anticancer mechanisms and may become part of future anticancer adjuvant strategies (36). Inflammation can induce changes in both the host and microbial Trp metabolism in colon cancer. For example, the overexpression of IDO1 (indoleamine-2,3-dioxygenase 1) shifts Trp metabolism towards the Kyn pathway, thereby promoting tumor immune evasion. By contrast, Trp metabolites, such as indole, can inhibit tumor occurrence and development. However, changes in the gut microbiota often lead to decreased indole levels, disrupting the symbiotic relationship between the host and microbes, consequently enhancing inflammation and exacerbating the vicious cycle (37). Therefore, abnormal

levels of indole metabolites are associated with diseases, such as inflammatory bowel disease, metabolic syndrome and gut microbiota dysbiosis, and thus have potential value as biomarkers. In summary, Trp metabolism via the indole pathway is vital for physiological and pathological processes in cells. Elucidating the specific mechanisms of action of indole and its derivatives on cell health is essential for exploring their potential applications in disease prevention and treatment.

3. Disruption of Trp metabolism in cancer

Disruption of Trp metabolism can induce alterations in various hallmark features of cancer across multiple systems, including the digestive, nervous, respiratory and hematological systems. Its role and underlying mechanisms in cancer are gradually elucidated (Fig. 2). The effects of Trp metabolism in cancer are summarized in Table I.

Table I. Role and mechanism of tryptophan in tumors.

First author, year	Tumor type	Tryptophan metabolism	Functions	Relative molecules	(Refs.)
Chen <i>et al</i> , 2015; Vermeulen <i>et al</i> , 2010; Pham <i>et al</i> , 2018	CRC	Kyn, AhR	Self-renewal of colon CSCs	PI3K/Akt, β -catenin	(43,44,48)
Zhu <i>et al</i> , 2022	CRC	5-HT	Self-renewal of colon CSCs and promotion of tumor angiogenesis	MMP-12	(45)
Shi <i>et al</i> , 2022	CRC	IDO1	Cause of T-cell dysfunction	-	(52)
Zheng <i>et al</i> , 2017; Gürsel <i>et al</i> , 2012	Glioma	Melatonin	Inhibition of the proliferation and tumorigenicity of glioma stem cells	EZH2, Notch	(46,47)
Guastella <i>et al</i> , 2018	Glioma	Kynurenic acid, AhR	Promotion of immunosuppression	-	(66)
Panitz <i>et al</i> , 2021	Glioma	TDO2, Kyn, AhR	Promotion of the motility of tumor cells and inhibit immune cells	Akt	(67)
Sahm <i>et al</i> , 2013	Glioma	NAD ⁺	Enhancement of resistance to oxidative stress	-	(71)
Sadik <i>et al</i> , 2020	Glioma	I3P, Kyn, AhR	Promotion of the motility and malignant phenotype of cancer cells	IL4I1	(74)
Bosnyák <i>et al</i> , 2015	Glioblastoma	Kyn, AhR	Promotion of the motility of tumor cells and inhibit immune cells	Trp catabolic enzymes	(77)
Panitz <i>et al</i> , 2021	Glioblastoma	TDO2, Kyn, 3-HAA	Facilitation of the preservation of tryptophan in tumor cells	HIF-1 α	(67)
Zhang <i>et al</i> , 2022; Pham <i>et al</i> , 2018	Esophageal cancer	TDO2	Participation in the formation of tumor spheres of esophageal CSCs	Oct4, EGFR	(39,48)
Zhao <i>et al</i> , 2012	Liver cancer	IDO	Facilitation of the immune escape of tumors	IFN- γ	(55)
Tummala <i>et al</i> , 2014	Liver cancer	NAD ⁺	Prevention of DNA damage and dysregulation of cell proliferation	URI	(56)
Yu <i>et al</i> , 2021	Liver cancer	TDO2	Inhibition of the proliferation of HCC cells	p21, p27, CDK2, CDK4	(57)
Wu <i>et al</i> , 2021	Liver cancer	TDO2, Kyn, AhR	Promotion of the progression of HCC cells	IL-6, STAT3, NF-kB	(58)
Li <i>et al</i> , 2021	Liver cancer	TDO2	Promotion of EMT of cancer cells	-	(59)
Jin <i>et al</i> , 2015	Liver cancer	KMO	Promotion of the progression of HCC cells	-	(60)
Shi <i>et al</i> , 2021	Liver cancer	3-HAA	Induction of apoptosis of HCC cells	YY1	(61)
Zhang <i>et al</i> , 2017; Koblish <i>et al</i> , 2010	Pancreatic cancer	IDO	Reflection of the malignancy of pancreatic adenocarcinoma	-	(63,65)
Hezaveh <i>et al</i> , 2022	Pancreatic cancer	Indole, AhR	Promotion of tumor growth and metastasis	-	(64)
Talari <i>et al</i> , 2016; Bosnyák <i>et al</i> , 2015	Meningioma	IDO2, TDO2, Kyn	Promotion of tumor growth and metastasis	-	(76,77)
Ino <i>et al</i> , 2008; Yoshida <i>et al</i> , 2008; Ino <i>et al</i> , 2006	Endometrial cancer	IDO	Promotion of the motility of tumor cells and inhibit immune cells	-	(78-80)
Inaba <i>et al</i> , 2009; Odunsi <i>et al</i> , 2022; Gostner <i>et al</i> , 2018	Ovarian cancer	IDO, NAD ⁺	Promotion of the motility of tumor cells and inhibit immune cells	-	(81-83)
Liu <i>et al</i> , 2014	Non-Hodgkin's lymphoma	IDO1	Facilitation of the immune escape of tumors	Lactate dehydrogenase	(87)

Table I. Continued.

First author, year	Tumor type	Tryptophan metabolism	Functions	Relative molecules	(Refs.)
El Kholy <i>et al</i> , 2011; Curti <i>et al</i> , 2007	Acute myeloid leukemia	IDO, kynurenic acid	Promotion of the motility of tumor cells and inhibit immune cells	-	(88,89)
Zhang <i>et al</i> , 2019	Pulmonary adenocarcinoma	IDO1	Promotion of the motility of tumor cells	EGFR	(90)
Tang <i>et al</i> , 2017; Hsu <i>et al</i> , 2016	Lung cancer	TDO2, Kyn, AhR	Promotion of the proliferation of CAFs and EMT in lung cancer cells	Akt/CREB, Akt/WNK1	(91,92)
Feng <i>et al</i> , 2022	Lung cancer	TDO, Kyn, AhR	Enhancement of the proliferation ability of NSCLC cells and their resistance to EGFR tyrosine kinase inhibitors	Akt, ERK	(93)
Tang <i>et al</i> , 2017	Lung cancer	IDO1	Promotion of the motility of tumor cells	P53	(91)
Karayama <i>et al</i> , 2021	NSCLC	3-HAA	Inhibition of the therapeutic efficacy of immune checkpoint inhibitors	-	(94)
Levina <i>et al</i> , 2012; D'Amato <i>et al</i> , 2015	Breast cancer	IDO1, TDO2, AhR	Promotion of tumor growth and metastasis	-	(95,96)
Li <i>et al</i> , 2021	Prostate cancer	AhR	Increase of the apoptosis rate of prostate cancer cells treated with Abi or Doc	c-Myc	(102)
Zhang <i>et al</i> , 2019	Bladder cancer	IDO1	Promotion of tumor angiogenesis	microRNA-153	(111)
Cecchi <i>et al</i> , 2024	Melanoma	TDO	Promotion of tumor angiogenesis	-	(112)

Kyn, kynurenine; AhR, aryl hydrocarbon receptor; 5-HT, 5-hydroxytryptamine; IDO1, indoleamine 2,3-dioxygenase 1; IDO, indoleamine 2,3-dioxygenase; TDO2, tryptophan 2,3-dioxygenase; NAD⁺, nicotinamide adenine dinucleotide; 3-HAA, 3-hydroxyanthranilic acid; KMO, kynurenine 3-monooxygenase; I3P, indole-3-pyruvate; EZH2, enhancer of Zeste Homolog 2; IL4I1, interleukin 4-induced 1; HIF-1 α , hypoxia-inducible factor 1- α ; Oct4, octamer-binding transcription factor 4; EGFR, epidermal growth factor receptor; IFN- γ , interferon- γ ; URI, unconventional prefoldin RPB5 interactor; IL-6, interleukin-6; STAT3, signal transducer and activator of transcription 3; NF-Kb, nuclear factor kappa-light-chain-enhancer of activated B cells; Akt, protein kinase B; CREB, cAMP response element-binding protein; ERK, extracellular signal-regulated kinase; P53, tumor protein P53; c-Myc, Myc proto-oncogene protein; Abi, abiraterone; Doc, docetaxel; HCC, hepatocellular carcinoma; EMT, epithelial-mesenchymal transition; CSCs, cancer stem cells; CRC, colorectal cancer; NSCLC, non-small cell lung cancer.

Correlation between Trp metabolism and CSC self-renewal.

Human pluripotent stem cells (hPSCs), which can differentiate into various cell types, hold great promise as a source of cells for regenerative therapies and drug discovery. Trp metabolism is critical for promoting hPSC proliferation without compromising their pluripotency (38). Several studies focused on the relationship between Trp metabolism and CSCs. Modulation of the Trp metabolic pathway can influence the self-renewal ability of CSCs. For example, the Trp metabolite Kyn can activate AhR to regulate self-renewal and differentiation of CSCs (39). In some diseases, colorectal CSCs represent a small subpopulation of cells with self-renewal and differentiation capabilities within CRC (40). These pathways are beneficial for the self-renewal of CSCs. Abnormal hyperactivation of specific signaling pathways in CSCs, such as the phosphoinositide 3-kinase/protein kinase B (PI3K/Akt) and β -catenin pathways, may induce uncontrolled cell proliferation and abnormal differentiation, leading to tissue-specific tumorigenesis (41-44). The neurotransmitter

5-HT promotes self-renewal and tumorigenesis of colorectal CSCs (45). The Trp-derivative melatonin may inhibit the proliferation and tumorigenicity of glioma stem-like cells by suppressing the EZH2 and Notch pathways, which are crucial for the survival of glioma stem cells (46,47). Overexpression of TDO2 is associated with tumor staging and recurrence status, as well as the CD44 CSC marker in esophageal squamous cell carcinoma (ESCC) and is involved in the formation of tumor spheres in esophageal CSCs. TDO2 may promote the generation of esophageal CSCs by inducing the expression of Oct4 and CD44, activating the epidermal growth factor receptor (EGFR) pathway, stimulating epithelial-mesenchymal transition (EMT) and invasion of esophageal CSCs, which are associated with poor prognosis in patients with ESCC (39,48). Additionally, indole-3-pyruvate, a Trp metabolite, reduces the expression of Oct4 in CSCs by activating the AhR transcriptional pathway, inducing CSC differentiation, and decreasing CSC tumorigenicity (39). Moreover, activating the Trp metabolic pathway

helps CSCs evade attacks from the host immune system through immune modulation and metabolic reprogramming, thereby maintaining survival. For example, Trp depletion and hypoxia preserve CSC phenotype by enhancing OCT4 transcription (49). Kyn inhibits the activity of effector T-cells via the AhR pathway, enhances Treg function, and suppresses antitumor immune responses. This immunosuppressive effect provides a favorable environment for CSC survival (7,39). In addition, Trp metabolites regulate the metabolic state of CSCs to adapt to hypoxia and nutrient deficiency in the TME (50). In summary, Trp metabolism and its key enzymes are vital for the maintenance and function of CSCs, promoting tumor progression and drug resistance by directly affecting CSC behavior and indirectly regulating immune responses in the TME.

Cancer cell proliferation, invasion and immune evasion Digestive system diseases

CRC. Kyn, a bioactive metabolite of the Trp metabolism, acts as an ‘oncometabolite’ in CRC cells. It maintains the proliferation of CRC cells by activating the transcription factor AhR and regulating genes that promote cell proliferation (51). Additionally, Kyn accumulation affects the TME, facilitating the proliferation and spread of CRC cells. USP14 promotes Trp metabolism in CRC by stabilizing the expression of IDO1, leading to T-cell dysfunction. This metabolic alteration enables tumor cells to evade immune surveillance, enhancing their proliferative capacity and metastatic potential (52). High expression of IDO is associated with the local depletion of Trp, which inhibits T-cell proliferation and activity, allowing tumor cells to escape immune attack and promote tumor proliferation and metastasis (53). The activity of IDO1 promotes immune tolerance in the TME and directly enhances the proliferation of CRC cells by activating the β -catenin signaling pathway (42). These studies indicate that modulation of Trp metabolism influences the development and progression of CRC. Therefore, in-depth studies on the relationship between Trp metabolism and CRC may facilitate the development of novel therapeutic strategies.

Hepatocellular carcinoma (HCC). In HCC, IDO inhibits the proliferation of cytotoxic T-cells by degrading Trp and promoting tumor immune evasion. High IDO expression is significantly associated with the metastasis rate and poor prognosis in patients with HCC, suggesting that IDO may play a crucial role in tumor cell proliferation, invasion and metastasis (54). CD69⁺ T-cells in the TME can induce high expression of IDO in tumor-associated macrophages (TAMs) through the secretion of interferon- γ (IFN- γ), which, in turn, inhibits T-cell proliferation and function, promoting tumor immune evasion (55). The role of Trp metabolism in HCC is reflected by its effect on NAD⁺ synthesis and DNA damage mechanisms. Overexpression of URI (an unconventional prefoldin RPB5-interacting factor) inhibits the Trp metabolism pathway, leading to decreased NAD⁺ levels, DNA damage and dysregulated cell proliferation, promoting the malignant transformation of hepatocytes and tumorigenesis (56). Overexpression of TDO2 inhibits HCC cell proliferation and induces cell cycle arrest by upregulating p21 and p27 and downregulating CDK2 and CDK4. The absence of TDO2 may promote tumor proliferation and metastasis, indicating that TDO2 is a potential biomarker and therapeutic target

for HCC (57). High TDO2 expression is associated with poor prognosis in patients with HCC. TDO2 promotes the conversion of Trp to Kyn, activates AhR, upregulates the secretion of interleukin-6 (IL-6), activating signal transducer and activator of transcription 3 (STAT3) and nuclear factor kappa B (NF- κ B) signaling pathways, and promotes HCC cell proliferation and metastasis (58). TDO2 promotes EMT in cancer cells by activating the Kyn-AhR pathway, thereby enhancing HCC cell proliferation, invasion and metastasis (59). High KMO expression in HCC tissues is associated with poor prognosis. *In vitro* experiments have shown that KMO overexpression promotes HCC cell proliferation, migration and invasion, whereas KMO knockdown inhibits these processes (60). 3-HAA, a derivative of Trp, is present at low concentrations in tumor cells. Exogenous 3-HAA induces apoptosis in HCC cells by binding to the transcription factor YY1. The mechanism involves protein kinase C Zeta (PKC ζ)-mediated phosphorylation of YY1, enhancing its binding to target genes, and regulating HCC cell proliferation, invasion and metastasis through modulation of 3-HAA levels (61). 5-HT1D is significantly upregulated in HCC tissues and cell lines, with its expression associated with poor clinical pathological features. 5-HT1D stabilizes PI3K1 to activate the PI3K/Akt signaling pathway, enhances FoxO6 expression, and promotes cancer cell proliferation, EMT and metastasis. Additionally, 5-HT1D inhibits the expression of TPH1 via the PI3K/Akt/CUX1 axis, thereby affecting 5-HT synthesis (62). In-depth research into the relationship between Trp metabolism and HCC may facilitate the development of novel therapeutic strategies against HCC.

Pancreatic cancer. High IDO expression is closely related to the malignancy of pancreatic adenocarcinoma, particularly in patients with poorly differentiated tumors, lymph node metastasis, and advanced TNM staging, and is associated with a poor prognosis. This suggests that IDO is involved in pancreatic cancer progression, making it a potential therapeutic target (63). The gut microbiota metabolizes Trp to produce indole compounds that activate the AhR, inhibit anti-tumor immunity, and promote tumor growth and metastasis. Macrophages lacking AhR function exhibit a stronger inflammatory phenotype, increased CD8⁺ T-cell infiltration and tumor growth inhibition (64). IDO catalyzes the conversion of Trp to Kyn, depleting Trp levels, causing immune suppression, and facilitating tumor cell evasion during immune attacks. Inhibition of IDO activity can reduce Kyn levels in the TME, enhance the function of tumor-infiltrating lymphocytes (TILs), and inhibit tumor growth and metastasis (65). These results indicate that modulation of Trp metabolism may be an effective strategy for cancer therapy.

CNS diseases

Glioma. Dysregulation of the Kyn pathway in primary brain tumors, such as gliomas, leads to local Trp depletion within cancer cells and promotes an immunosuppressive TME, affecting tumor cell proliferation and invasion capabilities. This pathway may also affect tumor metastasis by modulating the AhR signaling pathway (66). The upregulation of Trp catabolic enzymes in glioblastoma (GBM) promotes Trp degradation to produce metabolites, such as Kyn, which activate AhR and subsequently enhance tumor cell motility while suppressing immune cell function (67). TDO2 facilitates

the generation of Kyn from Trp metabolism, which activates the AhR and Akt signaling pathways, enhancing tumor cell proliferation and invasion. Moreover, Kyn inhibits the proliferation of functional T-cells, leading to immunosuppression and the promotion of glioma cell proliferation and metastasis (68). Under hypoxic conditions, hypoxia-inducible factor-1 α in GBM downregulates the expression of TDO2, reducing Trp degradation and consequently decreasing the production of Kyn and 3-HAA. This mechanism may help tumor cells conserve Trp in the hypoxic microenvironment and maintain their proliferative and survival properties (69). IDO expression in the brain increases with age. This enzyme generates immunosuppressive metabolites from Trp metabolism, weakening the efficacy of immunotherapy and resulting in poor treatment outcomes for GBM in elderly patients (70). Glioma cells generate QA via microglia and utilize it to synthesize NAD⁺, enhancing resistance to oxidative stress. Activation of this metabolic pathway is closely related to the malignant phenotype of tumors, and the accumulation of Quin endows glioma cells with a greater survival capacity when subjected to radiotherapy and chemotherapy (for example, temozolomide), promoting tumor invasion and metastasis (71). Positron emission tomography (PET) using α -¹¹C-methyl-L-Trp (AMT) can be used to assess 5-HT synthesis in the brain and track the upregulation of the Kyn pathway in tumor tissues in patients with malignant gliomas. Increased AMT uptake in the tumor tissues of patients with high-grade gliomas (grades III-IV) suggests that alterations in Trp metabolism may be closely related to the biological behavior of tumors such as proliferation and metastasis (72). Increased Trp metabolism, mainly through the Kyn pathway, observed using PET, positively correlates with tumor proliferative activity (assessed using the Ki-67 labeling index) (73). Finally, IL4I1 catalyzes Trp metabolism to generate indole-3-propionic acid (I3P) and its derivatives (for example, Quin and KynA), which activate AhR and promote cancer cell motility and a malignant phenotype, thereby correlating with reduced survival rates in patients with glioma (74). In low-grade brain tumors, such as dysplastic neuroepithelial tumors, widespread expression of the Trp-catabolic enzyme IDO may lead to local Trp depletion and inhibition of cell proliferation, as evidenced by a lower proliferative index (Ki-67). By contrast, IDO expression is less frequent in high-grade tumors such as GBM. It is mainly confined to endothelial cells and is possibly associated with tumor invasiveness and metastatic capability (75). Trp metabolism is important for immune evasion in gliomas and provides a survival advantage to glioma cells; thus, it is emerging as a potential therapeutic target.

Meningioma. Meningioma cells evade immune responses via the Trp metabolic pathway, particularly the Kyn pathway, resulting in elevated levels of Kyn and lower levels of Trp and its metabolites, thereby promoting tumor progression. This process is accompanied by the upregulation of enzymes such as IDO2 and INOS, highlighting the significant role of Trp metabolism in cancer cell proliferation and invasion (76). The grading of meningiomas is positively correlated with PET imaging parameters of Trp metabolism (for example, the k3' ratio). These parameters can be used to effectively distinguish meningiomas of different grades. The key enzyme in Trp metabolism, TDO2, exhibits significant immunostaining in

meningiomas, suggesting its potential role in tumor immune tolerance and proliferation (77). These findings indicate that Trp metabolism is associated with the biological characteristics of tumors and may provide new strategies for improving meningioma treatment outcomes.

Reproductive system diseases

Endometrial cancer. IDO is highly expressed in endometrial cancer and is significantly associated with tumor aggressiveness, lymph node metastasis and involvement of vascular lymphatic spaces. IDO exerts its effects by depleting Trp and generating toxic metabolites that inhibit the function of TILs and natural killer (NK) cells and promote tumor immune evasion (78). However, in mouse xenograft models, tumors overexpressing IDO exhibited faster growth rates, which correlated with a decrease in the number and function of NK cells, suggesting that IDO inhibits NK cell activity through Trp metabolism, thereby facilitating tumor progression (79). High IDO expression in endometrial cancer cells positively correlated with the clinicopathological features of the tumor. Elevated IDO expression is significantly associated with reduced overall and progression-free survival (PFS) (80). IDO influences endometrial cancer cell proliferation, invasion and metastasis by regulating Trp metabolism, making it a potential therapeutic target.

Ovarian cancer. High IDO expression is associated with an immunosuppressive state in tumor cells, reducing the number of TILs and affecting patient survival. Although *in vitro* experiments have shown no significant differences in the proliferation, migration and invasion capabilities of IDO-overexpressing ovarian cancer cells, mouse xenograft models have demonstrated a substantial increase in peritoneal metastasis in IDO-overexpressing cells (81). IDO1 inhibition alters Trp metabolism and suppresses immune evasion in tumor cells. It also induces metabolic adaptation by increasing NAD⁺ synthesis and inhibiting T-cell proliferation and function. This metabolic adaptation may limit the antitumor immune response and promote the proliferation, invasion and metastasis of ovarian cancer cells (82). An elevated Kyn/Trp ratio is associated with disease progression in patients with ovarian cancer. The presence of circulating tumor cells (CTCs) correlates with alterations in Trp metabolism and elevated levels of immune activation markers (such as neopterin), suggesting that CTCs continuously stimulate the immune system by releasing tumor antigens or cytokines, facilitating tumor immune evasion and metastasis (83).

Hematological system diseases

Non-Hodgkin's lymphoma (NHL). NHL is a hematological malignancy originating from lymph nodes and other extranodal lymphoid tissues (84-86). IDO1 expression is significantly upregulated in NHL tissues and is associated with the clinical stage of the tumor, tumor size and serum lactate dehydrogenase levels, indicating a poor prognosis. IDO1 promotes local immune tolerance by depleting Trp and its metabolites (for example L-kyn) and inhibiting the proliferation and activation of antigen-specific T-cells. Upregulation of IDO1 enhances the generation and infiltration of Tregs, possibly representing a mechanism by which NHL evades immune control (87), making it a potential target for treatment.

Acute myeloid leukemia (AML). IDO is expressed in patients with AML. It suppresses T-cell proliferation by reducing local Trp concentrations and generating immunosuppressive metabolites (for example, Quin), thereby promoting tumor immune tolerance. This mechanism may enhance the proliferation and survival of tumor cells, facilitating their invasion and metastasis (88). IDO expression is associated with increased circulating CD4⁺CD25⁺FOXP3⁺ regulatory T cells. AML cells directly convert CD4⁺CD25⁺ T cells into CD4⁺CD25⁺ Treg cells via Trp metabolism, inhibiting T-cell proliferation and activity and promoting tumor immune evasion. This process affects the TME and may contribute to cancer cell proliferation, invasion and metastasis (89). The inhibition of IDO may represent a novel therapeutic strategy against AML.

Other disease systems. The expression of IDO1 is significantly associated with tumor aggressiveness, smoking history, and the abundance of tumor-infiltrating CD8⁺ and T-bet⁺ cells; in some cases, it is related to EGFR mutations. Although IDO1 expression is associated with tumor growth and metastasis, its independent expression does not significantly affect patient survival, suggesting that its immunosuppressive role in lung adenocarcinoma may involve other mechanisms (90). High expression of IDO1 in lung cancer tissues correlates with clinical stage and lymph node metastasis. It enhances cancer cell migratory and invasive capacities, which are partially attenuated by p53 through suppression of the IDO signaling pathway (91). Lung cancer cells activate cancer-associated fibroblasts (CAFs) to promote Trp metabolism and generate Kyn via TDO2. Kyn inhibits DC function, promotes proliferation and EMT in lung cancer cells, and activates Akt/CREB and Akt/WNK1 signaling pathways to enhance cancer cell proliferation and migration (92). Kyn production is closely related to the activation in CAFs. It promotes activation of the AhR signaling pathway, activates Akt and ERK signaling, and enhances the proliferative capacity and resistance to EGFR tyrosine kinase inhibitors in non-small cell lung cancer (NSCLC) cells (93). Changes in Trp metabolite 3-HAA in the plasma of patients with NSCLC are associated with the efficacy of ICIs. Lower levels of 3-HAA correlate with improved treatment responses and longer PFS, indicating that 3-HAA may influence tumor growth and metastasis by modulating immune responses (94). IDO1 plays a significant role in Trp metabolism in breast cancer (BC), promoting tumor cell proliferation and metastasis through both immune and non-immune pathways (95). Upregulation of TDO2 and AhR renders triple-negative BC (TNBC) cells more resistant, allowing them to survive in the absence of matrix attachment, which is crucial for BC metastasis (96).

The complex relationship between cancer cells and cell death: Evasion and manipulation. Some metabolites generated during Trp metabolism can influence the immune system by regulating immune cell apoptosis, potentially promoting tumor progression (97).

Apoptosis. Kyn, the first metabolite of Trp degradation via IDO, also functions as an immunosuppressive molecule owing to the generation of its derivatives 3-HAA and Quin, which induce selective apoptosis in murine Th1 cells by activating

caspase-8 *in vitro* (9). T-cell apoptosis occurs at relatively low Kyn concentrations, independent of Fas/Fas ligand interactions, and is associated with caspase-8 activation and mitochondrial release of cytochromes (97,98). IDO and TDO deplete local Trp and accumulate Kyn in tumors and antigen-presenting cells, leading to T-cell anergy and apoptosis via the GCN2 pathway (99). Trp metabolites further enhance their immunosuppressive effects by inhibiting T-cell proliferation and inducing DC-mediated T-cell apoptosis (97). In addition to T-cell apoptosis, Trp metabolism also affects cancer cell apoptosis to some extent. Trp deprivation significantly increases the expression of ERRF1 in sensitive HCC cells, activating the apoptotic pathway and inducing cell death (100). Enhanced Kyn pathway activation leads to a substantial accumulation of Quin in the CNS in several inflammatory neurological diseases. By contrast, 3OH-Kyn and 3OH-anthranilic acids may induce neuronal apoptosis or necrosis. Kyn hydroxylase inhibitors reduce neuronal death in both *in vitro* and *in vivo* models of cerebral ischemia and excitotoxicity (101). AhR can cooperate with NF- κ B to promote c-Myc activation in prostate cancer cells, and overexpression of c-Myc upregulates the expression of Trp transporters and ABC transporters, further increasing the apoptosis rate of prostate cancer cells treated with Abi or Doc (102).

Autophagy. In addition to apoptosis, Trp metabolism, which involves various metabolic pathways involving Trp and its metabolites, is associated with autophagy. Trp metabolites modulate the autophagy pathway by activating AMPK and SIRT1, thereby affecting intestinal inflammation (103). For instance, Trp metabolites, such as IAA, regulate autophagy and ameliorate pulmonary fibrosis by inhibiting the PI3K/Akt signaling pathway (104). Trp metabolites also modulate autophagy via the mechanistic target of rapamycin (mTOR) signaling pathway. L-Trp enhances susceptibility to nonalcoholic fatty liver disease via the mTOR pathway (105). Trp metabolism is essential to the immune system, particularly in T-cells, where Trp metabolites modulate immune responses by affecting the autophagy pathway (106). However, Trp metabolism plays different roles in cancer cell autophagy. For example, extracellular vesicles derived from IDO1-high ovarian cancer cells upregulate SIRT3 expression in endothelial cells by increasing its acetylation, which is essential for promoting endothelial mitochondrial autophagy associated with tumor angiogenesis (107).

Necrosis. Trp metabolism generates Kyn and its metabolites (3-hydroxykynurenine and Quin), which may induce necrosis in tumor cells through multiple mechanisms. Metabolites in the Kyn metabolic pathway may induce oxidative stress, damaging the DNA and organelles of tumor cells and ultimately leading to cell necrosis (108). Although IDO/TDO primarily promote tumor growth through immune suppression, certain Kyn metabolites may activate immune cells under specific conditions, exerting cytotoxic effects on tumor cells, which may lead to alterations in the immune microenvironment. For example, Quin activates specific immune cell subsets and promotes tumor necrosis (109).

Ferroptosis. Ferroptosis is a newly discovered type of regulated cell death that is distinct from apoptosis and autophagy. The Trp metabolites, 5-HT and 3-hydroxykynurenine, are potent ferroptosis inhibitors capable of

suppressing ferroptosis in tumor cells and promoting their proliferation (110). These effects jointly influence cancer cell proliferation, survival and death and have significant implications for cancer progression and treatment.

Induction of cancer angiogenesis by Trp metabolites. Some metabolites formed during Trp metabolism promote tumor angiogenesis, which is crucial for tumor growth and metastasis. MicroRNA (miR)-153 inhibits tumor angiogenesis by suppressing the expression of IDO1. Downregulation of miR-153 leads to increased IDO1 expression in bladder cancer cells, promoting tumor angiogenesis (111). Angiogenesis is essential for the progression and metastasis of melanoma and is based on the production and release of pro-angiogenic molecules in the TME. The interaction between melanoma cells and endothelial cells affects the molecular signaling pathways involved in tumor growth and progression. TDO affects different melanoma cell lines, and its expression positively correlates with endothelial cell infiltration (112). The Trp metabolite 5-HT can modulate the function of tumor-infiltrating macrophages by regulating the expression of matrix metalloproteinase 12, which influences tumor angiogenesis. This mechanism has been validated in colorectal and lung cancers (113). Indole compounds related to Trp metabolism, such as melatonin, IAA, 5-hydroxytryptophan and 5-HT, significantly inhibit vascular endothelial growth factor (VEGF)-induced VEGF receptor-2 activation and subsequent angiogenesis in human umbilical vein endothelial cells, thereby suppressing tumor angiogenesis. These compounds provide potential molecular targets for developing anti-VEGF signaling pathway drugs that may help control tumor growth and progression (114,115). In summary, Trp metabolites induce tumor angiogenesis through significant tumor growth and metastasis.

4. Discoveries in targeting Trp metabolism in cancer

Recently, targeting Trp metabolism has led to significant progress in cancer therapy. The Trp metabolic pathway plays a crucial role in the TME, immune evasion and cancer progression, providing a wealth of targets for developing novel therapeutic strategies. It also offers theoretical support and practical evidence for applying multi-target strategies, combination therapies with ICIs, interactions with the microbiome, and the use of AhR antagonists.

Progress in multi-target strategies targeting Trp metabolism in cancer therapy. In recent years, therapeutic strategies targeting Trp metabolism have garnered widespread attention, with the potential for multi-target combination therapies gradually emerging as a research hotspot. The small-molecule IDO1 inhibitor navoximod (synonyms: GDC-0919, NLG-919) has demonstrated significant activity in combination therapy in various tumor models. It has been revealed that this inhibitor is well-tolerated and capable of reducing plasma Kyn levels, which is consistent with its pharmacokinetic (PK) half-life. In addition, a stable disease response has been observed in some patients (116). Further research has revealed that navoximod in combination with cisplatin can effectively reverse immune resistance mediated by the Kyn-AhR-IL6 axis induced by

IDO1-positive CAFs and chemoresistance triggered by tumor lymphoid structures by targeting IDO1. This mechanism has exhibited great potential in evaluating chemoresistance and biosafety in oral squamous cell carcinoma (117). Moreover, when navoximod is used in combination with another IDO1 inhibitor, indoximod, it exhibits synergistic effects, prolonging patient survival and enhancing therapeutic efficacy when combined with chemotherapy. Currently, research is underway to optimize prodrug formulations to improve their therapeutic effects (118). 1-Methyl-L-Trp (1-MT-L-Trp) is a non-specific competitive IDO1 inhibitor that is widely used in basic research (119). Notably, even in the absence of IDO expression, 1-MT can induce a strong inflammatory molecular genetic response by activating AhR. These data provide important insights into the potential clinical indications of 1-MT as a cancer immunotherapy and suggest that 1-MT may exert therapeutic effects through AhR-related mechanisms, even in IDO-deficient tumors (120). This finding also suggests that 1-MT may have a multi-target mechanism of action, thereby providing a new research direction for further exploration of its potential value in cancer therapy. Compared with 1-MT-L-Trp, 1-methyl-D-Trp (1-D-MT) is currently undergoing clinical trials for patients with recurrent or refractory solid tumors, with the aim of inhibiting tumor immune evasion mediated by IDO. However, studies have reported that 1-D-MT promotes immune evasion by upregulating the expression of IDO1 in cancer cells. This off-target effect has raised concerns regarding its safety and efficacy in clinical trials (121). Future research should combine high-throughput screening technologies to develop more selective IDO1 inhibitors and employ drug delivery systems (such as nanoparticles or prodrugs) to reduce non-specific effects on normal cells, which may help mitigate such off-target effects. TDO has long been considered constitutively expressed only in the liver. It has been identified that TDO is significantly expressed in various cancers, including BC, ovarian cancer and gliomas. TDO is involved in tumor progression and immune suppression through the TDO-L-Kyn-AhR pathway, and its inhibition is considered to help reverse immune evasion (29,36). Although TDO inhibitors remain in the preclinical stage, research is moving towards the development of dual-target inhibitors (IDO1 and TDO) that may enhance cancer immunotherapy efficacy by blocking L-kyn synthesis. However, the clinical feasibility of multi-target strategies faces challenges such as adverse reactions caused by drug interactions and heterogeneous responses of tumors. In the future, precise diagnostic tools need to be developed to identify tumor metabolic phenotypes and optimize multi-target therapeutic combination strategies.

Synergistic effects of Trp metabolism and ICIs. Recently, the synergistic effects of Trp metabolism and ICIs have become a popular research topic in the field of cancer immunotherapy. The Trp metabolic pathway, particularly the metabolic processes mediated by IDO and TDO, plays a crucial role in tumor immune evasion (99). It has been found that, in primary pulmonary squamous cell carcinoma, the co-expression of IDO1 and programmed death-ligand 1 (PD-L1) has significant prognostic implications and is closely related to TILs. Co-expression of IDO1 and PD-L1 may be an important target for immunotherapy in pulmonary squamous cell

carcinoma (122). The IDO1 enzyme inhibitor, BGB-5777, in combination with anti-PD-1 monoclonal antibodies and radiotherapy, demonstrated a robust immune-enhancing effect in GBM model studies. This mechanism may be related to an increase in tumor-infiltrating T-cells, reduction in immunosuppressive IDO1 levels, restoration of immune cell function following PD-1 blockade, and the pro-inflammatory effects of radiation therapy (123). Additionally, the novel IDO1 inhibitor PF-06840003 reversed the T-cell non-responsive state, reduced intra-tumoral Kyn levels, and inhibited tumor growth. It has been shown that the antitumor effect of this drug in combination with anti-PD-L1 antibody therapy is more pronounced, and preclinical data have supported Phase I clinical trials (27). Another IDO1 inhibitor, LY3381916, demonstrated high selectivity and efficacy. LY3381916, either as monotherapy or in combination with PD-L1 inhibitors, significantly inhibited IDO1 activity in tumors and increased CD8⁺ T-cell infiltration in studies on treating advanced solid tumors. However, the clinical activity of combination therapy is limited, and significant hepatotoxicity has been observed in patients with TNBC, highlighting the importance of dose adjustment and optimization (124). NLG-919, in combination with indoximod and ICIs (such as inhibitors of the PD-1/PD-L1/PD-L2 pathway), has shown synergistic antitumor effects in multiple models. For example, in the B16F10 melanoma model, NLG-919, in combination with indoximod, ICIs, chemotherapy and hgp100 peptide vaccine therapy, significantly inhibited tumor growth, further clarifying the mechanistic basis of such combination strategies. Future studies of the synergistic effects of Trp metabolism and ICIs should focus on several aspects. It has been previously revealed that tumors induce an immunosuppressive microenvironment by upregulating IDO1 expression. Specifically, IDO1 promotes immune tolerance under inflammatory stimulation by depleting Trp and generating metabolites, leading to the loss of effector T-cell function and enhanced activity of Tregs, making it an important target for immunotherapy (28). For example, epacadostat, a novel IDO1 inhibitor, can significantly inhibit Trp catabolism and has multifaceted effects on the maturation of DCs, activation of tumor antigen-specific cytotoxic T lymphocytes, regulation of Tregs and function of peripheral blood mononuclear cells, thereby enhancing the efficacy of immunotherapy (37). Additionally, linifanib mesylate, which occupies the heme cofactor-binding site, prevents the activation of IDO1. *In vitro* studies have shown that it can inhibit Kyn production and restore T-cell proliferation, while significantly reducing Kyn levels in tumor xenograft models *in vivo*, with favorable PK and pharmacodynamic properties, providing a basis for clinical development (125). The synergistic effects of Trp metabolism and ICIs offer new insights into cancer immunotherapy. However, their efficacy is influenced by the differential expression of IDO1 and PD-L1. Future studies should focus on patient stratification by using these biomarkers. This combination therapy has great potential to overcome the limitations of monotherapy and provide more efficient antitumor strategies. Further research is expected to drive the development of novel combination therapies.

Interactions between Trp metabolism and the microbiome. Tight interactions exist between Trp metabolism and the

gut microbiome, which has garnered widespread attention recently because of its implications in disease pathogenesis and treatment. The gut microbiota metabolizes Trp through various pathways into indole and its derivatives, which exhibit significant biological functions in immune regulation, metabolic homeostasis and suppression of inflammation. For instance, it has been identified that moderate dietary supplementation with Trp can generate indole compounds via microbial metabolism, modulating immune responses and effectively treating various immune-related diseases (126). Additionally, indole and its derivatives have shown considerable potential in treating metabolic and hepato-intestinal diseases, with mechanisms possibly involving multi-target regulation (127,128). Microbial indole metabolism is considered a potential therapeutic strategy for CRC (129). Recently, the discovery of novel microbial strains associated with Trp metabolism has increased the depth of research in this area. For example, certain strains isolated from the gut generate bioactive metabolites by modulating the Trp metabolic pathway, thereby influencing disease onset and progression. A representative example is the gut bacterium *Clostridium sporogenes*, which captures energy via the Stickland reaction. Its metabolic product, indolepropionic acid, which is known for its antioxidant and anti-inflammatory properties, is considered a probiotic with therapeutic potential for the prevention and treatment of inflammatory bowel disease (130,131). Similarly, *Lactobacillus plantarum* DPUL-S164 (S164) and its Trp metabolite, indole-lactic acid, demonstrated significant repair effects in mouse models of intestinal barrier damage induced by antibiotic mixtures and dextran sulfate sodium (132,133). The development of next-generation probiotics offers new insights into Trp-metabolism-targeted therapies. For example, by comparing the microbiota composition of healthy and diseased individuals and designing recombinant microbes that overexpress target genes, it is possible to achieve the local delivery of metabolites and regulation of signaling pathways. However, this strategy faces challenges such as regulatory requirements, manufacturing difficulties, complexity of disease models, and diversity of individual gut microbiota, which can lead to variable therapeutic outcomes. Current research has primarily focused on short-term efficacy, whereas long-term safety and effectiveness require further validation. The interactions between Trp metabolism and the gut microbiome provide new directions for disease treatment. An in-depth exploration of their metabolic pathways and microbial regulatory mechanisms can promote the development of novel compounds and optimize therapeutic strategies. However, future studies should address the challenges posed by complex disease models and the need for personalized treatments to achieve broader clinical applications and enhanced therapeutic outcomes.

AhR antagonists targeting Trp metabolism. Trp metabolites are closely related to AhR, and the potential role of AhR antagonists in targeting Trp metabolism in cancer therapy warrants further investigation. The AhR is a ligand-activated transcription factor that plays a key role in maintaining important physiological functions in the body. It exhibits dual pro- and antitumorigenic activities during tumorigenesis, with its expression and activity varying depending on the tumor type

and individual differences among patients (134-136). It has been revealed that Trp metabolites such as Kyn and indole, generated by endogenous enzymes or microbial metabolism, can bind to and activate AhR, forming the Trp-AhR pathway, which is closely related to cancer progression (137). For example, in melanoma and glioma, the continuous transcriptional activation of AhR is driven by ligands produced by the TME and the tumor itself, promoting tumor growth and suppressing immune defense functions. Moreover, IL4I1, a metabolic pathway parallel to IDO1 and TDO, can generate AhR ligands, further demonstrating the difficulty of completely inhibiting AhR ligand production (138). Based on these mechanisms, the potential applications of AhR antagonists in cancer therapy have attracted widespread attention. Various AhR antagonists have shown significant antitumor potential. For example, CH223191 is a selective competitive AhR antagonist that lacks antagonistic activity against non-aromatic hydrocarbon ligands. Although related research is still mainly focused on the basic scientific field, preliminary therapeutic effects have been demonstrated in pancreatic cancer models (139,140). Additionally, StemRegenin-1, an exogenously applied AhR antagonist, reversed the drug resistance of MCF-7/ADR cells through the AhR/ABC transport and AhR/UGT pathways (141). Furthermore, the antagonistic properties of BAY 2416964 were confirmed using transactivation assays. It effectively and selectively inhibits AhR activation in human and mouse head, head and neck squamous cell carcinoma, NSCLC and CRC cells *in vitro*, while restoring immune cell function and enhancing antitumor responses. BAY 2416964 exhibited favorable drug tolerance and significant antitumor efficacy *in vivo* by inducing a pro-inflammatory TME (142). CB7993113 inhibited the invasive capacity of human BC cells under three-dimensional culture conditions and blocked tumor cell migration in two-dimensional culture without affecting cell viability or proliferation. Moreover, this compound effectively inhibits bone marrow ablation induced by 7,12-dimethylbenz[a]anthracene *in vivo*, further proving that its absorption and distribution can produce pharmacological effects (143). Current research has clarified the dual role of AhR in tumorigenesis; however, the development of AhR antagonists remains in its early stages, with numerous obstacles facing clinical translation, such as balancing the pro-inflammatory and anti-inflammatory effects of AhR and avoiding off-target effects. Research targeting Trp metabolism is at a critical stage of transitioning from basic science to clinical applications, and there is still a need to address core issues such as optimizing drug targeting and safety, dealing with tumor heterogeneity, and integrating multi-target combination therapy strategies.

5. Concluding remarks

Trp metabolites are potential biomarkers for clinical features, such as inflammation, mental state and cognitive function, which can guide clinical decision-making. These metabolites may facilitate the development of novel therapeutic strategies for treating various diseases. Rate-limiting enzymes, including IDO, TDO, KMO and TPH, are critical for Trp metabolism, and research on their inhibitors has progressed. Although IDO/TDO inhibitors have shown limited efficacy as monotherapies for cancer treatment, they can significantly enhance the efficacy

of conventional therapeutic agents when used in combination with traditional drugs. Moreover, KMO inhibitors can reduce the neurological damage caused by acute pancreatitis, and the combination of telotristat ethyl with somatostatin analogs has been approved by the FDA for the treatment of carcinoid-associated diarrhea. Thus, specific inhibitors targeting TPH1 or TPH2 may be safer and more effective. Direct supplementation with indoles and their derivatives is a promising therapeutic strategy. Dysregulation of Trp metabolism in cancer is closely associated with clinical features such as tumor stage, size and lymph node metastasis, and the levels of Trp metabolites can thus serve as predictive biomarkers. Therefore, targeting Trp metabolism has emerged as a promising therapeutic approach for cancer treatment. However, despite preclinical evidence demonstrating the anticancer effects of Trp metabolism inhibition, its translation into clinical success remains challenging, as exemplified by the failure of IDO1 inhibitors in clinical trials. Similarly, although niacin can significantly increase HDL-C levels and has various lipid-modulating effects, it has not shown the expected clinical benefits of reducing the risk of cardiovascular events (144). Future research should delve into the resistance mechanisms, utilize multi-omic approaches to identify new biomarkers and therapeutic targets, and design combination therapies to enhance therapeutic efficacy and minimize resistance. Continued research on Trp metabolism combined with advanced technologies and innovative strategies holds promise for advancing cancer treatments and patient outcomes.

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Authors' contributions

JiZ, XB and JD contributed to conception and manuscript writing. YC and XG contributed to the proofreading and bioanalysis. JuZ and JG contributed to acquisition of data. PW, SC and XZ contributed to table and figure production. JY, JJ and LG contributed to manuscript editing. All authors read and approved the final version of the manuscript. Data authentication is not applicable.

Ethics approval and consent to participate

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Competing interests

The authors declare that they have no competing interests.

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