Molecular Cancer

REVIEW

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Molecular mechanisms and therapeutic significance of Tryptophan Metabolism and signaling in cancer

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Abstract

Tryptophan (Trp) metabolism involves three primary pathways: the kynurenine (Kyn) pathway (KP), the 5-hydroxytryptamine (serotonin, 5-HT) pathway, and the indole pathway. Under normal physiological conditions, Trp metabolism plays crucial roles in regulating inflammation, immunity, and neuronal function. Key rate-limiting enzymes such as indoleamine-2,3-dioxygenase (IDO), Trp-2,3-dioxygenase (TDO), and kynurenine monooxygenase (KMO) drive these metabolic processes. Imbalances in Trp metabolism are linked to various cancers and often correlate with poor prognosis and adverse clinical characteristics. Dysregulated Trp metabolism fosters tumor growth and immune evasion primarily by creating an immunosuppressive tumor microenvironment (TME). Activation of the KP results in the production of immunosuppressive metabolites like Kyn, which modulate immune responses and promote oncogenesis mainly through interaction with the aryl hydrocarbon receptor (AHR). Targeting Trp metabolism therapeutically has shown significant potential, especially with the development of small-molecule inhibitors for IDO1, TDO, and other key enzymes. These inhibitors disrupt the immunosuppressive signals within the TME, potentially restoring effective anti-tumor immune responses. Recently, IDO1 inhibitors have been tested in clinical trials, showing the potential to enhance the effects of existing cancer therapies. However, mixed results in later-stage trials underscore the need for a deeper understanding of Trp metabolism and its complex role in cancer. Recent advancements have also explored combining Trp metabolism inhibitors with other treatments, such as immune checkpoint inhibitors, chemotherapy, and radiotherapy, to enhance therapeutic efficacy and overcome resistance mechanisms. This review summarizes the current understanding of Trp metabolism and signaling in cancer, detailing the oncogenic mechanisms and clinical significance of dysregulated Trp metabolism. Additionally, it provides insights into the challenges in developing Trp-targeted therapies and future research directions aimed at optimizing these therapeutic strategies and improving patient outcomes.

Keywords Tryptophan metabolism, Expression changes, Clinical characteristics, Cancer, Targeted therapies

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Introduction

Trp, an essential amino acid not synthesized by the human body, must be obtained through diet [1–5]. It is a fundamental component of protein synthesis and a precursor for many crucial biomolecules, influencing various metabolic pathways [6–10]. Although a small fraction of free Trp contributes to protein synthesis and the production of neurotransmitters like serotonin and neuromodulators such as tryptamine, over 95% is utilized in the kynurenine (Kyn) pathway (KP) of Trp degradation. This pathway generates several metabolites with distinct biological activities in immune responses and neurotransmission [11–14].

Trp and its metabolites are crucial in various physiological processes, including biomass production, cellular energy, and cell growth [15–18]. They play a significant role in coordinating organismal responses to environmental changes, acting as key elements in both metabolic and signaling pathways [19–21]. The primary metabolic pathways for Trp include the synthesis of serotonin and the KP. Serotonin significantly influences the central nervous system and plays a critical role in regulating intestinal motility, emesis, vasoconstriction, platelet aggregation, and wound healing [22–26]. It also serves as a precursor to melatonin, which regulates sleep and circadian rhythms in diurnal animals. The KP produces a series of bioactive metabolites such as picolinic acid, quinolinic acid (QA), kynurenic acid (KynA), cinnabarinic acid (CA), xanthurenic acid (XA), and Kyn. These metabolites regulate the immune system by modulating the infiltration and activity of immune cells in the TME [27–29]. Another significant product of this pathway is nicotinamide adenine dinucleotide (NAD+), vital for cellular homeostasis [30–32]. Furthermore, Trp metabolites influence the gut microbiota's composition and functionality, affecting the gut microbiome balance and the gut-brain axis, which can alter the immune response and inflammation levels within the gastrointestinal tract [33–37].

Trp enzymes and metabolites are widely distributed across various cells and tissues, with their expression finely regulated [38–40]. Disruptions in Trp and its metabolites' levels have been linked to several diseasea, especially cancer [41–45]. Research indicates that key enzymes such as IDO1 and TDO2 are upregulated in various cancer types, including brain, digestive system, breast, and lung cancers [46–49]. This upregulation enhances Trp catabolism in tumors, creating immunosuppression, impairing multiple barriers, and promoting tumor growth and metastasis [41, 50–53]. Consequently, IDO1 has become a focal point for cancer therapy, with inhibitors currently being tested in various clinical trials to restore immune surveillance and enhance the efficacy of treatments like chemotherapy and immunotherapy [35, 52, 54–56]. However, results from later-stage trials have been mixed, highlighting the complexity of targeting metabolic pathways within the TME.

This review offers a comprehensive overview of the main metabolic pathways, abnormal expression features, and primary roles of Trp metabolism and signaling in cancer. Emphasis is placed on the molecular mechanisms by which dysregulated Trp metabolism and signaling contribute to oncogenesis across various tumor types. Furthermore, the latest advancements in anticancer therapies targeting Trp metabolism and signaling are discussed, alongside the current challenges and future prospects of these therapeutic strategies. This review highlights the critical importance of Trp metabolism and signaling in cancer biology and therapy, emphasizing its potential as a significant area for ongoing research and clinical development.

Physiological Properties of Trp and Its Metabolites

Trp: Dietary Sources, Absorption, and Degradation

Trp, an essential amino acid, is vital for human health due to its complex metabolic pathways and physiological effects. As humans cannot synthesize Trp, it must be obtained from dietary sources such as turkey, chicken, eggs, cheese, fish, and plant-based proteins like pumpkin seeds, soy products, and tofu [1, 57–59]. These sources provide the necessary intake to maintain adequate Trp levels essential for various biological functions [60–62]. Upon ingestion, Trp is absorbed in the intestines and transported through the blood to various tissues [63–66]. Key transporters, such as solute carrier family 1 member 5 (SLC1A5) and solute carrier family 7 member 5 (SLC7A5), facilitate the cellular uptake of Trp and its distribution to organs including the brain, heart, and muscles, where it undergoes further metabolism [67–70]. Beyond its role in protein synthesis, Trp is a precursor to several bioactive compounds [71–73]. Trp metabolism is orchestrated through three principal pathways, facilitated by distinct enzymatic reactions within barrier organs such as the intestines, lungs, and skin, largely influenced by resident microbiota [74–77]. The gut microbiota, which outnumbers human cells significantly, profoundly influences Trp metabolism [78–81]. The interaction between dietary Trp intake, bacterial utilization, and local turnover in the gastrointestinal tract has crucial implications for maintaining physiological balance and influencing disease states [82–84]. Recent evidence highlights the critical role of gut microbiota-mediated Trp metabolism in modulating immune responses and contributing to the pathogenesis of gastrointestinal cancers. Certain gut-resident microbes can metabolize Trp into bioactive compounds, such as

indole and its derivatives, including indole-3-propionic acid (IPA), indole-3-aldehyde (IAld), indole-3-carboxaldehyde (ICAld), and indole-3-acetaldehyde (IAAld) [43, 85–87]. These metabolites serve as key signaling molecules that interact with the aryl hydrocarbon receptor (AHR), which regulates genes crucial for maintaining intestinal barrier integrity, modulating immune cell differentiation, and promoting anti-inflammatory responses [88–91]. Notably, the gut-cancer axis has gained considerable interest, as dysbiosis-an imbalance in gut microbiota composition-has been linked to the progression of gastrointestinal cancers [92–94]. Gut microbes capable of converting Trp into indole derivatives may influence tumor growth by modulating local immune environments and epithelial cell proliferation. For example, IPA has demonstrated anti-inflammatory, antioxidant, and immunoregulatory properties, potentially reducing the risk of carcinogenesis [95, 96]. Conversely, the accumulation of certain metabolites, such as Kyn, through the KP, can promote immune escape mechanisms and tumor progression by activating immunosuppressive pathways such as AHR-mediated $CD8^+$ T-cell exhaustion [97, 98]. Besides gut microbes, Trp metabolism is also intricately affected by several factors, including genetic alterations, diet, stress, exercise, and aging, which further modulate enzymatic activity and determine the dominance of specific metabolic pathways [99–103].

The three primary metabolic pathways for Trp involve its conversion into serotonin, Kyn, and indole-3-pyruvate (I3P) and its derivatives (Fig. 1). Approximately 1% of dietary Trp is converted into serotonin, a crucial neurotransmitter [6, 104, 105]. The conversion process begins with Trp hydroxylase (TPH) converting Trp to 5-hydroxytryptophan (5-HTP), which is then decarboxylated by aromatic amino acid decarboxylase (AADC) to produce serotonin [106–109]. Serotonin is subsequently metabolized into several compounds, including 5-hydroxyindoleacetic acid (5-HIAA) by monoamine oxidase (MAO), N-acetylserotonin (NAS) by arylalkylamine N-acetyltransferase (AANAT), and ultimately melatonin by N-acetylserotonin O-methyltransferase (ASMT). The KP is the primary catabolic route for Trp, initiated by either IDO or TDO, which are pivotal in neuroprotection, neurotoxicity, immune modulation, and homeostatic balance within different cellular environments [110–114]. These heme-containing enzymes convert Trp to N-formylkynurenine (NFK). NFK is then metabolized to Kyn by arylformamidase (AFMID), which serves as a precursor for several bioactive metabolites. KMO and kynureninase (KYNU) further process Kyn into 3-hydroxykynurenine (3-HK) and anthranilic acid (AA), respectively. Kynurenine aminotransferase (KAT) also transforms Kyn into KynA and 3-HK into XA. Subsequently, 3-hydroxyanthranilic acid (3-HAA), derived from 3-HK by KYNU, is converted into QA and ultimately contributes to the synthesis of nicotinamide and NAD + by quinolinate phosphoribosyl transferase (QPRT) [115, 116]. Notably, Kyn serves as an endogenous ligand for the AHR, part of a cytoplasmic complex that dissociates upon ligand binding [14, 80, 117]. This dissociation allows AHR to bind with the aryl hydrocarbon receptor nuclear translocator (ARNT) and activate genes crucial for cytoprotection, including those encoding cytochrome P450 enzymes such as CYP1A1 and CYP1B1 [84, 85, 118, 119]. Metabolites like KynA are known for their neuroprotective properties, whereas others like 3-HK, 3-HAA, and QA have neurotoxic effects [120–123]. As the end product of the KP, NAD + is a crucial cofactor in cellular reactions vital for energy metabolism, influencing pathways like glycolysis, β-oxidation, and oxidative phosphorylation [118, 124–127].

Quantification Techniques of Trp Metabolism

Quantifying Trp and its metabolites in biological fluids such as plasma, urine, tissue samples, and cerebrospinal fluid is essential for identifying potential biomarkers for various diseases [128–132]. Trp's natural fluorescence facilitates the development of fluorometric detection methods [133–136]. Conventional techniques like liquid chromatography and gas chromatography, paired with UV detection, fluorescence, or mass spectrometry (MS), enhance the sensitivity and specificity of Trp metabolite detection [137–141]. These methods are foundational for assessing Trp metabolic profiles, providing insights into their roles in both physiological and pathological states. Additionally, refined Enzyme-Linked Immunosorbent Assay (ELISA) techniques quantify specific Trp metabolites within predefined detection limits, making them particularly useful for focused studies on individual metabolites, such as Kyn [142–145]. Immunohistochemistry, utilizing antibodies specifically targeting Trp metabolites, enables visualization and quantification within tissue samples, linking metabolic alterations to pathological states (Fig. 2) [146–148].

An advanced detection method, liquid chromatography-mass spectrometry (LC-MS), particularly ultra-high-performance LC-electrospray ionization-tandem MS (UHPLC-ESI-MS/MS), is robust for quantifying Trp and its metabolites, including Kyn [149, 150]. This approach offers comprehensive coverage of the Trp metabolic pathway, mapping intricate relationships between Trp and its derivatives. It is highly sensitive and specific, ideal for analyzing complex biological samples like blood and peritoneal fluid. Moreover, capillary electrochromatography-mass spectrometry (CEC-MS), using novel stationary phases like 4-vinylphenylboronic acid (4-VPBA)

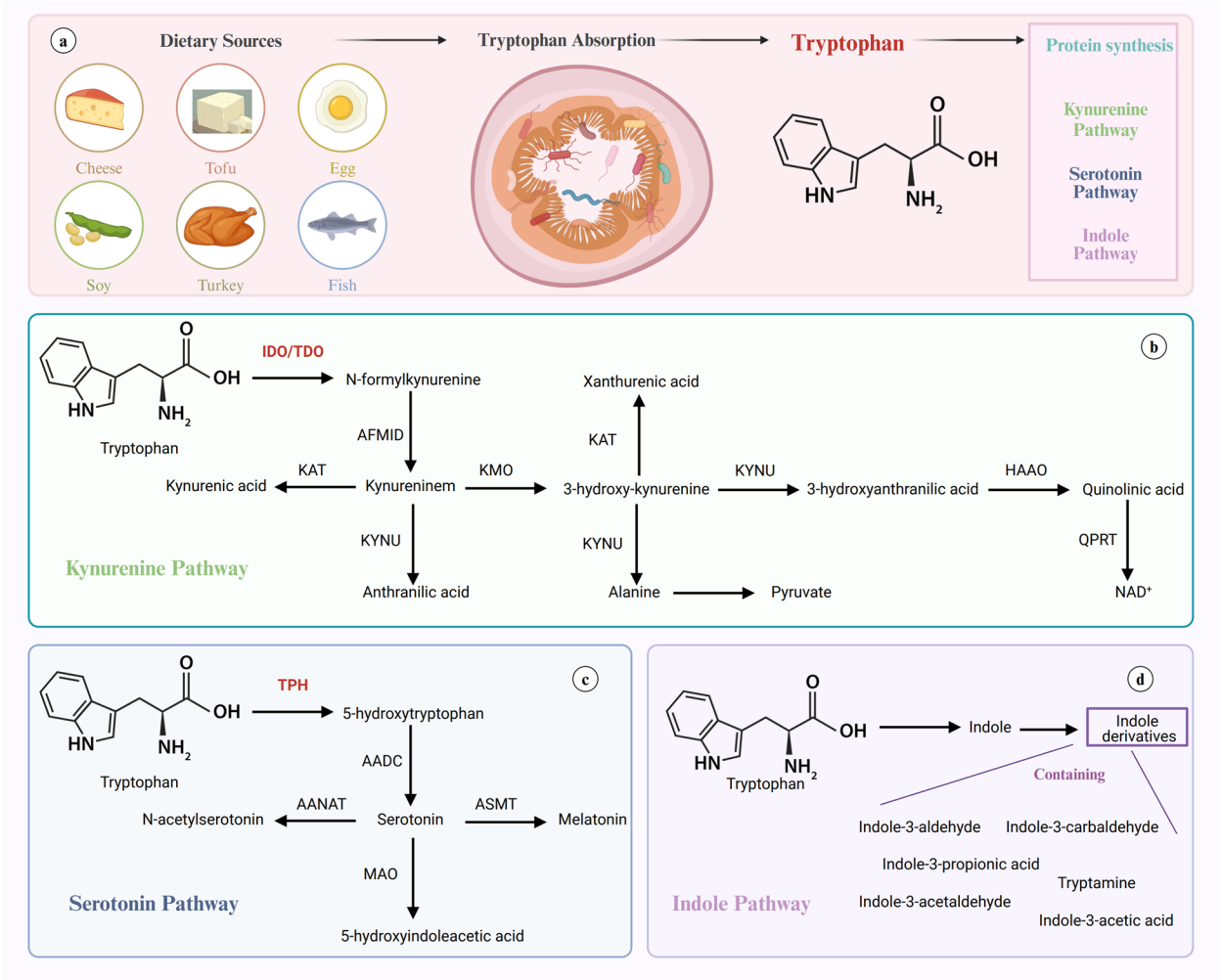

Fig. 1 Dietary Sources of Tryptophan and Main Pathways of Tryptophan Degradation (**a**) Tryptophan, an essential amino acid, is commonly acquired from dietary sources such as turkey, eggs, cheese, tofu, seeds, and fish. After ingestion, tryptophan is absorbed in the gut and enters the bloodstream for use in various metabolic processes. Besides protein synthesis, tryptophan undergoes three main catabolic pathways: the serotonin pathway, the kynurenine pathway, and the indole pathway. **b** In the kynurenine pathway, tryptophan is first converted into N-formyl-L-kynurenine by the enzymes indoleamine 2,3-dioxygenase (IDO) or tryptophan 2,3-dioxygenase (TDO), which is then broken down into several metabolites, including kynurenine, leading to the production of nicotinamide adenine dinucleotide (NAD+). **c** In the serotonin pathway, tryptophan is converted into serotonin via the enzyme tryptophan hydroxylase (TPH), followed by conversion to 5-hydroxytryptophan (5-HTP) and then to serotonin. Serotonin can further be converted into melatonin. **d** In the indole pathway, intestinal microbiota metabolizes tryptophan into various indole derivatives such as indole-3-acetic acid (IAA), indole-3-propionic acid (IPA), and indole-3-aldehyde (IAld)

columns, enables Trp and Kyn quantification in plasma [151, 152]. This method combines the high-resolution capabilities of capillary electrophoresis with the sensitivity of MS, offering a simple, fast, and repeatable approach for Trp metabolite analysis.

Advancements in high-technology methods have significantly improved the accuracy and efficiency of analyzing Trp and its metabolites, providing vital insights into the biological and pathological effects of Trp metabolism and supporting the development of therapeutic strategies targeting Trp metabolism in diseases [153–157].

Expression Changes of Trp Metabolism in Cancer

Increased Trp uptake and upregulation of Trp-metabolizing enzymes in various tumor types correlate with poor disease prognosis (Table 1) [158–162]. Among these enzymes, abnormal IDO1 levels are common in diverse cancers and are studied as a factor to enhance sensitivity to cancer therapy [51, 163, 164]. Conversely, TDO expression in cancers is less characterized due to the lack of validated bioassay systems for detecting TDO and identifying TDO-expressing cells [165, 166]. Recent advancements in TDO-specific monoclonal antibodies

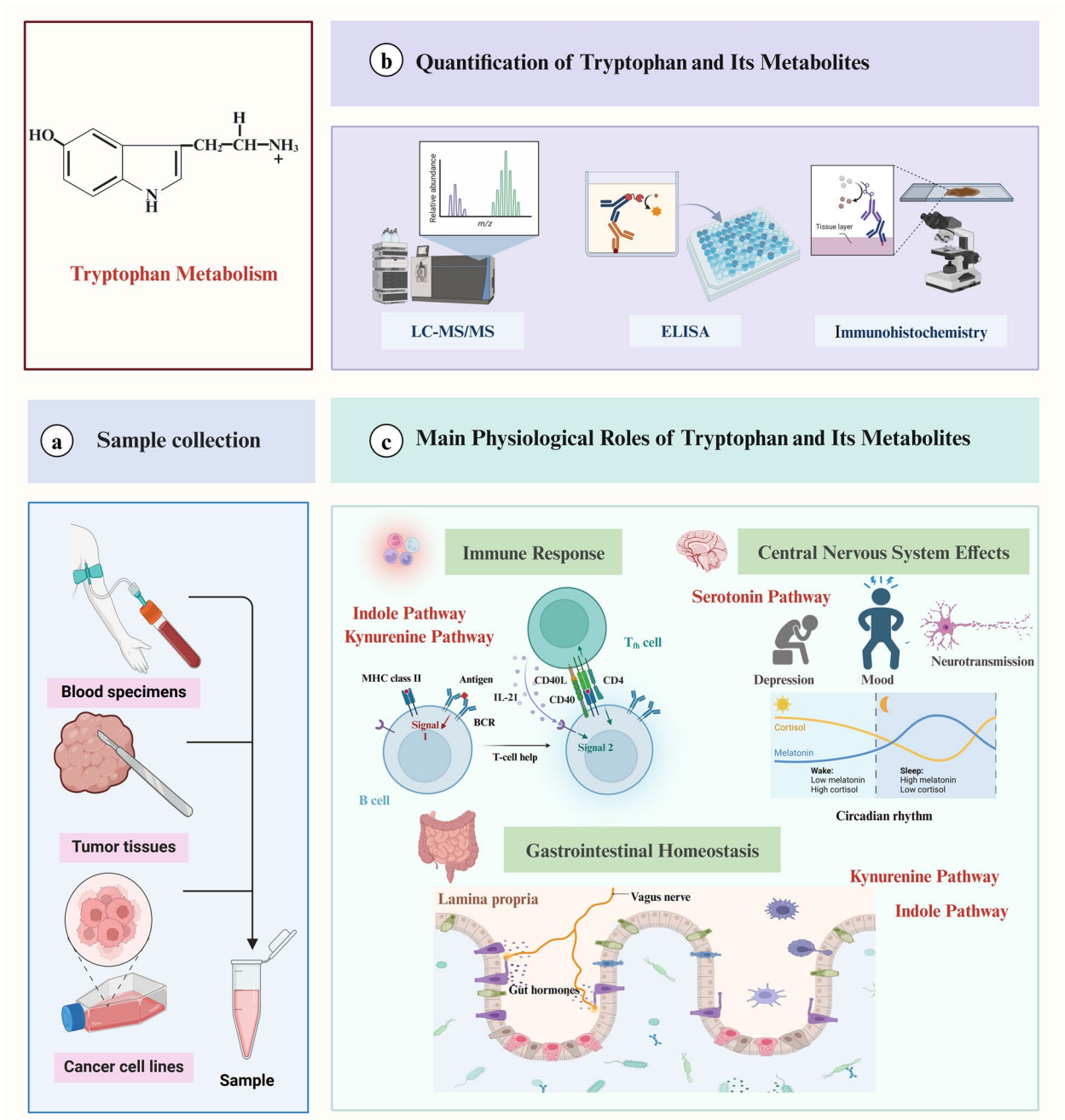

Fig. 2 Tryptophan Sample Collection, Detection Methods, and Biological Functions Samples for tryptophan detection are typically obtained from blood specimens, cancer tissues, and cancer cell lines. Detection methods for tryptophan and its metabolites include enzyme-linked immunosorbent assay (ELISA), liquid chromatography-tandem mass spectrometry (LC-MS/MS), and immunohistochemistry. Tryptophan plays crucial roles in various physiological processes. In the immune system, metabolites from the kynurenine pathway, such as kynurenine (Kyn), modulate immune responses by regulating immune cell development, activation, and infiltration, thereby contributing to immune suppression and tumor immune evasion. Additionally, indole derivatives significantly also impact the immune modulation and immune homeostasis, particularly through the activation of Aryl Hydrocarbon Receptor (AHR). In the central nervous system, it serves as a precursor for serotonin, which influences mood, depression, and circadian rhythms, while its derivative, melatonin, regulates sleep-wake cycles. In the gastrointestinal tract, tryptophan is metabolized by the gut microbiota into indole derivatives that help maintain gut health and microbial balance, promoting intestinal barrier integrity and mucosal immunity. Moreover, the kynurenine pathway also significantly impacts the gastrointestinal system, particularly in maintaining immune homeostasis, regulating inflammation, and shaping the gut microenvironment

Table 1 Expression changes and molecular mechanisms of tryptophan metabolism and signaling in cancers

Cancer type	Molecule in Tryptophan Metabolism	Expression changes	Downstream targets	Mechanisms	Functions	Cell lines	Year	Ref.
Glioma	IDO	Increased	CFH and FHL-1	IDO/CFH and FHL-1	Induce immunosuppression	human U87 cells and mouse GBM cells	2021	[167]
Glioma	IDO	Increased	GITR	IDO/GITR	Recruit Tregs to induce immunosuppression	GL261 cells	2012	[168]
Glioma	IDO	Increased	/	/	Inhibit T cell population and induce immunosuppression	Murine glioma GL261 cells and human glioma U87 cells	2016	[169]
Glioma	IDO	Increased	Trp	IFN-γ/IDO/Trp	Induce inactivation of the T cells and immune resistance	LN229, U251, T98G, and U87 cells	2009	[170]
Glioma	IDO	Increased	/	/	/	/	2018	[171]
Glioma	IDO	Increased	Kyn	IFN-γ/IDO/Kyn/AHR	Increase MDSC and Treg populations	GL261, and GSC-005 cells	2022	[172]
Glioma	IDO	Increased	/	IFN-γ/IDO	Induce immunosuppression	GL261 cells	2015	[173]
Glioma	IDO	Increased	/	/	Induce immunosuppression	/	2024	[174]
Glioma	IDO	Increased	/	/	/	/	2013	[175]
Glioma	IDO1 and TDO	Increased	Kyn	IDO1/TDO/Kyn/AHR/AQP4	Promote cell migration and invasion	U87MG, U251, A172, and GL261 cells	2020	[176]
Glioma	TDO	Increased	/	FKBP52/TDO	Suppress T-cell immunity	U87MG and LN-18 cells	2015	[177]
Glioma	TDO	Increased	/	OCT4 and SOX2/TDO	Inhibit the function and infiltration of $CD8^+$ T cells and expand immune-suppressive M2 macrophages and $Foxp3^+$ Tregs	GBM neurosphere lines (GBM1A and GBM1B), GL261 cells	2021	[178]
Glioma	TDO2	Increased	/	/	/	/	2015	[179]
Glioma	TDO2	Increased	Kyn	TDO2/Kyn/AHR	Promote cell viability	neuroblastoma cell lines (SK-N-AS, CHP-212, SK-N-BE (2), LA-N-5, NB-69, and SK-N-SH)	2024	[180]
CRC	SERT	Increased	mTORC1	SERT/mTORC1	Promote cancer growth	SW480 and HCT116 cells	2021	[45]
CRC	IDO	Increased	/	/	Induce immune inhibition	CRC CT26 cells	2022	[181]
CRC	IDO	Increased	/	/	/	/	2022	[182]
CRC	IDO1	Increased	CDC20	IDO1/Kyn/CDC20	Promote cell proliferation	HCT116 and HT29 cells	2018	[183]
CRC	SLC7A5, SLC1A5, and AFMID	Increased	Kyn	MYC/SLC7A5, SLC1A5, and AFMID/Kyn/AHR	Promote cell growth	DLD1, HT29, HCT116, HCT15, RKO, LoVo cells	2019	[184]

Table 1 (continued)

Cancer type	Molecule in Tryptophan Metabolism	Expression changes	Downstream targets	Mechanisms	Functions	Cell lines	Year	Ref.
PC	IDO1	Increased	nucleotide synthesis	IFNγ/JAK-STAT/IDO1/serine and purine nucleotide biosynthesis	Contribute one-carbon units to serine and purine nucleotide biosynthesis and support cancer cell proliferation	Human PC cell lines (BxPC-3, CFPAC-1, HPAF-II, Panc 10.05, AsPC-1, SW 1990, and SW 1990), and mouse PC cell lines (ImPSC and KPC)	2021	[185]
PC	3-IAA	Decreased	ROS	MPO/3-IAA/ROS/autophagy	Increase ROS accumulation and reduce autophagic activity and cancer cell proliferation	KPC cells	2023	[186]
PC	IDO1	Increased	/	/	Increase cellular proliferation and macropinocytic ability, decrease immunogenicity, lower IDO-1 activity, and accelerate distant metastasis	KPIC cells	2023	[187]
PC	IDO1 and TDO/	Increased	Kyn	IDO1 and TDO/Kyn/AHR/Cyp1a1	Promote migration and invasion	KPIC, PANC1, and Pan02 cells	2021	[188]
HCC	TDO	Increased	Kyn	TDO/Kyn/AHR	Inhibit $CD4^+$ and $CD8^+$ T cell proliferation	HepG2 cells	2021	[189]
HCC	TDO2	Increased	Kyn	TDO2/Kyn/AhR/IL-6/STAT3/NF-kB signals	Strengthen cell proliferation and cancer growth	SMC-7721 and HepG2 cells	2021	[190]
HCC	KMO	Decreased	3-HAA	KMO/3-HAA/	Induce cell apoptosis, inhibit cancer growth, and prolong survival		2022	[191]
HCC	IAA, ICAld, and IPA	Decreased	SREBP2	Gut Flora Disequilibrium/IAA, ICAld, and IPA/AhR/SREBP2	Prevent liver cancer initiation	Hep1-6 cells	2022	[115]
GC	IDO	Increased	/	/	/	/	2019	[192]
GC	IDO	Increased	/	/	/	/	2016	[193]
GC	Kyn	Increased	NK cells	IDO/Kyn/NK cells	Promote ferroptosis and NK cell loss	NK-92 cells, GC SGC-7901, and MGC-803 cells	2023	[194]
Melanoma	TPH1/2, IDO1, TDO2, and LAT1	Increased	/	/	Lead to defects in T cell effector function	SK-MEL-2 and MeWo cells	2023	[195]
Melanoma	AHR	Increased	/	IDO/TDO/Kyn/AHR	Induce immunosuppression	melanoma B16F10 cells	2020	[196]
Melanoma	IDO1	Increased	/	/	/	/	2019	[197]
Melanoma	TDO	Increased	CSC markers	dexamethasone/TDO/CSC markers	Promote melanospheres and stemness	SK-Mel-28 and A375 cells	2022	[198]

Table 1 (continued)

Cancer type	Molecule in Tryptophan Metabolism	Expression changes	Downstream targets	Mechanisms	Functions	Cell lines	Year	Ref.
BC	IL4I1, IDO1, KMO, and KYNU	Increased	/	/	Promote macrophage M1 polarization	M1 macrophages	2023	[199]
BC and Melanoma	IAN	Increased	/	Carbidopa/IAN	Promote cell proliferation	BC MCF-7 and melanoma A375 cells	2019	[200]
BC and Lymphoma	IDO	Increased	/	macrophages/FcγR signaling/AIM2/PD-L1 and IDO	Induce immunosuppression	BC HER2 + SKBR3 and BT-474 cells, and CD20 + Raji lymphoma cells	2018	[201]
BC, Melanoma, and CRC	Kyn	Increased	/	/	Inhibit the cancer infiltration and proliferation of polyfunctional $CD8^+$ cells	mouse B16-F10 melanoma (CRL-6475), 4T1 metastatic BC (CRL-2539) and CT26 CRC (CRL-2638) cell lines	2018	[202]
BC	IDO	Increased	/	/	/	/	2018	[203]
BC	IDO1	Increased	caspase-8 and caspase-9 pathways/MDR1, MRP 1/2, and BCRP	Thiosemicarbazide derivatives 1–3/IDO 1 and topoisomerase IIα/ Caspase-8 and Caspase-9 pathways/MDR1, MRP 1/2, and BCRP	Inhibit apoptosis and cell cycle arrest	MCF-7 and MDA-MB-231	2023	[204]
BC	IDO1 and TDO2	Increased	/	PDPN + CAFs/IDO1 and TDO2/NK cells	Suppress ADCC of NK cells and induce cell resistance to trastuzumab	Human trastuzumab-resistant HER2 + breast cancer cell JIMT-1, and CAFs	2023	[205]
BC	KMO	Increased	β-catenin	KMO /β-catenin/pluripotent genes	Increase cell growth, colony, mammosphere formation, migration, invasion, and stemness	MDA-MB-231 and MDA-MB-468	2020	[206]
OC	IDO1, IDO2, TDO2 and IL4I1	Increased	/	/	/	/	2023	[207]
LC	IDO1, IDO2, and TDO	Increased	Kyn	IDO1, IDO2, and TDO/Kyn	Inhibit the accumulation and infiltration of T cells	LC Lewis cells	2019	[208]
LC	IDO	Increased	Kyn	/	/	/	2018	[209]
LC	TDO	Increased	Kyn	TDO/Kyn/AHR/AKT/ERK	Promote cell proliferation, cancer growth, and development of EGFR TKI resistance	Human LC cells A549, and murine LC cells Lewis	2022	[210]
HCC, Glioma, PC and CRC	TDO	Increased	Kyn	TDO/Kyn	Induce immunosuppression	CRC MC38 and CT26, glioblastoma A172 cells	2020	[163]

have shown prevalent TDO expression in many human cancers, including hepatocarcinoma (HCC), glioblastomas, and kidney cancer. This understanding underscores the significance of Trp metabolism in cancer and highlights the potential of changes in Trp metabolism expression for prognosis prediction (Fig. 3). This section discusses the abnormal expression of Trp, key metabolic enzymes, and their products in various tumors, along with their potential clinical implications and prognostic value.

In glioma, analysis of TCGA data reveals that both IDO and complement factor H (CFH) mRNA levels increase with tumor grade, peaking in glioblastoma (GBM). IDO and CFH exhibit coordinated upregulation, with elevated CFH expression being inversely correlated with patient survival across all tumor grades [167]. Additionally, TCGA data highlights increased TPH-1 expression, which is associated with sustained glioma progression and poor overall survival [168]. Analysis of 343 glioma patients from the REpository of Molecular BRAin Neoplasia DaTa (REMBRANDT) confirms that upregulated IDO expression predicts significantly worse patient prognosis [169]. Immunohistochemical staining of 75 surgical specimens shows that stronger IDO expression is more prevalent in high-grade and secondary gliomas than in low-grade gliomas. Kaplan-Meier survival analysis demonstrated that patients with highly malignant gliomas and high IDO expression have worse prognoses compared to those with low IDO expression [170]. Furthermore, a positive correlation exists between IDO1 and TDO expression and glioma pathological grades. Both IDO1 and TDO expression are positively associated with overall survival (OS), and their co-expression represents independent prognostic values for OS of glioma patients [171]. AMT-PET, based on increased uptake of α-[11 C]-methyl-L-Trp (AMT) in glioma, shows high accuracy in distinguishing grade I from grade II/III gliomas. Additionally, TDO2 shows the highest immunostaining scores, particularly in grade I gliomas, followed by IDO2 and IDO1 [172]. Data from the Therapeutically Applicable Research to Generate Effective Treatments (TARGET) database (phs000467), involving 249 pediatric patients, indicates that high expression of Trp transporters SLC1A5 and SLC7A5 predicts worse prognosis for neuroblastoma patients (Fig. 4) [173].

In colorectal cancer (CRC), several studies have demonstrated elevated levels of Trp transporters SLC7A5 and SLC1A5, along with Kyn, AHR, and key KP enzymes (TDO2, IDO1, and AFMID) [174–176]. In patients with locally advanced rectal cancer (LARC) receiving preoperative chemoradiotherapy (CRT), IDO expression has been identified as a significant prognostic marker. Patients with IDO-positive tumors exhibit a markedly poorer 5-year OS compared to those with IDO-negative tumors, and multivariate analysis identifies IDO expression as an independent prognostic indicator, highlighting its potential as a marker for individualizing treatment strategies in LARC [177]. In pancreatic cancer (PC), prevalent expression of IDO1 and TDO is negatively correlated with patient OS and relapse-free survival (RFS) [178, 179]. IDO1 expression is upregulated during tumor formation in immunocompetent settings, especially in the presence of IFN-γ or through JAK/STAT signaling [178]. TCGA data confirms a negative correlation between high IDO1 expression and patient survival in PC [178]. The co-expression of IDO1 and TDO, rather than individual expression, offers independent prognostic value for PC [179]. Interestingly, IDO1 expression increases in cells within PC ducts but decreases in PC cells, contributing to epithelial-mesenchymal transition (EMT) [180]. Additionally, an increase in microbiota-derived 3-IAA is observed in the serum of both patients and mice with PC who are susceptible to chemotherapy, correlating with improved progression-free survival (PFS) and OS in the PC Hamburg cohort [181]. In HCC, advanced-stage cancer tissues exhibit enhanced TDO2 expression, which is correlated with poor prognosis, as validated by the TCGA database [182]. However, both KMO and its substrate 3-HAA are reduced in HCC cells and clinical HCC tissues, and patients with high KMO expression show longer disease-free survival (DFS) [183]. Dysbiosis of the gut flora in HCC reduces the levels of AhR ligands derived from Trp metabolism, such as 3-IAA, ICAld, and IPA [115]. In gastric cancer (GC), SGC-7901 cells exhibit significantly higher levels of Kyn compared to GES-1 and MGC-803 cells [184]. IDO is a powerful prognostic biomarker for GC following gastrectomy and is closely associated with the immunosuppressive GC TME [185–187]. Immunohistochemical staining analysis of 99 GC cancer tissues from patients who received radical resection reveals that larger tumors, advanced T stages, and poorer prognosis are more positively associated with IDO expression. Additionally, IDO-positive patients possess higher levels of $Foxp3^+$ Treg cells but lower levels of $CD4/CD8^+$ T cells in the TME [185]. Another involving 357 GC patients shows that high intratumoral IDO expression is associated with poor OS, deeper tumor invasion, and increased lymph node metastasis [186].

Melanoma exhibits dysregulation in Trp metabolism, characterized by high intratumoral expression of TPH1/2, IDO1, TDO2, and the transporter SLC7A5. Notably, higher SLC7A5 expression in melanoma cells is associated with worse OS, and baseline Trp levels strongly predict clinical benefits from the PD1 inhibitor pembrolizumab [188]. The LCCC1531 trial in

melanoma demonstrated that high Trp PET imaging correlates with shorter clinical benefits from pembrolizumab in PD1 inhibitor-naïve stage IIIB-IV melanoma patients. Additionally, the theragnostic value of baseline Trp metabolism effectively prolongs PFS, as shown by optimal cut-point post-hoc analysis [188]. In breast cancer (BC), analysis of single-cell transcriptome data indicates that elevated levels of Trp metabolic enzymes, such as IDO1, KMO, and KYNU, in macrophages are linked with a positive response to immunotherapy, suggesting that Trp metabolism could be a predictive marker for BC treatment [189]. Furthermore, the evaluation of 4 TMAs, containing 242 invasive primary BC and 39 metastatic BC cases, showed that IDO expression is prevalent in high-grade, triple-negative BC. Notably, 70% of PD-L1-positive BC cases also express IDO, contributing to poor outcomes with anti-PD-L1 treatment despite strong PD-L1 expression [190]. There is also a notable increase in indole-3-acetonitrile (IAN) levels over time in BC MCF-7 cells and melanoma A375 cells exposed to carbidopa, a DOPA decarboxylase inhibitor used in Parkinson's disease (PD) treatment [191]. Moreover, the investigation based on 86 clinical canine mammary tumor (CMT) cases indicates the ability of KMO for discriminating malignant from benign CMTs and the strong correlation of KOM expression with overall survival rates in patients with malignant CMTs [192]. In ovarian cancer (OC), IDO1, IDO2, TDO2, and IL4I1 exhibit high positive expression rates in cancer specimens, with IDO1-positive patients being more resistant to platinum-based chemotherapy. Increased IDO1 expression is also associated with advanced cancer stages and lymph node metastasis. In contrast, TDO2 expression negatively correlates with the presence of bilateral tumors and endometriosis, while negative IL4I1 expression is commonly observed in cases of cancer rupture [193]. Finally, radiotherapy (RT) in lung cancer (LC) patients impacts systemic IDO-mediated anticancer immune activity, evidenced by changes in serum levels of IDO-mediated Kyn production and the Kyn(K) ratios before, during, and after RT. The Kratio decreases during RT but returns to baseline levels post-RT. Notably, these changes in IDO-associated molecules correlate with clinical outcomes in RT-treated LC patients. Greater Kyn levels post-RT significantly indicate worse OS and PFS [194]. Additionally, an enriched distribution of cancer-associated fibroblasts (CAFs) with activated TDO and elevated secretion of Kyn is observed in epidermal growth factor receptor tyrosine kinase inhibitors (EGFR TKIs) resistant cancer tissues from LC patients [195].

Molecular Mechanisms of Tryptophan and Its Metabolites in Cancer

Involvement of KP in Carcinogenesis

Involvement of KP in Glioma

In glioma, cancer-derived IDO expression recruits immunosuppressive regulatory T cells (Tregs) and increases their glucocorticoid-induced TNFR-related protein (GITR) expression while decreasing $CD8^+$ T cell frequency. This immune imbalance triggers immunosuppression and tumor growth, relying on coordinated actions of $CD4^+$ and $CD8^+$ T cells [169]. Additionally, IFN-γ robustly induces IDO expression, leading to increased Trp consumption and Kyn accumulation, creating a local immunosuppressive environment that inactivates T cells and promotes glioma cell proliferation [196]. As an oncolytic adenovirus, Delta-24-RGD, engineered to selectively replicate in and destroy cancer cells, shows promising anti-glioma effects by enhancing the anticancer immune response [197–199]. Delta-24-RGD downregulates IDO expression in glioma cells and Foxp3 levels in Tregs, decreasing tumor-infiltrating $CD4^+$ $Foxp3^+$ Tregs and increasing IFN-γ-producing $CD8^+$ T cells, significantly improving the TME and systemic tumor-antigen-specific T cell therapy in GBM [200]. Additionally, tumor-propagating stem-like cells in glioblastoma (GSCs) contribute to the immunosuppressive TME, driven by reprogramming transcription factors OCT4 and SOX2. Co-expression of OCT4 and SOX2 in GSCs upregulates multiple immunosuppressive checkpoints, including TDO, and immunosuppressive cytokines and chemokines, inhibiting $CD8^+$ T cell function and infiltration while promoting the expansion of immunosuppressive M2 macrophages and $Foxp3^+$ Tregs [201]. Furthermore, recent findings indicate nonenzymic IDO in GBM U87 cells increases CFH and FHL-1 expression, independent of Trp metabolism, further enhancing immune suppression by raising intratumoral Tregs and myeloid-derived suppressor cells [202]. Recent studies have also shown that the IDO1/TDO/Kyn/AHR/AQP4 signaling pathway is central to glioma progression, particularly in cell motility. IDO1 and TDO facilitate Kyn generation, which activates AHR and increases AQP4 expression, enhancing the migratory and invasive capabilities of U87MG glioma cells (Fig. 4) [203].

Involvement of KP in Digestive System Cancers

In CRC, IDO generates Kyn to activate CDC20 transcription, maintaining HCT-116 and HT-29 cell proliferation and resisting cell cycle arrest-mediated apoptosis (Fig. 5a) [204]. Additionally, KMO knockdown suppresses the expression of cancer stem cells markers including Nanog and CD44 in CRC, thereby repressing CRC cell stemness, migration, and invasion [205].

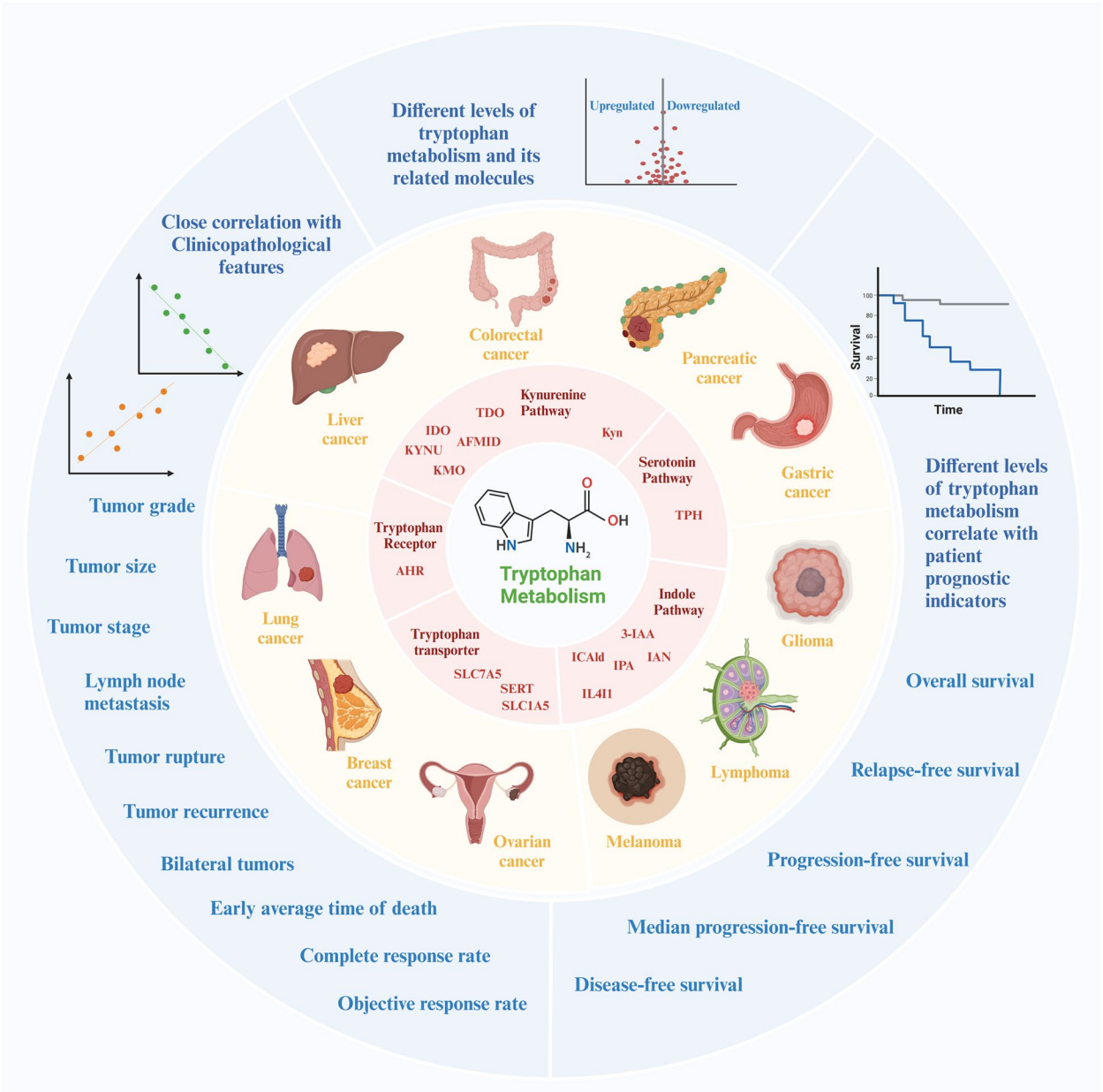

Fig. 3 Abnormal Expression of Tryptophan Metabolism in Cancers and Its Correlation with Clinicopathological Features and Prognosis Differentially abnormal expression of tryptophan metabolism and related molecules involved in cancer progression and patient outcomes. Critical enzymes in the tryptophan metabolism pathway, such as indoleamine 2,3-dioxygenase (IDO), tryptophan 2,3-dioxygenase (TDO), kynurenine 3-monooxygenase (KMO), kynureninase (KYNU), tryptophan hydroxylase (TPH), play significant roles in regulating tryptophan breakdown. Transporters such as solute carrier family proteins (SLC1A5, SLC7A5) and the serotonin transporter (SERT) facilitate cellular uptake and signaling of tryptophan and its metabolites, while the aryl hydrocarbon receptor (AHR) mediates biological effects of tryptophan-derived metabolites. These enzymes, transporters, and receptors are frequently found to be upregulated or downregulated in various cancers such as glioma, melanoma, lymphoma, and cancers of the digestive system, breast, and lung. The altered expression levels of these molecules are closely associated with clinicopathological features, including tumor grade, stage, size, and lymph node metastasis. Elevated or reduced levels of tryptophan metabolism-related molecules reflect the imbalance in tryptophan metabolism that influence disease progression. Furthermore, abnormal tryptophan metabolism and its associated molecules are strongly correlated with patient prognosis, usually as demonstrated by Kaplan-Meier survival curves. These alterations in tryptophan metabolism show a significant relationship with key prognostic indicators such as overall survival, relapse-free survival, and progression-free survival, suggesting that dysregulated tryptophan metabolism could serve as a prognostic biomarker and therapeutic target in cancer

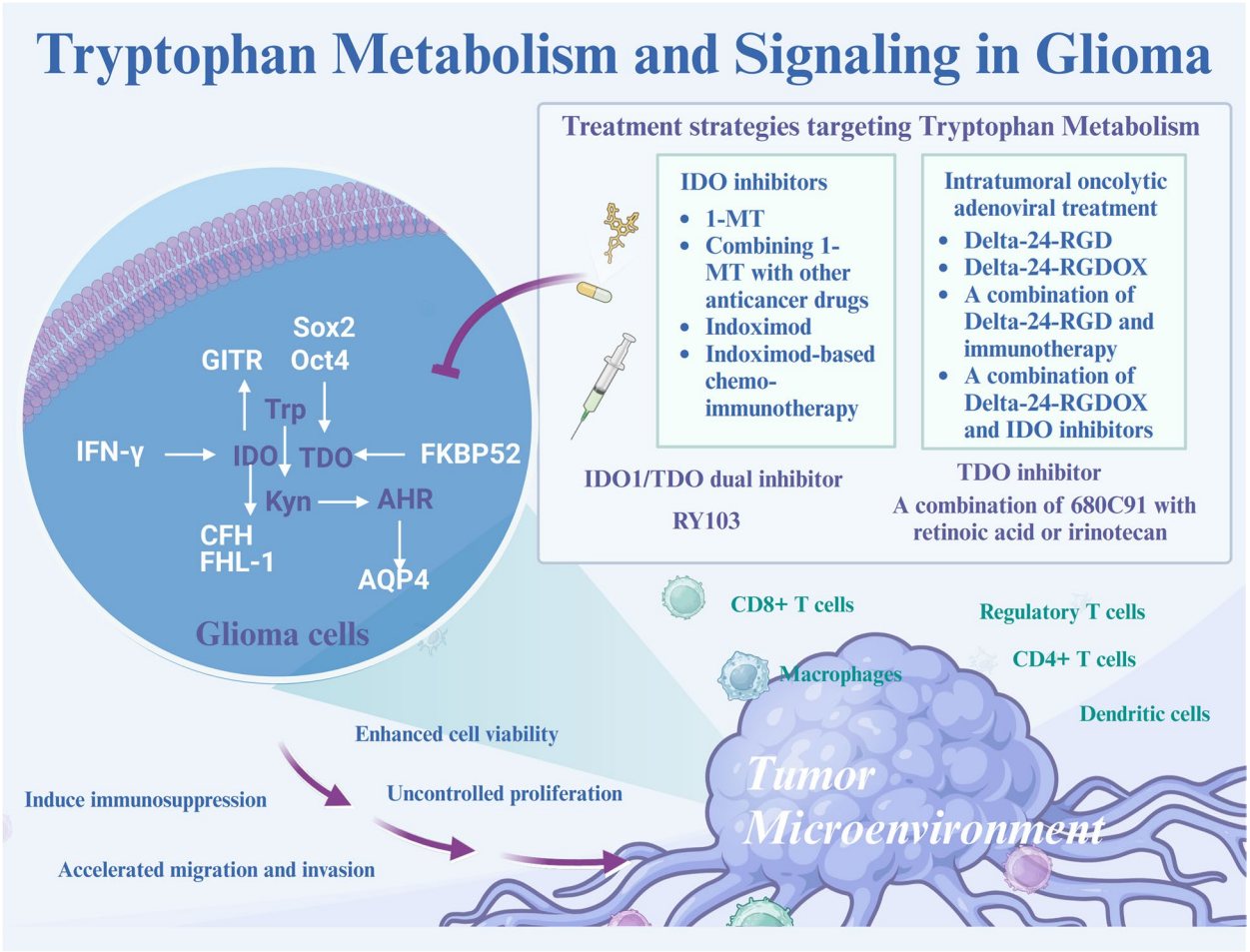

Fig. 4 Molecular Mechanisms and Therapeutic Strategies of Tryptophan Metabolism in Glioma In glioma, tryptophan metabolism plays a crucial role in tumor progression and immune evasion through the upregulation of key enzymes like indoleamine 2,3-dioxygenase (IDO) and tryptophan 2,3-dioxygenase (TDO). These enzymes increase kynurenine production, activating the aryl hydrocarbon receptor (AHR), which promotes glioma cell proliferation, migration, and invasion while inducing immunosuppression by depleting tryptophan and accumulating immunosuppressive metabolites. Therapeutic strategies targeting tryptophan metabolism include IDO inhibitors such as 1-MT and indoximod, which reduce immunosuppression and enhance the efficacy of other anticancer drugs. The TDO inhibitor 680C91 and the dual IDO/TDO inhibitor RY103 also lower kynurenine levels, mitigating its effects on AHR signaling. Additionally, combining oncolytic adenoviral treatments, such as Delta-24-RGD and Delta-24-RGDOX, with immunotherapy or IDO inhibitors enhances therapeutic outcomes by reducing the immunosuppressive environment within the glioma

In PC cancer with increased IDO1 expression, Trp serves as a viable one-carbon source for the tetrahydrofolate (THF) cycle, supporting PC cell proliferation and tumor growth. Liquid chromatography-mass spectrometry analysis confirms that Trp-derived one-carbon units integrate into serine and purine nucleotides in PC cells, offering an alternative to serine, particularly when serine availability is restricted. Pancreatic stellate cells also uptake and utilize Trp-derived formate released by PC cells for nucleotide biosynthesis in an IDO1-dependent manner [178]. However, recent studies show conflicting roles for IDO1 in PC, with evidence suggesting both pro-tumorigenic and anti-metastatic effects, depending on the immune context. In immunocompetent mice, deleting IDO1 in PC KPIC cells reduces tumor-forming ability, cellular proliferation, and macropinocytic capability. Conversely, IFN-γ-induced IDO1 inhibition using INB24360 triggers liver metastasis of PC organoid cancer [180]. Additionally, Kyn-mediated AHR activation in PC further leads to the induction of Cyp1a1 transcription, enhancing the migration and invasion capabilities of KPIC cells (Fig. 5b) [179]. In HCC, TDO2 overexpression significantly increases Kyn expression, leading to IL-6 secretion and activation of the STAT3/NF-kB signaling pathway. This enhancement boosts colony formation and cell proliferation capabilities of HCC cells, demonstrating

a key role for TDO in HCC pathogenesis [182]. Moreover, KMO knockdown has demonstrated a significantly inhibitory effect on HCC cancer progression, possibly through abnormal NAD concentration and subsequent destruction of NADH/NAD + redox homeostasis [183, 206]. While KMO overexpression are also confirmed to increase 3-HAA concentration, accelerating apoptosis in HCC SMMC7721 and HepG2 cells and impairing cancer growth (Fig. 5c) [183]. In GC, restoring the number of NK cells in the TME is crucial for effective treatment [207–209]. Kyn from GC cells induces ferroptosis in NK cells via an AHR-independent mechanism, leading to NK cell depletion and an immunosuppressive TME. Engineered NK cells with higher glutathione peroxidase 4 (GPX4) expression show resistance to Kyn-induced ferroptosis and therapeutic benefits in humanized GC cell-derived xenograft (CDX) cancer (Fig. 5d) [184].

Involvement of KP in Other Cancer

In BC, macrophages recruited to the TME via Fc gamma receptor (FcγR) signaling upregulate PD-L1, and IDO, leading to immunosuppression and cancer growth [210]. Furthermore, a novel population of podoplanin-positive (PDPN+) CAFs enriched in the BC TME secrete IDO1 and TDO2, leading to resistance to trastuzumab therapy [174]. Thiosemicarbazide derivatives (1–3), acting as dual inhibitors of topoisomerase IIα and IDO1, induce apoptosis in BC MCF-7 and MDA-MB-231 cells through caspase-8 and caspase-9 pathways. These derivatives also increase the proportion of BC cells in the G2/M phase and enhance sensitivity to anticancer treatments by inhibiting major ATP-binding cassette (ABC) transporters [211]. Overexpression of KMO functions as an oncogene in TNBC progression by preventing β-catenin degradation, upregulating pluripotent genes, leading to increased cell growth, colony and mammosphere formation, migration, invasion, and stemness in BC cells, and enhanced cancer metastasis and growth in vivo [212] (Fig. 6).

In melanoma, IFN-γ induces IDO1-mediated Trp depletion, diversifying the peptidome landscape at Trp residues. This altered peptidome is presented on HLA-I molecules, triggering peptide-specific T-cell responses crucial for immune recognition and melanoma therapy [213]. Melanoma cells exhibit a greater capacity for Trp uptake and metabolism within the competitive TME, depriving adjacent TILs of Trp and impairing their proliferation and survival. Additionally, Trp metabolism in melanoma cells produces Kyn and serotonin, which regulate TILs, leading to impaired T cell effector function [188]. TDO plays a crucial role in melanoma cancer stem cells (CSCs). Dexamethasone drives melanosphere formation and stemness in melanoma SK-Mel-28 and A375 cells in a TDO-dependent manner, resulting in a highly proliferative and metastatic phenotype [214]. In LC A549 and Lewis cells, CAFs produce Kyn and upregulate AHR expression to activate AKT and ERK signals, facilitating cell proliferation and resistance to EGFR TKIs [195].

Other Trp Metabolic Pathways and Signaling Mechanisms in Cancer

The serotonin and indole pathways, along with transport proteins and receptors involved in Trp signaling, play significant roles in carcinogenesis. Serotonin, as an important neurotransmitter, influences cancer growth and progression across various cancer types [215–219]. Previous research has shown that TPH1 overexpression increases serotonin production in prostate cancer, which activates the Axin 1/β-catenin signaling pathway. β-catenin then interacts with the transcription factor zinc finger binding protein (ZBP)-89 to further upregulate TPH1, forming a positive feedback loop (TPH1/5-HT/β-catenin/ZBP-89/TPH1), ultimately driving enhanced cell proliferation and migration [220]. In glioma, overexpressed TPH-1 facilitates serotonin generation to upregulate L1-cell adhesion molecule (L1CAM) and NF-κB signaling activation, subsequently promoting cell proliferative and migration ability [168]. Additionally, serotonin uptake via the serotonin transporter (SERT) is crucial for its recycling and degradation. In CRC, targeting SERT reduces mTORC1 serotonylation, leading to mTOR inactivation and increased Trp uptake. This process enhances Trp catabolism, boosting serotonin biosynthesis and accelerating cell proliferation and cancer growth in HCT116 and SW480 cells [45]. The serotonin receptor (5-HT(1D)R) is also promoted the activation of Axis Inhibition Protein 1(Axin1)/β-catenin/Matrix Metalloproteinase-7 (MMP-7) pathway, therefore enhancing cancer metastasis in an orthotopic CRC mouse model [221]. The intervention of a 5-HT(1D)R antagonist (GR127935) restrains CRC cancer invasion and migration activity. Furthermore, increased serotonin in BC interacts with 5-HTR2A/C to trigger ak1/STAT3 and ERK1/2 pathway, contributing to the upregulation of pyruvate kinase M2 (PKM2) and BC cell glycolysis. Administration of 5-HTR2A/C antagonist, ketanserin, significantly suppresses the glucose metabolism and cell growth rate in BC MCF-7 cells [222, 223].

It has also been demonstrated that metabolites from the indole pathway, primarily produced by gut microbiota, significantly impact systemic metabolism and the local TME [224–228]. Elevated levels of 3-IAA in PC cells increase reactive oxygen species (ROS) accumulation and reduce autophagic activity, contributing to cancer suppression [181]. Carbidopa, used to treat PD, alters Trp metabolism to increase production of the

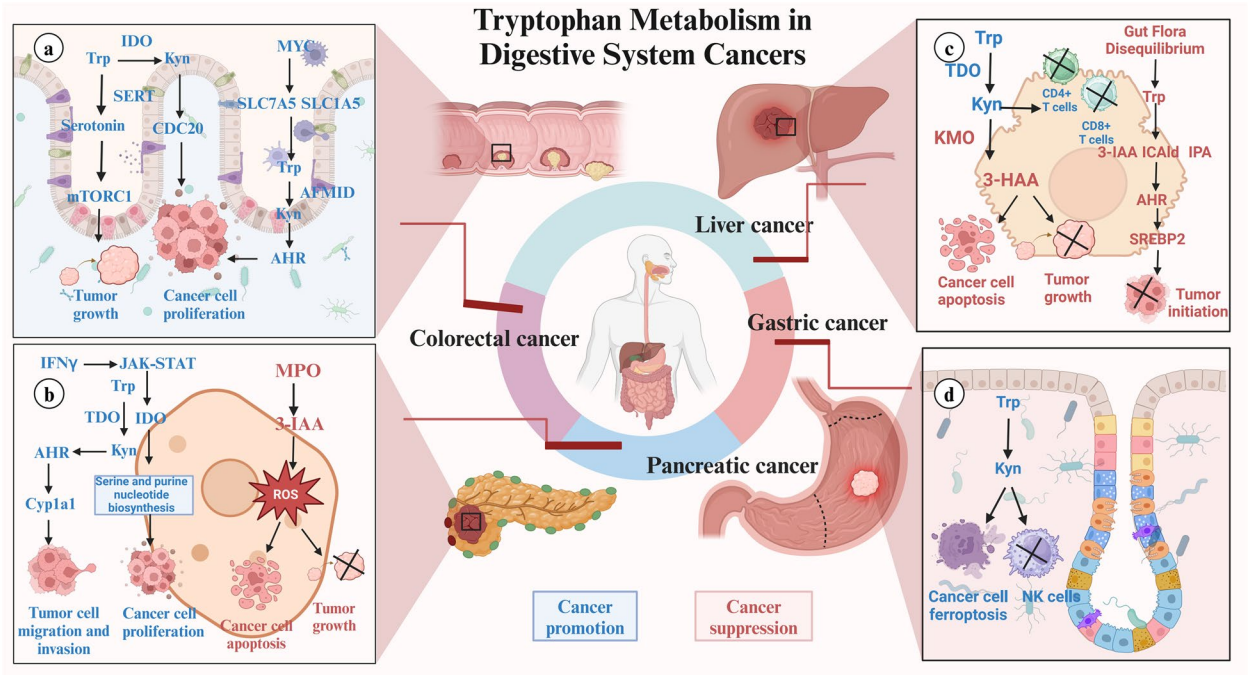

Fig. 5 Molecular Mechanisms of Tryptophan Metabolism in Digestive System Cancers (**a**) Tryptophan metabolism plays dual roles in digestive system cancers, promoting or suppressing tumor growth. In colorectal cancer, altered metabolism enhances tumor cell proliferation and survival through upregulated transporters like SLC1A5 and SLC7A5, increasing tryptophan uptake and metabolism. Kynurenine, via AHR signaling, supports cancer growth and immune evasion. **b** In liver cancer, gut microbiota-produced metabolites such as indole-3-acetic acid (IAA) and indole-3-aldehyde (IAld) inhibit tumor initiation and progression. **c** Pancreatic cancer progression is driven by the JAK-STAT signaling pathway, which increases IDO expression to support tumor growth and immune evasion. Conversely, the myeloperoxidase (MPO) pathway suppresses tumors by inducing oxidative stress and promoting cancer cell apoptosis. **d** In gastric cancer, kynurenine fosters cancer cell proliferation, migration, and NK cell loss, creating an immunosuppressive environment that facilitates tumor growth

pro-proliferative metabolite IAN in BC MCF-7 cells and melanoma A375 cells, enhancing cell viability and cancer incidence [191]. Upregulation of specific transport proteins that facilitate Trp import into cancer cells is vital for maintaining the altered metabolism supporting cancer growth and immune evasion [67, 229–232]. Moreover, transporters like SLC1A5 and SLC7A5 maintain the influx of Trp, meeting the high metabolic demand of cancer cells. In CRC, the oncogene MYC overexpresses Trp transporters (SLC7A5 and SLC1A5) and KP enzymes (AFMID), leading to increased Trp uptake and Kyn generation. Elevated Kyn supports CRC cell proliferation through AHR activation, an effect reversed by IDO, TDO, and AHR inhibitors (Epacadostat, 680C91, and CH223191) [174]. Additionally, Trp signaling receptors, such as AHR, significantly influence cancer growth and immune evasion [60, 233–236]. Gut microbiota dysbiosis reduces levels of AHR ligands, including 3-IAA, ICAld, and IPA, impairing AHR activation and increasing sterol regulatory element-binding protein 2 (SREBP2) levels, promoting HCC initiation [237]. These pathways underscore the multifaceted role of Trp metabolism in cancer and highlight the potential for targeted therapies to disrupt these processes.

Targeting Trp Metabolism and Signaling in Cancers

Considering the multifaceted roles of Trp metabolism, a significant exploration into small-molecule inhibitors targeting Trp metabolism, particularly IDO and TDO, has yielded promising advancements in cancer therapy [238]. Preclinical studies indicate that IDO1 and TDO inhibitors can reduce cancer growth and enhance the efficacy of existing treatments, such as immune checkpoint inhibitors [47, 239]. Additionally, dual inhibitors targeting both IDO1 and TDO are being developed for a broader and more effective approach to cancer therapy [240]. Various combination strategies involving IDO1 and TDO inhibitors with immune checkpoint inhibitors, chemotherapy, or radiotherapy are under investigation to maximize synergistic therapeutic efficacy (Table 2) [82, 241]. Moreover, increasing evidence supports the therapeutic potential of targeting other key enzymes in the tryptophan metabolism pathway, such as KMO and TPH, which have shown promise in a range of disorders, including neurodegenerative diseases [242, 243]. This suggests that investigating

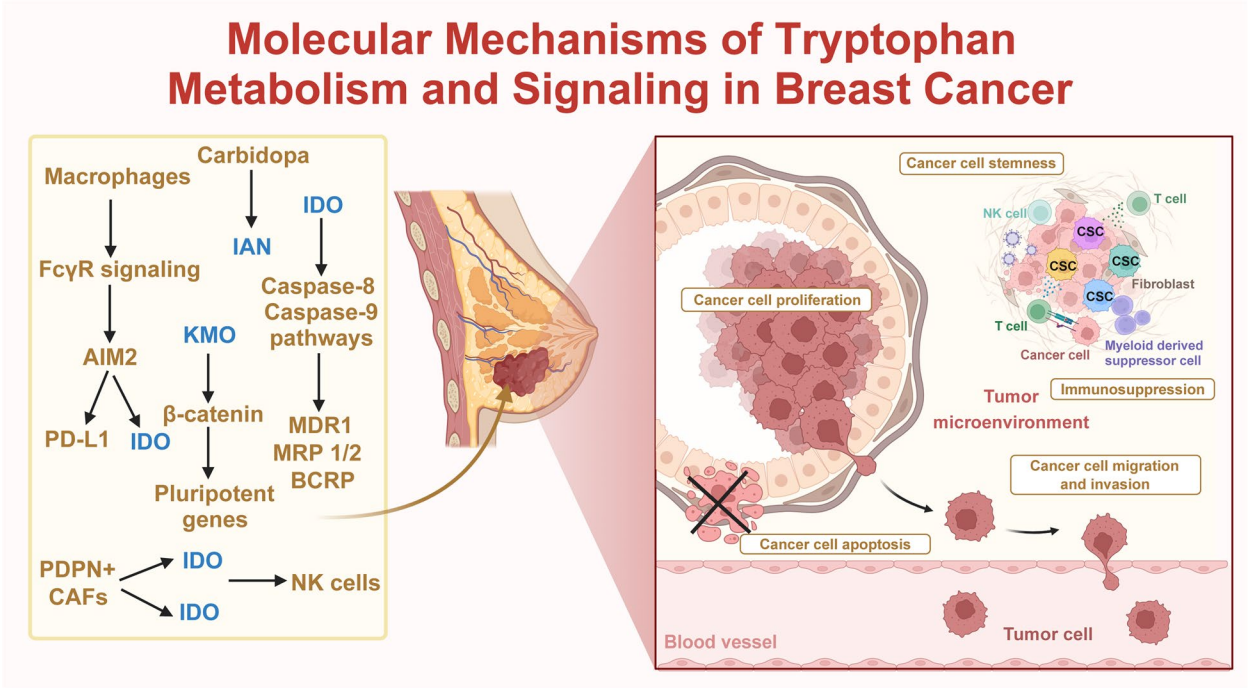

Fig. 6 Molecular Mechanisms of Tryptophan Metabolism and Signaling in Breast Cancer In breast cancer, key enzymes and metabolites in tryptophan metabolism, including indoleamine 2,3-dioxygenase (IDO), kynurenine 3-monooxygenase (KMO), and indole-3-acetonitrile (IAN), significantly contribute to creating an immunosuppressive tumor microenvironment. These factors promote cancer cell migration and invasion and maintain cancer stem cell (CSC) properties

these enzymes as potential therapeutic targets may also be crucial, broadening the scope of Trp metabolism as a therapeutic avenue.

Targeting Trp Metabolism in Glioma

In glioma, elevated IDO expression plays a significant role in promoting immunosuppression and cancer progression. Preclinical studies have shown that the IDO inhibitor 1-methyl-tryptophan (1-MT) significantly suppresses cancer growth in a subcutaneous glioma model, especially when used in combination with temozolomide (TMZ), an established chemotherapeutic agent. Mice with intracranially inoculated IDO knockdown glioma cells exhibit longer survival compared to control mice [244]. The combination of 1-MT with other chemotherapeutic agents (e.g., TMZ, bischloroethylnitrosourea, etoposide, cisplatin) in glioma cell lines has further demonstrated enhanced IDO inhibition, reversing immune resistance and impairing glioma cell proliferation [196]. Clinical trials are currently exploring the efficacy of IDO inhibitors in glioma treatment. A phase I trial (NCT02502708) of the oral IDO inhibitor indoximod in children with recurrent brain cancer, including diffuse intrinsic pontine glioma (DIPG), showed promising early results, such as reduced disease burden and extended periods of disease control [245]. Building on these findings, a phase II trial (NCT04049669) has been initiated, combining indoximod with chemo-immunotherapy, and a phase I salvage trial (NCT05106296) is testing its combination with ibrutinib to counteract immune evasion. Another promising approach involves oncolytic viruses, which have shown potent anti-immunosuppressive effects in glioma by lysing cancer cells and stimulating a stronger immune response [246–250]. In a phase I study, the oncolytic virus Delta-24-RGD (DNX-2401, AdCMVdelta24) led to complete cancer regression in 20% of patients with recurrent glioblastoma [251]. The third-generation adenovirus Delta-24-RGDOX (DNX-2440) demonstrated even more effective T-cell-mediated anticancer responses in preclinical models. When combined with IDO inhibitors, Delta-24-RGDOX increased $CD8^+$ T cells and decreased immunosuppressive cells like MDSCs and Tregs, leading to the complete eradication of glioma in murine models [202]. Clinical trials for Delta-24-RGDOX are ongoing in patients with malignant gliomas (NCT03714334) and liver metastases (NCT04714983). Targeting both IDO1 and TDO simultaneously has emerged as a promising strategy for overcoming the limitations of single-enzyme inhibition. The IDO1/TDO dual inhibitor RY103 demonstrated potent

anti-glioma effects by disrupting the IDO1/TDO/Kyn/AHR/AQP4 signaling axis, reducing tumor size and extending survival in orthotopic glioma models [171]. Additionally, novel therapeutic approaches targeting TDO have shown promise. The interaction between FKBP52 and the glucocorticoid receptor (GR) has been identified as a key regulator of TDO expression in gliomas. Treatment with FK506, an immunosuppressant that binds FKBP52, increases TDO expression and Kyn production, suggesting that modulating GR signaling could be a potential avenue for controlling TDO expression in gliomas [252]. The TDO2 inhibitor 680C91, when combined with chemotherapeutic agents such as retinoic acid or irinotecan, has demonstrated synergistic anticancer effects in neuroblastoma cells by inhibiting the Kyn/AHR pathway [173].

Targeting Trp Metabolism in Digestive System Cancers

In CRC therapy, combining the SERT inhibitor sertraline with dietary Trp restriction or the MEK inhibitor trametinib significantly weakens Trp uptake and degradation, leading to decreased CRC cell viability and cancer growth [45]. Additionally, local photothermal therapy (PTT) further induces cancer cells to release antigens, activating immune responses against residual lesions and distant metastases [253–255]. However, the immunosuppressive microenvironment often limits anticancer immunity by reducing the recognition efficiency of cancer antigens [256–260]. Recent advancements in in situ vaccines, such as outer membrane vesicles (OMVs) loaded with the IDO inhibitor 1-MT (1-MT@OMV-Mal), have shown promise in facilitating immune-mediated cancer clearance after PTT. This approach enhances the recognition and capture of cancer antigens by dendritic cells, leading to improved cancer-specific cytotoxic T cell (CTL) activation. In situ administration of 1-MT@OMV-Mal has demonstrated significant inhibition of both primary and distant CRC tumors [203]. In addition to vaccines, IDO1 inhibitors such as 1-MT and Epacadostat have been shown to reduce CRC cell viability by suppressing IDO expression and inhibiting Kyn-induced CDC20 transcription. A 1-MT-supplemented diet al.so prevents the development of sporadic colon cancer in mice induced by azoxymethane (AOM) and dextran sodium sulfate (DSS), suggesting its potential use in chemoprevention for colitis-associated CRC [204]. Moreover, PEGylated kynureninase (PEG-KYNase), a pharmacologically optimized enzyme, degrades Kyn into immunologically inactive metabolites. This enhances $CD8^+$ T cell proliferation and infiltration in the TME, impairing tumor growth. Notably, PEG-KYNase has demonstrated enhanced therapeutic efficacy when combined with checkpoint inhibitors or cancer vaccines, showing promising results in breast cancer, melanoma, and CRC treatment [261]. In PC, the IDO1 inhibitor Epacadostat, combined with serine starvation, effectively reduces the proliferation of IDO1-expressing cells, thus inhibiting cancer growth [178]. However, the dual functions of IDO1 in both cancerogenesis and metastasis complicate its application, contributing to setbacks in clinical trials [180]. In orthotopic PC mouse models, the dual IDO1/TDO inhibitor RY103 inhibits KPIC cell migration and invasion, reducing cancer metastasis by blocking the Kyn/AHR signaling pathway. Additionally, RY103 improves the immunosuppressive state by decreasing PMN-MDSCs and M-MDSCs in Pan02 cancer-bearing mice [179]. In a separate approach, a high-Trp diet in PC gnotobiotic mice elevates serum 3-indoleacetic acid (3-IAA) levels, which resulted in reduced cancer weight and enhanced responsiveness to FIRINOX treatment. Repeated cycles of 3-IAA combined with FIRINOX extends survival times in these orthotopic PC models [181]. In HCC, administering *Lactobacillus reuteri*, which produces Trp metabolites, or the AHR agonist 6-formylindolo(3,2-b) carbazole (Ficz), suppresses SREBP2 expression and inhibits cancer growth in mice with imbalanced gut flora [115]. Additionally, TDO-targeted conjugates, which combine the TDO inhibitor PVI with irinotecan (Ir), improves $CD4^+$ and $CD8^+$ T cell proliferation by inhibiting TDO expression and blocking Kyn production in the HCC TME. These conjugates also induce cell cycle arrest in the G2 phase and triggered apoptosis in HepG2 cells by releasing irinotecan, thus demonstrating the synergistic effects of combining immunotherapy and chemotherapy in HCC treatment [262]. Moreover, the combination of the AHR inhibitor PDM2 with chemotherapy agents such as Doxorubicin or 5-Fluorouracil enhances cancer-suppressive effects and prolongs OS duration in TDO2 overexpressing SMC-7721 bearing HCC mice by inhibiting AHR/IL-6/STAT3/NF-kB signaling [182]. The TDO inhibitor PF06845102/EOS200809 has also shown promise for treating TDO-expressing cancer, including HCC, glioblastomas, PC, and CRC, especially when used in combination with checkpoint inhibitors. Notably, TDO inhibitors increases Trp levels and enhances the efficacy of immunotherapy by overcoming IDO1-mediated immunosuppression, even in cancers without TDO expression at the tumor site [163]. Furthermore, in various HCC mouse models, overexpression of KMO or treatment with its substrate 3-HAA significantly enhances the efficacy of the IDO1 inhibitor Epacadostat, resulting in reduced cancer numbers and prolonged survival [183].

Table 2 Roles and clinical significance of tryptophan metabolism and signaling in cancers

Cancer type	Molecule in Tryptophan Metabolism	Role	Clinical characteristics	Drug/Treatment	Clinical samples and In vivo model	Year	Ref.
Glioma	IDO	Cancer promoter	tumor grade and OS	/	Peripheral blood from patients with GBM and aneurysm, tissues from patients with GBM, The Cancer Genome Atlas (TCGA), and syngeneic and humanized mouse GBM models database	2021	[167]
Glioma	IDO	Cancer promoter	OS, early average time of death, and tumor grade	/	The NCI Repository for Molecular Brain Neoplasia Data (REMBRANDT) database, the GL261 orthotopic mouse model, and the RasB8 transgenic mouse model	2012	[168]
Glioma	IDO	Cancer promoter	OS	1-MT	A subcutaneous ectopic model, a syngeneic intracranial orthotopic model, and an allogenic intracranial orthotopic model.	2016	[169]
Glioma	IDO	cancer promoter	/	1-MT	/	2009	[170]
Glioma	IDO	Cancer promoter	/	Delta-24-RGD	A phase I clinical trial involving 37 patients with recurrent malignant glioma	2018	[171]
Glioma	IDO	Cancer promoter	OS	a combination of Delta-24-RGDOX and IDO inhibitors	Orthotopic gliomas models	2022	[172]
Glioma	IDO	Cancer promoter	/	a combination of Delta-24-RGD and immunotherapy	A syngeneic GBM mouse model	2015	[173]
Glioma	IDO	Cancer promoter	/	Indoximod-based chemo-immunotherapy	A phase I clinical trial involving 81 children with recurrent brain cancer or newly DIPG	2024	[174]
Glioma	IDO	Cancer promoter	tumor grade and OS	/	75 tissue specimens from 68 patients with glioma	2013	[175]
Glioma	IDO1 and TDO	Cancer promoter	OS	RY103	75 glioma tissues, 34 blood samples, and GL261 orthotopic glioma mouse model	2020	[176]
Glioma	TDO	Cancer promoter	/	FK506	25 diffuse glioma tissues, GEO dataset: GSE18015, GSE16237, GSE9834, GSE9835, and U87MG orthotopic glioma mouse model	2015	[177]
Glioma	TDO	Cancer promoter	/	Pan-BET inhibitors	GlioVis and TCGA datasets and GL261 orthotopic glioma mouse model	2021	[178]
Glioma	TDO2	Cancer promoter	tumor grade	/	47 glioma tissues	2015	[179]
Glioma	TDO2	Cancer promoter	OS	a combination of 680C91 with retinoic acid or irinotecan	GSE89413 and TARGET database (phs000467)	2024	[180]

Table 2 (continued)

Cancer type	Molecule in Tryptophan Metabolism	Role	Clinical characteristics	Drug/Treatment	Clinical samples and In vivo model	Year	Ref.
CRC	SERT	Cancer promoter	/	a combination of SERT inhibition and dietary Trp restriction or trametinib	66 matched pairs of CRC tissues and adjacent tissues, alongside xenograft and primary CRC mouse model	2021	[45]
CRC	IDO	Cancer promoter	/	1-MT@OMV-Mal	Animal models	2022	[181]
CRC	IDO	Cancer promoter	OS	/	90 CRC tissue samples	2022	[182]
CRC	IDO1	Cancer promoter	/	1-MT and Epacadostat	Animal models	2018	[183]
CRC	SLC7A5, SLC1A5, and AFMID	Cancer promoter	/	TDO2 inhibitor (680C91), IDO inhibitor (Epacadostat), and AHR inhibitor (CH223191)	TCGA database and mouse organoids	2019	[184]
PC	IDO1	Cancer promoter	survival	a combination of Epacadostat and serine restriction	TCGA-PAAD dataset and subcutaneous allograft mouse models	2021	[185]
PC	3-IAA	Cancer suppressor	PFS or OS	FIRINOX/a high-tryptophan dietary intervention	Fecal and plasma samples of PC patients who do not respond and are responsive to the therapy and animal models	2023	[186]
PC	IDO1	Cancer promoter	/	Epacadostat	62 cancer samples from PC patients, KPIC organoids, and subcutaneous transplantation of organoids	2023	[187]
PC	IDO1 and TDO/	Cancer promoter	OS and RFS	RY103	TCGA database, KPIC orthotopic PC mice, and Pan02 cancer-bearing mice	2021	[188]
HCC	TDO	Cancer promoter	/	PVIS-Ir and PVIG-Ir	H22 BALB/c mice model	2021	[189]
HCC	TDO2	Cancer promoter	OS and tumor grade	a combination of PDM2 and chemotherapy	TCGA database as well as 16 HCC cancer tissues and subcutaneous mice models	2021	[190]
HCC	KMO	Cancer suppressor	DFS	/	A series of HCC animal models	2022	[191]
HCC	IAA, ICAld, and IPA	Cancer suppressor	/	Lactobacillus Reuteri/Ficz	Fecal samples of HCC patients and healthy subjects, and animal models	2022	[115]
GC	IDO	Cancer promoter	tumor size, tumor stage, and OS	/	99 GC cancer tissues and blood samples	2019	[192]
GC	IDO	Cancer promoter	OS, tumor invasion, and lymph node metastasis	/	357 GC cancer tissues from patients with GAC undergoing gastrectomy	2016	[193]

Table 2 (continued)

Cancer type	Molecule in Tryptophan Metabolism	Role	Clinical characteristics	Drug/Treatment	Clinical samples and In vivo model	Year	Ref.
Melanoma	TPH1/2, IDO1, TDO2, and LAT1	Cancer promoter	OS	a combination of Telotristat and Pembrolizumab	The Biomax Normal Skin/Benign Nevus/Primary Melanoma TMA, the UNC-CH 09–1737 Metastatic Melanoma TMA, and the LCCC1531 trial	2023	[195]
Melanoma	AHR	Cancer promoter	/	KYN-101/CH-223,191	Animal models	2020	[196]
Melanoma	IDO1	Cancer promoter	/	Epacadostat	706 patients with unresectable stage III or IV melanoma previously untreated with PD-1 or PD-L1 checkpoint inhibitors	2019	[197]
Melanoma	TDO	Cancer promoter	/	680C91	Melanospheres were generated from A375 and SK-Mel-28 human melanoma cells	2022	[198]
BC	IL4I1, IDO1, KMO, and KYNU	Cancer promoter	serve as a biomarker for predicting the efficacy of immunotherapy	/	GEO database (GSE75688, GSE176078, GSE210616), XENA database, and cBioPortal database	2023	[199]
BC and Melanoma	IAN	Cancer promoter	/	Carbidopa	/	2019	[200]
BC and Lymphoma	IDO	Cancer promoter	poor trastuzumab response	a combination of trastuzumab or rituximab with inhibitors of PD-L1 and IDO	307 paired biopsy samples and surgically resected samples from invasive HER2 + BC patients before and after neoadjuvant treatments and animal models	2018	[201]
BC, Melanoma, and CRC	Kyn	Cancer promoter	/	a combination of PEG-KYNase with approved checkpoint inhibitors or with a cancer vaccine	Animal models	2018	[202]
BC	IDO	Cancer promoter	tumor grade	/	4 TMA containing BC tissues from 242 invasive primary breast carcinomas, 20 nodal metastases, and 19 distant metastases	2018	[203]
BC	IDO1	Cancer promoter	/	Thiosemicarbazide derivatives 1–3	/	2023	[204]
BC	IDO1 and TDO2	Cancer promoter	/	IDO/TDO-IN-3	70 BC tissues and orthotopic BC mouse model	2023	[205]
BC	KMO	Cancer promoter	tumor metastasis, recurrence, RFS, and DFS	UPF 648 and Ro 61–8048	BC cancer tissues and paired mammary epithelial samples, TCGA database, and animal models	2020	[206]

Table 2 (continued)

Cancer type	Molecule in Tryptophan Metabolism	Role	Clinical characteristics	Drug/Treatment	Clinical samples and In vivo model	Year	Ref.
OC	IDO1, IDO2, TDO2 and IL4I1	Cancer promoter	late tumor stage, lymph node metastasis, bilateral tumors, endometriosis, and tumor rupture	Platinum	127 OC tissue samples	2023	[207]
LC	IDO1, IDO2, and TDO	Cancer promoter	/	F04	Immunocompetent C57BL6 mice and lung metastasis of Lewis cells model	2019	[208]
LC	IDO	Cancer promoter	OS and PFS	/	110 serum samples from patients with stage III inoperable/unresectable NSCLC	2018	[209]
LC	TDO	Cancer promoter	/	a combination of AhR inhibitor DMF and EGFR TKIs	20 LC cancer samples, and a xenograft mouse model using A549 or Lewis cells	2022	[210]
HCC, Glioma, PC and CRC	TDO	Cancer promoter	/	PF06845102/EOS200809	CT26 cancer and TDO-KO mice bearing MC38 cancer	2020	[163]

Targeting Trp Metabolism in BC

Antibody-dependent cellular cytotoxicity (ADCC) and antibody-dependent cellular phagocytosis (ADCP) are critical for the effectiveness of anticancer therapeutic antibodies. However, recent studies have highlighted the detrimental role of ADCP macrophages in cancer immunosuppression. In HER2 + BC patients receiving neoadjuvant trastuzumab therapy, cancer-associated macrophages (TAMs) significantly upregulate PD-L1 and IDO, creating an immunosuppressive TME and contributing to poor treatment responses to trastuzumab. Combining anti-PD-L1 and IDO inhibitors with therapeutic antibodies, such as trastuzumab or rituximab for BC and lymphoma treatment, has been shown to synergistically enhance therapeutic efficacy by boosting anticancer immunity [210]. The dual inhibitor IDO/TDO-IN-3 also restores NK cell-mediated cytotoxicity and enhances trastuzumab efficacy, effectively inhibiting cancer progression in orthotopic BC mouse models [263]. Thiosemicarbazide derivatives (1–3), as double inhibitors of topoisomerase IIα and IDO1, induce apoptosis, cause cell cycle arrest, and increase drug sensitivity in BC MCF-7 and MDA-MB-231 cells in a dose-dependent manner. Their pro-apoptotic efficacy is significantly higher than that of etoposide and they exhibit beneficial ADME-Tox properties [211]. Additionally, the novel pan IDO1/IDO2/TDO inhibitor F04 increases the accumulation and infiltration of T cells in the TME, suppressing cancer progression dose-dependently in immunocompetent C57BL6 mice and a lung metastasis model of Lewis cells. Notably, F04 demonstrates a more potent effect in reducing the Kyn/Trp ratio compared to Epacadostat, further emphasizing its therapeutic potential [264].

Targeting Trp Metabolism in Other Cancers

In metastatic melanoma, the phase I/II MM1636 trial (NCT03047928) involving thirty anti-PD1 therapy-naive patients showed encouraging results for an immunemodulatory vaccine (IO102/IO103) targeting IDO/PD-L1 combined with adjuvant Montanide and nivolumab. The trial achieved an objective response rate (ORR) of 80%, a complete response rate (CR) of 43%, and a median PFS (mPFS) of 26 months. Vaccine-specific T cells from vaccinated patients recognized cancer cells in a target- and HLA-restricted manner and polarized myeloid cells to a cancer-associated phenotype, enhancing vaccine-specific responses [265]. However, the phase III ECHO-301/KEYNOTE-252 trial (NCT02752074) with 706 patients with unresectable or metastatic melanoma, who were randomly assigned to receive the IDO1 selective inhibitor Epacadostat plus the PD-1 inhibitor pembrolizumab ($n = 354$) or placebo plus pembrolizumab ($n = 352$), did not show additional benefits in PFS or OS over the placebo group [266]. The AHR pathway exhibits selective activity in cancer overexpressing IDO/TDO and is associated with resistance to immune checkpoint inhibitors. The AHR pathway drives T cell dysfunction by promoting a suppressive axis between Tregs and macrophages within the melanoma TME. Selective AHR blockade with CH-223,191 reverses IDO-Kyn-AHR-mediated immunosuppression and delays melanoma progression. Additionally, using the AHR antagonist KYN-101 in IDO/TDO-expressing cancer improves the limitations of targeting IDO or TDO alone and sensitizes cancer to anti-PD-1 therapy in melanoma [267]. IFN-γ prompts endogenous frameshifting events at Trp residues, leading to their presentation on HLA-I molecules and triggering peptide-specific T-cell responses in melanoma MD55A3 cells. This process diversifies the peptidome landscape, driving IDO1-mediated Trp depletion, and plays a crucial role in enhancing immune recognition in anti-melanoma treatments [213]. In LC xenograft mouse models, the combined administration of the AHR inhibitor DMF and TKIs also significantly inhibits cancer growth, reverses resistance to TKIs, and prolongs survival time [193]. Furthermore, a Phase I trial (NCT01219348) is currently underway to evaluate a novel immunotherapeutic strategy for patients with locally advanced or metastatic LC. This strategy involves IDO peptide vaccination in combination with the immune-stimulating agent Aldara and the adjuvant Montanide to enhance the immune response. Additionally, targeting the serotonin pathway in carcinogenesis has emerged as a promising approach in various cancers, showing anticancer effects in some preclinical trials. In prostate cancer, the TPH1 inhibitor 4-chloro-dl-phenylalanine (PCPA) disrupts the TPH1/5-HT/β-catenin/ZBP-89/TPH1 feedback loop, significantly enhancing the anticancer effects of paclitaxel and suppressing lung metastasis in prostate cancer-bearing mice [220].

Current Status and Future Prospects of Trp Metabolism in Cancer

Trp metabolism plays a crucial role in cancer progression and immune modulation, with research primarily focusing on the KP, which generates multiple bioactive compounds with immunosuppressive properties. However, despite significant attention on KP, the serotonin and indole pathways are less frequently explored in cancer [53, 64, 268]. Recent insights suggest that a more nuanced understanding of these alternative pathways is necessary to broaden the scope of therapeutic applications targeting Trp metabolism.

Current Status of IDO1 and TDO inhibitors

Early research efforts were largely concentrated on developing IDO1 inhibitors, as IDO1 is a key enzyme that suppresses anticancer immunity by driving the conversion of Trp into Kyn [269–273]. While preclinical studies yielded promising results, translating these findings into clinical success has been more challenging. A notable example is the ECHO-301 phase III trial, which evaluated the selective IDO1 inhibitor Epacadostat (INCB24360) in combination with pembrolizumab (anti-PD-1 antibody) in patients with advanced melanoma. Unfortunately, the trial did not show significant improvement in PFS or OS compared to the placebo group, prompting a reevaluation of the therapeutic potential of IDO1 inhibition alone [274–277]. This result has shifted the focus toward understanding the broader role of Trp metabolism in cancer and exploring more effective combination therapies. One key limitation of these trials is the absence of reliable biomarkers to assess IDO1 levels and activity before and during treatment. Given that the efficacy of IDO1 inhibitors hinges on the presence and functionality of the enzyme, the development of robust clinical tools to stratify patients based on IDO1 expression and to monitor enzyme activity in real time is crucial [278]. Additionally, the lack of standardized methods for measuring metabolite and drug concentrations at target sites complicates the evaluation of treatment efficacy [279, 280].

In response to these challenges, recent research has expanded beyond IDO1 to include dual inhibitors that target both IDO1 and TDO. Preclinical data suggest that dual IDO1/TDO inhibitors may offer a more comprehensive blockade of Trp metabolism, potentially overcoming the limitations of selective IDO1 inhibition [51, 55, 281]. In addition, an open-label, Phase I multicenter study (NCT03208959) is currently underway to assess the preliminary efficacy and safety of a novel orally administered small-molecule IDO1/TDO dual inhibitor, HTI-1090, in patients with advanced solid tumors.

Expanding the Scope: KMO and TPH Inhibitors

Since KMO is overexpressed in several cancer types and plays a role in cancer development, the development of KMO inhibitors represents a novel strategy for cancer treatment [282–284]. In recent years, research into KMO inhibitors has shown potential as a promising therapeutic approach for various diseases. However, the majority of KMO inhibitors currently under investigation are focused on neurodegenerative diseases [243, 285, 286]. Due to the relatively poor efficacy of these inhibitors and limited preclinical trials, few have successfully completed clinical trials in cancer treatment. Expanding the focus of KMO inhibitors to cancer may open new therapeutic avenues, particularly by targeting KMO's immunosuppressive and pro-tumorigenic effects [242]. Similarly, the TPH-serotonin signaling pathway has gained attention as a contributor to cancer progression. Several TPH inhibitors and serotonin receptor antagonists have shown the anticancer effects in animal models [287, 288]. Notably, TPH inhibitors have shown promising results in the treatment of diverse disorders, such as neuropsychiatric conditions, gastrointestinal dysfunction, osteoporosis, and bone homeostasis. Additionally, the excessive secretion of serotonin by cancer cells can lead to the typical symptoms of carcinoid syndrome and in 2017, TPH inhibitors were approved by the United States Food and Drug Administration (FDA) for managing gastrointestinal symptoms associated with this condition [289–291]. Additionally, excessive serotonin secretion by cancer cells can cause the typical symptoms of carcinoid syndrome. In 2017, TPH inhibitors were approved by the United States Food and Drug Administration (FDA) for managing gastrointestinal symptoms associated with this condition. A pilot clinical trial (NCT03453489) is also investigating TPH levels in neuroendocrine cancer to assess the efficacy of Etiprate treatment. Despite these findings concerning the secretion pathway, its specific role in cancer progression and the therapeutic efficacy of targeting serotonin, TPH, and its receptors in cancer treatment remains limited.

Overcoming Translational Challenges

Despite significant advancements, the development of selective, potent, and safe inhibitors for Trp-metabolizing enzymes remains a challenge. Inhibitors targeting IDO1, TDO, and other enzymes within the Trp metabolic pathway must balance efficacy with safety, as Trp metabolism is essential for normal physiological processes [292]. Off-target effects and toxicity continue to be concerns, underscoring the need for improved detection tools to monitor tissue-specific Trp concentrations and metabolite levels throughout treatment.

Combination Therapies and Future Directions

Given the challenges encountered with IDO1 inhibitors, there is growing interest in combining Trp metabolism inhibitors with immune checkpoint inhibitors, chemotherapy, or radiotherapy to enhance anticancer immune responses and improve clinical outcomes [293]. Recent clinical trials (NCT03291054, NCT01961115, NCT02785250, NCT03006302, NCT03516708, NCT03661320, NCT02077881 and NCT02835729) have tested novel combinations, such as combining IDO1 inhibitors with immunotherapies, or with radiotherapy and/or chemotherapy [82]. While some trials have demonstrated improvements in PFS and OS for specific patient populations, broader success remains elusive. Understanding the optimal sequencing and timing of combination therapies is critical, as Trp metabolism modulation may need to occur

in specific stages of the immune response to maximize therapeutic benefit [294–296].

Furthermore, researchers are increasingly focused on uncovering downstream effector mechanisms in Trp metabolism that may be relevant to cancer progression [180, 297]. While the immunosuppressive effects of kynurenine are well-established, emerging studies suggest that indole derivatives may also promote cancer through activation of the AHR [88–91]. AHR regulates genes involved in immune suppression, inflammation, and cell proliferation, making it a promising target for future therapies.

Addressing these challenges necessitates uncovering additional oncogenic mechanisms of Trp metabolism, identifying the relevance of Trp-related molecules, and evaluating the roles and therapeutic significance of other enzymes within Trp metabolism [298–300]. The integration of cutting-edge technologies such as multi-omics, CRISPR gene editing, and single-cell sequencing could help identify new therapeutic targets within Trp metabolism [269, 294, 301–303]. Moreover, the strategic combination of Trp metabolism inhibitors with other immunotherapies, guided by improved biomarker detection and patient stratification, represents a forward-looking approach that could enhance treatment outcomes in cancer.

Conclusion

Trp, an essential amino acid, influences various physiological and pathological processes through its metabolism into serotonin, Kyn, and indole derivatives. Dysregulated Trp metabolismis observed in many cancers and is strongly linked to clinical features such as tumor stage, size, and lymph node metastasis. Additionally, Trp metabolite levels correlate with patient prognosis, serving as robust predictive markers. Aberrant Trp metabolism affects multiple malignant processes in cancer, including cell proliferation, migration, invasion, and immune evasion, primarily through interactions with various cancer-related molecules and signaling pathways. Consequently, targeting Trp metabolism has emerged as a promising avenue in cancer therapy. While numerous preclinical trials have demonstrated the anticancer effects of inhibiting Trp metabolism, translating these findings into clinical success remains a challenge. The failure of IDO1 inhibitors in clinical trials highlights the complexity of the TME, the compensatory activation of alternative immune-suppressive pathways, and the heterogeneity of Trp metabolism across different cancer types and patient populations. To overcome these clinical challenges, future research should prioritize a deeper exploration of the underlying mechanisms driving resistance, as well as utilizing multi-omics approaches to identify novel biomarkers and therapeutic targets. Another critical area for future research is the design of combination therapies that address the limitations of current Trp metabolism inhibitors. Given the compensatory activation of alternative immune-suppressive pathways, combining Trp-targeted therapies with immune checkpoint inhibitors, targeted therapies, or even next-generation cancer vaccines to simultaneously target multiple metabolic pathways may enhance therapeutic efficacy while minimizing resistance.

In summary, although significant progress has been made in understanding the role of Trp metabolism in cancer, addressing these research gaps is essential for clinical translation. The continued investigation of Trp metabolism, coupled with advanced technologies and innovative combination strategies, holds substantial promise for advancing cancer therapy and ultimately improving patient outcomes.

Abbreviations

Trp	Tryptophan
KP	kynurenine pathway
IDO	indoleamine-2,3-dioxygenase
TDO	Trp-2,3-dioxygenase
KMO	kynurenine monooxygenase
TME	tumor microenvironment
Kyn	kynurenine
AHR	aryl hydrocarbon receptor
KynA	kynurenic acid
QA	quinolinic acid
CA	cinnabarinic acid
XA	xanthurenic acid
NAD+	nicotinamide adenine dinucleotide
SLC1A5	solute carrier family 1 member 5
SLC7A5	solute carrier family 7 member 5
I3P	indole-3-pyruvate
TPH	Trp hydroxylase
5-HTP	5-hydroxytryptophan
AADC	aromatic amino acid decarboxylase
5-HIAA	5-hydroxyindoleacetic acid
MAO	monoamine oxidase
NAS	N-acetylserotonin
AANAT	arylalkylamine N-acetyltransferase
ASMT	N-acetylserotonin O-methyltransferase
AFMID	arylformamidase
KYNU	kynureninase
3-HK	3-hydroxykynurenine
AA	anthranilic acid
KAT	Kynurenine aminotransferase
3-HAA	3-hydroxyanthranilic acid
QPRT	quinolinate phosphoribosyl transferase
ARNT	aryl hydrocarbon receptor nuclear translocator
ELISA	Enzyme-Linked Immunosorbent Assay
LC-MS	liquid chromatography-mass spectrometry
UHPLC-ESI-MS/MS	ultra-high-performance LC-electrospray ionization-tandem MS
GBM	glioblastoma
OS	overall survival
PC	pancreatic cancer
RFS	relapse-free survival
PFS	progression-free survival
DFS	disease-free survival
TILs	tumor-infiltrating lymphocytes
PD	Parkinson's disease
CAFs	cancer-associated fibroblasts

Tregs	regulatory T cells
GSCs	stem-like cells in glioblastoma
HCC	hepatocellular carcinoma
CRC	colorectal cancer
GC	gastric cancer
BC	breast cancer
OC	ovarian cancer
LC	lung cancer
ROS	reactive oxygen species
ADCC	antibody-dependent cellular cytotoxicity
TKIs	tyrosine kinase inhibitors
TMZ	temozolomide

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Dongming Yan, Hongjiang Li, Lixia Xu, and Jingliang Cheng designed the structure of the review. Jing Yan, Di Chen, and Zi Ye wrote the article. Xuqiang Zhu, Xueyuan Li, and Henan Jiao draw the figures. Mengjiao Duan, and Chaoli Zhang completed the tables. Jing Yan, Jingliang Cheng, and Dongming Yan helped with the final revision of the review. All authors reviewed the manuscript and approved the final manuscript.

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No datasets were generated or analysed during the current study.

Declarations

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Not applicable.

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The authors declare no competing interests.

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