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Targeting the Kynurenine Pathway: A Novel Approach in Tumor Therapy

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Abstract

Complex interactions between cancer cells and their microenvironment promote tumor development and metastasis, a procedure which often requires a continuous supply of amino acids. Reprogramming of tryptophan metabolism is highly activated in tumors to provide biological raw material and energy for malignant tumor advancement. Targeting the most important kynurenine pathway in tryptophan metabolism provides new possibilities for tumor therapy. The aim of this study is to comprehensively analyze the roles of kynurenine pathway metabolites and their mechanisms in tumor development, and to propose therapeutic strategies targeting this pathway to address the above mentioned process. These strategies include traditional targeting of key enzymes, novel targeting of key enzyme drug delivery systems, and mechanism-derived targeting and combination therapies, with the goal of improving the precision and efficacy of tumor therapy targeting the kynurenine pathway.

Keywords: targeted therapy, kynurenine pathway, cancer, precision medicine, combinational therapy

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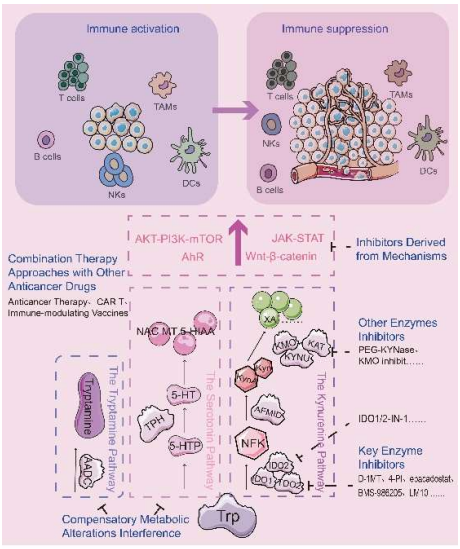
Graphical Abstract



Conventional targeting of key enzymes, novel targeting of key enzyme delivery systems, and mechanism-derived targets and combination therapies for tumor therapy targeting the kynurenine pathway

Abstract

Cancer cells interact with their surroundings to promote tumor formation and spread, which typically requires a constant supply of amino acids. Reprogramming of tryptophan metabolism is highly activated in tumors to provide biological raw material and energy for malignant tumor advancement. Targeting the most important kynurenine pathway in tryptophan metabolism provides new possibilities for tumor therapy. The purposes of this research are to thoroughly examine the functions of metabolites of the kynurenine pathway and how they work in tumor growth, as well as to suggest therapeutic approaches that target this route in order to address the aforementioned process. These strategies include traditional targeting of key enzymes, novel targeting of key enzyme drug delivery systems, and mechanism-derived targeting and combination therapies, with the goal of improving the precision and efficacy of tumor therapy targeting the kynurenine pathway.

Keywords: targeted therapy, kynurenine pathway, cancer, precision medicine, combinational therapy

1 Introduction

In the 21st century, cancer is a significant social, public health, and economic issue. It is anticipated that in 2022, there will be roughly 20 million newly diagnosed cancer instances, and 9.7 million individuals will perish from the disease [1]. While

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traditional anti-cancer therapies such as surgery, chemotherapy and radiation have shown progress, the field of cancer treatment is on a quest aimed at improving survival rates [2]. The emerging therapeutic avenues including immunotherapy, gene therapy and molecularly targeted therapies offer great promise in this context [3]. A characteristic of cancer is the abnormal control of cellular metabolism, whereby cancer cells must modify the processes that enable them to absorb extracellular metabolites and optimize the activity of these enzymes in order to adapt and endure extreme environmental stressors [4]. Targeting energy metabolism reprogramming has therefore become a hot new area of tumor therapy [5].

Tryptophan (Trp) metabolic reprogramming is extraordinarily active in tumors, and the main tryptophan metabolism process is called the kynurenine pathway (KP), through which >95% of tryptophan is degraded into a wide range of biologically active compounds by the pathway's key enzyme, indoleamine 2,3 dioxygenase1 (IDO1), and the levels of these metabolites are strongly correlated with the malignant characteristics of the tumor [6,7]. Studies using inhibitors of key enzymes involved in the metabolism of the canine uridine pathway have shown improved efficacy both in vitro and in vivo[8]. The most extensively researched important enzyme that targets this pathway at the moment is IDO1, and when used in conjunction with targeted immune checkpoint therapies, its inhibitors work in concert to stimulate anti-tumor immune responses in animal tumor models [9]. However, a phase III therapeutic trial using the PD-1 checkpoint inhibitor pembrolizumab in conjunction with the IDO1 inhibitor epacastat to treat malignant melanoma failed [10]. This leads us to think that targeting the kynurenine pathway is problematic in tumor therapy.

This article aims to clarify a few questions: Targeting the KP in the past has prioritized the inhibition of crucial enzymes while ignoring the regulation of other enzymes. Can other metabolic enzymes be used as therapeutic targets? How to choose between targeting other metabolic enzymes and key enzymes? Meanwhile, cancer cells interact with their surroundings, leading to tumor formation. So will the newly discovered regulatory effects of the kynurenine pathway metabolites on tumors and the tumor microenvironment (cells as well as infiltrating bacteria) shed new light on drug design? And does the modulating effect provide a theoretical basis for drug combination?

2 Tryptophan Metabolism and its Role in Tumor Progression

2.1 Kynurenine pathway is the principal route of tryptophan catabolism

In addition to being a necessary amino acid for protein synthesis, L-Trp also contributes to homeostasis by generating a range of metabolites via intricate metabolic processes. Only a small portion of Trp ingested by the body is used for anabolic processes, and the rest of Trp has three catabolic pathways (Figure 1): First, tryptamine is created when aromatic L-amino acid decarboxylase (AADC)

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decarboxylates It [11]. Secondly, about 5% of tryptophan forms serotonin (5-HT) through tryptophan hydroxylase (TPH) [12]. Thirdly, three rate-limiting enzymes, IDO1, IDO2, and TDO2, convert approximately 95% of free Trp to N-formyl kynurenine (NFK). Arylformamidase (AFMID) then converts NFK to kynurenine (Kyn), and kynurenic aminotransferase (KYNU) then converts Kyn to anthranilic acid (AA). Kynureninase (KYNU) converts kyn to anthranilic acid (AA), while kynurenic aminotransferase (KATI-KATIII) converts kyn to kynurenic acid (KA). Through Kynurenine 3-monooxygenase (KMO), Kyn also produces 3-hydroxy-kynurenine (3-HK), which is subsequently processed by KYNU to produce 3-hydroxyanthranilic acid (3-HAA). 3-hydroxyanthranilic acid (HAAO) transforms 3-HAA into neurotoxic quinolinic acid (QA), which certain cells can then transform into NAD+, a crucial coenzyme in energy metabolism. 3-HK can also be converted by KATI-KATIII catalysis to produce xanthurenic acid (XA) [13].

The tryptophan metabolites listed above play a role in the organism's control of inflammation, immunological response, and excitatory neurotransmission[14]. The function of tryptophan metabolites generated by the kynurenine pathway (KP) in tumor growth is the focus of this article. The technique known as single-cell RNA sequencing, or scRNA-seq, is used to highlight the diversity of intricate biological systems. Ashley et al. collected samples before targeted therapy (TKI naive [TN]) and residual lesions (RD) during progressive disease (PD) for single-cell sequencing analysis, revealing upregulation of KP metabolic pathway enzyme gene expression during PD [15]. Based on high-throughput data, it is evident that tryptophan metabolism is abnormally activated in various cancers, with KP metabolic pathway activation being particularly pronounced. Therefore, this paper aims to summarize in which cancers tryptophan metabolism is abnormally activated and plays a role in promoting tumor development, providing a theoretical basis for subsequent targeting of the tryptophan metabolic pathway.

2.2 Significance of targeting the kynurenine pathway: the kynurenine pathway metabolites facilitate in carcinogenesis

In various tumors, metabolites of the kynurenine pathway contribute to the malignant progression of tumor proliferation, stemness, and migratory invasion to varying degrees. Despite differences in the mechanisms by which metabolites act, most of them advance the malignant progression of tumors, revealing an important role for the targeted kynurenine pathway in tumor therapy. Clarifying the regulatory mechanisms of metabolites facilitates tumor treatment strategies that more precisely target the kynurenine pathway, so later we summarize the potential mechanisms of action for different metabolites.

Increased IDO1 expression in the intestinal epithelium of colorectal cancer patients promotes colon tumorigenesis and affects their prognosis, probably due to the

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activation of β-catenin by Kyn, a metabolite of the KP pathway, which increases cancer cell proliferation and inhibits the apoptotic process through the PI3K/AKT signaling pathway [16]. In colorectal cancer, TDO2 enhances tumor proliferation by increasing glycolysis, and a decrease in tryptophan also reduces the quality of life of colorectal cancer patients [17]. The prognosis and pathological grading of gliomas are favorably connected with IDO1/TDO expression and activity, and the possible mechanism is to activate the aromatic hydrogen receptor (AhR) by catabolism of tryptophan to produce Kyn, and to stimulate glioma cell motility and invasion by acting on the downstream aquaporin protein AQP4 [18]. In melanoma, Kyn and 6-formylbenzo[3,2-b]carbazole (FICZ) have anti-proliferative activity on human melanoma cells. 1 pM L-Kyn significantly inhibits the proliferation of A375 cells, while 5 mM of L-Kyn inhibits DNA synthesis in normal human melanoma cells HEMA, and 50 μM FICZ and 5 mM kynurenic acid KynA both markedly cause apoptosis to A375 cells line [19]. This suggests that different concentrations of KP metabolites may also play different roles in tumors. KMO is abnormally expressed in the cell membranes of breast cancer and other types of tumors, thereby promoting tumor migration and invasion [20]. In HepG2 hepatoma cells, kyn is a significant byproduct of tryptophan breakdown by TDO2, and its buildup in HepG2 cells may be a key mechanism of tumor immune resistance [21]. Kyn is a major metabolite of tryptophan degradation by TDO2 in HepG2 hepatoma cells, and its accumulation in HepG2 cells may be an important mechanism of tumor immune resistance [22]. PD-L1-mediated immune evasion and stemness maintenance facilitate liver metastases from colon cancer when the TDO2-Kyn-AHR pathway is activated [23]. In cervical cancer, Kyn increased the ability of tumor spheroid formation and the expression of tumor stem cell genes (e.g. Oct4 and Sox2) [24]. In non-small cell lung cancer, Kyn can increase the stemness of cells from non-small cell lung cancer by activating aromatic hydrocarbon receptors via the JAK2/STAT3 signaling pathway [25]. In addition, tobacco smoke nitrosamines produced by smoking activates c-Jun upregulation of IDO1 to promote non-small cell lung cancer carcinogenesis [26]. In pancreatic cancer, nitric oxide induces IDO1-Kyn-AhR signaling thereby enhancing the disease aggressiveness [27]. The conversion of Kyn to 3-HK in Diffuse Large B Cell Lymphoma (DLBCL) is catalyzed by KMO, and the resultant 3-HK may be implicated in controlling DLBCL cell survival through NAD+ production [28]. In addition, it has also been claimed that Kyn can promote vascular endothelial proliferation, which may provide blood supply to tumors [29].

Tryptophan metabolism can provide new ideas for tumor therapy in addition to new horizons for tumor diagnosis. Currently, Mandarano et al. have demonstrated the promise of tryptophan metabolites as markers of tumor prognosis: IDO1 catabolic activity is indicated by serum KTR (Kyn/Trp Ratio, KTR), which can be utilized as a stand-alone prognostic factor for a number of tumor types [30]. In patients undergoing immunotherapy for several solid tumor types, the serum Kyn/Trp ratio may be predictive and prognostic, and it may represent the main mechanisms of immune

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resistance [31]. High Kyn/Trp levels were linked to higher tumor stages (II and III), a high density of tumor-infiltrating lymphocytes, and a tendency toward connection with the likelihood of recurrence, just like in non-small cell lung cancer [32,33]. IDO activity, on the other hand, might be a possible cause and predictive indicator of resistance to anti-PD-1 therapy [34]. In addition, serum Kyn/Trp ratio serve as a predictor of early intervention and disease outcome in melanoma sub-stratification [35]. Additionally, KTR can be employed as a predictive factor for progression-free survival (PFS) and cancer specific survival (CSS) as well as a marker of ccRCC aggressiveness in clear cell renal cell carcinoma [36]. In conclusion, IDO1 is commonly highly expressed in pan-cancer and its expression is significantly elevated compared to normal tissues, which has the potential to be a diagnostic marker. The fact that the above metabolites have the potential to be used as tumor diagnostic markers is also a side point to the fact that they are more different in cancerous and normal tissues, which makes tumor therapy targeting the kynurenine pathway safer.

3 Tumor Therapeutic Strategies Targeting the Kynurenine Pathway

3.1 Direct targeting of key enzymes in tryptophan metabolism

3.1.1 Key enzymes in kynurenine pathway

By targeting key enzymes of metabolism, it can effectively reduce the amount of downstream unfavorable metabolites, thus achieving tumor suppression. Tryptophan catabolism can also be divided into the following two types according to the mode of action of the key enzymes of metabolism: either shattering the indole ring to generate kynurenine or retaining it (as in the case of 5-hydroxytryptamine, melatonin, and indole pyruvate) [37]. Three enzymes—IDO1, IDO2, and TDO2—break the indole ring in mammals, which are named for their ability to catalyze the binding of two oxygen atoms to the product. Each of these enzymes exhibits controlled expression and a distinct tissue specialization. TDO is considered to be the main regulator of Trp catabolism and is in charge of controlling Trp contents [9], while under pathological conditions IDO1 plays an important role in Trp catabolism [38]. Meanwhile, the enzymatic activities of these enzymes towards the substrate tryptophan differed greatly, with IDO1 (K_m~20 μmol•L^{-1}) > TDO2 (K_m~90 μmol•L^{-1}) > IDO2 (K_m~6.8 mmol•L^{-1}) [39]. Therefore, we believed that IDO1 and TDO2 may be closely related to immune function, thus making it potential for intervention in tryptophan metabolism to regulate tumor immunity.

IDO1 is a 45 kDa monomeric enzyme containing haemoglobin, which can usually be crystallized into a dimeric form (Figure 2A) [40], the active site consists of two lipophilic regions: one region contains the heme, which is the large container for the tryptophan catalytic site, and the other region is the entrance to the binding site [41]. Two phosphorylated tyrosine residues, Y115 and Y253, control IDO1 activity. Through the phosphorylation process, Y115 and Y253 can alter the IDO1

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conformation and reduce its activity [42]. IDO1 can be found in a diverse range of immune cells, including astrocytes, macrophages, and dendritic cells (DC) [43]. Moreover, it exhibits widespread presence in tumor cells (Figure 3A) [44].

TDO2 is a homotetrameric cytosolic enzyme with a molecular mass of 35-45 kDa encoded by the TDO2 gene. hTDO monomers consist of 15 α-helices that can be divided into three major regions: the N-terminal region, the large structural domain and the small structural domain. Three bidirectional axes that are perpendicular to each other connect the four monomers, with stronger interaction between the two connected monomers, in which the two C-shaped dimers are clamped perpendicular to each other to form a tight tetramer (Figure 2B) [45]. Compared to hIDO1, hTDO necessitates a highly specific substrate for binding, with L-Trp being the sole relevant native substrate [46]. TDO2 is predominantly localized within hepatic tissues, with marginal expression detected in adrenal glands, lungs, and brain (Figure 3B) [47]. In response to regulation by certain stimuli, such as glucocorticoids and norepinephrine, TDO2 can be expressed in different tissues, such as the epididymis, placenta, testis, brain, and pregnant uterus [41].

Clarifying the structure of the key enzyme is beneficial to drug design, and drugs with high selectivity can reduce side effects, while clarifying the distribution of the key enzyme in different tissues is beneficial to the selection of more targeted inhibitors according to the location and characteristics of the tumor.

3.1.2 Traditional Key Enzyme Inhibitors

Based on the relevance of high IDO1 and TDO expression in many tumors and their poor prognosis, and the role of many products of the KP metabolic in driving tumor development, we believe it is reasonable to explore IDO inhibitors, TDO inhibitors, and dual IDO1/TDO inhibitors. IDO expression and activity are influenced by a variety of factors and are regulated at the transcriptional level by the following modalities: (1) NF-κB pathway; (2) CCCTC-binding factor (CTCF)[48]; (3) Specific DC response elements bind to AhR and promote Kyn-dependent IDO1 expression [49]. IDO1 is primarily governed by the immunogen-stimulated proteasomal degradation mechanism. No selective TDO inhibitors have entered clinical studies yet, and three dual IDO1/TDO inhibitors have entered clinical studies. The common IDO inhibitors are: tryptophan analogs (D-1MT), aryl imidazoles and their derivatives (4-PI), N-hydroxyamidine (epacadostat), quinones, quinolines and others (BMS-986205), etc. Among them, D-1MT can indirectly inhibit the KP by reversing tryptophan depletion-induced mTORC1 inhibition in human Teff cells[50,51]; N-Hydroxyamidine is more common in many clinical trials, but unfortunately some studies have shown a lack of efficacy, such as the study by Georgina et al, which showed that in individuals with pembrolizumab-treated melanoma that is incurable or metastatic, it is ineffective when used in conjunction with a placebo [52]. In addition,

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the data show that the end product of epacadostat metabolized in vivo by the enzyme UGT1A9 has a half-life of only 2.5 h, is relatively poorly hydrophobic (CLogP = 0.09), and has low oral bioavailability [53]. IDO1 can be considered as a moonlighting protein [54], i.e., it has additional functions in addition to its catalytic activity. Moonlighting proteins exhibit a distinct behavior, as they transition between functions by adjusting their structural shape in response to shifts in external conditions. These variations encompass alterations in the cell's redox status, temperature fluctuations, post-translational modifications (such as phosphorylation), changes in where they are located within the cell, and their interactions with other peptides. The currently available studies suggest that epacadostat is capable of inhibiting both [55]. However, recent research indicates that epacadostat inhibits the activity of the IDO1 enzyme while stabilizing its lipid form. This promotes tyrosine phosphorylation and binding with the phosphatase SHP-2, contributing to the oncogenic phenotype of SKOV-3 cells [56]. This suggests that, the development of IDO1 inhibitors should focus on their enzymatic as well as non-enzymatic activities. Typical TDO inhibitors include: indoles (LM10), naphthalenetriazodiones, aminoisoxazoles and other structures (catechol, L-adrenaline, p-benzoquinone, etc.). The aminoisoxazole TDO inhibitors are less stable in whole blood. Dual IDO1/TDO inhibitors contain: indoles, quinone derivatives, indazoles, etc[45].

Traditional drugs have achieved some success in clinical trials, but they have gradually revealed problems such as adverse reactions and low bioavailability. Therefore, scholars have begun to utilize new technologies to improve the shortcomings of traditional drugs.

3.1.3 Novel Delivery and Drug Carrier Methods Combined with Traditional Inhibitors

In order to address the shortcomings of traditional inhibitors mentioned above, such as short half-life, poor hydrophilicity, and low cellular uptake, researchers are striving to load effective inhibitors onto new nanocarrier and delivery systems to enhance drug efficacy. Chemical crosslinking of engineered bacteriophage hydrogels (M13 gel) may yield photothermal palladium nanoparticles (PdNPs) in situ on the pVIII coat protein, resulting in M13@Pd gel. Loading the IDO1 inhibitor NLG919 onto the gel's biologically active gel system can reverse immune suppression and dramatically increase the anti-breast chemotherapy outcomes [57]. Sonodynamic therapy (SDT)-triggered prodrug-loaded hydrogel delivery systems have also been used to load NLG919. When irradiated with SDT, the generated $^1O_2$ not only induces immunogenic cell death but additionally disrupts the $^1O_2$-cleavable linker to precisely activate NLG919 prodrug [58] NLG919 has also been loaded onto other nanozyme therapeutic agents to enhance therapeutic efficacy [59-61] and its combination with platinum-based drugs has been designed to provide a new approach for combined chemotherapy and immunotherapy for osteosarcoma[62]. In addition to NLG919,

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other IDO1 inhibitors have been designed to be loaded onto nanoparticles to improve their bioavailability and significantly improve immune cascade reactions and tumor microenvironment (TME) improvement in vivo, resulting in remarkable tumor suppression and prolonged survival [63,64]. Indeed, novel delivery and drug carrier systems have effectively addressed the shortcomings of traditional inhibitors. However, certain design aspects of traditional inhibitors, such as non-enzymatic activity, cannot be simply compensated for by improving delivery methods alone. Further improvements are required in the structural design, starting from the mechanism.

3.2 Targeted Inhibition of Other Enzymes and Metabolites in Tryptophan Metabolism

3.2.1 Other enzymes in kynurenine pathway

IDO2 is a 45 kDa enzyme, which has a bis (His) six coordinate heme iron site with two distinct Fe–NHis distances[65]. IDO2 has a large predicted domain with thirteen α-helices and two 3_{10}-helices. Mouse IDO2 has a smaller predicted domain with six α-helices, two short β-sheets, and three 3_{10} helices (Figure 2C) [66]. The amino acid similarity between human and mouse IDO1 and IDO2 proteins stands at 43%. IDO2 has little or no tryptophanolytic activity, plays distinct immunomodulatory roles in cancer and autoimmune diseases, depending on the context [67]. Recent studies have suggested that IDO2 may modulate disease processes by virtue of its non-enzymatic activity [68]. IDO2 is mostly expressed in the liver, kidney, brain, placenta, and colon (Figure 3C) [69].

hIL4I1 is an N-glycosylated secretory protein consisting of 567 amino acids that is predominantly found in immune organs, with lymph nodes and the spleen expressing the most of it. In addition to B cells, it has also been reported to be present in germinal center macrophages, inflammatory myeloid cells, and antigen-presenting cells [70,71]. Nevertheless, there remains a scarcity of information regarding the present enzymology and functionality of IL4i1 [72], which also increases the difficulty of designing IL4i1 inhibitors.

KMO is a class A FAD monooxygenase typically characterized by a single gene encoding a FAD-binding domain [73]. hKMO consists of 486 amino acids, has a molecular weight of about 50 kDa, and contains two structural domains, in addition to a large FAD-binding region it also contains a small N-terminal structural domain consisting of an α helix and an antiparallel β-sheet. hKMO has a small N-terminal domain consisting of an α helix and antiparallel β-sheet [74].

3.2.2 Other enzymes inhibitors

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3.2.2.1 IDO2 inhibition

Since a variety of KP metabolites are able to affect tumors and IDO2 has been shown to have a role in certain tumors that cannot be ignored. In addition, IDO2, which is structurally similar to IDO1, was knocked down in several animal models resulting in tumor growth inhibition, suggesting that it also has the potential to serve as a viable target for cancer therapy [75] more and more scholars are placing their research focus on the development of combined inhibitors of IDO1 and IDO2. The dual inhibitor of IDO1/IDO2, IDO1/2-IN-1, significantly inhibits tumor progression. Notably, in a xenograft mouse model, IDO1/2-IN-1's in vivo antitumor potency (TGI = 69.7%) was much greater than epacadostat's (TGI = 49.4%), highlighting the benefits of dual IDO1/2 inhibitors in tumor immunotherapy [76]. We are also looking forward to the clinical application of this dual inhibitor. However, since it is downregulated in some tumors (e.g., cervical cancer[77]), Therefore, we suggest that the development of new IDO2 inhibitors should be highly selective, distinguish between IDO1 and IDO2, which will better enable personalized therapy.

3.2.2.2 IL4i1 inhibition

In many tumors, IDO1 is highly expressed, AhR levels are also elevated. Sadik et al. analyzed 32 types of tumors using weighted gene co-expression network analysis (WGCNA) and found that in 9 of them, other tryptophan metabolism enzymes activated the aryl hydrocarbon receptor, specifically Interleukin 4 inducible protein 1 (IL4i1) [78]. Thus far, tryptophan metabolism enzyme inhibitors have not been successful in clinical trials, possibly due to the overlooked role of IL4i1. In the tumor microenvironment, especially in myeloid cells, IL4i1 and IDO1 show overlapping expression patterns. We speculate that blocking IDO1 is still a viable supplementary treatment. Consideration must be given to the overlapping effects of IL4i1, as simultaneous inhibition of both enzymes may be necessary for a positive impact in cancer treatment [79]. Several small molecule inhibitors are being designed [80], but given the limited understanding of IL4i1's role in regulating tumor immunity, we believe that further basic research is needed to better inform drug design.

3.2.2.3 Other enzymes inhibition and metabolites degradation products

Utilizing a pharmacologically optimized enzyme (polyethylene glycolylated kynureninase; hereafter referred to as PEG-KYNase), which degrades Kyn into non-toxic and easily removed metabolites, has been shown to prevent development of tumors. Combining PEG-KYNase with approved checkpoint inhibitors or cancer vaccines has demonstrated notable therapeutic efficacy in treating large B16-F10 melanoma, 4T1 breast cancer, and CT26 colon cancer tumors [81]. Due to restricted bioavailability and the inherent instability of proteins in vivo, maintaining sufficiently high concentrations of KYNase in TME has been challenging. Some studies have addressed this issue by loading KYNase onto biodegradable and implantable

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nanoparticle carriers called "BIND," enabling sustained release around the tumor [82]. A different immunomodulatory pathway linked to decreased KMO expression and increased KYNA synthesis, in addition to IDO1, also leads to defective effector $CD4^+$ T cell responses, indicating that KMO could be a viable target for cancer treatment [83]. Research by Kesarwani et al. found that tumors in $Kynu^{-/-}$ glioma mice exhibited higher levels of $CD8^+$ $CD69^+$ T cell infiltration and significantly reduced expression of $CD206^+$ M2 macrophages. This might be explained by the transcription factor Foxo1 being phosphorylated and degraded by QA. Foxo1 binds to the promoter of PPARγ and inhibits its production endogenously. Therefore, they propose that targeting downstream tryptophan metabolism may alter the immune characteristics of tumors more effectively than solely targeting IDO1 or TDO [84].

3.3 Inhibitors Derived from Mechanisms Regulating Tryptophan Metabolism to Modulate the Microenvironmen

Metabolic changes in the tumor micro-environment (TME) not only affect the biological activity of tumor cells, which become more aggressive in migration and proliferation, but also affect the immune response of the body, either by inhibiting tumor development or by supporting tumor immune escape[85]. A better knowledge of the variables affecting the local immunological balance within TME will be necessary to enhance clinical responses to immune checkpoint inhibition. Stewart et al. integrated multi-omics data such as single-cell RNA sequencing and spatial transcriptomics of classical Hodgkin's lymphoma, revealing the tumor's immune microenvironment rich in classical monocytes, macrophages, and DC cell infiltration. Among them, cDCs and monocytes express immune checkpoint PD-L1, TIM-3, and IDO[86]. This suggests that tryptophan metabolism not only affects tumor cells but also regulates the immune microenvironment through immune cell expression. Meanwhile, some scholars characterized the tumor microenvironment where cancer cells overexpressing the IDO1 gene are located through MALDI MSI. The findings indicate that Trp depletion and Kyn elevation suppress T cell effector function and metabolism, while fostering a regulatory T cell phenotype, M2 macrophages, and the generation of tolerant dendritic cells[87].

3.3.1 T cells

γδT cells are immune cells that recognize cancer antigens and belong to the atypical T cell family. MHC I and II do not limit these atypical T cells' ability to recognize antigens, and they exhibit potent cytotoxic effects against cancer cells, tumor stem cells and solid tumors while protecting normal tissues [88]. Kyn inhibits degranulation and cytotoxicity of γδT cells in PDAC of pancreatic ductal adenocarcinoma [89]. $FOXP3^+$ Tregs is a distinct subpopulation of lymphocytes that promote tumorigenesis by clearing self-reactive T cells from the thymus and peripheral organs, FOXP3 loss-of-function mutations in animal models and humans result in loss of potential for differentiation to Treg cells and cause highly aggressive,

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lethal, systemic immune-mediated inflammatory disease, Kyn reduces Th1/Th22 development while massively inducing AhR-dependent cells to produce FoxP3$^+$ Tregs, and IDO inhibitors reverse that process [90-94]. Th17 cells' expression of IL-23 and IL-17 was suppressed when KynA was present [95]. Inhibiting KMO increases CD4$^+$ T cell counts in SIV-infected rhesus monkeys, suggesting a regulation of CD4$^+$ T cells by KP metabolism [96]. KynA strongly suppressed CD4$^+$ T proliferation and IFN-γ release in melanoma [97]. L-Kyn, 3-HK, 3HAA and QA also can inhibit T cell activation and proliferation [98-100]. Nevertheless, it has been proposed that kynurenine uses SLC7A5 to pass through the T cell membrane. Consequently, only T cells that express SLC7A5 may be affected by kynurenine [101]. Trp catabolic enzymes also play a role in driving adaptive immune resistance mechanisms by inhibiting the cytolytic function of CD8$^+$ T cells [102,103]. According to a study, Kyn-AhR increases the expression of the programmed cell death protein 1 (PD-1) on CD8$^+$ T lymphocytes, indicating a possible therapeutic approach to target this network in cancer [104,105].

3.3.2 Tumour-associated macrophages (TAMs)

TAMs are the most prevalent immune cells in the majority of tumors and make up the diverse and changeable cell type of TME, making up around 30% of all the cells in tumor tissues [106]. TAMs give malignant cells nutritional assistance, which promotes disease development and treatment resistance [107]. TDO2 and IDO1 silencing in mouse glioma cells decreased the expression of the immunosuppressive gene Arg-1 (M2 polarization) in TAM, suggesting that Kyn secreted by gliomas may regulate the phenotype of TAMs [108]. Low systemic kynurenine levels are linked to a lower overall survival rate. Glioblastoma cell-produced kyn activates AhR in TAMs to enhance CCR2 expression, drives TAM recruitment in response to CCL2, drives KLF4 expression, and inhibits NF-κB expression in TAMs [108,109]. IDO1 expression and kynurenine metabolism may promote autophagy in cervical cancer cells and facilitate its clearance by macrophages [110].

3.3.3 B cells

It is yet unknown how Trp metabolism directly affects B cell development and proliferation. According to some theories, IDO1 is a crucial feedback mechanism that restricts the antibody response and B cell proliferation. It also promotes apoptosis and adversely controls B cell proliferation following LPS stimulation [111]. Myeloid-derived suppressor cells MDSC expressing IDO cause B cells proliferation [112]. It has recently been demonstrated that IDO1 and IDO2 seem to have opposing functions in the control of B cells, with IDO2 promoting inflammatory B cell responses and IDO1 suppressing them [113].

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3.3.4 Natural killer cells (NK cells)

L-Kyn inhibits the cytokine-mediated upregulation of the expression and function of particular trigger receptors, such as NKp46 and NKG2D, that cause NK cells to kill target cells by specific identification, which results in tumor immune escape [114,115]. In multiple myeloma, KMO inhibits the activation of defective plasmacytoid dendritic cells and initiates the cytolytic activity of certain NK cells and cytotoxic T lymphocytes against tumor cells [116]. The activation of T and NK cells is facilitated by the increased expression of "CXCL11" as well as "KLRD1" that results from altered 3-HAA concentration [117]. IDO in thyroid cancer cells produces kynurenine, which leads to NK cells dysfunction by a possible mechanism that reduces NK cells function through the signal transduction and transcriptional activator STAT1 and STAT3 pathways [118]. Through the AhR-IDO axis, both acute and long-term endurance exercise can control NK cells and contribute to immunological modulation [119].

3.3.5 Dendritic cells (DCs)

Binding of IFN-γ to IDO promoter region induces IDO expression in DC cells[120,121]. DC regulation of T cells induction may be through intracellular IDO, and the data suggest that under specific conditions, cDC1 selectively expresses IDO, which inhibits T cells proliferation and triggers tumor immune escape [122]. Kyn-AhR helps maintain the DC tolerance phenotype by maintaining self-amplification of IDO [123]. In DCs, IDO downregulation also results in a rise in CD4+ T cell proliferation and a decrease in Treg cells [124]. KynA Plays an crucial role in regulating DC by blocking GPCR35 and the downregulation of IFN-γ and cAMP [95].

3.3.6 Cancer associated fibroblasts (CAFs)

By promoting the growth, invasion, and metastasis of cancer cells, CAFs contribute significantly to the advancement of tumors [125,126]. Itoh et al. found that CAFs supernatants stimulate normal fibroblasts (NFs) to become CAF-educated fibroblasts (CEFs), which further express IDO1 and KYNU by secreting extracellular matrix proteins, ultimately leading to tumor cell dissemination [127]. CAFs up-regulate tryptophan TDO expression, leading to enhanced secretion of Kyn. Kyn produced by CAFs can upregulate AhR expression and activate AhR-AKT-STAT3, which causing tumor cell proliferation [128]. $PDPN^+$ CAF (podoplanin-positive CAFs) $PDPN^+$ CAFs (podoplanin-positive cancer-associated fibroblasts) promote resistance of HER2-positive breast cancer to trastuzumab by secreting immunosuppressive factors IDO1 and TDO2 [129].

3.3.7 Local or Global Tumor Microenvironment

The regulatory role of tryptophan metabolism on specific cells within the microenvironment appears relatively clear in current research. However, existing

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studies may overlook some practical considerations. For example, in vitro inhibition of T cell proliferation requires tryptophan concentrations to be below 0.5-1 μM, whereas human plasma concentrations vary from 50 to 100 μM. This suggests that in future research, we need to consider the microenvironment as a whole and validate the accuracy of in vitro experimental results in vivo.

Some of the latest research has begun to view the local balance of the tumor microenvironment as a whole, for instance, considering antigen-presenting cells collectively. When tryptophan metabolism enzymes are active, antigen-presenting cells that would normally produce inflammatory cytokines (such as IL-12) instead generate inhibitory cytokines (such as IL-10). This suggests that the upregulation of tryptophan metabolism enzymes can alter the characteristics of antigen-presenting cells themselves and shift the entire local environment from immunogenicity to tolerance [130]. The communication between immune cells has also received more attention. Luis et al. established that the contact between Tregs and tumor-associated macrophages is necessary for the immunological suppression mediated by IDO-Kyn-AHR [131]. Mature DCs can express IDO1 and interact with tumor-reactive exhausted $CD8^+$ T cells and Tregs, collectively forming a malignant immune suppression cycle and mediating immune escape in cervical cancer [132]. These findings suggest that tryptophan metabolism does not act independently on specific immune cells but rather facilitates communication among various cells to create an environment conducive to tumor immune evasion. Various alterations in tumor cells and the surrounding tumor microenvironment are caused by abnormalities in tryptophan metabolism in gliomas. Glioblastomas may be able to avoid immune system responses thanks to these metabolic alterations, which would encourage the growth of tumors [133]. To acquire a better insight into global influence of tryptophan metabolism on the microenvironment, Zhang et al[134] Analyzed data from multiple public databases and 1,523 patient samples. The results suggest that the high-scoring group of tryptophan metabolism-related genes (TRGs) is correlated with more infiltration of immune cells and a "hot" immune phenotype, which is related to shorter overall survival in this group. This indicates that tryptophan and its metabolism play an important role in reshaping the immune landscape. Similarly, research in low-grade gliomas has also demonstrated this phenomenon [135]. The above results collectively indicate that future research on tryptophan metabolism is transitioning from its inhibitory effects on specific microenvironment cells to interactions among multiple cells and even the microenvironment as a whole. This research is not limited to malignant tumor cells or immune cells themselves. It is anticipated that new mechanistic research will aid in the development of new inhibitors or the enhancement of current ones.

In conclusion, the metabolism of tryptophan is crucial for controlling the tumor microenvironment. Its regulatory effects on tumors extend beyond the tumor cells themselves, mostly affecting other cells (figure 4). Only by grasping the regulatory

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role and mechanism of tryptophan metabolism in the complex microenvironment as a whole can we propose a better response.

3.3.8 AhR inhibition

Although there are still questions about IDO1 inhibition, there is a lot of preclinical data to support the ongoing development of inhibitors of the Trp-Kyn-AhR pathway to improve immune checkpoint and other cancer treatments [136]. A highly selective exogenous or endogenous AhR ligand inhibitor, BAY 2416964, exhibits good tolerability upon oral administration in vivo, inducing a pro-inflammatory tumor microenvironment and demonstrating anti-tumor efficacy in syngeneic mouse models [137]. Additionally, activation of AhR by tryptophan metabolites can induce T cell expression of PD1, an effect significantly abolished by the AHR antagonist CH223191. The role of KP metabolites and key enzymes in the tumor immune-suppressive icroenvironment is primarily mediated through activation of the AhR receptor, which was one potential imitation of past IDO1 inhibitor clinical trials—some inhibitors themselves act as AhR agonists [138]. Hence, drug design should avoid this aspect. However, AhR inhibitors also remain controversial, primarily due to the dual nature of AhR. Besides serving as a ligand-activated transcription factor that promotes tumor immune evasion, AhR can also act as a ligand-dependent E3 ubiquitin ligase, promoting the degradation of β-catenin by tryptophan metabolites in intestinal carcinogenesis, thereby inhibiting cancer development [139]. Therefore, optimizing the anticancer properties of AhR will be a focal point of future research.

3.3.9 Compensatory metabolic alterations interference

In addition to the paradoxical role of AhR in tryptophan immune regulation, the immunosuppressive environment caused by aberrant activation of the KP pathway can also be counteracted by compensatory metabolic alterations induced by KP activation. Tryptophan degradation via the kynurenine pathway is efficiently blocked by IDO1 inhibition, which also causes metabolic adaptation that redirects tryptophan degradation to the serotonin pathway. This contributes to the clinical failure of IDO1 inhibitors by raising nicotinamide adenine dinucleotide levels, which in turn impair T cell proliferation and function. Coupling IDO1 inhibition with A2a/A2b receptor blockade enhances the survival of ovarian cancer mice overexpressing IDO1 and strengthens anti-tumor immune features, suggesting the importance of understanding the regulatory role and mechanisms of tryptophan metabolism in the immune environment for devising new therapeutic strategies[140]. It is essential to not only focus on the modulation of the microenvironment by KP itself but also consider the impact of compensatory pathways alterations following KP changes on the microenvironment.

3.4 Combination Therapy Approaches with Other Anticancer Drugs

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3.4.1 Combination with other anticancer therapy

Combining targeted therapies with other drugs often enhances the efficacy of treatments targeting tryptophan metabolism. Song et al. utilized a self-amplifying ROS-responsive nanocarrier co-loaded with the immunogenic inducer paclitaxel (PTX) and the IDO1 inhibitor 1-MT. This nano-platform demonstrated efficient immunogenic cell death, leading to robust T cell infiltration and triggering anti-tumor immune responses. In 4T1 tumor-bearing mice, immune-suppressive tumor microenvironment controlled by IDO inhibition-mediated Tregs and M2-TAMs infiltration simultaneously resulted in considerable primary tumor regression and decreased lung metastasis. These results imply that employing ROS-amplifying nanoplatforms to co-deliver immunogenic inducers and IDO inhibitors has enormous potential for tumor chemotherapeutic immunotherapy [141].

Numerous cancer types can go into remission as a result of viral infections that occur naturally in humans. Clinical trials for the oncolytic virus Delta-24-RGD are presently underway to treat liver metastases (NCT04714983) and malignant gliomas (NCT03714334). Combining it with IDO inhibitors can improve resistance of human glioblastoma to oncolytic viruses, leading to enhanced immunotherapeutic efficacy. This suggests that IDO1 inhibition's molecular and immunological effects could enhance the results of other virotherapy-treated malignancies [142].

One of the most well-known combination therapies is epacadostat and pembrolizumab. While the combination therapy of epacadostat and pembrolizumab demonstrates good tolerability, its anti-tumor activity is limited in clinical trials. Phase III clinical trial of IDO1 inhibitor epacadostat in combination with PD-1 checkpoint inhibitor pembrolizumab for melanoma declared a failure in 2018 [52]. Relevant data indicate that obtaining maximum suppression of IDO1 activity in the setting of anti-PD-1 therapy may require greater dosages of epacadostat than those tried in prior clinical studies [143]. Increasing the local concentration of IDO1 inhibitors is indeed effective, and understanding the mechanism behind the need for higher concentrations of IDO1 inhibitors in anti-PD-1 therapy can better optimize treatment regimens.

Additionally, recent research has shown that the kynurenine pathway interacts with and modifies the activity of numerous other transduction systems, that pharmacologically modulating the kynurenine pathway can indirectly affect anticancer protection, and that altering these interacting pathways can indirectly affect inflammatory states and tumor development [7]. It may also be a unique strategy to increase activity to combine IDO inhibitors with medications that block other signals, like those produced by PIK3CA mutations that may accompany IDO1 overexpression [144].

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3.4.2 Chimeric Antigen Receptor T-cell Therapy（CAR T）

Several challenges have impeded the use of CAR T treatment for solid malignancies. IDO1 inhibition in conjunction with immune checkpoint blockade has been demonstrated in preclinical and clinical research to produce long-lasting cancer therapeutic benefits. For example, in mice models of colorectal cancer, miR-153 inhibits IDO1 expression in colorectal cancer cells, increasing the therapeutic efficacy of CAR T-cell treatment [145]. IDO1 has the ability to suppress anti-GD2 CAR (GD2.CAR) T cells and NK cells primarily by preventing them from producing IFNγ. Combining NK or GD2.CAR T cells with IDO1 inhibitors provides a fresh approach to immunotherapy's long-term efficacy [146].

3.4.3 immune-modulating vaccines

One promising approach to cancer immunotherapy is antigen peptide vaccination. However, due to low antigenicity and insufficient immune response stimulation, cationic liposomes co-delivering tumor vaccines and IDO inhibitors stimulate anti-tumor T cell immunity while simultaneously reversing immune-suppressive tumor microenvironments. This provides a promising platform for cancer immunotherapy[147]. Targeting both malignant and regulatory cells, the T-win® immune-modulating anti-cancer medicines work by triggering the body's natural anti-Tregs. Because they can identify proteins like IDO or PD-L1 that are produced by regulatory immune cells, anti-regulatory T cells are naturally occurring T cells that can target these cells directly. In the end, they draw pro-inflammatory cells to the tumor microenvironment, which has a direct effect on immune suppression mechanisms and may change tumor antigen tolerance. IFN-γ causes circulating IDO or PD-L1-specific anti-Tregs to proliferate, and pre-incubation with IFN-γ improves their sensitivity to target cell recognition of IDO or PD-L1-specific anti-Tregs. Thus far, vaccines that target IDO or PD-L1 have been shown to be safe and to have little harm [148]. A deeper understanding of tryptophan metabolism's regulatory role in the tumor microenvironment can aid in the development of new immunotherapeutic approaches.

In summary, tryptophan metabolism plays a crucial role in the initiation and progression of tumors, intimately intertwined with shaping a microenvironment conducive to tumor evasion. As scholars delve deeper into its mechanisms in tumor regulation, strategies targeting tryptophan metabolism for cancer treatment are becoming increasingly refined.

Author contributions

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SL, GZ, YX and TL had a substantial contribution to the conception of the work, drafted the work, revised it critically and approved it for publication. BS and DZ were responsible for project administration and funding acquisition. All authors contributed to the article and approved the submitted version.

Conflict of Interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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Figures

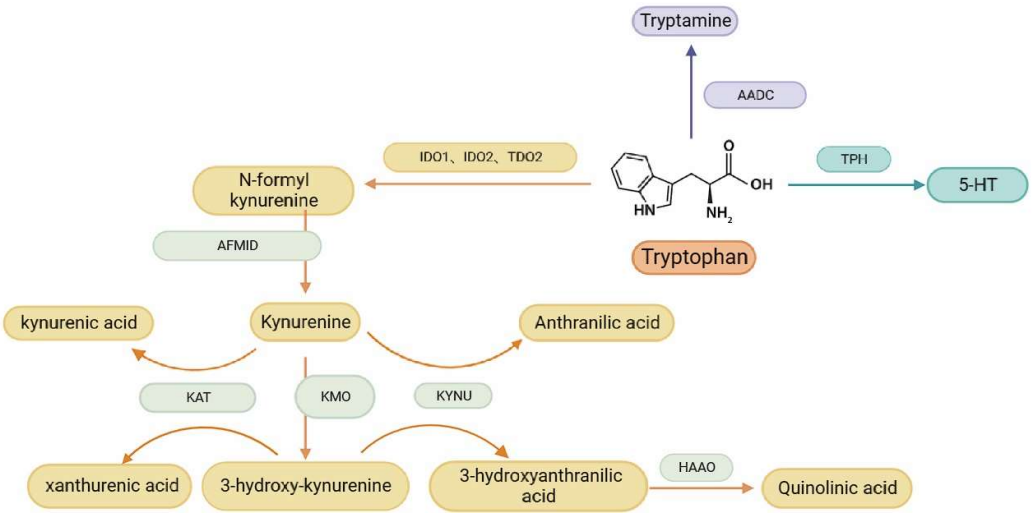

Figure 1: The kynurenine pathway, the tryptamine pathway and the serotonin pathway together constitute the tryptophan catabolic pathway.

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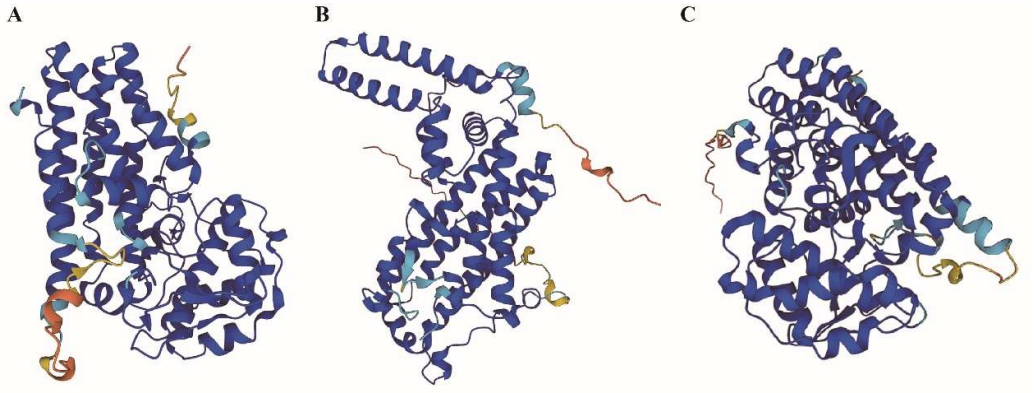

Figure 2: Structure of key enzymes in tryptophan metabolism. (A)1DO1.(B) TDO2. (C)IDO2.

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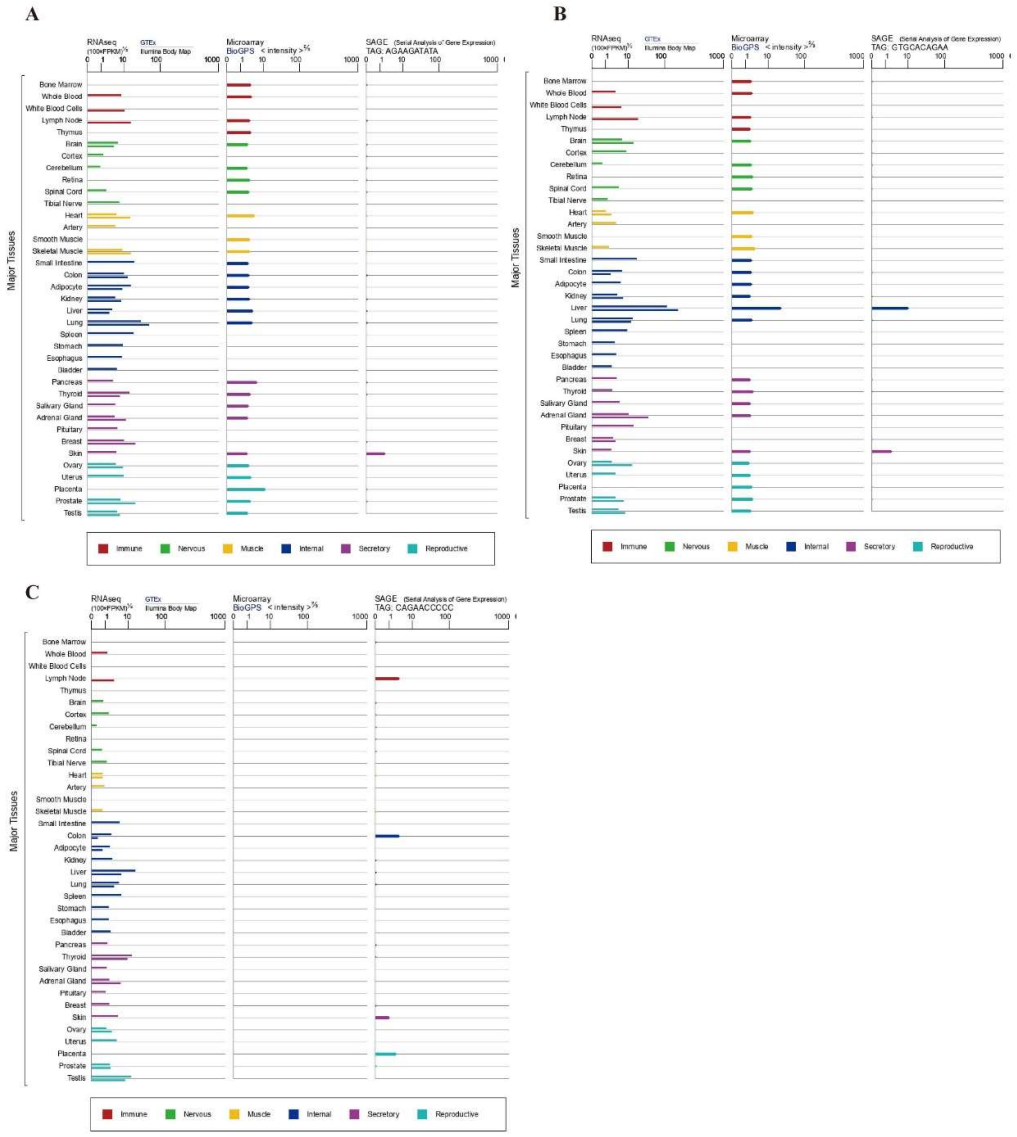

Figure 3. mRNA expression in normal human tissues from GTEx, llumina, BioGPs, and SAGE.(A) IDO1.(B) TDO2. (C)IDO2.

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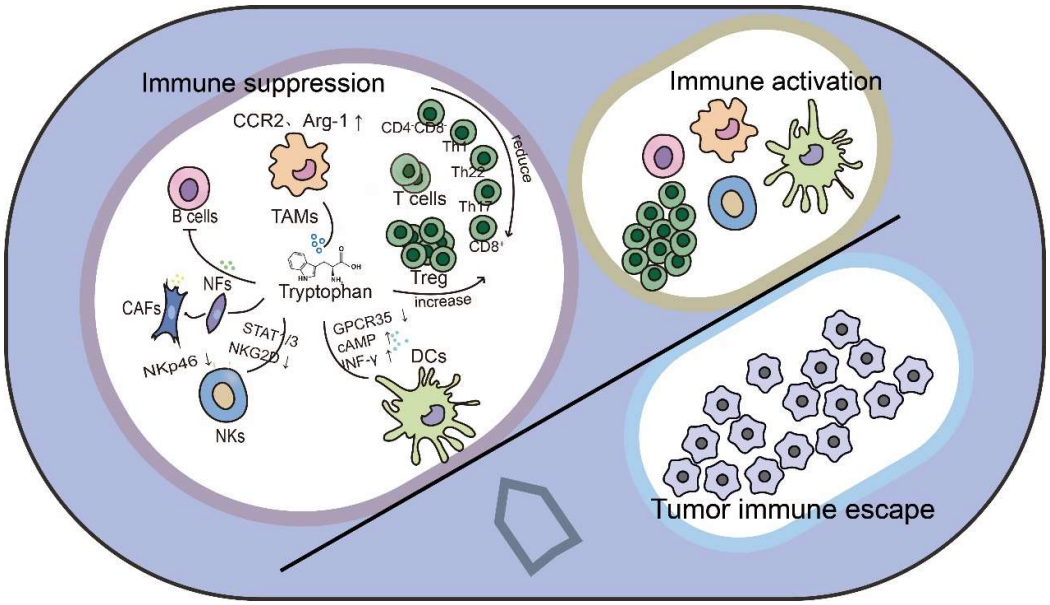

Figure 4. Effect of tryptophan metabolism on cells in the tumor microenvironment.

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