

Targeting amino acid metabolism in cancer growth and anti-tumor immune response

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Abstract

Recent advances in amino acid metabolism have revealed that targeting amino acid metabolic enzymes in cancer therapy is a promising strategy for the development of novel therapeutic agents. There are currently several drugs in clinical trials that specifically target amino acid metabolic pathways in tumor cells. In the context of the tumor microenvironment, however, tumor cells form metabolic relationships with immune cells, and they often

compete for common nutrients. Many tumors evolved to escape immune surveillance by taking advantage of their metabolic flexibility and redirecting nutrients for their own advantage. This review outlines the most recent advances in targeting amino acid metabolic pathways in cancer therapy while giving consideration to the impact these pathways may have on the anti-tumor immune response.

Key words: Amino acid metabolism; T cells; Anti-tumor immune response; Tumor microenvironment; Cancer therapy

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Core tip: Amino acid metabolism has been a focus of increased attention by cancer researchers and immunologists due to its importance for the metabolic reprogramming of proliferating cells. Many amino acid enzymes are described as immunosuppressive in the tumor microenvironment and targeted for cancer therapy. This review addresses the metabolic control of tumor progression in the context of anti-tumor immunity and discusses current and future therapeutic approaches. Special emphasis is given to the emerging role of branched chain amino acid metabolism in cancer and immunity highlighting some recent work by our research group.

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INTRODUCTION

Two functionally distinct types of cells, cancer and T cells, undergo similar metabolic reprogramming during

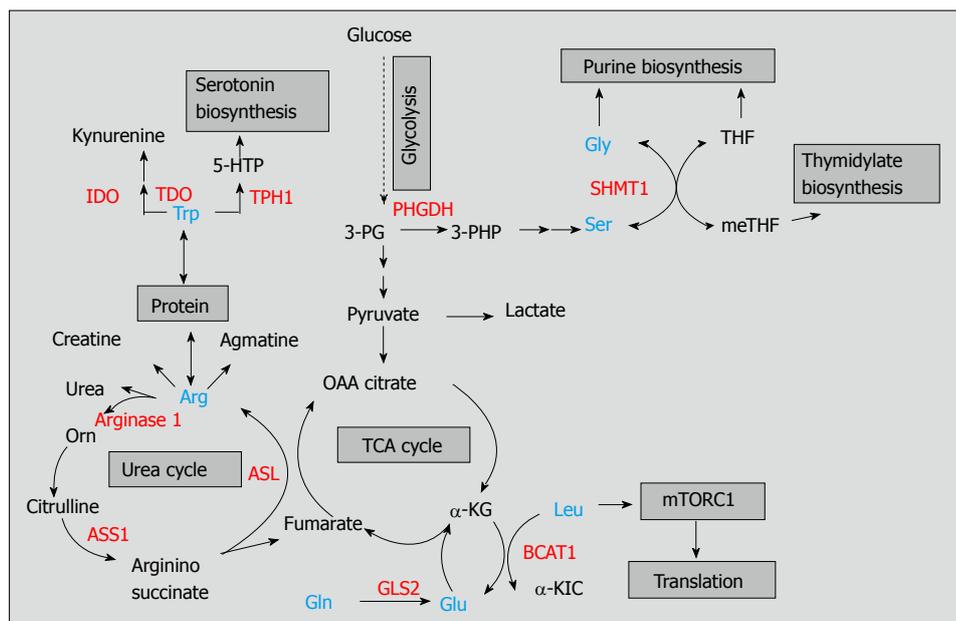


Figure 1 Schematic representation of amino acid metabolic pathways targeted in cancer therapy. The amino acid metabolism of Arg, Trp, Ser, Gly, Gln, Glu, and BCAAs interconnects with major catabolic and biosynthetic pathways shown in gray. Arg is an important precursor for creatine, urea, and agmatine synthesis while Trp is important for kynurenine and serotonin biosynthesis; Ser and Gly are major sources of methyl groups during purine and thymidylate biosynthesis; Leu is a known activator of complex 1 of mTOR pathway and Gln/Glu provide intermediates for the TCA cycle and restore glutathione to its reduced form. Metabolic enzymes catalyzing important steps in the metabolism of these amino acids are involved in clinical and/or preclinical cancer studies and are denoted in red. 5-HTP: 5-hydroxytryptophan; 3-PG: 3-phosphoglycerate; 3-PHP: 3-phosphohydroxy pyruvate; THF: Tetrahydrofolate; meTHF: Methyltetrahydrofolate; OAA: Oxaloacetate; α -KG: α -ketoglutarate; α -KIC: α -ketoisocaproate; Trp: Tryptophan; Arg: Arginine; Gln: Glutamine; Glu: Glutamate; BCAAs: Branched chain amino acids; Ser: Serine; Gly: Glycine; mTORC1: Complex 1 of the mammalian target of rapamycin; IDO: Indoleamine-2,3-dioxygenase; TDO: Tryptophan-2,3-dioxygenase; TPH1: Tryptophan hydroxylase-1; BCATc: Cytosolic branched chain aminotransferase; ASS1: Argininosuccinate synthetase 1; ASL: Argininosuccinate lyase; GLS2: Glutaminase 2; PHGDH: Phosphoglycerate dehydrogenase; SHMT1: Serine hydroxymethyl transferase 1.

proliferation to support their increased biosynthetic and energy demands^[1,21]. To meet these demands, cancer cells need a continuous supply of nutrients that maintain abnormal growth and rapid division during cancer progression. Activated T cells also rely on a continuous nutrient supply to ensure proper differentiation and performance during cell-mediated immunity against pathogen attacks or while fighting cancer^[3]. In areas with poor nutrient and oxygen access, such as the tumor microenvironment^[4] and inflammatory sites^[5], cellular metabolism must adapt to promote continued survival and function of the cells residing in and/or migrating to these areas. Not surprisingly, both cancer and T cells rely on high rates of glycolysis while retaining mitochondrial respiration, a phenomenon known as the Warburg effect^[6,7]. Ever since Otto Warburg observed that cancer cells produced lactate from glucose even under non hypoxic conditions^[7], subsequent reports demonstrated that high rates of glycolysis are beneficial for cell survival, providing energy and biosynthetic material for the synthesis of new proteins, lipids, and nucleic acids in proliferating cells^[8-13]. Recent advances in cancer biology and cellular immunity reveal that not only glucose but also amino acids are essential to support the high metabolic demands of tumor and/or immune cells and different strategies for targeting amino acid metabolism and corresponding enzymes are now a focus of innovative treatment approaches^[14-17]. The purpose of

this review is to highlight the importance of amino acid metabolism in the tumor microenvironment and use this knowledge to generate more effective immunotherapies while keeping in mind that both cancer and immune cells have similar metabolic requirements for growth and function and therefore may compete for common nutrients.

ARGININE AND TRYPTOPHAN METABOLISM IN THE TUMOR MICROENVIRONMENT

The amino acid arginine has considerable nutritional and physiological significance as it is recognized as an important precursor for the synthesis of proteins, urea, and creatine as well as for the synthesis of signaling molecules such as glutamate, nitric oxide, and agmatine^[18] (Figure 1). Although arginine is a dispensable (nonessential) amino acid for healthy humans, it is conditionally essential under certain physiological conditions or disease state^[10,19,20]. For example, many tumors are dependent on exogenous arginine for growth as they lack the enzyme argininosuccinate synthetase 1 (ASS1)^[21]. ASS1 catalyzes the conversion of citrulline into argininosuccinate in an ATP-dependent manner, completing one of the last steps in the arginine biosynthetic pathway^[18] (Figure 1). Loss of ASS1 prevents the production of arginine and may lead

to arginine depletion. Osteosarcoma and bladder cancer cell lines expressing low levels of ASS1 failed to grow in an arginine-free medium, indicating that ASS1 behaves as a tumor suppressor^[22,23]. However, arginine depletion in ASS1-negative tumor cells is usually associated with an aggressive phenotype and negative prognostic impact^[22]. Kobayashi *et al*^[22], showed that ASS1 deficiency in osteosarcoma patients correlated with the development of pulmonary metastasis in patients with osteosarcoma and can be used as a predictive biomarker for unfavorable prognosis. The aggressiveness of ASS1-negative tumors can be explained partially by the ability of these tumors to utilize more efficiently exogenous arginine coming from the tumor microenvironment. It is hypothesized that tumor associated myeloid cells (TAMCs), that consist of macrophages, monocytes, myeloid suppressor cells, and neutrophils^[24], form metabolic relationship with the tumor cells in the tumor microenvironment. They provide arginine to help the tumor cells by-pass the effect of arginine deprivation^[25]. In addition, TAMCs express high levels of another enzyme in the arginine metabolism, arginase 1, that hydrolyses arginine into urea and ornithine and sustains tumor growth by providing precursors for polyamine synthesis^[26,27]. By producing high levels of arginase 1 in the tumor microenvironment, TAMCs reduce arginine availability for other immune cells such as T cells. However, TAMCs can arrest cytotoxic T cell proliferation and induce T cell dysfunction by more than one mechanism, including generation of nitric oxide from arginine by nitric oxide synthase^[28]. Additionally, these cells can induce regulatory T cell differentiation^[29] potentially promoting immune tolerance in the tumor microenvironment. Thus, TAMCs have the ability to suppress the protective anti-tumor immune response by targeting arginine metabolism and helping tumors escape immune destruction. While immunotherapeutic targeting of arginine metabolism in the tumor microenvironment is still in its infancy, several decades of substantial *in vitro* and *in vivo* studies on arginine metabolism led to the development of arginine deprivation therapy, which is currently the subject of ongoing clinical trials with several arginine depleters, such as pegylated arginine deiminase (ADI-PEG20, Polaris group) and bioengineered forms of human arginase^[25,30,31] (Table 1). A small study group of patients with hepatocellular carcinoma revealed response rates to ADI-PEG20 between 25%-47% and this compound holds great potential in the arginine deprivation therapy^[30]. ADI-PEG20 is not limited to cancer therapy as there is ADI-PEG20 with anti-viral activity designed for treatment of hepatitis C by Polaris group.

Tryptophan is another amino acid linked to the regulation of immune tolerance and anti-tumor immune responses^[32-35]. Tryptophan degradation occurs *via* the kynurenine pathway where two different enzymes, indoleamine-2,3-dioxygenase (IDO) and tryptophan-2,3-dioxygenase (TDO), catalyze the conversion of tryptophan into kynurenine, while tryptophan hydroxylase-1 (TPH-1) converts tryptophan to 5-hydroxytryptophan

and provides precursors for serotonin biosynthesis^[32,36] (Figure 1). IDO is the most studied enzyme in tryptophan metabolism expressed by both immune cells (dendritic cells, macrophages) and tumor cells^[33,37-39]. Due to the fact that tryptophan readily crosses the plasma membrane, dendritic cells expressing IDO are capable of depleting tryptophan in the extracellular space, limiting tryptophan supply to surrounding T cells. T cell activation is sensitive to local tryptophan concentrations, and lack of tryptophan blocks their proliferation^[40]. By degrading tryptophan, IDO inhibits T cell proliferation and plays a role in autoimmunity and anti-inflammatory responses^[41-43]. For example, *ApoE*^{-/-} mice treated with the IDO inhibitor, 1-methyl-Trp, showed a significant increase in atherosclerotic lesions in the aortic arch and root of their hearts along with enhanced vascular inflammation^[41]. Additionally, IDO-expressing dendritic cells suppressed the allograft rejection and increased the survival time of small bowel transplanted mice^[44]. In the tumor microenvironment, however, IDO limits the T cell response to tumor growth^[45-47]. By using an IDO-negative subline of the mouse tumor model P815B, Uyttenhove *et al*^[45] elegantly showed that mice transfected with this subline completely rejected the tumor challenge while mice transfected with IDO-expressing cells developed progressive tumors and died. These results suggest that effector T cells that infiltrate the tumor microenvironment are more susceptible to the effects of IDO than are tumor cells. Indeed, immunohistochemical staining for IDO expression in endometrial cancer tissues revealed significant correlation between high IDO expression and low numbers of CD3⁺, CD8⁺, and CD57⁺ immune cells, which possibly contributed to disease progression and impaired clinical outcome for patients with endometrial cancer^[48]. In addition to IDO, tumors use other enzymes in tryptophan metabolism to resist immune destruction^[36,49]. TDO, a well described liver enzyme, is another immunosuppressive enzyme found in bladder carcinomas, melanomas, and hepatocarcinomas^[50]. In a preclinical model, Pilotte *et al*^[50] demonstrated that systemic treatment of immunized mice with a TDO inhibitor prevented the growth of TDO-expressing tumor cells. Lastly, TPH-1 expressed by mast cells is also necessary for long-term graft tolerance and a suppressive anti-tumor microenvironment^[51]. Therefore, more than one tryptophan catabolic enzyme contribute to the establishment of immune tolerance and could be suitable for combinatorial therapies. Thus far, IDO inhibitors, specifically designed for cancer immunotherapy, have been broadly used in preclinical and clinical trials alone or in combination with T cell checkpoint inhibitors^[52-54], while systemic inhibition of TDO, although promising, may raise safety concerns^[54] (Table 1). Another limitation of cancer trials targeting tryptophan metabolism is that they do not select cancer patients based on assessment of systemic IDO/TDO activities or by analysis of their metabolites in patients' serum^[54]. Nevertheless, combinatorial approaches targeting tryptophan metabolism will continue to deliver novel therapeutic avenues in cancer therapy.

Table 1 Amino acid metabolic enzymes targeted in cancer therapy

Amino acid metabolism	Targeted enzyme	Drug design	Drug toxicity, adverse events	Cancer type	Response rate	Clinical studies	Ref.
Arginine	ASS1, Arginine deaminase	ADI-PEG20	¹ Grade 3-4: Fatigue, hyperuricemia, anemia	HCC (nonresectable and metastatic)	31%-47%	Phase I / II	[30,94,95]
		ADI-PEG20	¹ Grade 3-4: Pain in extremity, arthralgia, pruritus, lymphedema, seizure	Melanoma (stage III and IV)	25%	Phase I / II	[96,97]
	Arginase 1	rhArgIpeg5000	¹ Grade 3-4: Elevated ALT, AST, bilirubin and GGT	HCC (advanced)	26.70%	Phase I	[31]
		Co-hArgI	Nude BALBc mouse model: Weight loss, hunch posture, lethargy, bone marrow injuries (> 15 mg/kg)	HCC (HepG2), pancreatic cancer (Panc-1); tumor site (right flank)	Smaller tumors	Preclinical studies	[98]
Tryptophan	IDO	Indoximod and docetaxel	Grade 1: Anemia, fatigue, hyperglycemia Grade 3-4: Headache, hypotension, infection	Various metastatic solid tumors	41% PD	Phase I	[99]
		1-D-MT	Grade 1: Fatigue; Grade 2: Hypophysitis	Various metastatic solid tumors	4P (SD), 3P (PD)	Phase I	[100]
		Indoximod and anti-CTLA4	C57BL/6 mouse model: No weight loss or acute/delayed toxicity observed	B16 F10 melanoma cell line, tumor site -flank	Delayed tumor growth	Preclinical studies	[101]
Tryptophan	TDO	Indole LM10	DBA/2 mouse model: No liver toxicity observed for 3 mo	P815B tumor cell line, tumor site -peritoneal cavity	Delayed tumor progression	Preclinical studies	[50]
Serine	PHGDH	NA	NA	Melanoma and breast cancer cell lines (SkBr3, MCF7)	NA	Preclinical studies	[15]
		NA	NA	Murine mammary fat pad tumors with MDA-MB-468 cells expressing PHGDH-shRNA	Reduced tumor growth	Preclinical studies	[63]
Glycine	SHMT1	NA	λ -Myc <i>Shmt1</i> ^{-/-} transgenic mice: no toxicity observed	Accelerated lymphomagenesis	NA	Preclinical studies	[102]
Glutamine	Glutamine -dependent enzymatic steps	L-DON ² , azaserine ²	None reported	Various animal and human xenografted tumors	Tumor growth inhibition	Preclinical studies	[80]
		Acivicin ²	Grade1-3: neurological toxicity Grade 2: vomiting, infections	High grade astrocytoma	Median 128 day survival	Phase II	[103]
Leucine, Isoleucine, Valine	BCATc	NA	CD-1 nude mouse model bearing tumors with BCATc knockdown: lethargy and uncoordinated motor activity	U-87MG glioblastoma cells with BCATc-shRNA; tumor site-intracerebral transplantation	Smaller tumors	Preclinical studies	[16]
		NA	NA	Nasopharyngeal carcinoma (5-8F, 6-10B), colorectal cancer	Induced cell proliferation	Preclinical studies	[92,93]

¹The highest grade is shown (Grade 3-4) and is summarized for either one or more studies; ²Discontinued. ADI-PEG20: Pegylated arginine deiminase; rhArgIpeg5000: Pegylated recombinant human arginase I; HCC: Hepatocellular carcinoma; Co-hArgI: Co²⁺ substitution of the Mn²⁺ metal cofactor in human arginase I; Indoximod (NLG8189, 1-D-MT1): 1-methyl-D-tryptophan; Indole LM10, tetrazolyl-vinyl substituted (fluoro)indole; L-DON: 6-diazo-5-oxo-L-norleucine; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma glutamyltransferase; PD: Progressed disease; SD: Stable disease; P: Patient; NA: Not available.

SERINE AND GLYCINE METABOLISM IN TUMORIGENESIS

Serine and glycine metabolism are interconnected *via* the glycine cleavage system, a major metabolic pathway in one-carbon metabolism that provides cofactors for purine and pyrimidine nucleotide biosynthesis for proliferating lymphocytes, cancer cells, and/or fetal tissues^[55-57]

(Figure 1). Studies from the late 1980s to more recent years, strongly suggest that cancer cells have an increased capacity for *de novo* serine synthesis *via* the phosphoglycerate dehydrogenase (PHGDH) pathway. PHGDH oxidases around 10% of 3-phosphoglycerate produced during glycolysis by converting it to 3-phosphohydroxypyruvate^[58-61]. This compound is then transaminated, forming 3-phosphoserine, and dephos-

phorylated to yield serine (Figure 1). PHGDH along with other enzymes in the serine biosynthetic pathway were upregulated in highly metastatic breast cancer, a finding associated with overall poor patient survival^[62]. Two independent studies published in 2011 reported that the gene encoding PHGDH was recurrently amplified in melanoma and breast cancers and this amplification was not associated with oncogene regulation^[15,63]. Apart from PHGDH, serine hydroxymethyl transferase (SHMT), that converts serine to glycine, has also been implicated in tumorigenesis. Two isoforms of SHMT (cytoplasmic SHMT1 and mitochondrial SHMT2) were both described as targets of c-myc oncogene^[64], a transcriptional factor abnormally expressed in many tumors that controls transcription of up to 15% of the genes in human cells^[65]. Both SHMT1 and SHMT2 were described as downstream effectors of c-myc function and rescued the growth defects of c-myc-null cells^[64]. At first glance, the role of serine and glycine metabolism in tumorigenesis may appear disadvantageous as PHGDH diverts metabolites from glycolysis to *de novo* synthesis of serine followed by conversion to glycine by SHMT (Figure 1). However, both serine and glycine are major sources of methyl groups for the one carbon pool required for a variety of biosynthetic pathways and/or DNA methylation that tumor cells use. Similar to cancer cells, immune cells are also shown to use glycolytic intermediates for serine/glycine biosynthesis with the ultimate goal of synthesizing building materials for cell growth and proliferation^[66]. Preclinical studies are underway to test the efficacy of many one carbon metabolic enzymes, including PHGDH^[67], as anti-tumor targets (Table 1). Dietary intervention is another strategy to target cancer metabolism and although preclinical studies restricting serine and glycine metabolism showed promising results^[68,69], global or systematic interventions need to be carefully examined in the context of the immune system that rely on the same metabolic pathways for proper function.

GLUTAMINE METABOLISM, A HALLMARK OF PROLIFERATING CELLS

As early as 1951, Mider^[70] described that tumors behaved as “nitrogen traps” where glutamine was the preferred nitrogen donor^[70,71]. More reports from the 1980’s, demonstrated that not only cancer cells but also rapidly dividing cells such as lymphocytes, thymocytes, and colonocytes had high glutamine consumption rates^[72-74]. Despite the fact that glutamine is a nonessential amino acid, proliferating cells display addiction to glutamine implying that glutamine plays more roles in cell metabolism than simply being a nitrogen donor. As such, glutamine is a conditionally essential amino acid for the proliferating cells as well as critically ill humans^[75]. Glutamine provides intermediates for the TCA cycle, restores glutathione to its reduced form suppressing oxidative stress, and maintains mitochondrial membrane integrity thus contributing to the survival of proliferating cells (reviewed

by Wise and Thompson)^[76]. Tumor suppressors (p53) and oncogenes (c-myc) were shown to regulate glutamine metabolism. Hu *et al*^[77] demonstrated that p53 targeted the mitochondrial isoform of glutaminase [glutaminase 2 (GLS2)], that converts glutamine to glutamate (Figure 1). p53 increased GLS2 expression and led to enhanced mitochondrial respiration and generation of ATP along with reduction in reactive oxygen species due to increased glutathione levels^[77]. Likewise, introduction of an inducible c-myc transgene in mouse embryonic fibroblasts led to induction of glutaminase 1 along with lactate dehydrogenase and glutamine transporters, suggesting that c-myc is required to support cellular dependence on glutamine^[78]. Cancer “addiction” to glutamine had been explored in cancer therapeutics and three compounds, 6-diazo-5-oxo-L-norleucine (L-DON), azaserine, and acivicin, showed significant activity as glutamine analogs^[79]. In early preclinical and clinical studies, these compounds showed promising results against different tumor types by inhibiting ribonucleotide biosynthesis, glutamine oxidation and reducing cell viability^[80,81] (Table 1). However, due to the important role of glutamine metabolism for normal tissue physiology, these compounds were discontinued while better tumor-targeting options with less general toxicity are currently considered^[76,82].

EMERGING ROLE OF BRANCHED CHAIN AMINO ACID METABOLISM IN CANCER THERAPY

Branched chain amino acids (BCAAs, leucine, isoleucine, and valine) constitute about 40% of the essential amino acid requirements of healthy individuals^[83]. They play an important role in protein synthesis and serve as major nitrogen donors for alanine and glutamine synthesis^[84]. Increasing evidence shows that BCAAs, especially leucine, are not merely building blocks necessary to support biosynthetic demands but also nutrient signals regulating the mammalian target of rapamycin (mTOR) pathway^[85,86]. By controlling protein translation, cell growth, proliferation, and autophagy, the mTOR pathway is recognized as a critical regulator of cellular function^[87]. Immune cells are particularly sensitive to mTOR regulation as mTOR pathway responds to environmental cues and coordinates immune cell differentiation and function, accordingly^[88]. For example, inhibition of mTOR pathway in T cells promoted T cell tolerance and the mechanism responsible for the maintenance of tolerance was failure of T cells to upregulate mTOR activity in the presence of metabolic inhibitors including leucine antagonists^[89]. In this regard, leucine appears to be an important nutrient signal that is sensed by the immune cells *via* mTOR pathway and is critical for their proliferation. Leucine supply to mTOR pathway is regulated through BCAA metabolism as shown recently in T cells^[90]. The cytoplasmic branched chain aminotransferase (BCATc), that catalyzes leucine transamination, was induced in activated T cells, where

it regulated leucine supply to complex 1 of the mTOR pathway. Loss of BCATc expression eliminated cytosolic leucine catabolism leading to upregulation of complex 1 of the mTOR pathway and increased glycolysis^[90]. While mTOR pathway is upregulated in many cancer types and mTOR-targeted cancer therapy has been a part of clinical research^[91], a direct link between mTOR pathway and leucine/BCAA metabolism in the tumor microenvironment awaits to be explored. Similar to the tryptophan degrading enzymes, BCATc may play an immunosuppressive role in the tumor microenvironment possibly contributing to tumor escape mechanisms. Another mechanism of BCATc function in cancer was explored in glioblastomas^[16]. Tönjes *et al*^[16] demonstrated that BCATc and BCAA metabolism are attractive targets for the development of therapeutic approaches to treat glioma patients. The majority of gliomas show mutations in their isocitrate dehydrogenase enzyme 1 (IDH1^{mut}) and although IDH1 mutation status is a powerful prognostic factor, it was insufficient to induce tumors in mice alone. BCATc was overexpressed in normal (wild type) IDH1^{wt} gliomas but not in gliomas with mutated IDH1, demonstrating a connection between IDH1 mutation and BCATc^[16]. Additionally, BCATc was identified as a c-myc target in nasopharyngeal carcinoma and BCATc overexpression induced cancer cell proliferation and migration^[92]. Although the majority of these studies imply that cancer cells require BCAA metabolism to sustain growth, and overexpression of BCATc results in increased cell proliferation^[92,93], the mechanism through which changes in BCAA metabolism affect cancer growth is currently unknown. It is possible that T cells and cancer cells share similar requirements for BCAA catabolism, where mTOR pathway is dependent on leucine regulation. Thus, future use of leucine antagonists or specific inhibitors aimed at BCATc may be suitable for targeted cancer therapies.

CONCLUSION

Research on amino acid metabolism in cancer cells in the last decades has provided valuable insights on the potential impact of metabolic control and regulation in the tumor microenvironment. Amino acids are no longer regarded solely as building materials but also as nutrient signals that regulate important signaling pathways. A number of amino acid metabolic enzymes are regulated by oncogenes and tumor suppressors and have been explored as targets for cancer therapies. Design and use of inhibitors targeting tryptophan, arginine and/or glutamine metabolism either alone or in combination with anti-tumor drugs has been introduced in clinical trials. However, cancer and immune cells share similar requirements for amino acid metabolic enzymes and often compete for the same nutrients. Therefore, therapeutic interventions in the tumor microenvironment must be cautiously explored to eliminate potential negative impacts on the anti-tumor immunity. Understanding the underlying mechanisms of metabolic interplay between tumor and immune cells will provide new directions to manipulate the tumor

microenvironment and unleash the anti-tumor immune response.

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