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REVIEW

Amino acids shape the metabolic and immunologic landscape in the tumor immune microenvironment: from molecular mechanisms to therapeutic strategies

Ziyou Lin[1,2]*, Chang Chang[1,2]*, Shuyu Zhao[1,2]*, Lan Fang[1], Ping Wang[1]

[1]Tongji University Cancer Center, Shanghai Tenth People's Hospital, School of Medicine, Tongji University, Shanghai 200072, China; [2]School of Medicine, Tongji University, Shanghai 200072, China

ABSTRACT The tumor immune microenvironment (TIME) represents a complex battlefield where metabolic competition and immune evasion mechanisms converge to drive cancer progression. Amino acids, with their multifaceted biological roles, have emerged as pivotal regulators of tumor cell proliferation and immune cell functionality. The sensing mechanisms by which amino acids within the tumor microenvironment influence cellular growth, survival, and immune function are systematically explored in this review; the latest advances in understanding amino acid metabolism in tumor biology are also reviewed. In addition, the multifaceted roles of key amino acids in shaping the TIME with particular emphasis on tumor immunity and malignant growth were investigated. Finally, emerging therapeutic strategies targeting amino acid metabolism to reprogram the TIME are discussed, highlighting promising approaches, such as CAR-T cell therapy and engineered bacterial interventions. Through this comprehensive analysis, critical insights into future research directions and potential clinical translation of amino acid-targeted interventions are provided.

KEYWORDS Tumor microenvironment (TME); amino acid sensing; amino acid metabolism; metabolic reprogramming; immunotherapy

Introduction

The tumor microenvironment (TME) is a complex and dynamic ecosystem where the interactions between cancer cells, immune cells, and various molecular signals determine the trajectory of cancer progression and the effectiveness of therapeutic interventions[1]. Within this intricate network, amino acids serve multiple essential roles, ranging from nutrient supply and metabolic regulation to signal transduction and immune modulation[2]. These functions position amino acids as key elements in tumor initiation, progression, and metastasis.

In addition to serving as building blocks for protein synthesis, amino acids are deeply involved in metabolic and epigenetic reprogramming within tumors. The influence of amino acids extends to shaping the immune landscape of the TME, making amino acids crucial for understanding cancer biology[3]. Tumor cells meet the heightened demands of rapid proliferation and adjust to the often nutrient-depleted conditions of the TME by reprogramming metabolic pathways. While amino acids are traditionally recognized for metabolic roles, the ability of amino acids to modulate immune responses within the TME has gained increasing attention. Recent studies have illuminated how amino acids affect immune cell function, alter tumor progression, and even serve as targets for innovative cancer therapies. Mechanisms that sense and respond to amino acid levels, such as the mechanistic target of rapamycin (mTOR) pathway and amino acid transporters, act as central hubs that integrate metabolic and immunologic signals[4]. These sensing pathways enable cells within the TME to adapt to nutrient-scarce conditions, ultimately influencing survival, growth, and immune cell behavior.

Traditional strategies, such as dietary modulation of amino acids or direct inhibition of amino acid metabolic enzymes,

*These authors contributed equally to this work.
Correspondence to: Lan Fang and Ping Wang
E-mail: lanfang@tongji.edu.cn and wangp@tongji.edu.cn
ORCID ID: https://orcid.org/0000-0001-8477-0528 and https://orcid.org/0000-0002-9922-5407
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have shown some clinical efficacy. However, these approaches often face obstacles, such as variable response rates and insufficient specificity[5]. Recent advances have focused on more sophisticated interventions to overcome these challenges. Emerging strategies now aim to exploit the reliance of tumor cells on some amino acids and metabolic pathways[6,7]. These approaches seek to disrupt tumor metabolic adaptations, boost anti-tumor immunity, or achieve both simultaneously by targeting amino acid transport, metabolism, or sensing mechanisms.

A comprehensive overview of the latest findings on amino acid sensing and the roles of amino acid sensing in the TME is provided in this review. How these molecules influence tumor cell survival and immune cell function are explored, offering insights into the dual contributions to tumor growth and immune suppression. In addition, the most recent clinical research efforts aimed at targeting amino acid metabolism to enhance anti-tumor immunity are highlighted. Finally, the challenges facing amino acid-based cancer therapies are discussed, potential solutions are proposed, and future directions for research and clinical application are suggested. By integrating these findings, we hope to illuminate new therapeutic avenues and guide the development of combination treatments that harness the power of amino acid targeting to improve cancer outcomes.

Amino acid sensing in the tumor immune microenvironment (TIME)

Amino acids serve as metabolic substrates and function as key signaling molecules that influence tumor cell behavior and the surrounding immune microenvironment. Understanding the interplay between amino acid sensing and signaling pathways holds promise for unraveling novel therapeutic targets and strategies in cancer immunotherapy and metabolic modulation.

Amino acid metabolism is regulated by several intricate signaling pathways that have a crucial role in tumor progression, immune modulation, and metabolic reprogramming. These pathways ensure that tumor cells adapt to fluctuating nutrient levels and hostile microenvironments, while also influencing immune responses in the TME. The roles of the mTOR pathway, HIF-1α, and MYC in amino acid sensing and the impact on tumor metabolism and immune evasion were therefore explored.

mTOR pathway and amino acid sensing

The mTOR pathway is a central regulator of cell growth, metabolism, and survival, integrating signals from nutrients, growth factors, and cellular energy status. Among the two distinct complexes (mTORC1 and mTORC2), mTORC1 has the more prominent role in sensing amino acids. Amino acids, particularly leucine, methionine, threonine and arginine, are key signals for mTORC1 activation, which enables tumor cells to adjust metabolism according to nutrient availability. The sensing of these amino acids involves complex mechanisms, which enable mTORC1 to respond to fluctuations in amino acid levels and modulate various cellular processes, including protein synthesis, autophagy, and cell growth (**Figure 1**).

mTORC1 is primarily regulated by Rag GTPases, which mediate the detection of leucine, methionine, and threonine, and by CASTOR proteins, which sense arginine[8]. Leucine is detected by leucyl-tRNA synthetase (LRS), Sestrin2, and SAR1B, which interact with GATOR2, relieving GATOR1-mediated inhibition of mTORC1[9-11]. Methionine availability is linked to SAMTOR, which regulates mTORC1 *via* S-adenosylmethionine (SAM) levels[12]. Under low arginine conditions, CASTOR proteins interact with the GATOR1 complex, leading to inhibition of mTORC1[8]. Conversely, high arginine levels disrupt CASTOR-GATOR1 interactions, allowing mTORC1 activation[13]. Additionally, the lysosomal transporter, SLC38A9, which is responsible for the uptake of amino acids (e.g., arginine and glutamine) and directly regulates mTORC1 by interacting with Rag GTPases[13,14]. When arginine levels rise in the lysosome, SLC38A9 activates mTORC1 *via* Rag GTPase signaling, facilitating cell growth and metabolic reprogramming. TM4SF5, which was discovered in 2019, binds free L-arginine in the lysosome and interacts with mTOR, forming a complex with SLC38A9 to activate mTOR/S6K1 signaling. Cells lacking TM4SF5 fail to phosphorylate ribosomal protein S6 kinase beta-1 (S6K1) and eukaryotic translation initiation factor 4E-binding protein 1 (4EBP1)[15]. Both S6K1 and 4EBP1 are classical downstream targets of mTORC1 that regulate mRNA translation, protein synthesis, and cell proliferation. High TM4SF5 expression in liver cancer suggests a role in mTOR/S6K1 activation during cancer progression or recurrence[16]. Leucyl-tRNA synthetase (LARS) has been identified as a leucine sensor mediating the mTORC1 pathway. Recent studies have identified mitochondrial seryl-tRNA synthetase 2 (TARS2) as a novel threonine

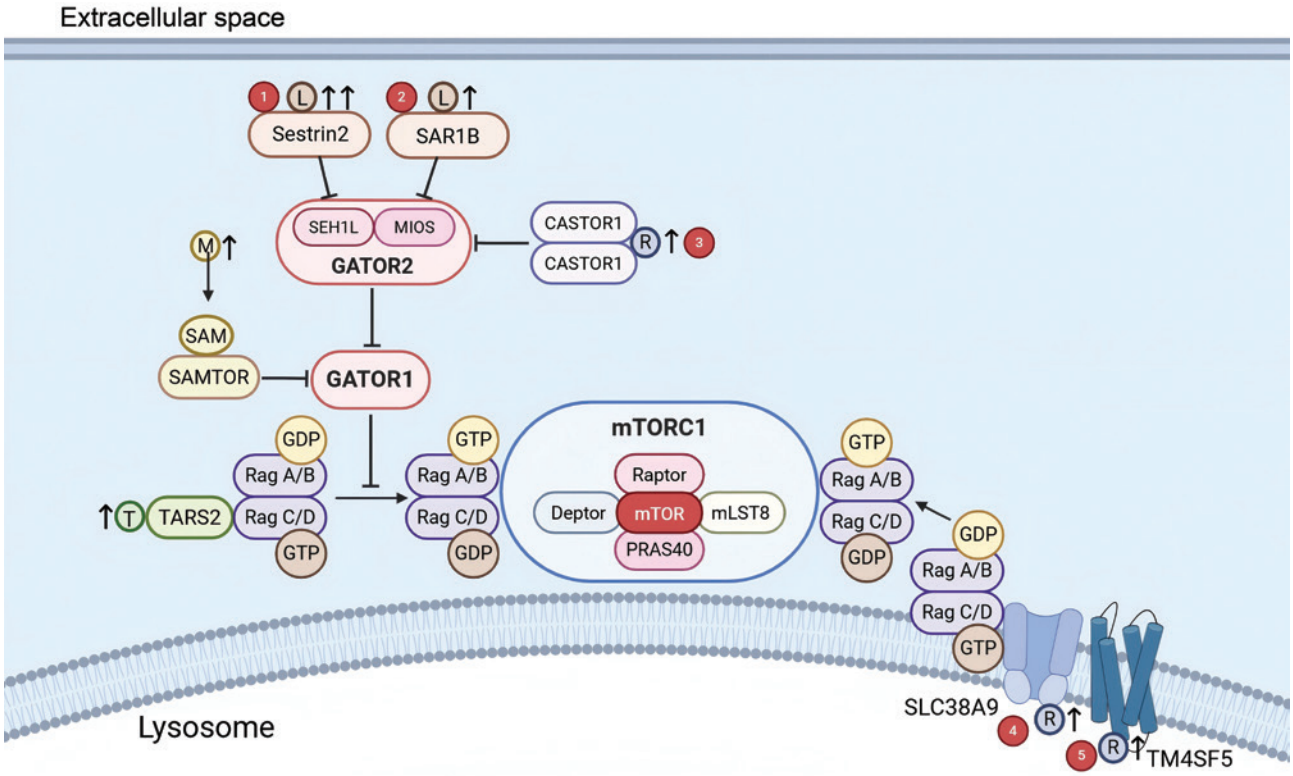


Figure 1 Regulation of mTORC1 signaling by amino acid sensors and the GATOR complex. This schematic depicts how amino acid availability regulates mTORC1 through a network of cytosolic and lysosomal sensors. Leucine (L) is sensed by two distinct proteins: ① Sestrin2 [a leucine-binding GTPase involved in mTORC1 inhibition (Kd ≈ 20 μM)]; and ② SAR1B [a stress-responsive regulator of cell viability with high leucine affinity (Kd ≈ 2 μM)]. Upon binding leucine, both sensors undergo conformational changes and dissociate from the GATOR2 complex (SAR1B from MIOS; Sestrin2 from SEH1L), which relieves GATOR1 inhibition. GATOR1 acts as a GTPase-activating protein (GAP) for RagA/B, promoting the conversion to the GDP-bound (inactive) state. The inactive RagA/B–GDP:RagC/D–GTP heterodimer is unable to recruit mTORC1 to the lysosomal membrane. When amino acids are sufficient, GATOR2 inhibits GATOR1, thereby relieving GAP activity. This situation enables formation of the active RagA/B–GTP:RagC/D–GDP heterodimer, which facilitates recruitment and activation of mTORC1. Methionine (M) is detected *via* SAMTOR, which binds SAM and modulates GATOR1 activity, acting in parallel to the leucine pathway. Threonine (T) activates mTORC1 *via* TARS2. Upon threonine binding, TARS2 preferentially associates with GTP-bound RagC, which promotes RagA GTP-loading and facilitates mTORC1 recruitment. Arginine (R) is monitored by three spatially distinct sensors: ③ CASTOR1, a cytosolic sensor that interacts with GATOR2 to regulate mTORC1 in response to cytoplasmic arginine; ④ SLC38A9, a lysosomal arginine transporter that interacts with inactive Rag dimers and promotes activation in response to luminal arginine; and ⑤ TM4SF5, a lysosomal lumen sensor that binds free arginine and cooperates with SLC38A9 and mTOR to activate the mTOR/S6K1 signaling axis. The figure was created with BioRender.com. CASTOR1, cytosolic arginine sensor for mTORC1 regulation; GDP, guanosine diphosphate; GTP, guanosine triphosphate; Kd, dissociation constant; mTORC1, mechanistic target of rapamycin complex 1; SAM, S-adenosylmethionine; SAMTOR, SAM sensor regulating mTORC1 *via* GATOR1; SLC, solute carrier; TARS2, threonyl-tRNA synthetase 2; TM4SF5, transmembrane 4 L six family member 5.

sensor. When bound to threonine, TARS2 interacts with inactive Rag GTPases (especially GTP-RagC), which promotes GTP loading of RagA and subsequent mTORC1 activation. TARS2 regulates cell proliferation and mRNA translation in a threonine-dependent manner through this mechanism[17]. This intricate regulation of mTORC1 through amino acid sensing ensures that tumor cells maintain optimal metabolic conditions for survival and proliferation, linking nutrient availability to tumor progression.

The MYC family of oncogenes (c-Myc, N-Myc, and L-Myc) has a pivotal role in driving tumor growth by reprogramming cellular metabolism, especially amino acid metabolism. MYC enhances the expression of multiple amino acid transporters and metabolic enzymes, ensuring a sufficient

supply of nutrients to meet the demands of rapidly proliferating tumor cells. Notably, MYC-induced upregulation of transporters, such as SLC7A5, increases the uptake of large neutral amino acids (e.g., leucine), which in turn activates the mTORC1 pathway and promotes protein synthesis. This metabolic adaptation supports sustained tumor cell growth and survival under nutrient-limited conditions[18]. This metabolic adaptation creates a feed-forward loop because increased amino acid influx further activates mTORC1 signaling. Additionally, MYC regulates glutamine metabolism by enhancing glutaminase (GLS) activity, which provides essential metabolic intermediates for the TCA cycle[19]. Understanding the interplay between mTOR and MYC in amino acid sensing reveals therapeutic opportunities to disrupt tumor metabolism and boost anti-tumor immunity, offering novel strategies for cancer treatment.

AMP-activated protein kinase (AMPK) and cystine sensing

Cysteine exists primarily as cystine, a disulfide-bonded dipeptide, in the oxidizing extracellular environment. The cystine/glutamate antiporter, xCT, mediates cystine uptake in exchange for intracellular glutamate with cystine undergoing rapid reduction to cysteine by NADPH inside the cell[20]. Several key proteins regulate xCT expression, including mutant KRAS, p53, and BAP1, highlighting the crucial role of cysteine in tumorigenesis[21-23].

CARS, a tRNA synthetase, has been identified as a cysteine sensor that directly influences AMPK activation. CARS interacts with AMPKγ2 when cysteine levels drop, facilitating AMPK activation through upstream kinases, like CaMKK2. This activation helps cells adapt to cysteine deprivation by promoting catabolic processes that generate energy and suppressing anabolic processes that require cysteine. In nutrient-stressed conditions, such as exist in triple-negative breast cancer (TNBC) cells, AMPK activation by CARS supports cell survival. By linking amino acid sensing to energy balance and metabolic reprogramming, the CARS-AMPK axis provides a crucial adaptive mechanism for cancer cells under cysteine-limited conditions[24]. Additionally, EglN1 functions as another cysteine sensor, modulating HIF activity in response to cysteine levels. When intracellular cysteine levels drop, EglN1 undergoes oxidative self-inactivation, which prevents normal functioning of prolyl-hydroxylating HIF1α[25].

Sterol regulatory element-binding proteins (SREBPs) and SREBP cleavage-activating protein (SCAP)

SREBPs are transcription factors best known for a role in lipid metabolism but SREBPs are also influenced by amino acid availability, especially glutamine. SCAP acts as a sensor that monitors intracellular glutamine levels. SCAP facilitates the activation of SREBPs when glutamine levels are sufficient, which promotes the transcription of genes involved in lipid synthesis. This connection between glutamine and lipid metabolism is especially important in cancer cells, where increased glutamine metabolism supports bioenergetic needs and membrane synthesis for rapidly proliferating cells. By coupling amino acid sensing to lipid biosynthesis, the SCAP-SREBP axis highlights a unique metabolic adaptation strategy in tumor cells[26].

Aryl hydrocarbon receptor (AhR)

AhR functions as a receptor and sensor for tryptophan-derived metabolites, such as kynurenine (Kyn). AhR translocates to the nucleus upon binding to these metabolites, where AhR influences gene expression patterns that modulate immune responses[27]. Tryptophan catabolism *via* the Kyn pathway generates metabolites that engage AhR in the TME, which promotes regulatory T cell (Treg) differentiation and the expression of immunosuppressive cytokines[28]. This sensing mechanism effectively helps tumors evade immune surveillance by reshaping the immune landscape. AhR also regulates genes involved in oxidative stress responses, cellular metabolism, and even vascularization, making AhR a multifaceted sensor that integrates metabolic cues with immune and environmental signals[29].

Lymphocyte-specific protein tyrosine kinase (LCK)

LCK is a novel amino acid sensor in the tumor immune microenvironment. LCK, primarily known for its role in T-cell receptor signaling, has emerged as a direct sensor for arginine, establishing a previously unknown link between amino acid availability and immune cell activation. This kinase undergoes specific conformational changes upon arginine binding, leading to distinct phosphorylation patterns at Tyr394 and Tyr505

residues. The resulting enhanced LCK activity amplifies TCR signaling cascade, thereby modulating T-cell responses in the TME[19].

Human histone deacetylase 6 (HDAC6)

HDAC6 is a unique member of the HDAC family, primarily regulating non-histone protein deacetylation with key roles in cellular stress responses, cytoskeletal dynamics, and protein homeostasis. Unlike nuclear HDACs, HDAC6 mainly functions in the cytoplasm but the localization and activity are dynamically regulated by environmental cues[30]. Recent studies identify HDAC6 as a valine sensor, linking amino acid availability to epigenetic regulation and DNA damage responses. HDAC6 directly binds valine through its SE14 repeat domain unlike traditional amino acid sensors (e.g., mTORC1 and GCN2), regulating nuclear-cytoplasmic shuttling. HDAC6 accumulates in the nucleus under valine deprivation, where HDAC6 deacetylates TET2, promoting DNA demethylation and damage *via* thymine DNA glycosylase. Functionally, dietary valine restriction suppresses tumor growth in xenograft models and enhances PARP inhibitor efficacy[31].

General control nonderepressible 2 (GCN2) pathway

GCN2 is a serine/threonine-protein kinase that has a pivotal role in cellular adaptation to amino acid deprivation[32]. When amino acids are scarce, uncharged tRNAs accumulate and bind to the GCN2 HisRS-like domain, triggering activation. Once active, GCN2 phosphorylates eIF2α and reduces global protein translation to conserve resources, while selectively enhancing the expression of stress response genes. This translational control allows cells to maintain homeostasis and survive periods of nutrient stress. Beyond translation inhibition, GCN2 modulates metabolic pathways, autophagy, and even immune responses, making GCN2 a central sensor that integrates amino acid availability with broader cellular adaptive programs[33].

Sensor-unknown amino acids inducing signal transduction in TIME

While the sensing mechanisms of amino acids, such as arginine, leucine, and methionine, in activating the mTORC1 pathway are well-established, emerging evidence suggests that several other amino acids, the specific sensors of which remain unidentified, also have critical roles in regulating signaling within the TIME. These amino acids may modulate cellular metabolism, transcriptional networks, and immune cell interactions through as-yet undefined signaling pathways.

Proline

Proline has been implicated in tumor cell signal transduction, especially under metabolic stress conditions. Proline biosynthesis is primarily regulated by the enzyme, pyrroline-5-carboxylate reductase 1 (PYCR1), the expression of which is upregulated in response to proline precursor deprivation. PYCR1 is frequently overexpressed in invasive breast carcinoma and other aggressive tumors, supporting cancer cell proliferation and redox balance. Knockdown of PYCR1 significantly suppresses tumor growth *in vitro* and *in vivo*, indicating that proline metabolism may act as a critical regulator of oncogenic signaling under stress conditions[34-36].

Serine

Similarly, serine deprivation has been shown to exert profound effects on tumor cell signaling. In addition to metabolic functions, limiting serine availability has been shown to enhance cancer treatment efficacy when combined with dietary serine and glycine restriction[37]. Moreover, serine deprivation increases the antitumor activity of biguanides through specific signaling mechanisms, while also inducing cellular stress responses and activating p53-dependent pathways, ultimately leading to metabolic reprogramming[38,39]. Serine deprivation triggers p53-mediated activation of the p21 axis in tumor cells, shifting metabolic flux from nucleotide biosynthesis to glutathione production, thereby enhancing antioxidant capacity. p53 can limit non-specific $CD4^+$ T cell proliferation in T cells and modulate immune responses under metabolic stress, suggesting that serine metabolism is tightly linked to immune cell function beyond tumor-intrinsic effects[40]. Although much of the existing research on serine depletion has focused on metabolic consequences, further investigation is needed to uncover direct roles in tumor cell signaling.

Other amino acids, such as histidine, have been proposed to influence immune or tumor cell behavior in the TIME, although the sensing mechanisms and downstream signaling have not been established[41]. Preliminary studies suggest that these amino acids may regulate redox state, metabolic flux, or epigenetic remodeling[42]. Identifying the molecular sensors and signaling networks of these underexplored amino acids is critical. Uncovering how these amino acids mediate immune

regulation, tumor progression, and therapy response may provide novel targets for metabolic intervention in cancer.

Amino acids shape the tumor metabolic landscape

Amino acids, in addition to traditional roles as building blocks of proteins, have a central role in shaping the molecular landscape of tumor cells. Metabolism of amino acids is closely linked to epigenetic modifications, transcriptional regulation, redox balance, and adaptive stress responses. By influencing key regulatory pathways, amino acids enable cancer cells to survive in nutrient-deprived environments, evade immune surveillance, and maintain rapid proliferation.

Epigenetic and transcriptional regulation in tumor cells

Amino acid metabolism (especially methionine metabolism) has a key role in shaping the epigenetic and transcriptional landscape of tumor cells. Methionine-derived SAM serves as a methyl donor for DNA and histone methylation. Elevated MAT2A activity boosts SAM levels, which promotes oncogene activation and silences tumor suppressors. Inhibiting methionine cycling reduces histone methylation, which leads to cell cycle arrest and senescence[43].

Branched-chain amino acids (BCAAs) also influence epigenetic regulation. Overexpression of BCAT1 in cancers, including acute myeloid leukemia (AML) and gliomas, lowers α-ketoglutarate (α-KG), which impairs dioxygenase activity and leads to hypermethylation of DNA and histones. This epigenetic modulation supports tumor growth. In IDH-mutant glioblastomas, BCAT1 promoter hypermethylation suppresses transcription, whereas hypomethylation in hepatocellular carcinoma upregulates transcription[44].

Serine and threonine also connect amino acid metabolism to epigenetic and transcriptional regulation. Serine supports one-carbon metabolism and nucleotide biosynthesis with ATF4 driving serine synthesis pathway (SSP) gene expression under stress conditions[45]. ATF3, induced by ATF4, amplifies this transcriptional response, enabling tumor growth under nutrient deprivation[45]. Threonine metabolism modifies N^6-threonylcarbamoyladenosine (t^6A) tRNA *via* YRDC, which enhances oncogenic transcript translation and maintains the transcriptional landscape needed for proliferation[46].

Phenylalanine serves as a precursor to tyrosine and has been implicated in cancer metabolism[47]. Recent studies have revealed that genetic alterations in hepatocellular carcinoma GSTZ1 lead to succinylacetone accumulation, a byproduct of phenylalanine/tyrosine metabolism. This process activates the NRF2/IGF1R axis and inhibits tumor cell apoptosis[48]. Cancer cells adopt a W > F codon switch under tryptophan depletion by substituting phenylalanine for tryptophan. These substitutions are enriched across cancers and linked to elevated IDO1 expression, oncogenic signaling, and immune microenvironment remodeling[49].

In addition to these epigenetic effects, amino acid metabolism is tightly regulated at the transcriptional level. Transcription factors, such as hypoxia-inducible transcription factors (HIFs), c-Myc, and activating transcription factor 4 (ATF4), coordinate cellular responses to metabolic stress. HIF-1α and HIF-2α upregulates amino acid transporters and metabolic enzymes under hypoxia, securing a steady nutrient supply[50]. In addition, ATF4 activates genes related to amino acid biosynthesis and stress responses during nutrient deprivation, which enhances cellular resilience[51]. These epigenetic and transcriptional mechanisms highlight how amino acid metabolism drives tumor growth, survival, and immune evasion by reprogramming chromatin, altering methylation, and shaping gene expression networks.

Antioxidant defense and stress response by amino acids

Amino acids have a pivotal role in maintaining redox balance and responding to cellular stress. Methionine acts as an endogenous antioxidant, effectively scavenging reactive oxygen species (ROS) and mitigating oxidative stress[52]. Similarly, cysteine contributes to glutathione (GSH) synthesis, supporting cellular redox stability and protecting against oxidative damage[53]. The cystine/glutamate antiporter, SLC7A11, facilitates cysteine import for GSH biosynthesis, although SLC7A11 expression can be downregulated by interferon-gamma (IFNγ) from CD8+ T cells, leading to lipid peroxidation and ferroptosis in tumor cells[54]. Additionally, tryptophan metabolites, such as serotonin (5-HT) and 3-hydroxyanthranilic acid (3-HA), function as radical-trapping antioxidants (RTAs), eliminating lipid peroxidation and preventing cellular ferroptosis[55]. The cysteine–GSH–GPX4–ferroptosis axis is vital for redox balance and ferroptosis regulation in the TIME. Cysteine supports GSH synthesis, which sustains GPX4 activity to

prevent lipid peroxidation. Cysteine depletion or GPX4 inhibition induces ferroptosis, especially in tumors dependent on SLC7A11-mediated cystine uptake for survival[56,57].

Proline, another key amino acid, has been increasingly recognized for a role in cancer metabolism and stress adaptation. Proline biosynthesis enzymes sense environmental stresses and participate in metabolic signaling. Hypoxia can drive phosphorylation of pyrroline-5-carpoxylate reductase-1 (PYCR1) by insulin-like growth factor 1 receptor (IGF1R) in the nucleus, helping cells avoid growth arrest[58]. Proline degradation, catalyzed by proline dehydrogenase (PRODH), generates ROS that upregulate inflammatory genes, such as CXCL1, LCN2, and IL17C, and causes DNA damage[59]. This ROS-mediated signaling, supported by the LSH-p53-PRODH axis, contributes to epithelial-mesenchymal transition (EMT), inflammatory signaling, and tumor progression in non-small cell lung cancer[60].

In summary, these amino acids support tumor growth through common mechanisms, including metabolic reprogramming, regulation of key signaling pathways, epigenetic modifications, immune modulation, antioxidant defense, stress response, and genetic adaptation. These processes underscore the critical roles in cancer metabolism and highlight potential targets for therapeutic intervention.

Metabolic tug-of-war: amino acids in the TIME

The TIME is comprised of tumor cells, immune cells, and stromal components that form a network crucial for tumor progression and immunotherapy response[61]. Amino acids serve essential metabolic functions and regulate immune responses within this environment. Competition for amino acids between tumor and immune cells significantly drives immune evasion[62]. Tumor cells often outcompete immune cells for uptake of critical amino acids, leading to nutrient depletion in the TME. This depletion hinders the function of immune cells, particularly effector T cells (Teffs) and antigen-presenting cells (APCs), thereby contributing to immune suppression and tumor progression[63]. The availability and metabolism of specific amino acids in the TME influence tumor growth, immune modulation, and immune escape mechanisms (**Figure 2**). To provide a structured overview of how key amino acids influence T cell metabolism and function within the TIME, the corresponding transporters and downstream signaling pathways are summarized in **Table 1**. This summary serves as a foundation for the detailed discussion below, in which the roles of several key amino acids in shaping the TIME and the impact on tumor and immune cell functions are explored.

Glutamine and glutamate

Glutamine is one of the most abundant amino acids in the body and has a critical role in cellular metabolism. Glutamine metabolism is extensively reprogrammed to support rapid cell division and tumor growth in the TME. To meet high metabolic demands, tumor cells upregulate glutamine transporters, such as SLC1A5, facilitating increased glutamine uptake[65]. This process ensures a constant intracellular supply of glutamine, which is essential for biosynthetic pathways and maintaining oxidative stress resistance.

Glutamine is converted to glutamate by glutaminase (GLS), which fuels the TCA cycle, supports protein synthesis, and maintains redox balance *via* glutathione (GSH) production. Tumor cells rely on glutamine-derived glutamate to sustain anaplerosis and rapid proliferation[66]. Although glutamine also supports T cell function, inhibiting glutamine metabolism can paradoxically enhance T cell antitumor activity[67]. This finding may stem from a tumor cell glutamine addiction, making tumors more vulnerable to glutamine deprivation. Differential MAPK/ERK pathway activation in tumors and T cells likely influences glutamine dependence[68,69]. Notably, the glutamine transporter inhibitor, V-9302, selectively blocks glutamine uptake in TNBC cells without affecting $CD8^+$ T cells, thereby boosting GSH synthesis and effector function. These findings support tumor-selective glutamine metabolism inhibition as a promising strategy for TNBC immunotherapy[67].

In addition a role in fueling the TCA cycle, glutamate also has a critical role in immune regulation. Tumor cells exploit the glutamine axis to regulate glutamate levels in the TME, thereby limiting the availability of glutamate for immune cells[70]. T cells depend on glutamine metabolism for optimal activation and effector function; glutamine scarcity weakens the ability to mount an effective anti-tumor response[71]. This reduction in glutamate disrupts the redox balance in these cells, impairing the ability to generate ROS. Glutamate signaling has a dual role in immune regulation, as follows: glutamate enhances T cell activation and proliferation *via* glutamate

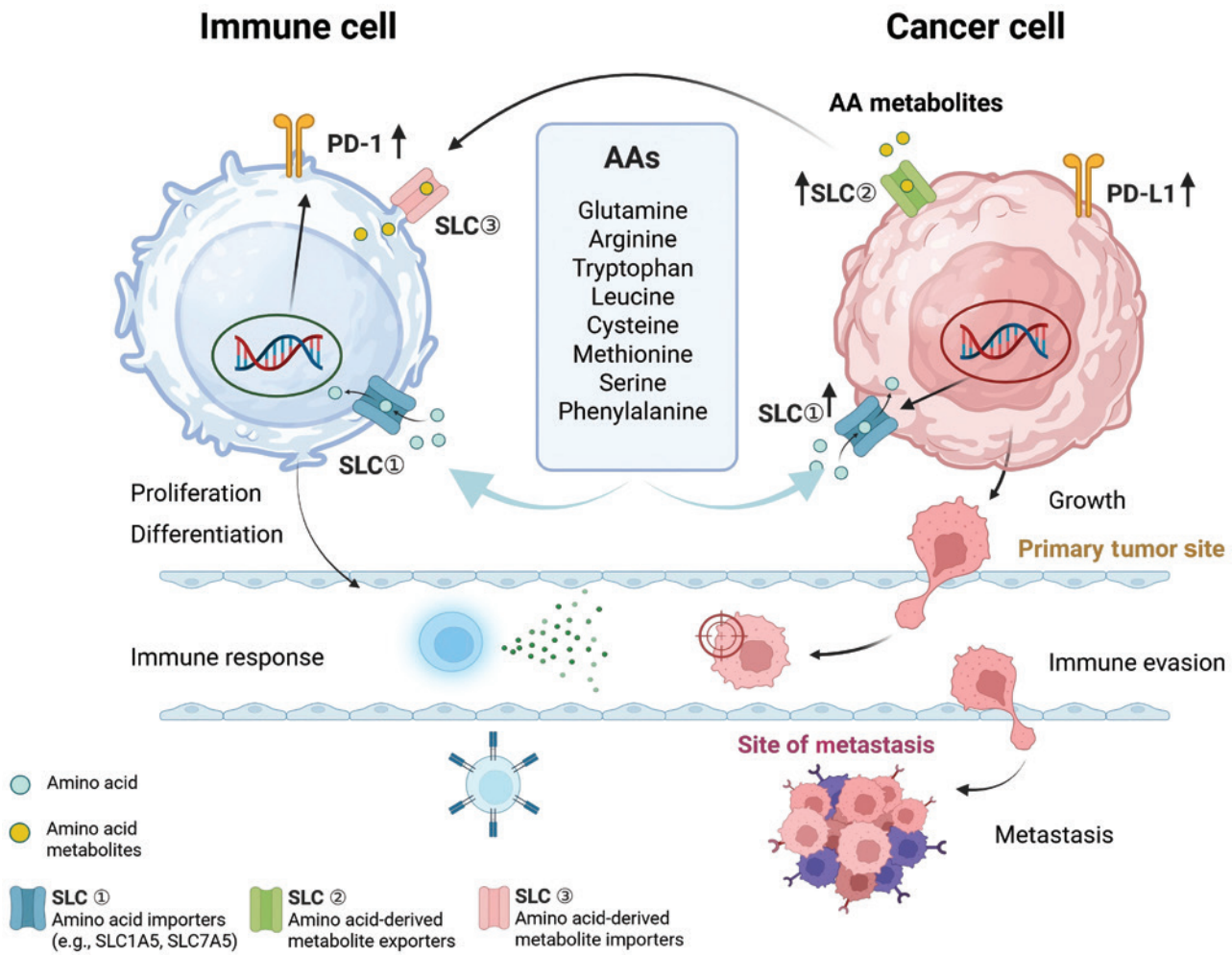


Figure 2 The metabolic tug-of-war for amino acids between cancer cells and immune cells. Within the tumor immune microenvironment (TIME), cancer cells upregulate various solute carriers (SLCs) to enhance amino acid uptake and amino acid-derived metabolite transport, which supports proliferation, immune evasion, and metastasis. SLCs are functionally categorized and labeled, as follows: SLC① (e.g., SLC1A5 and SLC7A5) mediates amino acid import and is commonly upregulated in tumor cells to meet biosynthetic and energetic demands. SLC② (e.g., SLC7A5 and MCT1) exports tumor metabolites, such as Kyn and lactate, and is frequently upregulated[64], while SLC③ mediates amino acid uptake by immune cells with stable expression. In contrast, immune cells also rely on amino acids for proliferation, differentiation, and effective anti-tumor responses. Competition for amino acids and amino acid derivatives within the TIME impairs immune cell function and promotes tumor progression. PD-L1 and PD-1 are upregulated in response to metabolic stress. Blue and yellow dots represent amino acids and amino acid-derived metabolites, respectively. The figure was created with BioRender.com. AAs, amino acids; Kyn, kynurenine; MCT, monocarboxylate transporter; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SLC, solute carrier; TIME, tumor immune microenvironment.

receptors; and reduces the immunosuppressive function of myeloid-derived suppressor cells (MDSCs)[72].

Glutamine metabolism influences immune checkpoint expression on tumor cells. Glutamine deprivation activates the EGFR/ERK/c-Jun and NF-κB pathways, upregulating PD-L1 expression[73]. Interestingly, another study revealed that limiting glutamine consumption by tumor cells increases tumor PD-L1 expression, a process linked to reduced intracellular GSH levels. Because glutamine is a key precursor for GSH synthesis, glutamine restriction leads to lower GSH levels, which in turn inhibits the activity of sarcoplasmic reticulum Ca^{2+}-ATPase (SERCA) and activates the NF-κB signaling pathway. This cascade of events triggers PD-L1 induction, ultimately suppressing T cell function. Notably, combining glutamine inhibition

Table 1 Structure-functional relationships of amino acids and their associated transporters

Amino acid	Transporter	Function and downstream pathway
Glutamine	SLC1A5 SLC38A1/2	Glutamine fuels the TCA cycle, supports biosynthesis and redox balance *via* glutathione production, and activates mTORC1 signaling to promote T cell survival and antitumor activity.
Arginine	SLC7A1 SLC6A2	Arginine supports mTORC1 signaling, nitric oxide (NO) production, and T cell effector functions. Arginine is critical for T cell proliferation and metabolic fitness in the tumor microenvironment.
Asparagine	SLC1A5	Asparagine enhances T cell activation and memory T cell function by supporting amino acid exchange and metabolic reprogramming under stress conditions.
Leucine	SLC7A5	Leucine activates mTORC1 and c-Myc pathways, promoting protein synthesis and effector T cell differentiation during immune responses.
Alanine	SLC6A19 SLC38A1	Alanine is utilized for protein synthesis and contributes to energy production *via* entry into glycolysis, regulated by mTOR signaling in activated T cells.
Methionine	SLC43A2	Methionine is a precursor for SAM, a universal methyl donor. Methionine regulates epigenetic modification and transcriptional programming *via* histone/DNA methylation.
Cysteine	SLC7A11	Cysteine is imported for glutathione (GSH) synthesis *via* xCT, maintaining redox homeostasis. GSH protects T cells from oxidative stress and ferroptosis.
Tryptophan	SLC7A8	Tryptophan is catabolized by IDO1 to Kyn, which activates AhR and upregulates PD-1 on T cells, leading to T cell exhaustion and immune suppression.
GABA	SLC6A13	GABA inhibits T cell activation and proliferation *via* GABAergic signaling, representing a negative regulatory mechanism in T cell function.

with anti-PD-L1 therapy enhances antitumor immunity in mouse models[74].

Arginine

Arginine is a key amino acid that shapes the TME and regulates antitumor immunity. The TME is often arginine-deficient, impairing immune cell function. While tumor cells adapt by expressing arginine succinate synthetase (ASS) to synthesize arginine from citrulline, T cells lack this capability and are more susceptible to arginine deprivation[75,76]. Tregs, which also express arginase-2 (ARG2), contribute to depletion of arginine in the TME, further suppressing Teff activity[77].

Regulation of arginine metabolism in the TME involves complex interactions between multiple cell types and enzymatic pathways. Two primary metabolic routes dominate: the arginine/arginase (ARG)/ornithine decarboxylase (ODC)/polyamine pathway; and the arginine/inducible nitric oxide synthase (iNOS)/NO pathway[78]. These pathways are differentially utilized by various cell types within the TME, leading to distinct functional outcomes. Tumor-associated macrophages (TAMs) and MDSCs express arginase-1 (ARG1), which depletes extracellular arginine and creates an immunosuppressive environment[79,80].

The impact of arginine metabolism on immune cell function is especially evident in T cells. Arginine enhances T cell oxidative metabolism, promoting vitality, persistence, and antitumor activity[81]. Under arginine starvation, ASS1 transcription is induced by activating transcription factor 4 (ATF4) and CCAAT/enhancer-binding protein beta (CEBPb) binding to an enhancer within the ASS1 gene. T cells fail to induce ASS1, despite active ATF4 and CEBPb, due to repression of the gene. Arginine deprivation drives chromatin compaction and repressive histone methylation, disrupting ATF4/CEBPb binding and impairing gene transcription. Consequently, T cell activation is impaired with significant metabolic disturbances linked to incomplete chromatin remodeling and misregulation of key genes[82]. Additionally, low arginine conditions trigger adaptive responses, including upregulation of SLC7A11 and CGN2 expression, and enhanced glutathione synthesis to maintain redox balance[83].

The role of TAMs in tumor progression is particularly noteworthy and evolves with tumor development. Initially, TAMs exhibit pro-inflammatory (M1-like) effects that suppress tumor growth[84]. However, as tumors progress, Th2 cells drive TAMs toward an M2-like phenotype, transforming TAMs into tumor-supportive cells. This phenotypic switch is accompanied by distinct patterns of arginine metabolism;

specifically, M1-like macrophages generate NO, while M2-like macrophages utilize ARG1 to support tumor growth and suppress immune responses[85,86]. The hypoxic tumor environment elevates HIF1α and HIF2α expression in macrophages. These factors drive TAM-mediated immunosuppression by upregulating ARG1 and iNOS, which modulate arginine and NO levels in the TIME[86]. NO produced by TAMs and MDSCs inhibit T cell activation, while promoting tumor progression[87].

Recent therapeutic advances have focused on manipulating arginine metabolism to enhance antitumor immunity. Modifying ASS or ornithine transcarbamylase (OTC) enzymes during chimeric antigen receptor (CAR)-T cell therapy has shown promise in enhancing CAR-T cell proliferation without compromising cytotoxicity, leading to improved tumor clearance[88]. Metabolic intervention strategies, such as using methotrexate to increase NO levels while reducing polyamine synthesis, have demonstrated potential in reprogramming M2-like TAMs toward an immunostimulatory M1-like phenotype[89].

Tryptophan

Tryptophan is an essential amino acid involved in the synthesis of proteins, neurotransmitters, and various bioactive metabolites. Tryptophan metabolism is primarily regulated in the TME by the enzyme, indoleamine 2,3-dioxygenase (IDO), which catalyzes the first step in the Kyn pathway[90]. IDO expression is often upregulated in tumor cells and immune cells, such as dendritic cells and macrophages, as a mechanism of immune suppression. By degrading tryptophan into Kyn, IDO limits the availability of tryptophan for immune cells (especially T cells)[91]. Kyn acts on the AhR to induce production of immunosuppressive cytokines, such as IL-10, and to inhibit the expression of co-stimulatory molecules (CD80 and CD86), as well as upregulate PD-1 expression on T cells, further dampening T cell activation[92]. Depletion of tryptophan and accumulation of Kyn in the TME lead to immune suppression, especially in CD8+ T cells and Th1 cells. Tumor cells utilize tryptophan-degrading enzymes to generate Kyn, which acts as a mechanism of immune evasion by promoting T cell exhaustion and preventing effective anti-tumor responses[93].

Recent research revealed that the Kyn-AhR axis affects T cell function and has a crucial role in shaping the immunosuppressive landscape of the TME through an impact on TAMs. Tryptophan-derived microbial metabolites, especially indoles produced by gut microbiota, activate AhR in TAMs within pancreatic ductal adenocarcinoma (PDAC), promoting an immunosuppressive phenotype marked by elevated IL-10. AhR deletion or inhibition reprograms TAMs, reduces tumor growth, and improves response to immune checkpoint blockade, highlighting the role of microbiota–AhR signaling in shaping the immunosuppressive TME[29,94].

Serine

Serine metabolism is closely linked to T cell activation, proliferation, and differentiation. Serine is crucial for supporting the metabolic needs of immune cells in the TME, especially T cells and macrophages. During T cell activation, serine provides the building blocks for nucleotide synthesis and supports the generation of ATP through a one-carbon metabolism pathway[95]. Serine is also essential for maintaining redox balance in immune cells by contributing to the synthesis of GSH. Serine deficiency impairs T cell activation and proliferation, leading to reduced immune responses in the TME. In addition, serine availability regulates macrophage polarization. Macrophages tend to adopt an immunosuppressive M(IL-4)-like phenotype under serine-sufficient conditions. In contrast, serine deprivation or inhibition of the serine biosynthesis pathway promotes pro-inflammatory M(IFN-γ) polarization. Mechanistically, serine deficiency reduces SAM levels, leading to decreased H3K27me3 enrichment at the LGF1 gene promoter. The resulting upregulation of IGF1 expression activates the p38-dependent JAK–STAT1 signaling pathway, which drives M1-like polarization[96]. Thus, serine metabolism orchestrates epigenetic and transcriptional regulation of macrophage fate, shaping the immune landscape in the TME.

Asparagine

Asparagine restriction has stage-specific effects on T cells. Asparagine suppresses early activation and cell cycle entry but enhances $CD8^+$ T cell proliferation and function during differentiation *via* NRF2-mediated stress responses. Metabolically, Asn deprivation reduces glucose and glutamine use, while increasing nucleotide availability. Tumor cells upregulate ASNS to compete for Asn in the TME, potentially impairing immune responses. Asparagine also promotes tumor growth and metastasis by acting as an amino acid exchange factor that regulates mTORC1 activity, serine metabolism, and nucleotide synthesis, thereby supporting anabolic metabolism and proliferation[97]. These findings highlight the potential of asparagine

as a therapeutic target, although further studies are needed to clarify the dual role in tumor progression and immunity[98].

Methionine

Methionine is an essential amino acid that serves as the precursor of SAM, the principal methyl group donor involved in epigenetic regulation and nucleotide synthesis. Methionine availability critically influences tumor and immune cell behavior in the TIME. Tumor cells competitively uptake methionine by overexpressing the methionine transporter, SLC43A2, leading to methionine deprivation in T cells, which subsequently impairs survival and function[99].

In contrast to tumor cells, T cells lack compensatory mechanisms to acquire or retain methionine under competitive conditions. Methionine restriction in T cells results in reduced levels of the histone, H3K79me2, a marker associated with active gene transcription that ultimately leads to defective T cell activation and immune dysfunction[100]. Although methionine deprivation impairs T cell function, emerging evidence suggests that methionine also enhances antitumor immunity through epigenetic reprogramming. Specifically, methionine restriction induces chromatin demethylation and cGAS activation, which promotes cytosolic DNA sensing and immune activation in tumor and APCs. This dual effect reflects a context-dependent metabolic checkpoint, where tumor cells are more susceptible to methionine starvation and appropriate metabolic modulation may selectively rewire the TIME in favor of immune activation[101].

The TIME is a battleground where tumors and immune cells compete for critical amino acids and shape the balance between tumor progression and antitumor immunity. Glutamine, tryptophan, serine, and arginine have pivotal roles in this metabolic tug-of-war (**Figure 3**). Tumors often gain the upper hand by monopolizing these nutrients, leading to immunosuppression and immune evasion. However, by strategically manipulating amino acid pathways and combining these approaches with immunotherapy, the scales may be tipped in favor of immune activation and enhanced therapeutic outcomes. Deciphering the intricate metabolic networks within the TIME will pave the way for novel precision therapies. To facilitate a clearer understanding of how specific amino acids orchestrate the immunologic dynamics within the TIME, the respective roles of tumor and immune cells with potential therapeutic strategies are summarized in **Table 2**.

Amino acid therapy in tumor targeting: clinical insights

The treatment of cancer initially involved resection and radiation therapy relying on X-rays. The first tumor chemotherapy drug was nitrogen mustard, which was developed by Goodman and Gilman at Yale University[102,103]. Although some progress was made, there were still two bottlenecks (imprecise killing and insufficient intensity) and there was no progress for a long time. However, in recent years the development of new technologies, such as reprogramming of amino acid metabolism and the development of small molecule amino acid carrier drugs, have largely compensated for the previous shortcomings. The following will provide a detailed introduction to tumor-targeted amino acid therapy in recent years (**Table 3**).

Targeting amino acid metabolic enzymes

IDO 1 inhibitors

Tryptophan is essential for T cell-mediated immunity. High IDO1 expression is associated with a poor prognosis in a range of cancers. Therefore, IDO1 inhibition is the goal of anticancer therapy. Currently, the combined application of IDO and TDO inhibitors, as well as IDO/TDO dual-target inhibitors, mainly focuses on IDO, TDO, and indoleamine 2,3-dioxygenase, and has made important progress in the treatment of melanoma, and lung, liver, and colorectal cancers (CRCs), demonstrating promising prospects. However, complete blockade of tryptophan metabolism may lead to a series of adverse reactions, including a significant increase in tryptophan concentration, and a reduction in downstream metabolites of Kyn, including compounds that have neuroprotective and tumor growth-inhibiting effects, which may in turn promote the occurrence and development of tumors. This strategy still faces many challenges[104,105].

Arginase inhibition

In a mouse model of osteosarcoma, arginine administration synergistically acts against PD-L1. CB-1158 is a potent Arg1 small molecule inhibitor that attenuates MDSC-mediated T cell inhibition *in vitro*, increases the number and function of CD8+ T cells in the TME, and inhibits tumor growth in multiple tumor models. CB-1158 treatment synergistically enhances the antitumor effects of checkpoint blockade in a mouse model. This approach is being tested in a clinical study

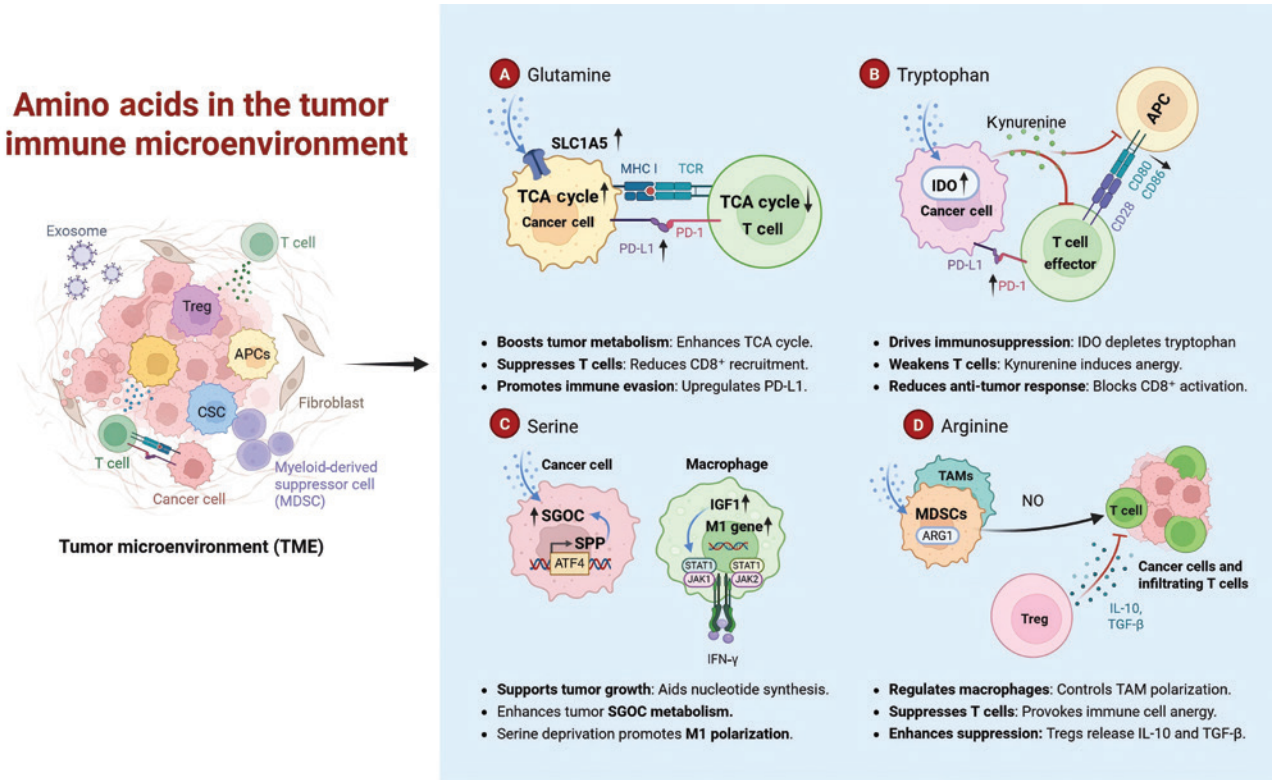


Figure 3 Amino acid metabolism in the TIME. The TIME is shaped by metabolic competition between tumor and immune cells. Amino acids have key roles in modulating immune responses and tumor progression. (A) Glutamine: tumor cells upregulate the glutamine transporter, SLC1A5, increasing glutamine uptake to fuel the TCA cycle and promote PD-L1 expression. PD-L1 on tumor cells interacts with PD-1 receptors on $CD8^+$ T cells, inhibiting TCR signaling initiated by MHC I–TCR antigen presentation and thereby suppressing T cell activation and inducing exhaustion. Excessive glutamine uptake by tumor cells reduces glutamine availability in the microenvironment, thereby limiting TCA cycle activity and metabolic fitness in T cells. (B) Tryptophan: tumor cells overconsume tryptophan and convert tryptophan into kynurenine *via* IDO. Kynurenine activates AhR signaling in T cells, which leads to downregulation of co-stimulatory molecules (e.g., CD80/CD86) and upregulation of PD-1, thereby suppressing T cell activation and fostering an immunosuppressive microenvironment. (C) Serine: tumor cells excessively uptake serine to fuel SGOC metabolism *via* ATF4, supporting nucleotide biosynthesis and proliferation. In contrast, serine deprivation promotes M1 macrophage polarization by upregulating IGF1 and activating STAT1 signaling. (D) Arginine: TAMs and MDSCs express ARG1 to deplete extracellular arginine and produce NO, both contributing to immune suppression. Tregs secrete IL-10 and TGF-β, further reinforcing immunosuppression and shaping the TIME. The figure was created with BioRender.com. AhR, aryl hydrocarbon receptor; ARG1, arginase-1; ATF4, activating transcription factor 4; CD80, cluster of differentiation 80; CD86, cluster of differentiation 86; IDO, indoleamine 2,3-dioxygenase; IGF1, insulin-like growth factor 1; IL-10, interleukin-10; Kyn, kynurenine; MDSC, myeloid-derived suppressor cell; NO, nitric oxide; PD-1, programmed cell death protein 1; PD-L1, programmed death-ligand 1; SGOC, serine–glycine–one-carbon; SLC, solute carrier; STAT1, signal transducer and activator of transcription 1; TAM, tumor-associated macrophage; TCR, T cell receptor; TGF-β, transforming growth factor-beta; TIME, tumor immune microenvironment; Treg, regulatory T cell.

(NCT02903914) in patients with advanced or metastatic solid tumors. Therefore, arginine depletion (e.g., ADI-PEG20) and arginine supplementation may have clinical benefits for R-depleting and non-auxotrophic tumors, respectively[106]. Arg2-deficient T cells exhibit a 20% increase in baseline intracellular L-arginine levels and an extended survival duration *in vitro*. Activation in the presence of the arginase inhibitor, norNOHA, elevates the survival rate of wild-type T cells without affecting Arg2-null T cells[3].

Glutamine metabolic enzyme inhibition

The quest for targeting glutamine metabolism, despite initial setbacks due to toxicities, has been revitalized with the development of compounds, such as JHU-083[7]. This prodrug,

Table 2 Comparative overview of key amino acids in tumor *vs.* immune cells and therapeutic implications

Amino acid	Role in tumor cells	Role in immune cells	Therapeutic strategy
Glutamine	Supports proliferation, TCA cycle fueling, and redox balance *via* GSH synthesis	Required for T cell activation, proliferation, and redox homeostasis	GLS inhibitors (e.g., CB-839); glutamine transporter inhibitors (e.g., V-9302); combined with ICIs
Arginine	Tumors express ASS1 for *de novo* synthesis; used for polyamine and NO synthesis	Essential for T cell function and memory; T cells cannot synthesize it *de novo*	Arginase inhibitors; ASS1/OTC-modified CAR-T cells; methotrexate-induced NO boost
Tryptophan	Degraded *via* IDO to Kyn to promote immune evasion *via* AhR pathway	Required for T cell proliferation and activation	IDO inhibitors; AhR blockers; modulation of microbial-derived indoles
Serine	Promotes nucleotide biosynthesis, redox balance, and tumor growth	Essential for T cell and macrophage activation and differentiation	Targeting PHGDH/serine synthesis pathway; modulation of macrophage polarization
Asparagine	Promotes tumor survival and metastasis *via* ASNS upregulation	Dual role: depletion impairs early activation but enhances effector function *via* NRF2	Asparaginase treatment; dietary asparagine restriction; ASNS inhibition
Methionine	Enhances histone methylation and immune evasion *via* SAM synthesis	Required for T cell epigenetic activation and cytokine production	Methionine restriction; SLC43A2 inhibition; combination with cGAS-STING activation and ICIs

Table 3 Summary of amino acid-targeting approaches in cancer therapy

Targeting	Methods	Mechanisms
Targeting amino acid metabolic enzymes	IDO 1 inhibitors	Therapy mainly focuses on IDO, TDO, and indoleamine 2,3-dioxygenase.
	Arginase inhibition	Arginine administration synergistically acts against PD-L1.
	Glutamine metabolic enzyme inhibition	Some compounds like JHU-083 have solved the toxicity problem of targeted glutamine blockade methods.
	Serine synthetases inhibition	PHGDH plays a key role in the biosynthesis of serine from glucose sources.
Amino acid combination microflora		Probiotics degrade dietary tryptophan into dialdehyde-3-aldehyde (I3A), which then activates aromatic hydrocarbon receptors (AhR). This activation leads to local expansion of $CD8^+$ T cells that produce interferon-γ, enhancing tumor immunity and increasing melanoma responsiveness to immune checkpoint inhibitors (ICIs).
Small-molecule amino acid carrier medications		Innovations in multivesicular liposome technology have led to the continuous supply of alkaline l-arginine (l-arg), modifying the acidic and l-arg-deficient tumor microenvironment (TME).
Diet-related treatment		Leucine can activate the mTOR signaling pathway. Restricting dietary methionine induces a sulfur deficiency, attenuating tumor immunogenicity within the TME.
Immune cell modification		T cells can be redesigned to express functional ASS or OTC enzymes together with different chimeric antigen receptors.
Reprogramming of the amino acid metabolism		PEG bound cysteine enzymes can induce selective cancer cell death, while addressing pharmacokinetic limitations.
Others		Anti-SLC7A5 can block the uptake of Gyn by T cells and enhance the immunity of anti-tumor T cells. L-ASNase GRASPA® encapsulated in red blood cells demonstrates good tolerability, reducing the occurrence of allergic reactions and coagulation disorders.

activated within the TME, signifies a targeted approach to glutamine blockade, showcasing the efficacy in multiple cancer models through a $CD8^+$ T cell-dependent mechanism. This strategy exemplifies the nuanced understanding.

Serine synthetases inhibition

Targeting 3-phosphoglycerate dehydrogenase (PHGDH) disrupts serine synthesis, a critical pathway in the metastatic potential of various cancer types. Inhibition of PHGDH, which is pivotal in glucose-derived serine biosynthesis, attenuates brain metastasis without impeding extracranial tumor growth, delineating a targeted approach to disrupt metabolic dependencies of tumor cells and enhancing survival outcomes in animal models[107].

Amino acid combination microflora

Emerging research underscores the potential of *Lactobacillus reuteri* (Lr) in melanoma treatment through probiotic intervention. Lr facilitates tumor immunity by translocating to, colonizing within, and enduring in the melanoma microenvironment. This process involves probiotic' degradation of dietary tryptophan into indole-3-aldehyde (I3A), subsequently activating the AhR. This activation spearheads the local amplification of IFN-γ-producing $CD8^+$ T cells, bolstering tumor immunity and enhancing melanoma' responsiveness to immune checkpoint inhibitors (ICIs)[108]. Furthermore, the production of I3A by Lr is necessary and sufficient to drive antitumor immunity, an effect enhanced by a tryptophan-rich diet *via* AhR signaling in $CD8^+$ T cells. Additionally, an engineered attenuated *Salmonella* strain overexpressing methioninase effectively targets tumors and depletes intratumoral methionine, exploiting cancer cell methionine dependence, while sparing systemic levels. This approach significantly inhibited tumor growth and metastasis in prostate, breast, and liver cancer models in nude mice[109]. *Salmonella*-induced methionine depletion activates the immune system and enhances the effectiveness of ICI therapy in melanoma[110].

Small-molecule amino acid carrier medications

Innovations in multivesicular liposome technology have led to the continuous supply of alkaline l-arginine (l-arg), modifying the acidic and l-arg-deficient TME. This strategy not only facilitates tumor cell access to l-arg from the microenvironment but also ensures immune cell provision with l-arg. Selective inhibition of the CAT-2 transporter protein concurrently maintains tumor l-arg deprivation and enriches tumor-killing immune cells within the TME. This dual action promotes $CD8^+$ T cell infiltration and activation, elevates M1 macrophage ratios, and suppresses melanoma growth, thereby extending survival. When combined with anti-PD-1 antibodies, this approach reverses the low response of tumors to immune checkpoint blockade therapy, manifesting a synergistic antitumor effect[111].

Immunosurveillance activation nanomedicine (MRIAN) represents a novel approach to T-ALL therapy by targeting MDSCs in the bone marrow. T-ALL cells and MDSCs show elevated uptake of L-phenylalanine and MRIANs, which in combination with doxorubicin (MRIAN-Dox), selectively eliminate leukemic cells while sparing normal hematopoietic cells and reducing cardiotoxicity. Mechanistically, MRIANs decompose into L-phenylalanine, inhibiting PKM2 and reducing ROS in MDSCs, thus impairing the suppressive function and promoting differentiation[112]. Biodegradable L-phenylalanine polymer (8P6) encapsulating venetoclax forms nanoparticles (Vene@8P6) with high drug loading capacity and stability. This nano-delivery system precisely targets AML cells in leukemic mouse bone marrow, effectively damaging tumor cell DNA and ROS clusters, inducing cell death[113].

Diet-related treatment

Some studies have demonstrated that B cells in CRC have an addiction for leucine, which promote *in vitro* induction of leucine-tRNA-synthase-2 (LARS2) and transforming growth factor-β1 (TGF-β1) expression. The generation of LARS2-expressing B cells is enhanced *in vivo* when applying a L-rich diet to mouse models of CRC, which was shown to be associated with an increased tumor burden[114]. Restricting dietary methionine induces a sulfur deficiency, attenuating tumor immunogenicity within the TME. Conversely, methionine supplementation in diets boosts antitumor immunity in immunocompetent mice and inhibits tumor progression. Investigations reveal that reduced methionine or protein intake diminishes T cell prevalence in such mice, undermining the efficacy of antitumor immunotherapy. This effect correlates with a decrease in hydrogen sulfide production by the gut microbiota, impairing antitumor immunity, fostering colon cancer advancement,

and suppressing antitumor immune responses through microbial interactions[115].

Immune cell modification

Blood and solid cancers catabolize the semi-essential amino acid, arginine, to drive cell proliferation. However, the resulting hypoarginine microenvironment can also impair CAR-T cell proliferation, limiting efficacy in clinical trials targeting hematologic and solid malignancies. T cells are sensitive to the low arginine microenvironment due to low expression of the arginine resynthetases [arginine succinate synthase (ASS) and OTC]. T cells can be redesigned to express functional ASS or OTC enzymes in conjunction with different CARs. Enzymatic modifications increase CAR-T cell proliferation without losing CAR cytotoxicity or increasing depletion. Enzyme-modified CAR-T cells enhance clearance of leukemia or solid tumor burden *in vivo*, providing the first metabolic modification for enhanced CAR-T cell therapy[116].

Reprogramming of the amino acid metabolism

The lysosome-nuclear signaling axis, which is pivotal in sensing lysosomal cysteine, presents a novel therapeutic avenue through modulation of the AhR. Interventions targeting lysosomal cysteine efflux have been shown to sensitize cancer cells to ferroptosis[117]. CysRx, a synthetic mRNA therapeutic, exemplifies this therapeutic potential by strategically converting cytosolic cysteine to lysosomal cystine, thereby reprogramming intracellular nutrient distribution. This targeted metabolic intervention demonstrates that it is possible to selectively kill cancer cells while maintaining normal systemic functions in healthy tissues, providing a more selective approach to cancer treatment[117].

Cysteine ligandability varies significantly across different cancer contexts, with particular relevance for previously "undruggable" transcription factors that comprise 19% of all oncogenes. Specific probes targeting critical transcription factors were developed through cysteine-directed chemical screening, including NF-κB1 at C61 using SH-7346 and SOX10 using SH-0029, effectively disrupting DNA-binding and transcriptional activity in melanoma. This chemical proteomics approach establishes general principles governing tumor cysteine ligandability, providing promising avenues for expanding small-molecule therapeutics beyond the current 10% of targetable oncogenic drivers, particularly into the previously inaccessible realm of transcription factor inhibition[118].

Others

SLC7A5 (LAT1) is a key transporter of BCAAs and Kyn. Monoclonal antibodies against SLC7A5 have shown strong antitumor activity in colorectal and breast cancer xenograft models by inhibiting nutrient uptake and suppressing tumor proliferation. Beyond blocking BCAA and Kyn transport, these antibodies also induce antibody-dependent cell-mediated cytotoxicity (ADCC), further enhancing the therapeutic potential[119]. Kyn mediates T cell dysfunction by activating AHR signaling. By preventing Kyn uptake, anti-SLC7A5 can block the uptake of Kyn by T cells and enhance the immunity of antitumor T cells[120].

Recent advances in nanomedicine have facilitated the development of delivery systems that improve the tumor specificity of metabolic inhibitors, including delivery systems targeting amino acid transporters. pH-responsive nanoparticles, for example, are designed to release therapeutic payloads specifically within the acidic TME, thereby reducing off-target toxicity and enhancing treatment efficacy[121]. Some studies have reported the use of lipid-polymer hybrid nanoparticles to deliver inhibitors of amino acid transporters, such as SLC7A11, which has a critical role in glutathione biosynthesis and ferroptosis resistance[122]. Targeting SLC7A11 using nanoparticle-based systems has shown promise in promoting ferroptotic cell death in preclinical models[123]. In addition, bispecific antibodies (BsAbs) offer a promising approach to simultaneously target immune checkpoints and metabolic pathways. Emerging BsAbs aim to co-target molecules, such as PD-1 or CTLA-4, alongside amino acid transporters, like LAT1 (SLC7A5) or xCT (SLC7A11), potentially restoring T cell function while disrupting tumor nutrient acquisition for synergistic antitumor effects[124].

ASNase can serve as a chemotherapeutic agent targeting free asparagine, has been approved for cancer treatment, and has demonstrated success in the clinical treatment of leukemia patients[125]. Currently, many modified asparaginases have emerged. For example, recombinant L-asparaginase from the *Anoxybacillus* genus exhibits good thermal stability but lacks glutaminase activity[126]. L-ASNase GRASPA® encapsulated in

red blood cells demonstrates good tolerability, reducing the occurrence of allergic reactions and coagulation disorders. However, most studies involving ASNase have focused on leukemia cells. Further *in vitro* and *in vivo* research may be needed to evaluate the actual efficacy against other solid tumors if considered for treatment.

These strategies remain under preclinical or early clinical investigation. Further research is required to optimize delivery efficiency, minimize immunogenicity, and evaluate the safety and efficacy across diverse tumor types.

Conclusions and future perspectives

Amino acids are no longer viewed as mere building blocks of proteins. The profound roles of amino acids in regulating the TME and influencing cancer progression have been thoroughly elucidated. This review has highlighted how amino acids, acting both as nutrients and signaling molecules, shape tumor growth, immune cell function, and therapeutic responses. By deepening our understanding of the complex interplay between amino acid metabolism and cancer biology we open new doors to targeted therapies that may revolutionize cancer treatment paradigms.

Strategies targeting key metabolic enzymes, such as IDO1, TDO2, and glutamine metabolism enzymes, are moving from concept to clinical trials. These approaches not only aim to starve tumor cells of critical nutrients but also to restore immune cell functionality, enhance antigen presentation, and reduce immune checkpoint expression. Additionally, novel methods involving engineered microbiota to modulate amino acid profiles, small-molecule amino acid mimetics, and innovative dietary interventions offer promising complementary avenues[127].

Despite these advances, numerous challenges remain. Tumor heterogeneity limits the universal applicability of amino acid-targeted therapies. In light of the metabolic plasticity of tumor cells, which often drives resistance to amino acid-targeted therapies, real-time monitoring of metabolic biomarkers, such as circulating amino acid levels or pathway-specific metabolites, may enable early detection of adaptive changes[128]. In parallel, dual targeting strategies have shown enhanced efficacy in preclinical models. By dynamically adjusting therapeutic strategies in response to these metabolic changes, clinicians can maintain treatment pressure on tumor cells and delay the onset of resistance.

Another key concern is systemic toxicity. Systemic depletion of amino acids can lead to off-target effects, including neurologic symptoms, immune suppression, or gut microbiota imbalance[129]. To mitigate these risks, precision delivery approaches, such as engineered bacteria and pH-sensitive nanocarriers, are being developed to restrict therapeutic activity to the tumor site while sparing normal tissues. These strategies are expected to enhance safety and tolerability in clinical applications.

Future research should continue to integrate emerging knowledge from systems biology, single-cell metabolomics, and spatial transcriptomics to map amino acid fluxes in the TME and identify context-specific metabolic vulnerabilities. Clinical trials should evaluate the efficacy and safety of amino acid-targeted therapies across a broader spectrum of cancer types and stages. Importantly, new biomarkers that reflect metabolic states and treatment responses will be essential to guide patient selection, monitor therapy, and detect resistance early.

In conclusion, amino acid metabolism represents a cornerstone of cancer biology and a fertile ground for therapeutic innovation. By building on our expanding understanding of these metabolic networks, we can develop more precise, effective, and personalized approaches that improve patient outcomes and quality of life.

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Conflict of interest statement

No potential conflicts of interest are disclosed.

Author contributions

Conceived and designed the analysis: Lan Fang, Ping Wang.
Wrote the paper: Ziyou Lin, Chang Chang, Shuyu Zhao.
Figure preparation: Ziyou Lin, Chang Chang.

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