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Amino acid sensors as key regulators of tumor biology

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Highlights:

- Amino acid sensors integrate nutrient signals to coordinate tumor adaptation.
- Amino acid sensing remodels metabolism, epigenetics, immunity, and redox balance.
- Targeting amino acid sensors offers new strategies for cancer therapy.

Abstract: Amino acid sensors are central regulators that link nutrient availability to tumor adaptation. They coordinate metabolic homeostasis, modulate epigenetic landscapes via metabolite-driven chromatin remodeling, shape the immune microenvironment by controlling nutrient competition and stress signaling, and maintain redox balance under oxidative stress. This review examines how amino acid sensing circuits sustain tumor growth, plasticity, and immune evasion, highlighting their potential as therapeutic targets to exploit metabolic vulnerabilities and enhance anti-cancer efficacy.

Keywords: amino acid sensors; tumor metabolic homeostasis; epigenetic regulation; immune microenvironment; oxidative stress

1. Introduction

Cancer is a complex disease characterized by sustained proliferation and remarkable adaptability. Its evolution is not solely driven by the stepwise accumulation of genetic mutations, but rather by the dynamic interplay among genetic alterations, metabolic reprogramming, and microenvironmental pressures [1,2]. Within this complex network, amino acids play diverse and essential roles, serving not only as nutrients but also as key regulators of metabolism, signaling pathways, and immune responses [3]. These diverse roles position amino acids as key determinants of tumor initiation, progression, and metastasis.

Beyond serving as substrates for energy production and macromolecular biosynthesis, amino acids also function as critical signaling molecules that actively participate in the regulation of cellular fate and homeostasis. Cells rely on molecular sensors and associated signaling cascades to detect amino acid levels, coordinating nutrient availability with context-specific signaling responses. By integrating these

signals, nutrient-sensing circuits coordinate anabolic and catabolic processes to maintain growth homeostasis under stress conditions [4]. The mechanistic target of rapamycin complex 1 (mTORC1) and general control nonderepressible 2 (GCN2) are two evolutionarily ancient and deeply conserved amino acid-sensing pathways that safeguard nutrient homeostasis in eukaryotic cells [5,6]. Under physiological conditions, they coordinate cell growth, protein synthesis, autophagy, and energy metabolism in response to nutrient availability, ensuring survival during amino acid deprivation and restoring metabolic balance upon nutrient replenishment. In cancer, however, these nutrient-sensing mechanisms are profoundly altered. Rather than constraining growth under metabolic stress, oncogenic signaling, ubiquitin-system dysregulation, and aberrant post-translational modifications (PTMs) of nutrient sensors uncouple amino acid scarcity from mTORC1 inhibition [7,8]. As a result, tumor cells sustain anabolic growth despite fierce competition with immune cells for limited nutrients. Concurrently, the GCN2-activating transcription factor 4 (ATF4) stress-response program is transformed from a transient cytoprotective mechanism into a chronic adaptive network that promotes nutrient acquisition, redox homeostasis, epigenetic plasticity, and the persistence of therapy-resistant cancer cells. Collectively, by precisely tuning signaling thresholds and reallocating metabolic resources, tumor cells adapt to diverse stressors and dynamically shift among proliferative, survival, and drug-tolerant states, thereby promoting malignant progression and therapeutic resistance [5,9].

Increasing evidence now indicates that amino acid metabolism is structurally coupled to long-term tumor adaptation and evolution through its capacity to reshape the epigenetic landscape and remodel the immune microenvironment [10,11]. Within cancer cells, rewiring of amino acid metabolic pathways directly modulates the intracellular pools of key metabolites and cofactors required for epigenetic processes, including histone modifications and deoxyribonucleic acid (DNA) methylation. These alterations drive transcriptional reprogramming programs that sustain tumor heterogeneity, cellular plasticity, and the maintenance of stemness-associated states [9,12,13]. In the tumor microenvironment (TME), intense competition between tumor cells and immune cells for limited amino acids is a key driver of metabolic immune suppression [14]. This competition not only deprives immune cells of essential nutrient substrates required to support activation and effector function, but also activates nutrient-sensing stress signaling pathways within immune cells. As a result, immune cell proliferation, cytokine production, and cytotoxic activity are directly suppressed, collectively promoting immune evasion and diminishing the efficacy of immunotherapeutic interventions [15].

Accordingly, this review synthesizes recent advances from a systems-level perspective, highlighting how amino acid sensing and signal integration are connected to downstream phenotypic outcomes. We focus on the molecular mechanisms by which amino acid sensors perceive amino acid availability and transmit these signals to signaling and metabolic networks. We also discuss their functional significance in cancer biology and provide a mechanistically informed framework for developing combination therapeutic strategies that exploit metabolic vulnerabilities and alleviate tumor-associated immunosuppression.

2. Amino acid sensors regulate tumor metabolic homeostasis

Within the complex network of tumor metabolic reprogramming, cells rely on a series of highly coordinated amino acid sensors to monitor intracellular and extracellular amino acid availability and convert this information into downstream signaling outputs that regulate cell growth, proliferation,

survival, and metabolic activity [4,8]. The mTORC1 is a central regulator of cell growth and represents a key signaling hub that links amino acid sensing to metabolic reprogramming. Activation of mTORC1 is essential for ribosomal protein synthesis and cancer cell growth, whereas its inhibition leads to cell cycle arrest, induction of autophagy and apoptosis, and a reduction in overall cellular viability [16]. Leucine and arginine sensors transmit amino acid availability signals to mTORC1, thereby coordinating anabolic and catabolic metabolism and providing the biosynthetic precursors and energy required to support rapid tumor cell proliferation (Figure 1).

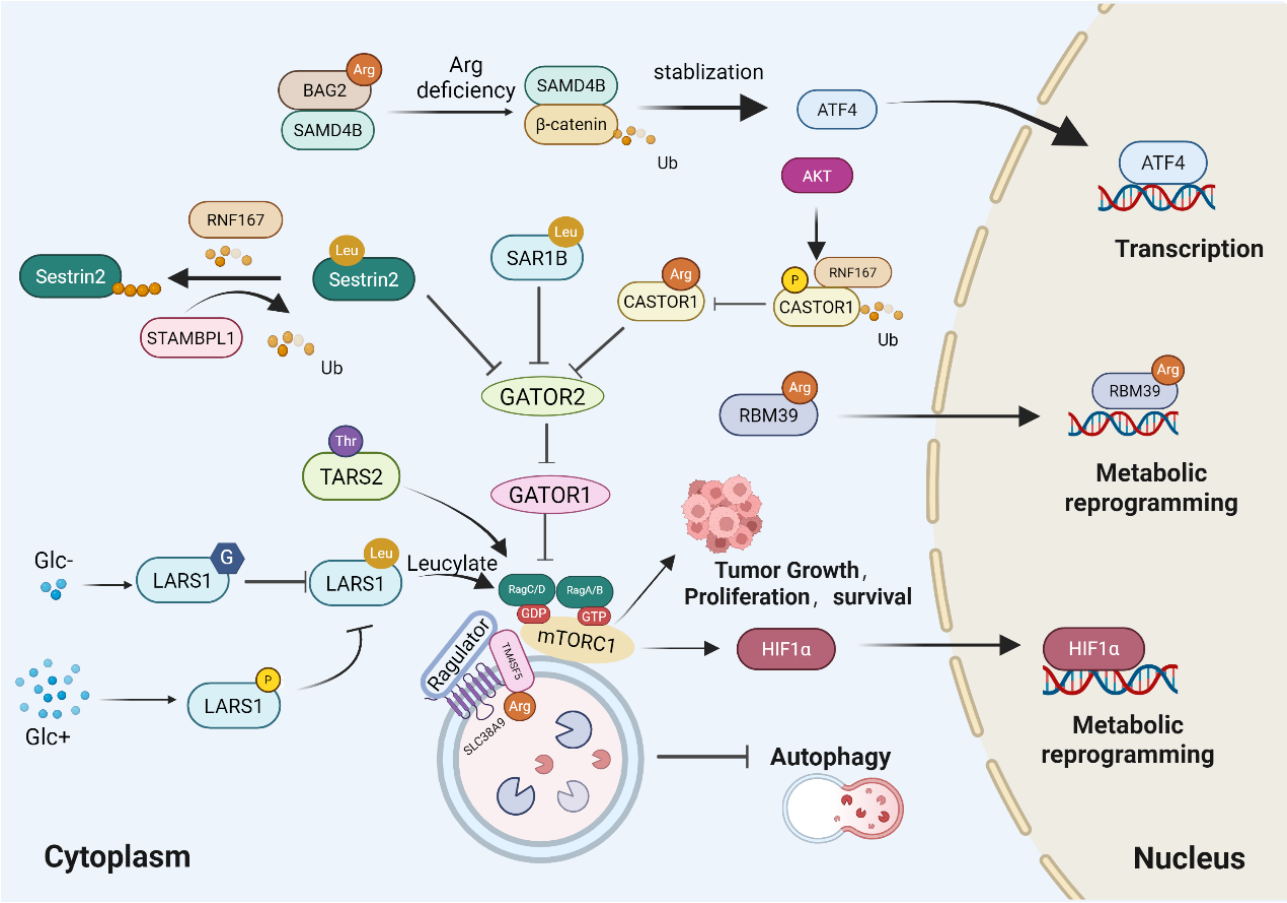

Figure 1. Amino acid sensing in tumor metabolic homeostasis. Representative amino acid sensors and their downstream signaling pathways coordinate tumor metabolic homeostasis. Leucine, arginine, and threonine sensors, including Sestrin2, secretion-associated Ras-related GTPase 1B (SAR1B), Leucyl-tRNA synthetase 1 (LARS1), cytosolic arginine sensor for mTORC1 subunit 1 (CASTOR1), Solute carrier family 38 member 9 (SLC38A9), RNA-binding motif protein 39 (RBM39), Bcl-2-associated athanogene 2 (BAG2), and threonyl tRNA synthetase 2 (TARS2), regulate mTORC1 activity through distinct mechanisms, integrating nutrient availability with metabolic reprogramming, autophagy, and tumor growth. Arg, Arginine; Leu, Leucine; Thr, Threonine; G, GlcNAcylation; Glc, Glucose; P, Phosphorylation.

2.1. Leucine sensing by its sensors in tumor metabolic control

Leucine is an essential branched chain amino acid and represents one of the most potent activators of mTORC1 signaling. In cancer, leucine sensing mechanisms are frequently reprogrammed to sustain elevated levels of protein synthesis and proliferative signaling [17,18].

Sestrin2 functions as a key metabolic regulator in cancer cells by determining whether intracellular leucine availability is sufficient to support growth [19,20]. Sestrin2 directly binds leucine and modulates mTORC1 activity through its interaction with the GTPase-activating protein activity toward Rags 2 (GATOR2) complex, thereby controlling Ras-related GTP-binding GTPase (Rag GTPase) signaling and the recruitment of mTORC1 to the lysosomal surface [21,22]. Under conditions of leucine deprivation, Unc-51-like autophagy-activating kinase 1 (ULK1) phosphorylates Sestrin2 and enhances its interaction with GATOR2, leading to inhibition of Ras-related GTP-binding protein A (RagA) and Ras-related GTP-binding protein B (RagB) activation and preventing mTORC1 localization to lysosomes. In contrast, under leucine-rich conditions, Sestrin2 undergoes dephosphorylation, which facilitates mTORC1 activation [23]. Beyond phosphorylation, leucine availability further modulates mTORC1 signaling through regulation of Sestrin2 polyubiquitination, which critically determines its interaction with GATOR2. In gastric and colorectal cancers, elevated expression of the E3 ligase RING finger protein 167 (RNF167) and reduced expression of the deubiquitinase STAM binding protein like 1 (STAMBPL1) lead to decreased polyubiquitination of Sestrin2, whereas genetic ablation of STAMBPL1 or correction of its heterozygous mutations significantly suppresses xenograft tumor growth [7]. In parallel, the deubiquitinase OTU deubiquitinase 5 (OTUD5) has been shown to promote bladder cancer progression through the OTUD5-RNF186-Sestrin2-mTOR axis by deubiquitinating and stabilizing ring finger protein 186 (RNF186), thereby facilitating Sestrin2 degradation [24,25]. These modifications thereby fine-tuning Sestrin2-mediated leucine sensing and downstream mTORC1 signaling and indicate that PTMs modulate amino acid sensing through regulating sensor activity.

Functionally, Sestrin2-dependent regulation of mTORC1 signaling has profound consequences for cellular metabolism and stress adaptation. In brain tissue, the absence of the local phosphorylated mTOR (p-mTOR)/hypoxia-inducible factor-1α (HIF-1α) pathway within Sestrin2-enriched regions results in enhanced glycolysis [26]. In tumor core regions characterized by severe hypoxia and nutrient deprivation, suppression of mTORC1 activity cooperates with sustained activation of HIF-1α to drive a metabolic shift from anabolic programs toward catabolic states [27,28]. A hallmark of this adaptive response is the induction of autophagy. As a key negative regulator of autophagy initiation, inhibition of mTORC1 directly relieves repression of the autophagic machinery, leading to enhanced autophagic flux [29]. In line with this mechanism, Sestrin2 promotes cancer cell death through autophagy in bladder cancer models [30,31], while its overexpression in osteosarcoma cells suppresses mTORC1 and HIF-1α signaling, accompanied by increased autophagy and apoptosis [32]. Beyond its role in autophagy regulation, Sestrin2 functions as a metabolic stress sensor by forming a complex with AMP-activated protein kinase (AMPK) and regulating liver kinase B1 (LKB1)-dependent phosphorylation events, thereby linking autophagic activity to cellular energy metabolism and metabolic homeostasis [33]. In line with this notion, in breast cancer, Sestrin2 regulates the expression of AMPK subunits and modulates cellular responses to ionizing radiation, whereas in colorectal cancer, Sestrin2 suppresses tumor cell proliferation through activation of the AMPK/mTORC1 signaling axis [33,34].

SAR1B is a small GTPase best known for its canonical role in COPII vesicle formation during endoplasmic reticulum to Golgi transport [35]. Strikingly, beyond this classical trafficking function, SAR1B acts as an intracellular leucine sensor that couples nutrient availability to mTORC1 signaling. SAR1B directly binds leucine through a leucine binding pocket located within its amino terminal alpha helical domain, leading to conformational changes upon ligand binding [36]. Under leucine limiting

conditions, SAR1B interacts with the GATOR2 complex to modulate mTORC1 activity. Conversely, SAR1B dissociates from the meiosis regulator for oocyte development (MIOS) subunit of GATOR2, suppresses mTORC1 activity, and establishes a negative feedback regulatory loop. Loss of SAR1B is associated with lung cancer progression, and silencing of SAR1B or its homolog SAR1A promotes mTORC1-dependent lung tumor growth in mouse models [36]. Another study reports that SAR1B plays a functional role in liver tumor initiating cells and in hepatocellular carcinoma (HCC) cells that exhibit resistance to mTORC1 inhibition. Baicalein induced chemosensitivity can be restored through SAR1B expression, and deletion of SAR1B in hepatocellular carcinoma cells treated with mTORC1 inhibitors recapitulates this phenotype [37].

LARS1, beyond its canonical role in catalyzing leucyl-tRNA charging during protein synthesis, has emerged as a key intracellular leucine sensor. In response to leucine availability, LARS1 directly binds leucine and regulates mTORC1 activity through its C-terminal RagD GTPase activating domain [38,39]. This dual functionality enables cells to coordinate translational capacity with nutrient availability, ensuring that protein synthesis occurs only under favorable metabolic conditions. Glucose serves as the primary energy source for most cells, and cancer cells frequently enhance glucose uptake and glycolytic flux to support rapid growth and proliferation [40,41]. Notably, LARS1 activity is modulated by glucose availability and the overall cellular energy status. O-GlcNAcylation of LARS1 at S1042 dynamically regulates its leucine-sensing activity by enhancing its interaction with RagD, thereby promoting leucine-dependent mTORC1 activation. In addition, O-GlcNAcylation of LARS1 promotes phosphorylation of the leucine binding site by the autophagy initiating kinase ULK1, reduces leucine affinity, and suppresses mTORC1 activity [42]. These modifications highlight that PTMs fine-tune amino acid sensing rather than act as independent signaling events. In addition, glucose starvation activates AMPK, which further stimulates ULK1 activity. ULK1 subsequently phosphorylates LARS1 at serine 720, thereby reducing leucine binding affinity and downregulating mTORC1 signaling [43]. In thyroid cancer, knockdown of LARS1 suppresses cellular viability through modulation of autophagy activation by inhibiting mTOR activity *in vitro* [44]. Furthermore, LARS1 is significantly downregulated in intrahepatic cholangiocarcinoma (iCCA). The downregulation of LARS1 can disrupt the biosynthesis of N-glycans in iCCA and enhance the chemotherapy resistance mediated by ATP-binding cassette sub-family C member 1 (ABCC1) [45].

Collectively, these findings indicate that amino acid sensors are regulated not only by fluctuations in nutrient availability but also by diverse PTMs, including phosphorylation, ubiquitination, and O-GlcNAcylation. Rather than serving as static nutrient detectors, these sensors integrate nutrient availability with oncogenic signaling through dynamic PTM-mediated regulation. Such modifications influence sensor stability, ligand-binding affinity, subcellular localization, and interactions with downstream signaling complexes, thereby fine-tuning mTORC1 activity and metabolic adaptation under different nutrient conditions. These observations suggest that PTMs constitute an additional regulatory layer controlling amino acid sensing and may provide novel therapeutic opportunities for selectively targeting nutrient-sensing pathways in cancer.

2.2. Regulatory roles of arginine sensing in tumor metabolic homeostasis

During tumor growth and metabolic reprogramming, arginine functions as a semi essential amino acid with dual roles as both a metabolic substrate and a signaling molecule, thereby exerting a central influence on the regulation of tumor growth [46,47]. On the one hand, arginine directly contributes to the biosynthesis of proteins, nucleotides, polyamines, and nitric oxide, providing essential building blocks for rapid tumor cell proliferation. On the other hand, arginine is sensed by tightly coordinated intracellular nutrient-sensing systems that translate its availability into signaling cues, thereby sustaining the activation of multiple growth promoting and metabolism supporting pathways.

At the signaling level, the CASTOR1-GATOR2-mTORC1 axis has been identified as a key regulatory module linking arginine availability to mTORC1 activation. Arginine regulates mTORC1 activity through a dual-sensing mechanism involving both cytosolic and lysosomal components, thereby ensuring metabolic homeostasis and coordinated cellular growth. CASTOR1, a member of the GATS protein family, serves as a cytosolic arginine sensor that modulates mTORC1 signaling in response to intracellular amino acid status [48,49]. Under arginine deprivation, CASTOR1 reversibly associates with the upstream GATOR2 complex via its aspartate kinase-chorismate mutase-TyrA (ACT) domain, leading to suppression of Rag GTPase-dependent mTORC1 activity [50]. In contrast, arginine binding triggers dissociation of CASTOR1 from GATOR2, thereby relieving its inhibitory effect and allowing mTORC1 activation. Competitive binding assays demonstrated that the dissociation constant (Kd) for the interaction between arginine and CASTOR1/2 is approximately 30 μM. Mutations within the ACT domain completely abolished CASTOR1's ability to bind arginine *in vitro*, confirming that arginine binding to CASTOR1 is essential for the mTORC1 pathway's response to arginine availability. Similarly, SLC38A9, a lysosomal transmembrane transporter, acts as a luminal arginine sensor that promotes mTORC1 activation through its interaction with Rag GTPases and the Regulator complex on the lysosomal surface [51,52]. In addition, the lysosomal membrane protein TM4SF5 directly binds extracellular free arginine through its extracellular loop and facilitates arginine efflux via SLC38A9, thereby further enhancing Rag and Rheb-dependent mTORC1 signaling output [53]. These convergent signals are ultimately integrated at the Rag and Rheb mTORC1 axis, tightly coupling intracellular arginine availability to cell growth, suppression of autophagy, and metabolic reprogramming.

In lung adenocarcinoma, the expression of CASTOR1 is significantly reduced, and CASTOR1 regulates lung adenocarcinoma by controlling the activation of mTOR [54]. Kirsten rat sarcoma viral oncogene homolog (KRAS) mutant tumor cells exhibit a pronounced dependence on the arginine mTORC1 axis. In non-small-cell lung cancer (NSCLC), CASTOR1 serves as a critical negative regulator of arginine sensing. Its loss significantly accelerates KRAS G12D driven lung tumorigenesis. Mechanistically, CASTOR1 deletion leads to constitutive GATOR2 activation, sustaining mTORC1 activity even under arginine-deprived conditions. Persistent mTORC1 activation further amplifies crosstalk between the PI3K-AKT and KRAS-ERK pathways, thereby conferring strong resistance to therapies targeting KRAS or PI3K signaling. In breast cancer, regulation of tumor growth by arginine displays features of arginine independent activation. AKT phosphorylates CASTOR1 at serine 14, promoting its interaction with the E3 ubiquitin ligase RNF167 and inducing K29 linked polyubiquitination, which accelerates CASTOR1 protein degradation and modulates its interaction with

GATOR2 and downstream mTORC1 signaling [55]. Thus, PTMs serve as regulatory mechanisms that fine-tune amino acid sensing rather than functioning as independent signaling pathways. In HCC, arginine sensing is tightly coupled to mitochondrial metabolic reprogramming. Primary mitochondrial defects can promote fermentative glycolysis, which is commonly referred to as the Warburg effect, thereby supplying energy and metabolic intermediates that fuel uncontrolled anabolic growth in cancer cells [56]. Transmembrane 4 superfamily member 5 (TM4SF5) enriched lysosome-like multivesicular compartments directly bind to free L arginine and facilitate its efflux through SLC38A9, leading to activation of mTORC1 signaling. Simultaneously, TM4SF5 promotes the efflux of cholesterol and remodeling of mitochondrial membrane architecture, triggering mitochondrial functional reprogramming and conferring Warburg-like metabolic features in hepatocellular carcinoma cells. This arginine driven metabolic remodeling not only sustains glycolytic energy production but also provides intermediates for lipid and nucleotide biosynthesis, thereby substantially enhancing tumor growth capacity [57].

Beyond canonical sensing pathways, the roles of RBM39 and Bcl-2-associated athanogene 2 (BAG2) in specific tumor contexts further highlight the hierarchical diversity of arginine mediated regulation. RBM39 has been identified as an arginine sensitive RNA binding protein whose stability is directly regulated by intracellular arginine levels. In hepatocellular carcinoma, accumulation of arginine to high intracellular concentrations promotes direct binding to RBM39, thereby regulating the expression of metabolic genes. At the same time, RBM39 mediated upregulation of asparagine synthesis enhances arginine uptake, establishing a positive feedback loop that sustains elevated arginine levels and oncogenic metabolic programs [58]. Small molecule degraders targeting RBM39 have been shown to disrupt tumor metabolic homeostasis, underscoring its critical role in arginine-dependent metabolic vulnerability.

BAG2 is increasingly implicated in metabolic-stress adaptation in cancer. In metabolically active tumors such as gastric cancer and breast cancer, high expression of BAG2 is strongly associated with aggressive behavior and poor clinical outcome [59,60]. Beyond its role in proteostasis regulation, BAG2 has been reported to modulate oncogenic signaling pathways including AKT/mTOR [61], and recent work identifies BAG2 as an arginine-responsive factor that supports tumor cell survival under arginine limitation. In hepatocellular carcinoma and colorectal cancer characterized by highly active arginine metabolism, BAG2 acts as an arginine sensor that directly interacts with arginine and regulates sterile alpha motif domain containing 4B (SAMD4B). Under arginine deprived conditions, BAG2 releases SAMD4B, leading to degradation of beta catenin and stabilization of ATF4 protein, which enhances cell survival. In contrast, under arginine replete conditions, strengthened interaction between BAG2 and SAMD4B prevents β-catenin degradation and activates Wnt/β-catenin signaling, thereby supporting tumor cell growth [62].

2.3. Regulatory roles of threonine sensing in tumor metabolic homeostasis

Mitochondrial TARS2 has been identified as a threonine sensor that links amino acid availability to mTORC1 signaling. TARS2 interacts with inactive Rag GTPases, particularly GTP bound RagC, leading to increased GTP loading of RagA and subsequent activation of mTORC1. In cells lacking TARS2, mTORC1 activity is no longer responsive to threonine supplementation [63]. In addition, *in vitro* studies

demonstrate that variants within the 301 to 381 amino acid region of TARS2 exhibit reduced binding to Rag GTPases, which may impair mTORC1 activation [64].

Clinical evidence indicates that TARS2 is highly expressed in lung adenocarcinoma tissues and that elevated TARS2 expression is associated with poorer overall survival. Functional studies further show that downregulation of TARS2 suppresses cell proliferation through the retinoblastoma protein pathway and promotes mitochondrial reactive oxygen species induced apoptosis [65]. However, whether the oncogenic effects of TARS2 are directly mediated through mTORC1 activation remains to be fully elucidated.

Collectively, these findings establish amino acid sensors as central coordinators of tumor metabolic homeostasis, integrating nutrient availability with anabolic signaling, stress adaptation, and metabolic reprogramming. Importantly, the consequences of amino acid sensing extend well beyond metabolic regulation. By reshaping intracellular metabolic states and the availability of metabolites required for chromatin modification, these nutrient-sensing pathways provide a mechanistic link between metabolic adaptation and epigenetic remodeling, thereby supporting transcriptional plasticity during tumor progression.

3. Amino acid sensors in the regulation of tumor epigenetic programs

Tumor initiation and progression constitute a highly complex multistep process in which metabolic reprogramming and epigenetic dysregulation are not independent events but are tightly interconnected through metabolite mediated signaling [66,67]. Metabolic intermediates within tumor cells function not only as sources of energy or substrates for macromolecular biosynthesis, but also as direct regulators of epigenetic modifying enzymes [68,69]. Through these mechanisms, cellular metabolic states are translated into stable or reversible changes in gene expression, forming a central nexus between tumor metabolism and epigenetic regulation.

Within this context, intracellular amino acid sensors play a critical role. These sensing proteins precisely detect fluctuations in the levels of specific amino acids or their metabolic derivatives and convert this information into downstream signaling cascades or directly modulate the activity of epigenetic enzymes. Through these mechanisms, amino acid sensors enable dynamic regulation of the epigenetic landscape, thereby contributing to tumor cell plasticity and malignant progression.

3.1. Methionine sensors link mTORC1 signaling to histone methylation control

Methionine is a sulfur-containing essential amino acid that plays a fundamental role in epigenetic regulation. Through the action of methionine adenosyl transferases (MAT), methionine is converted into S-adenosylmethionine (SAM), which serves as the universal methyl donor for DNA, RNA, and histone methylation reactions [70,71]. The intracellular abundance of SAM and the SAM/S-adenosylhomocysteine (SAH) ratio directly determine global methylation potential [72]. In multiple tumor types, methionine adenosyltransferase 2A (MAT2A) is frequently upregulated or becomes a functional dependency, thereby enhancing methionine to SAM flux and supporting tumor growth [73–75]. For example, in HCC, reprogramming of the methionine cycle is accompanied by elevated levels of SAM/MAT. Genetic deletion of MAT2A not only suppresses tumor growth but also alleviates immunosuppressive phenotypes [76]. In gastric cancer, silencing of MAT2A inhibits tumor cell proliferation, migration, and invasion while activating p53-associated tumor suppressive programs,

supporting its oncogenic role [77]. In colorectal cancer associated metastasis models, tumor derived secretion of MATα2, the protein encoded by MAT2A, influences the tumor liver metastatic niche, further expanding the functional landscape of MAT2A in tumor progression [78].

Recent studies have identified S-adenosylmethionine sensor upstream of mTORC1 (SAMTOR) as a key intracellular sensor of SAM availability. When intracellular SAM levels are elevated, SAMTOR dissociates from the GATOR1 complex, thereby relieving GATOR1 mediated inhibition of Rag GTPases and activating downstream mTORC1 signaling [79,80]. Importantly, SAMTOR function depends on coordinated regulation with the KICSTOR complex (KICSTOR) [81]. Under conditions of low SAM availability, SAMTOR associates with KICSTOR to maintain suppression of mTORC1 by GATOR1. In contrast, increased SAM weakens the interaction between SAMTOR and KICSTOR, releases GATOR1 mediated inhibition, and activates mTORC1 signaling (Figure 2). Through this mechanism, metabolic advantages in methionine utilization are converted into amplified growth promoting and epigenetic remodeling signals [80].

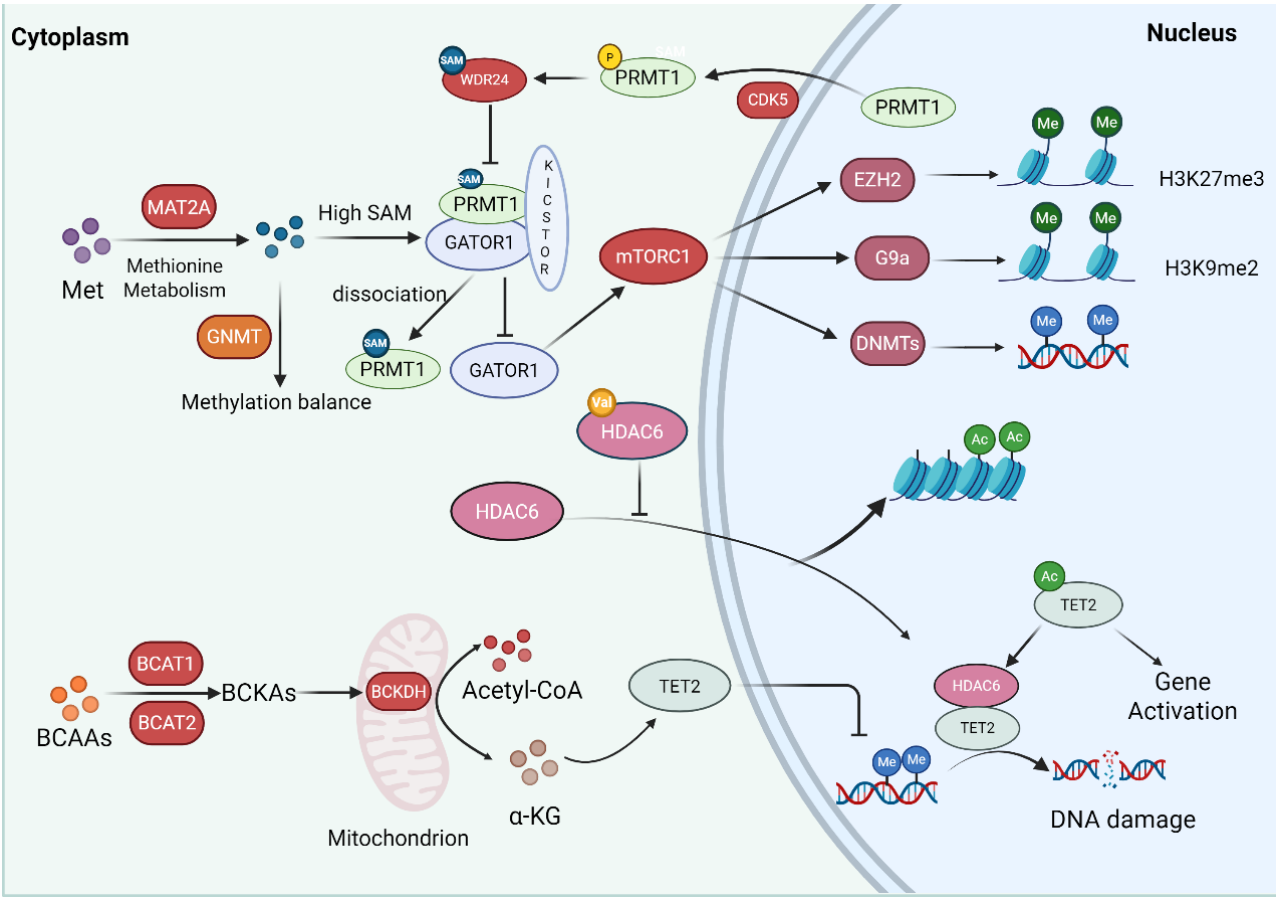

Figure 2. Amino acid sensors regulate tumor epigenetic programs. SAMTOR and Protein arginine methyltransferase 1 (PRMT1) sense methionine-derived SAM and connect nutrient availability to GATOR1-mTORC1 signaling and methylation-dependent gene regulation. Histone deacetylase 6 (HDAC6) senses valine availability and modulates tet methylcytosine dioxygenase 2 (TET2)-dependent DNA demethylation. In parallel, BCAT1/2-dependent branched-chain amino acid metabolism alters acetyl-CoA and α-KG availability, thereby influencing histone acetylation and DNA demethylation. Met, Methionine; SAM, S-adenosylmethionine; Val, Valine; Me, Methylation; Ac, Acetylation; P, Phosphorylation; BCAAs, Branched-chain amino acids; BCKAs, Branched-chain keto acids; α-KG, α-ketoglutarate.

Sustained activation of mTORC1 may lead to aberrant expression or activity of DNA methyltransferases and histone methyltransferases, thereby promoting oncogene activation through hypomethylation or silencing of tumor suppressor genes through hypermethylation [82,83]. These alterations are frequently accompanied by widespread changes in histone methylation patterns that contribute to tumor initiation and progression [84]. Enhancer of zeste homolog 2 (EZH2) functions as the catalytic core of polycomb repressive complex 2 (PRC2) and mediates di-methylation and trimethylation of histone H3 lysine 27 (H3K27) through its SET domain, resulting in transcriptional repression [85]. Trimethylated histone H3 at lysine 27 (H3K27me3) has been shown to suppress multiple genes associated with cancer cell survival, and its abundance is closely linked to tumor progression and malignancy. mTORC1 signaling has been reported to upregulate EZH2 protein levels, enhance H3K27me3, and promote cell proliferation [86]. EZH2 promotes mammary tumor initiation through epigenetic regulation of the Wnt and mTORC1 signaling pathways [87]. In human glioblastoma, coordinated activation of mTORC1 and mTORC2 drives tumor progression through specific epigenetic regulatory mechanisms, highlighting these complexes as therapeutically actionable targets [88]. In addition to EZH2, mTORC1 also cooperates with the histone methyltransferase G9a to regulate autophagy related gene expression. By increasing the repressive histone mark dimethylated histone H3 at lysine 9 (H3K9me2) at promoters of autophagy associated genes, mTORC1 suppresses autophagic programs and supports tumor cell growth [89].

PRMT1 as an additional methionine and SAM sensor that cooperates with SAMTOR to regulate mTORC1 signaling. Elevated cytosolic SAM promotes dissociation of SAMTOR from GATOR1, which facilitates the interaction between GATOR1 and PRMT1. This interaction leads to methylation of nitrogen permease regulator-like 2 (NPRL2) and suppression of GATOR1 GAP activity, thereby activating mTORC1 signaling [90]. PRMT1 is aberrantly expressed across multiple tumor types [91,92]. In pancreatic cancer, PRMT1 is highly expressed, and loss of PRMT1 reduces glycolysis and impairs tumor forming capacity. Pharmacological inhibition of PRMT1 synergizes with gemcitabine to suppress pancreatic tumor growth *in vitro* and *in vivo* [93]. Increased PRMT1 protein expression has also been reported in hepatocellular carcinoma [94,95]. Mechanistically, enhanced PRMT1 activity is linked to increased mTORC1 signaling. Under amino acid replete conditions, cyclin-dependent kinase 5 (CDK5) phosphorylates PRMT1 at serine 307, promoting its translocation from the nucleus to the cytosol and lysosomes. In these compartments, PRMT1 not only acts on GATOR1 but also methylates WD repeat domain 24 (WDR24), a key component of GATOR2, thereby activating mTORC1 through an additional mechanism. Disruption of the CDK5-PRMT1-WDR24 axis suppresses HCC proliferation and inhibits xenograft tumor growth [96].

Glycine N-methyltransferase (GNMT) functions as a key hepatic methyl-group buffering enzyme that regulates intracellular SAM homeostasis and methylation potential [97,98]. By catalyzing the transfer of methyl group from SAM to glycine, GNMT modulates the intracellular SAM/SAH ratio and thereby influences global methylation balance. GNMT predominantly exists as an active tetramer, whereas disruption of its quaternary structure markedly reduces enzymatic activity [99]. Through these mechanisms, GNMT serves as an important regulator of hepatic methyl donor flux and epigenetic stability. Genetic deletion of GNMT results in hepatic SAM accumulation, aberrant DNA methylation patterns, and spontaneous development of HCC in murine models. In human HCC, GNMT expression is frequently downregulated, and its loss is considered an early event in hepatocarcinogenesis [100].

Restoration of GNMT expression suppresses proliferation and promotes apoptosis in HCC cells, consistent with a tumor-suppressive role. Mechanistically, GNMT has been reported to interact with components of the mTOR signaling pathway, including DEP domain containing MTOR interacting protein (DEPTOR) and mTORC1, thereby modulating downstream S6K1 activation and cell-cycle progression [101].

3.2. Coupling of branched chain amino acid sensing to histone acetylation and methylation

In contrast to methionine, which primarily regulates cellular methylation reactions, branched-chain amino acids (BCAAs) are more closely associated with other major epigenetic processes, particularly histone acetylation and histone or DNA demethylation. Catabolism of BCAA, including leucine, isoleucine, and valine, not only supplies energy and biosynthetic precursors but also generates key metabolites that directly regulate epigenetic enzymes [102,103]. Acetyl-CoA serves as the obligate substrate for histone acetyltransferases, whereas α-ketoglutarate (α-KG) functions as an essential cofactor for dioxygenases, including TET family DNA demethylases and JmjC domain containing histone demethylases [104]. As a result, branched chain amino acid sensing constitutes an important pathway that links nutrient availability to the dynamic balance between histone acetylation and demethylation [105]. Ranched-chain amino acid transaminase 1 (BCAT1) and BCAT2, particularly BCAT1, represent key metabolic checkpoints connecting branched chain amino acid metabolism with epigenetic regulation in cancer cells [106,107]. In glioblastoma, BCAT1 is markedly upregulated, and its high expression is strongly associated with poor patient prognosis [108,109]. In acute myeloid leukemia, aberrant overexpression of BCAT1 reduces intracellular α-KG levels, suppresses TET2 activity, and promotes DNA hypermethylation, thereby driving leukemic cell proliferation and maintenance of AML properties [110]. These findings identify the BCAT1-α-KG axis as an important non genetic mechanism for regulating TET enzyme activity in cancer.

Following transamination, BCKA are oxidatively decarboxylated by the branched-chain α-keto acid dehydrogenase complex (BCKDH) complex in mitochondria, generating Acetyl-CoA derivatives that ultimately enter the TCA cycle and contribute to an Acetyl-CoA production [111,112]. Because Acetyl-CoA is the sole acetyl donor for histone acetylation reactions, flux through BCAA catabolism directly influences the nuclear Acetyl-CoA pool available for chromatin modification [102,113]. In KRAS mutant pancreatic cancer, BCAA catabolism is rewired in a manner that may promote incorporation of BCAA derived Acetyl-CoA into histone acetylation processes [114,115]. Conversely, acetylation of metabolic enzymes involved in BCAA degradation, such as BCAT2, exerts feedback regulation on pathway activity, indicating a bidirectional regulatory relationship between BCAA metabolism and acetylation-dependent epigenetic control [116].

Notably, restriction of valine, one of the branched chain amino acids, has been shown to exert a direct effect on demethylase activity. Histone deacetylase 6 HDAC6 functions as a direct valine sensor that coordinates epigenetic responses under nutrient stress conditions [37]. The SE14 repeat domain of HDAC6 contains a hydrophobic binding pocket that confers specific affinity for valine (Kd ≈ 1.95 μM) while showing negligible binding to leucine, isoleucine, or other amino acids. Under nutrient replete conditions, the HDAC6 valine complex remains localized in the cytoplasm, where HDAC6 primarily deacetylatesα-tubulin. Upon valine depletion, dissociation of valine exposes a nuclear localization

signal, enabling translocation of HDAC6 into the nucleus. Nuclear HDAC6 associates with the DNA demethylase TET2 and deacetylates it, thereby activating DNA demethylation processes that promote DNA damage through thymine DNA glycosylase mediated base excision. This mechanism demonstrates that valine binding represents not merely a metabolic event but a nutrient-dependent signaling input capable of regulating chromatin structure. Functionally, dietary valine restriction suppresses xenograft tumor growth and enhances the therapeutic efficacy of poly(ADP-ribose) polymerase 1 (PARP) inhibitors, indicating that the HDAC6 valine TET2 axis constitutes a critical regulatory node linking tumor epigenetic plasticity to treatment sensitivity.

Collectively, BCAA metabolism not only supplies Acetyl-CoA and α-KG to directly support histone acetylation and demethylation reactions, but also fine tunes the activity of key epigenetic enzymes through nutrient sensing mechanisms. Through these coordinated inputs, branched chain amino acid metabolism is deeply embedded within the epigenetic regulatory network of tumor cells. Accordingly, the branched chain amino acid BCAT acetylation and demethylation axis represents an important hub that links metabolic state to chromatin plasticity, thereby shaping tumor progression and responses to therapy.

4. Amino acid sensors in the regulation of antitumor immunity

The tumor microenvironment is a complex and dynamic ecosystem characterized not only by extensive interactions among diverse cell types but also by a distinct metabolic landscape [117,118]. Within this environment, nutrient availability, particularly the concentration of amino acids, constitutes a critical battleground that shapes both tumor progression and immune cell function. To meet the demands of rapid proliferation and biosynthesis, tumor cells consume large amounts of essential amino acids and, through their metabolic activities, actively remodel the chemical composition of the tumor microenvironment [119–121]. This remodeling results in localized depletion of specific amino acids or abnormal accumulation of metabolic byproducts, thereby imposing substantial metabolic stress on infiltrating immune cells and constraining effective anti-tumor immunity.

4.1. Tryptophan sensor mediated regulation of immune cell metabolism

Tryptophan is an essential amino acid that contributes to protein synthesis as well as the production of neurotransmitters and diverse bioactive metabolites. Within the tumor immune microenvironment, tryptophan metabolism is predominantly regulated by indoleamine 2,3 dioxygenase, which catalyzes the first and rate limiting step of the kynurenine pathway [122] (Figure 3). Across multiple tumor types, increased tryptophan uptake and upregulation of indoleamine 2,3-dioxygenase (IDO) are associated with poor clinical outcomes. For example, in pancreatic cancer, widespread expression of IDO1 and tryptophan 2,3-dioxygenase (TDO) correlate negatively with overall survival and recurrence free survival.

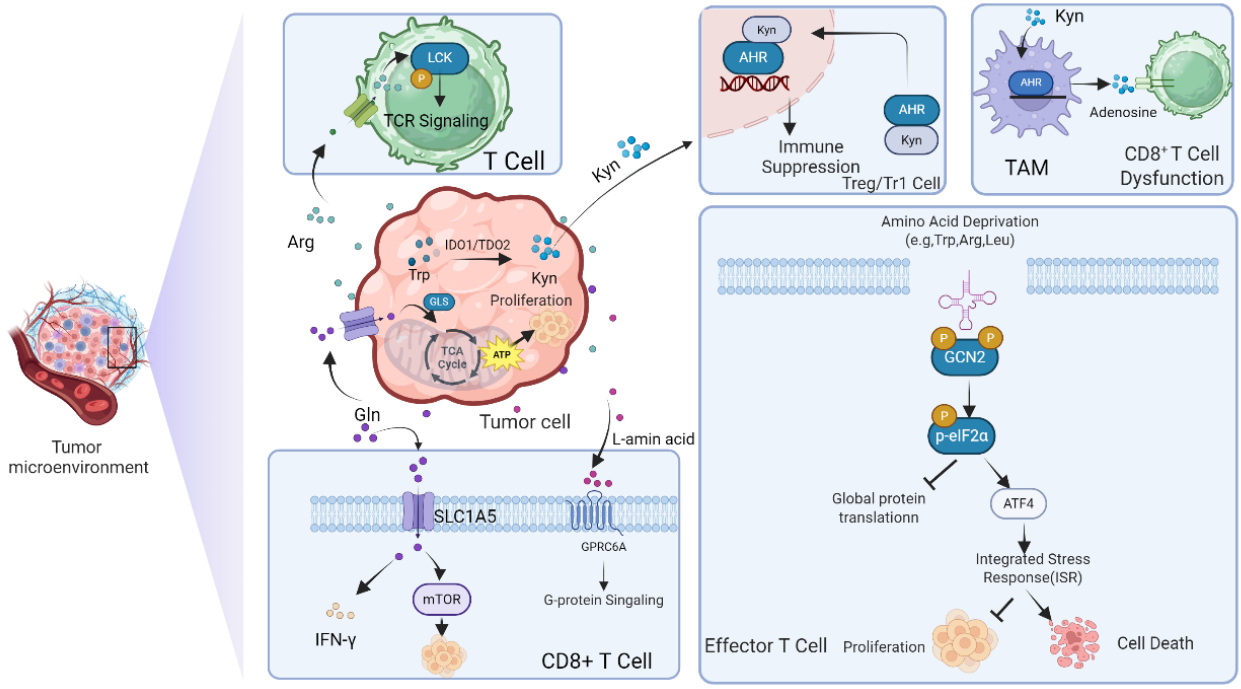

Figure 3. Amino acid sensors coordinate antitumor immunity by integrating nutrient availability with immune and stress signaling. Aryl hydrocarbon receptor (AHR) senses tryptophan-derived kynurenine to promote immune suppression, GCN2 detects amino acid deprivation to activate the integrated stress response, and G protein-coupled receptor class C group 6 member A (GPRC6A) senses extracellular amino acids to regulate T cell function. Glutamine metabolism further shapes metabolic competition between tumor and immune cells. Trp, Tryptophan; Kyn, kynurenine; TMA, Tumor-associated macrophage; Gln, Glutamine; Arg, Arginine; Leu, Leucine.

The AHR functions as a key endogenous receptor for kynurenine and plays a central role in the differentiation and function of regulatory T cells, particularly type 1 regulatory T cells [123,124]. Activation of Aryl hydrocarbon receptor is not restricted to regulatory T cells, but broadly induces immunosuppressive programs across multiple immune cell populations. Through these effects, AHR signaling reshapes the tumor microenvironment at a systemic level and promotes tumor immune evasion. Macrophages represent major cellular targets of kynurenine within the tumor microenvironment. In macrophages, activation of the kynurenine AHR signaling axis induces multiple immunosuppressive effects, including downregulation of costimulatory molecule expression and impairment of antigen presentation capacity. These changes effectively limit T cell activation and effector function [125,126]. In glioblastoma, for instance, kynurenine driven activation of AHR in tumor associated macrophages induces expression of the ecto-nucleotidase ectonucleoside triphosphate diphosphohydrolase 1 (CD39), which cooperates with ecto-5′-nucleotidase (CD73) to generate adenosine and promote cluster of differentiation 8 (CD8) positive T cell dysfunction [127].

In dendritic cells, AHR activation suppresses the expression of costimulatory molecules such as CD80 and cluster of differentiation 86 (CD86), as well as major histocompatibility complex class II (MCH-II) molecules including human leukocyte antigen-DR (HLA-DR). In parallel, AHR signaling inhibits the secretion of proinflammatory cytokines such as interleukin-12 (IL-12), interleukin-6 (IL-6), and tumor necrosis factor-α (TNF-α) [128]. Importantly, AHR activation also upregulates a set of immunosuppressive

mediators, including IDO1, interleukin-10 (IL-10), and programmed death-ligand 1 (PD-L1) [129]. These changes impair the ability of dendritic cells to function as effective antigen presenting cells and instead promote their conversion into tolerogenic dendritic cells that actively induce regulatory T cell differentiation and T cell anergy. In effector T cells, AHR activation directly promotes the expression of inhibitory receptors such as programmed cell death protein 1, thereby predisposing these cells to enter an exhausted state [39]. Collectively, AHR functions as a central signaling node downstream of the tryptophan metabolite kynurenine and establishes a robust immunosuppressive network within the tumor microenvironment. Targeting AHR or its upstream metabolic regulators, including IDO1 and TDO2, has therefore emerged as an important direction in cancer immunotherapy research.

4.2. GCN2 integrates stress responses to regulate antitumor immunity

GCN2 is an evolutionary conserved serine and threonine protein kinase that functions as a central intracellular sensor of amino acid deprivation. Within the tumor microenvironment, essential amino acids such as tryptophan, arginine, and leucine are frequently depleted as a consequence of aberrant tumor metabolism and competitive nutrient consumption. This depletion leads to accumulation of uncharged transfer RNAs within immune cells. Uncharged transfer RNAs directly bind to the histidyl tRNA synthetase related domain of GCN2, relieving its autoinhibitory conformation and inducing GCN2 dimerization and autophosphorylation, thereby activating the kinase [130]. Activated GCN2 phosphorylates its canonical substrate eukaryotic initiation factor 2 alpha (eIF2α), generating phosphorylated eIF2α (p-eIF2α). p-eIF2α suppresses the activity of its guanine nucleotide exchange factor eIF2B, resulting in a global reduction in protein translation rates that conserves energy and amino acid resources. Despite this general translational repression, selective translation of stress responsive transcripts is enhanced, most notably activating transcription factor 4. This GCN2-eIF2α-ATF4 cascade constitutes a core component of the integrated stress response, which enables cells to adapt to a wide range of intrinsic and extrinsic stresses, including nutrient limitation [131,132].

Importantly, the impact of the GCN2 mediated integrated stress response on T cell fate is highly context dependent and functionally complex. This pathway can operate either as an executor of immunosuppressive programs or as an essential adaptive mechanism that allows T cells to survive within hostile metabolic environments [133–135]. Beyond direct growth suppression, amino acid stress and tryptophan catabolism may also initiate immunoregulatory programs through GCN2-dependent pathways. These include induction or expansion of Foxp3 positive regulatory T cell, and under conditions of moderate or transient activation, promotion of adaptive metabolic reprogramming characterized by enhanced mitochondrial oxidative phosphorylation. In contrast, chronic activation of the integrated stress response within tumors, accompanied by persistent ATF4 upregulation, is frequently associated with dysfunction of tumor infiltrating lymphocytes, increased apoptosis, and resistance to immunotherapy [134]. In contrast to its immunosuppressive roles, GCN2 has been shown to be essential for the survival and effector function of tumor infiltrating CD8 positive T cells in extremely nutrient deprived glioblastoma models. Loss of GCN2 results in marked apoptosis and necrosis of intratumoral CD8 positive T cells, thereby compromising antitumor immunity. Furthermore, in preclinical adoptive cell transfer models, *ex vivo* pretreatment of CD8 positive T cells with GCN2 agonists such as halofuginone enhances oxidative metabolism and effector function. Upon reinfusion, these metabolically conditioned T cells exhibit superior tumor control and can even eradicate established tumors.

Collectively, these findings suggest that the GCN2 pathway may present a therapeutically exploitable window. Controlled and context appropriate activation of GCN2 may function as a form of metabolic training that enhances T cell adaptability and antitumor efficacy within the metabolically hostile tumor microenvironment.

4.3. Glutamine metabolism as a central regulator of tumor-immune interactions in the tumor microenvironment

Glutamine exerts its regulatory functions in TME not only through its abundance as a metabolic substrate, but more importantly through a network of glutamine-binding proteins that sense, transport, and metabolize this amino acid [136,137]. These proteins, including glutamine transporters such as SLC1A5 (ASCT2) [138,139], glutaminases (GLS1/GLS2) [140], and glutamine synthetase (GS) [141] serve as molecular nodes that integrate nutrient availability with signaling pathways, epigenetic remodeling, and immune regulation.

In multiple solid tumors, SLC1A5 is frequently upregulated, enabling enhanced glutamine uptake to sustain rapid proliferation [142–144]. Once internalized, glutamine is converted by GLS1 into glutamate and subsequently into α-KG, fueling the tricarboxylic acid (TCA) cycle and supporting nucleotide biosynthesis [145]. Elevated GLS1 expression correlates with tumor aggressiveness and metastatic potential [146,147], whereas GLS2, often downregulated in HCC, exhibits tumor-suppressive properties linked to redox balance and metabolic restraint [148]. Beyond supporting tumor growth, glutamine-binding proteins critically shape immune cell function. Activated $CD8^+$ T cells depend on SLC1A5-mediated glutamine uptake to sustain mTOR signaling, clonal expansion, and effector molecule production [149]. However, in the TME, tumor cells often outcompete immune cells for glutamine due to higher transporter expression and GLS activity, leading to localized glutamine deprivation. This metabolic imbalance impairs T cell proliferation, reduces interferon-γ and granzyme B production, and promotes exhaustion phenotypes [150]. In ovarian cancer and melanoma models, pharmacological inhibition of GLS has been shown to alleviate metabolic competition, enhance $CD8^+$ T cell infiltration, and improve responses to immune checkpoint blockade [151,152].

Glutamine sensors also regulate immunosuppressive cell populations. In breast and lung cancers, glutamine metabolism supports tumor-associated macrophage (TAM) polarization toward an M2-like phenotype, while myeloid-derived suppressor cells (MDSCs) rely on glutamine-dependent metabolic pathways to maintain suppressive function [119,153]. Conversely, targeting tumor-intrinsic GLS1 activity can shift the metabolic balance within the TME, indirectly restoring T cell functionality.

4.4. Other amino acid sensors in the sensing and regulation of antitumor immunity

Arginine is a key amino acid that shapes the tumor immune microenvironment. Recent work identifies lymphocyte specific protein tyrosine kinase as an arginine sensor in this setting. Lymphocyte-specific protein tyrosine kinase (LCK) is a central component of T cell receptor signaling and is required for T cell activation. Binding of arginine induces a conformational change in LCK that alters the phosphorylation pattern of tyrosine 394 and tyrosine 505. The resulting increase in LCK activity augments downstream T cell receptor signaling cascades and modulates T cell responses within the tumor microenvironment.

GPRC6A is a cell surface G protein coupled receptor of the class C family that senses the extracellular availability of specific amino acids. Studies demonstrate that GPRC6A functions as a direct sensor for basic L amino acids, including arginine and lysine. In the tumor microenvironment, extracellular arginine levels are strongly influenced by tumor cell metabolism and by arginase 1(ARG1) expressed by myeloid derived suppressor cells, creating spatially heterogeneous arginine gradients. Expression of GPRC6A enables immune cells to monitor and respond to these fluctuations in extracellular arginine. Upon ligand binding, including arginine, GPRC6A activates downstream G protein signaling pathways that coordinate immune cell functional programs.

5. Amino acid sensors in the regulation of tumor oxidative stress

Within the metabolically and structurally hostile tumor microenvironment, the survival and proliferative capacity of cancer cells critically depend on their ability to adapt to metabolic stress and oxidative stress. Maintenance of redox homeostasis represents a central component of this adaptive capacity. In tumor cells, specific amino acid sensors function not only as carriers for metabolic substrates but also as nutrient sensors and allosteric regulators that continuously monitor intracellular and extracellular nutrient states. Through mechanisms that include allosteric control, transcriptional reprogramming, and noncanonical translation, these proteins dynamically tune the global reducing capacity of cancer cells and support redox balance under stress conditions.

5.1. Serine mediated allosteric activation of PKM2 in the control of tumor oxidative stress

Pyruvate kinase M2 (PKM2) is a key terminal enzyme of glycolysis and a central hub in tumor metabolic reprogramming. PKM2 can reversibly switch between a highly active tetrameric form and a low activity dimeric form, and this oligomeric transition directly determines the fate of upstream glucose derived carbon flux. Through this mechanism, PKM2 profoundly influences the rate of reduced nicotinamide adenine dinucleotide phosphate (NADPH) production and thus cellular reducing capacity. NADPH is essential for maintaining redox homeostasis, as it provides the reducing power required for the glutathione and thioredoxin systems and is indispensable for the catalytic activity of glutathione reductase and thioredoxin reductase.

PKM2 contains a unique amino acid binding pocket that enables it to sense intracellular amino acid availability [154]. Serine functions as a natural allosteric activator by directly binding to this pocket and enhancing PKM2 catalytic activity [155]. Under conditions of amino acid limitation, such as serine deprivation, PKM2 shifts toward a low activity state. This promotes accumulation of glycolytic intermediates and their diversion into the pentose phosphate pathway, thereby increasing NADPH generation. The resulting enhancement of antioxidant capacity supports cell survival under oxidative stress [156,157]. These findings indicate that PKM2 can function as a metabolic emergency valve during oxidative stress, trading reduced ATP production for increased reducing power to preserve redox balance and promote stress tolerance [158].

5.2. Cysteine binding proteins in the regulation of tumor oxidative protection

Cysteine is a critical precursor within the cellular antioxidant system and serves as an essential component for glutathione synthesis. Tumor cells are highly dependent on uptake of extracellular cystine

through the cystine glutamate antiporter system xc, which is frequently upregulated to sustain intracellular redox balance. In tumor microenvironments such as breast cancer, cancer cells export glutamate through system xc^-, thereby inhibiting cystine uptake by surrounding cells and leading to depletion of intracellular free cysteine pools. Cysteine deprivation triggers oxidative self- inactivation of EglN1 also known as prolyl hydroxylase domain protein 2 (PHD2), rendering it unable to efficiently hydroxylate hypoxia inducible HIF-1α even under normoxic conditions (Figure 4). This results in pseudohypoxic stabilization of hypoxia inducible HIF-1α and activation of adaptive transcriptional programs that promote tumor survival and progression [159,160].

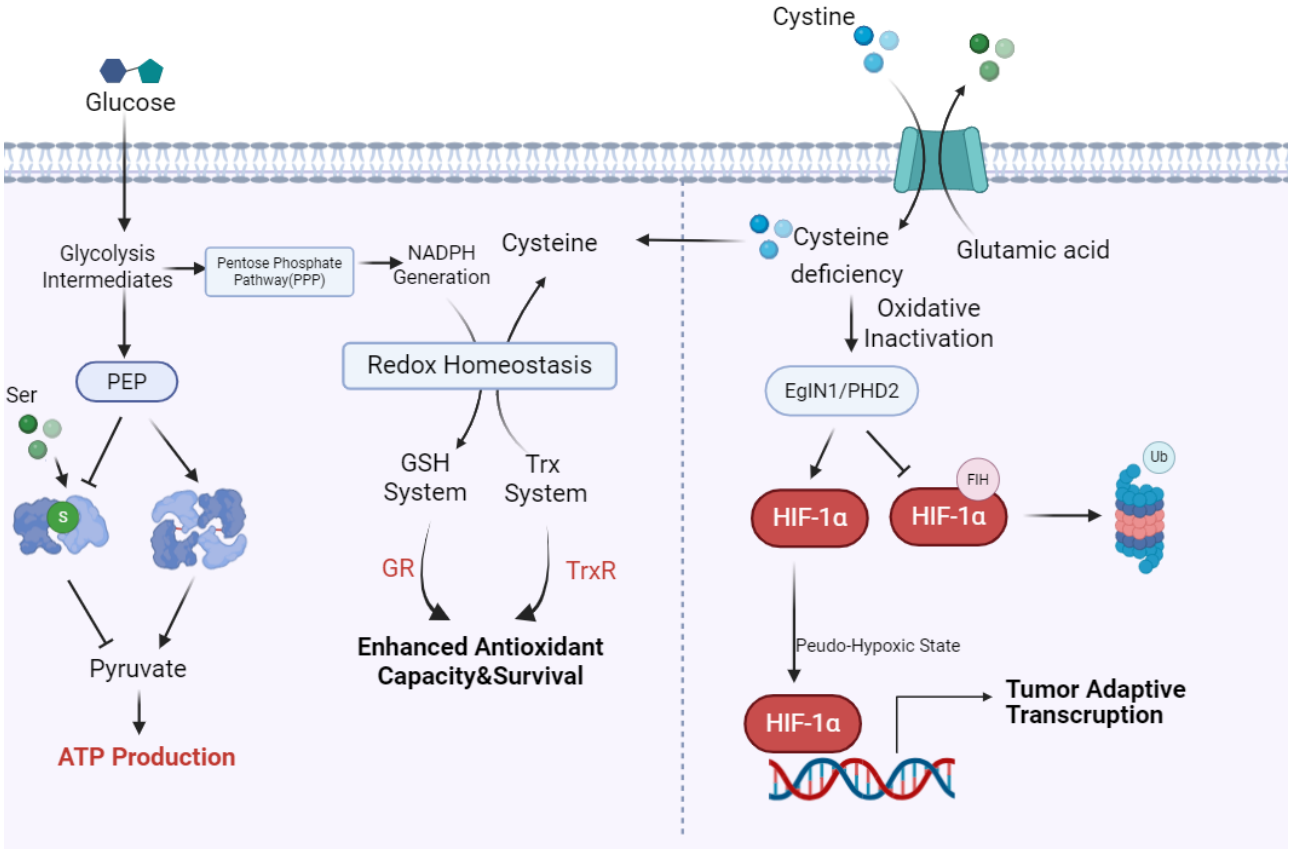

Figure 4. Glucose and cystine sensing coordinate metabolic and redox homeostasis by regulating NADPH production, antioxidant capacity, and stress-responsive signaling. These adaptive responses support tumor cell survival under oxidative stress. Ser, Serine; GR, Glutathione reductase; TrxR, Thioredoxin reductase; FIH, Hypoxia-Inducible Factor.

6. Dietary restriction and targeted therapeutic strategies based on tumor amino acid sensing networks

During rapid proliferation and malignant progression, tumor cells exhibit aberrant dependencies on multiple amino acids and achieve metabolic reprogramming by remodeling pathways of amino acid uptake, synthesis, and utilization. These adaptations support energetic demands, biosynthetic output, and epigenetic regulation required for tumor growth and survival [161,162]. It is important to note that the current understanding of amino acid sensing is not equally advanced across different amino acids. While several amino acid-sensing pathways have been well characterized, the molecular machinery governing serine, cysteine and other amino acids remains poorly characterized, a discrepancy stemming from the

current progress of research rather than their biological significance. Building on this concept, a range of therapeutic strategies centered on amino acid metabolism has emerged in recent years. These approaches include dietary interventions that restrict amino acid availability as well as precision therapies that achieve selective amino acid deprivation through enzymes or pharmacological agents. By disrupting tumor amino acid homeostasis at distinct levels, such strategies provide new avenues for anticancer intervention.

6.1. Amino acid restriction

6.1.1. Dietary methionine restriction

Dietary methionine restriction exhibits consistent and repeatable antitumor effects in various solid tumor models and currently represents one of the most extensively studied and clinically translatable amino acid based dietary interventions (Table 1). In colorectal cancer and soft tissue sarcoma models, methionine restriction significantly suppresses tumor growth and enhances the efficacy of 5-Fluorouracil or radiotherapy, effects that are closely linked to reprogramming of one carbon metabolism [163]. In hematologic malignancies, methionine depletion has been identified as a metabolic vulnerability in acute myeloid leukemia. Dietary methionine starvation is well tolerated in mice and markedly delays disease progression in both cell line based and patient derived acute myeloid leukemia models [164]. A phase I clinical study further tested methionine-restricted diet paired with radiotherapy in solid tumor patients, verifying acceptable safety yet highlighting poor patient compliance and insufficient plasma methionine reduction as critical obstacles to clinical implementation [165].

Table 1. Dietary restriction strategies based on tumor amino acid sensing networks.

Amino acid	Tumor types	Key mechanisms	Therapeutic implications	Clinical Stage
Methionine	CRC, sarcoma, AML, HCC, GBM	Disruption of one-carbon metabolism; cell-cycle arrest; senescence; ferroptosis	Tumor inhibition; sensitization to therapy	Phase I [165]
Cysteine	GBM	Glutathione depletion	Enhanced response to ferroptosis inducers	Preclinical
Serine/Glycine	CRC	One-carbon metabolism inhibition; metabolic stress	Tumor suppression; enhanced $CD8^+$ T cell immunity	Preclinical
BCAAs	KRAS-mutant PDAC, CHOL	Inhibition of BCAT2-PPDPF-mTORC1 axis	Suppressed tumor initiation and progression	Preclinical

In hepatocellular carcinoma, methionine deprivation *in vitro* induces irreversible cell cycle arrest. Inhibition of MAT2A-dependent methionine catabolism triggers cell cycle arrest and DNA damage, ultimately leading to cellular senescence in liver cancer cells [166]. In addition, methionine restriction exerts antitumor effects through induction of glutathione depletion. In mouse glioma models, combinatorial cysteine deprivation and methionine-restricted diets improve responses to the ferroptosis inducer RAS-selective lethal 3 (RSL3) and significantly extend survival [167].

However, methionine also serves as a critical nutrient for immune cell function within the tumor microenvironment. T cell activation and proliferation require sustained exogenous methionine supply, and intratumoral methionine supplementation enhances CD8 positive T cell mediated antitumor

immunity. Methionine deficiency within the tumor microenvironment has been shown to reduce histone H3K79 methylation [168].

Importantly, the impact of methionine restriction on responses to immunotherapy exhibits strong temporal dependence. When implemented after tumor establishment, methionine restriction synergizes with antitumor immunotherapies to inhibit tumor growth [169,170]. In contrast, methionine restriction initiated prior to tumor development compromises the efficacy of immunotherapeutic interventions [168]. Collectively, these findings highlight the pronounced context dependence of dietary methionine restriction in cancer therapy. Its anti-tumor efficacy and immunological consequences are jointly influenced by tumor type, disease stage, and timing of intervention, underscoring the need for precise and stage specific design of methionine restriction strategies in clinical applications.

6.1.2. Dietary serine restriction

Dietary serine restriction exerts pronounced antitumor effects in tumors that are highly dependent on exogenous serine supply. Early studies demonstrated that removal of serine markedly suppresses proliferation of colon cancer cells, and that p53 plays a central role in coordinating metabolic stress responses induced by serine starvation. Cancer cells lacking p53 display heightened sensitivity to serine deprivation [171]. In mouse xenograft models of colorectal cancer, simultaneous dietary restriction of serine and glycine induces accumulation of deoxy sphingolipids and leads to significant inhibition of tumor growth [172]. More recent studies indicate that serine and glycine free diets suppress colorectal cancer cell growth and enhance CD8 positive T cell mediated antitumor immunity. However, serine and glycine restriction also promotes lactylation of programmed cell death protein 1 (PD-1), delaying its degradation and thereby facilitating immune evasion. Blockade of the programmed cell PD-1 and PD-L1 signaling axis restores the function of $CD8^{+}$T cells recruited under serine and glycine restricted conditions, highlighting the therapeutic potential of combining serine and glycine dietary restriction with immune checkpoint inhibition [173].

6.1.3. Dietary restriction of BCAA

Evidence indicates that BCAA catabolism, mediated in part by BCAT2, is functionally required for the initiation and progression of KRAS mutant pancreatic ductal adenocarcinoma [174]. In corresponding mouse models, reduction of dietary branched chain amino acids suppresses or delays pancreatic tumor development and progression [114]. In cholangiocarcinoma, metabolic rewiring of branched chain amino acid utilization promotes tumor progression through the pancreatic progenitor cell differentiation and proliferation factor (PPDPF) mTORC1 axis. Consistently, dietary leucine restriction or pharmacological targeting of PPDPF markedly inhibits tumor growth, further supporting the potential of BCAA restriction as a metabolism-based intervention in selected tumor contexts [175].

Nevertheless, accumulating evidence suggests that the therapeutic efficacy of dietary amino acid restriction is influenced not only by tumor-intrinsic metabolism but also by systemic metabolic regulators. Among these, the gut microbiome has emerged as a key determinant of amino acid availability and treatment response. Emerging evidence indicates that the therapeutic efficacy of dietary amino acid restriction is also shaped by the gut microbiome. Intestinal microorganisms actively synthesize, degrade, and transform amino acids and their metabolites, thereby influencing systemic

amino acid availability and the metabolic state of the tumor microenvironment [117,168]. Microbiota composition may therefore modify the response to methionine, serine/glycine, or branched-chain amino acid restriction, and may also affect the efficacy of therapies targeting amino acid-sensing pathways by regulating host metabolism and antitumor immunity [18]. These findings suggest that integrating microbiome modulation with amino acid restriction or sensor-targeted therapies may further improve therapeutic outcomes.

Despite encouraging preclinical results, caution is warranted when interpreting data derived from conventional cancer cell lines and xenograft models [176]. Most xenograft studies are performed in immunodeficient mice, preventing accurate assessment of interactions between amino acid sensing pathways and antitumor immunity [177]. Furthermore, dietary interventions frequently employ severe amino acid restriction regimens that are difficult to replicate safely in humans [163]. Such interventions may induce systemic metabolic adaptations that differ substantially from those occurring in patients. Therefore, future studies should increasingly incorporate genetically engineered mouse models, humanized immune models, patient-derived organoids, and clinically relevant dietary interventions to improve translational relevance.

6.2. Targeting amino acid sensors

Compared with systemic amino acid restriction, directly targeting amino acid sensors that mediate nutrient sensing and signal integration in tumor cells offers a more selective therapeutic strategy. For example, inhibitors that disrupt the interaction between LARS1 and RagD, such as BC-LI-0186, have been shown to suppress the noncanonical mTORC1 activating function of LARS1. When combined with mitogen-activated protein kinase kinase 1 (MEK1) and mitogen-activated protein kinase kinase 2 (MEK2) inhibitors, this approach produces enhanced anti-tumor effects in non-small cell lung cancer models [178]. However, small molecule interventions targeting other amino acid sensors or sensors that converge on mTORC1 signaling largely remain at an early stage of development, with current efforts focused primarily on structural and mechanistic characterization.

Beyond direct inhibition of amino acid sensing pathways upstream of mTORC1, selective targeting of HDAC6 has been widely explored as a combination sensitization strategy through remodeling of non-histone acetylation and proteostatic stress. Representative examples include ricolinostat, also known as ACY-1215, a selective HDAC6 inhibitor, which has demonstrated feasibility in early clinical combination studies with lenalidomide and dexamethasone in relapsed and refractory multiple myeloma [179]. Similarly, citarinostat, also known as ACY-241, an orally-bioavailable selective HDAC6 inhibitor, has been evaluated in combination with nivolumab in a phase Ib study in previously treated non-small-cell lung cancer, and further development of next generation candidates such as KA2507, a potent orally-bioavailable selective HDAC6 inhibitor, remains ongoing [180,181].

In parallel, small-molecule targeting RBM39 in cancer primarily relies on aryl sulfonamide based molecular glues that induce proteasomal degradation. Compounds such as indisulam, E7820, and tasisulam promote formation of a ternary complex between RBM39 and the CRL4-DCAF15 ubiquitin ligase, triggering RBM39 ubiquitination and degradation. This leads to widespread splicing disruption and suppression of tumor growth [182,183]. A phase II clinical trial of E7820 confirmed in vivo RBM39 degradation and splicing interference in patients with splicing factor-mutant myeloid malignancies, yet single-agent E7820 exhibited modest anti-tumor activity in heavily pretreated cohorts [184] (Table 2).

From a translational perspective, RBM39 degradation has been explored as a sensitization strategy in combination therapies. For instance, in ovarian cancer models, indisulam enhances sensitivity to cisplatin and poly ADP ribose polymerase inhibitors [185].

Table 2. Targeting amino acid sensors or binding proteins.

Target	Tumor types	Key mechanisms	Therapeutic implications	Clinical Stage
LARS1	NSCLC	Blockade of non-canonical mTORC1 activation	Synergistic efficacy with MEK1/2 inhibitors	Preclinical
HDAC6	MM, NSCLC	Proteostasis stress via non-histone deacetylation	Sensitization to immunotherapy and IMiD-based regimens	Phase I/II [179]
RBM39	Ovarian and other solid tumors	CRL4-DCAF15-mediated splicing disruption	Increased sensitivity to platinum and PARP inhibitors	Phase II [184]

Collectively, compared with single nutrient restriction approaches, targeting amino acid sensors and binding proteins represents a next generation strategy with the potential to achieve greater selectivity and an improved therapeutic window for interventions aimed at tumor metabolism and signaling pathways.

7. Conclusions and future perspectives

Amino acid metabolism reprogramming is not only an important way for cells to obtain energy and biosynthetic precursors, but also a core regulatory mechanism for cells to sense nutritional status, regulate growth programs, adapt to fluctuations in nutrient supply, and resist environmental stress [186,187]. Notably, the current mechanistic understanding of amino acid sensing remains uneven across different amino acids. While leucine- and arginine-sensing pathways have been extensively characterized because of their central roles in mTORC1 regulation, the sensing mechanisms for serine, cysteine, and several other amino acids remain comparatively less well defined and warrant further investigation. Increasing evidence from spatial transcriptomics, spatial metabolomics, and mass spectrometry imaging has demonstrated that tumors exhibit profound spatial metabolic heterogeneity, characterized by steep gradients of oxygen and nutrient availability between the well-perfused tumor periphery and the hypoxic, nutrient-deprived tumor core, thereby establishing region-specific metabolic microenvironments [188,189]. In the nutrient-rich tumor periphery, abundant leucine uptake mediated by solute carrier family 7 member 5 (SLC7A5) enables coordinated activation of the amino acid sensors LARS1 and Sestrin2, resulting in robust mTORC1 signaling [38,190]. Conversely, in nutrient-deprived tumor regions, persistent Sestrin2 activation suppresses mTORC1 activity, promoting metabolic adaptation, autophagy, and cellular dormancy, thereby facilitating the persistence and accumulation of therapy-resistant cell populations [21,191]. This spatial segregation of nutrient-sensing activity highlights that amino acid sensors function as context-dependent regulators that establish distinct signaling thresholds according to local nutrient availability. Such metabolic compartmentalization has important therapeutic implications, as conventional mTOR-targeted therapies preferentially eliminate proliferative cells while often sparing quiescent, therapy-resistant cells in nutrient-deprived regions [192]. Future therapeutic strategies may therefore benefit from simultaneously targeting amino acid transport, nutrient-sensing pathways, and metabolic adaptation to overcome spatially heterogeneous therapeutic responses. Advances in spatial metabolomics, spatial transcriptomics, and integrated spatial multi-omics will further facilitate the characterization of nutrient gradients and amino acid sensor activation *in situ*, providing new insights

into the regulation of metabolic plasticity and therapeutic resistance and enabling the development of spatially informed precision metabolic therapies [192,193].

Importantly, within the tumor microenvironment, amino acid availability shapes the metabolic competition and functional crosstalk between tumor cells and immune cells. By establishing the balance between immune activation and suppression, these nutrient-dependent interactions provide a key metabolic foundation for sustained tumor growth and immune evasion [194].

However, despite the robust antitumor activity of amino acid restriction strategies exhibit strong anti-tumor activity in various preclinical tumor models, there are still significant challenges in its effective clinical implementation [3,195]. Amino acid restriction does not only affect tumor cells. By altering the overall nutritional supply status of the tumor microenvironment, it can simultaneously reshape the metabolic characteristics and functional phenotypes of both tumor cells and immune cells [122]. Consequently, the impact of amino acid restriction on immunity is often complex and highly context dependent. Such interventions may enhance antitumor immune responses in some settings, yet in others they may compromise therapeutic efficacy by limiting immune cell proliferation and effector function [196]. Therefore, future intervention strategies based on amino acid restrictions should not merely focus on evaluating the intrinsic metabolic inhibitory effect of tumor cells, but should prioritize the overall immune net effect. This will require more refined intervention designs that explicitly account for immune context, disease stage, and the timing of dietary modulation.

Future work should be carried out in several directions. First, context dependence and systemic compensation represent major challenges for amino acid restriction strategies. Because amino acid limitation can exert dual effects on tumor cells and immune cells, its net impact must be rigorously evaluated across distinct immune microenvironments, tumor types, and treatment schedules. This highlights the need for clinically stratified implementation, with tailored approaches for defined patient subsets, such as immune inflamed *versus* immune cold tumors. Second, the spatial and cell state dependent logic of metabolism and signaling integration requires systematic investigation. Nutrient gradients, metabolite accumulation, and the metabolic heterogeneity of immune cells within the tumor microenvironment drive context-dependent functional divergence of signaling axes across distinct cell types and tissue locales. Studies integrating single cell omics, spatial metabolomics, and *in vivo* functional tracing will be critical for unraveling the spatial heterogeneity of amino acid restriction effects on both tumors and immunity. Third, targeting nodes that mediate amino acid sensing and signal integration represents a promising direction. By modulating amino acid sensing proteins and their downstream signaling pathways, it may be possible to more precisely control tumor metabolic responses while coordinating immune cell function.

In summary, although amino acid restriction strategies hold considerable promise in cancer therapy, major challenges remain for clinical translation. Future studies should prioritize a refined characterization of the metabolism immunity tumor interface, optimize intervention designs around net immunological outcomes, and develop more precise and personalized therapeutic paradigms. By integrating mechanistic metabolism research with immunology and clinical trial data, it should be feasible to maximize the therapeutic benefit of amino acid restriction-based interventions.

Declaration of generative AI and AI-assisted technologies

During the preparation of this manuscript, the authors used ChatGPT (GPT-4, OpenAI) to assist in checking linguistic errors and improving sentence readability. No other generative AI or AI-assisted tools were utilized. The authors take full responsibility for all content presented in this manuscript.

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Authors' contribution

Conceptualization, S.Z.; literature collection, S.Z., X.S. and R.W.; writing—original draft preparation, X.S. and R.W.; writing—review and editing, S.Z.; supervision, S.Z.; funding acquisition, S.Z. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no competing interests.

References

[1] Hanahan D. Hallmarks of cancer: new dimensions. *Cancer Discovery* 2022, 12(1):31–46.

[2] Mao Y, Xia Z, Xia W, Jiang P. Metabolic reprogramming, sensing, and cancer therapy. *Cell Rep.* 2024, 43(12):115064.

[3] Chen J, Cui L, Lu S, Xu S. Amino acid metabolism in tumor biology and therapy. *Cell Death Dis*. 2024, 15(1):42.

[4] Jiang C, Tan X, Jin J, Wang P. The molecular basis of amino acids sensing. *Adv. Sci.* 2025, 12(26):e2501889.

[5] Saxton RA, Sabatini DM. mTOR signaling in growth, metabolism, and disease. *Cell* 2017, 169(2):361–371.

[6] Pakos-Zebrucka K, Koryga I, Mnich K, Ljujic M, Samali A, *et al.* The integrated stress response. *EMBO Rep*. 2016, 17(10):1374–1395.

[7] Wang D, Xu C, Yang W, Chen J, Ou Y, *et al.* E3 ligase RNF167 and deubiquitinase STAMBPL1 modulate mTOR and cancer progression. *Mol. Cell* 2022, 82(4):770–784 e9.

[8] Lin Z, He L, Wang J, Zhang H, Yao S, *et al.* Amino acid sensing in cancer. *Pharmacol Res.* 2025, 221:108003.

[9] Jiang C, Tan X, Liu N, Yan P, Hou T, *et al.* Nutrient sensing of mTORC1 signaling in cancer and aging. *Semin. Cancer Biol.* 2024, 106:1–12.

[10] Ishak Gabra MB, Yang Y, Li H, Senapati P, Hanse EA, *et al.* Dietary glutamine supplementation suppresses epigenetically-activated oncogenic pathways to inhibit melanoma tumour growth. *Nat. Commun.* 2020, 11(1):3326.

[11] Zhu Y, Zhou Z, Du X, Lin X, Liang ZM, *et al.* Cancer cell-derived arginine fuels polyamine biosynthesis in tumor-associated macrophages to promote immune evasion. *Cancer Cell* 2025, 43(6):1045–1060 e7.

[12] Reid MA, Dai Z, Locasale JW. The impact of cellular metabolism on chromatin dynamics and epigenetics. *Nat. Cell Biol.* 2017, 19(11):1298–1306.

[13] Su B, Chen Q, Li X, Fang M, Wang Y, *et al.* A methionine allocation nanoregulator for the suppression of cancer stem cells and support to the immune cells by epigenetic regulation. *Adv. Sci.* 2025, 12(15):e2415207.

[14] Chang Y, Wang N, Li S, Zhang J, Rao Y, *et al.* SLC3A2-Mediated lysine uptake by cancer cells restricts t-cell activity in hepatocellular carcinoma. *Cancer Res*. 2025, 85(12):2250–2267.

[15] Leone RD, Powell JD, Metabolism of immune cells in cancer. *Nat. Rev. Cancer* 2020, 20(9):516–531.

[16] Goul C, Peruzzo R, Zoncu R. The molecular basis of nutrient sensing and signalling by mTORC1 in metabolism regulation and disease. *Nat. Rev. Mol. Cell Biol*. 2023, 24(12):857–875.

[17] Wang N, Lu S, Cao Z, Li H, Xu J, *et al.* Pyruvate metabolism enzyme DLAT promotes tumorigenesis by suppressing leucine catabolism. *Cell Metab*. 2025, 37(6):1381–1399 e9.

[18] Chen J, Liu X, Zou Y, Gong J, Ge Z, *et al.* A high-fat diet promotes cancer progression by inducing gut microbiota-mediated leucine production and PMN-MDSC differentiation. *Proc. Natl. Acad Sci. U. S. A.* 2024, 121(20):e2306776121.

[19] Xu D, Dai W, Kutzler L, Lacko HA, Jefferson LS, *et al.* ATF4-mediated upregulation of REDD1 and Sestrin2 suppresses mTORC1 activity during prolonged leucine deprivation. *J. Nutr.* 2020, 150(5):1022–1030.

[20] Chen, F, Peng S, Li C, Yang F, Yi Y, *et al.* Nitidine chloride inhibits mTORC1 signaling through ATF4-mediated Sestrin2 induction and targets IGF2R for lysosomal degradation. *Life Sci.* 2024, 353:122918.

[21] Wolfson RL, Chantranupong L, Saxton RA, Shen K, Scaria SM, *et al.* Sestrin2 is a leucine sensor for the mTORC1 pathway. *Science* 2016, 351(6268):43–48.

[22] Machado IF, Palmeira CM, Rolo AP. Sestrin2 is a central regulator of mitochondrial stress responses in disease and aging. *Ageing Res. Rev*. 2025, 109:102762.

[23] Kimball, SR, Gordon BS, Moyer JE, Dennis MD, Jefferson LS, *et al.* Leucine induced dephosphorylation of Sestrin2 promotes mTORC1 activation. *Cell Signal.* 2016, 28(8):896–906.

[24] Hou T, Dan W, Liu T, Liu B, Wei Y, *et al.* Deubiquitinase OTUD5 modulates mTORC1 signaling to promote bladder cancer progression. *Cell Death Dis.* 2022, 13(9):778.

[25] Lear TB, Lockwood KC, Ouyang Y, Evankovich JW, Larsen MB, *et al.* The RING-type E3 ligase RNF186 ubiquitinates Sestrin-2 and thereby controls nutrient sensing. *J. Biol. Chem.* 2019, 294(45):16527–16534.

[26] Wang Z, Huang Y, Zhang Y, Zhu H, Amin MR, *et al.* Knockdown of SESN2 exacerbates cerebral ischemia-reperfusion injury through enhancing glycolysis via the mTOR/HIF-1alpha pathway. *CNS Neurosci. Ther.* 2025, 31(3):e70314.

[27] Li J, Quan C, He YL, Cao Y, Chen Y, *et al.* Autophagy regulated by the HIF/REDD1/mTORC1 signaling is progressively increased during erythroid differentiation under hypoxia. *Front. Cell Dev. Biol.* 2022, 10:896893.

[28] Fu J, Lin J, Dai Z, Lin B, Zhang J. Hypoxia-associated autophagy flux dysregulation in human cancers. *Cancer Lett.* 2024, 590:216823.

[29] Li X, He S, Ma B. Autophagy and autophagy-related proteins in cancer. *Mol. Cancer* 2020, 19(1):12.

[30] Hua X, Xu J, Deng X, Xu J, Li J, *et al.* New compound ChlA-F induces autophagy-dependent anti-cancer effect via upregulating Sestrin-2 in human bladder cancer. *Cancer Lett.* 2018, 436:38–51.

[31] Liang Y, Zhu J, Huang H, Xiang D, Li Y, *et al.* SESN2/sestrin 2 induction-mediated autophagy and inhibitory effect of isorhapontigenin (ISO) on human bladder cancers. *Autophagy* 2016, 12(8):1229–1239.

[32] Yen JH, Huang ST, Huang HS, Fong YC, Wu YY, *et al.* HGK-sestrin 2 signaling-mediated autophagy contributes to antitumor efficacy of Tanshinone IIA in human osteosarcoma cells. *Cell Death Dis*. 2018, 9(10):1003.

[33] Sanli T, Linher-Melville K, Tsakiridis T, Singh G. Sestrin2 modulates AMPK subunit expression and its response to ionizing radiation in breast cancer cells. *PLoS One* 2012, 7(2):e32035.

[34] Wei J, Fang M, Fu Z, Zhang S, Guo J, *et al.* Sestrin 2 suppresses cells proliferation through AMPK/mTORC1 pathway activation in colorectal cancer. *Oncotarget* 2017, 8(30):49318–49328.

[35] Zanetti G, Pahuja KB, Studer S, Shim S, Schekman R. COPII and the regulation of protein sorting in mammals. *Nat. Cell Biol.* 2011, 14(1):20–28.

[36] Chen J, Ou Y, Luo R, Wang J, Wang D, *et al.* SAR1B senses leucine levels to regulate mTORC1 signalling. *Nature* 2021, 596(7871):281–284.

[37] Wu R, Murali R, Kabe Y, French SW, Chiang YM, *et al.* Baicalein targets GTPase-mediated autophagy to eliminate liver tumor-initiating stem cell-like cells resistant to mTORC1 inhibition. *Hepatology* 2018, 68(5):1726–1740.

[38] Han JM, Jeong SJ, Park MC, Kim G, Kwon NH, *et al.* Leucyl-tRNA synthetase is an intracellular leucine sensor for the mTORC1-signaling pathway. *Cell* 2012, 149(2):410–424.

[39] Kim, M, Tomek P. Tryptophan: a rheostat of cancer immune escape mediated by immunosuppressive enzymes IDO1 and TDO. *Front Immunol.* 2021, 12:636081.

[40] Guo D, Meng Y, Zhao G, Wu Q, Lu Z. Moonlighting functions of glucose metabolic enzymes and metabolites in cancer. *Nat. Rev. Cancer* 2025, 25(6):426–446.

[41] Pan BS, Hsu CC, Wu HE, Chen Y, Zhou X, *et al.* Glucose metabolism and its direct action in cancer and immune regulation: opportunities and challenges for metabolic targeting. *J. Biomed. Sci.* 2025, 32(1):71.

[42] Kim K, Yoo HC, Kim BG, Kim S, Sung Y, *et al.* O-GlcNAc modification of leucyl-tRNA synthetase 1 integrates leucine and glucose availability to regulate mTORC1 and the metabolic fate of leucine. *Nat. Commun.* 2022, 13(1):2904.

[43] Yoon I, Nam M, Kim HK, Moon HS, Kim S, *et al.* Glucose-dependent control of leucine metabolism by leucyl-tRNA synthetase 1. *Science* 2020, 367(6474):205–210.

[44] Jin C, Li C, Chen L, Liu H, Yu Y, *et al.* LARS1 knockdown suppresses the biological activities of thyroid cancer cells by stimulating autophagy. *Tissue Cell* 2025, 97:103075.

[45] Liu H, Wang J, Yao Y, Xia T, Zhang S, *et al.* Restoration of N-glycosylation via leucine-activated leucyl-tRNA synthetase 1 overcomes chemoresistance in intrahepatic cholangiocarcinoma. *J. Hepatol.* 2026, 84(1):150–164.

[46] Zhang J, Wang S, Liu H, Luo L, You J. Arginine competition in tumor microenvironment: a potential target for cancer therapy. *Med. Res. Rev.* 2026, 46(2):382–407.
[47] Feng T, Xie F, Lyu Y, Yu P, Chen B, *et al.* The arginine metabolism and its deprivation in cancer therapy. *Cancer Lett.* 2025, 620:217680.
[48] Chantranupong L, Scaria SM, Saxton RA, Gygi MP, Shen K, *et al.* The CASTOR proteins are arginine sensors for the mTORC1 pathway. *Cell* 2016, 165(1):153–164.
[49] Valenstein ML, Wranik M, Lalgudi PV, Linde-Garelli KY, Choi Y, *et al.* Structural basis for the dynamic regulation of mTORC1 by amino acids. *Nature* 2025, 646(8084):493–500.
[50] Saxton RA, Chantranupong L, Knockenhauer KE, Schwartz TU, Sabatini DM, *et al.* Mechanism of arginine sensing by CASTOR1 upstream of mTORC1. *Nature* 2016, 536(7615):229–233.
[51] Wang S, Tsun ZY, Wolfson R, Shen K, Wyant GA, *et al.* Metabolism. lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1. *Science* 2015, 347(6218):188–194.
[52] Rebsamen M, Pochini L, Stasyk T, De Araújo ME, Galluccio M, *et al.* SLC38A9 is a component of the lysosomal amino acid sensing machinery that controls mTORC1. *Nature* 2015, 519(7544):477–481.
[53] Jung JW, Macalino SJ, Cui M, Kim JE, Kim HJ, *et al.* Transmembrane 4 L six family member 5 senses arginine for mTORC1 signaling. *Cell Metab.* 2019, 29(6):1306–1319 e7.
[54] Zhou X, Cheng Z, Chen H, Shi S, Wang X, *et al.* CASTOR1 suppresses the progression of lung adenocarcinoma and predicts poor prognosis. *J. Cell Biochem.* 2018, 119(12):10186–10194.
[55] Li T, Wang X, Ju E, da Silva SR, Chen L, *et al.* RNF167 activates mTORC1 and promotes tumorigenesis by targeting CASTOR1 for ubiquitination and degradation. *Nat. Commun.* 2021, 12(1):1055.
[56] Schwartz L, Supuran CT, Alfarouk KO, The warburg effect and the hallmarks of cancer. *Anti-Cancer Agents Med. Chem.* 2017, 17(2):164–170.
[57] Kim JE, Park SY, Kwak C, Lee Y, DG Song, *et al.* Glucose-mediated mitochondrial reprogramming by cholesterol export at TM4SF5-enriched mitochondria-lysosome contact sites. *Cancer Commun*. 2024, 44(1):47–75.
[58] Mossmann D, Müller C, Park S, Ryback B, Colombi M, *et al.* Arginine reprograms metabolism in liver cancer via RBM39. *Cell* 2023, 186(23):5068–5083 e23.
[59] Huang X, Shi D, Zou X, Wu X, Huang S, *et al.* BAG2 drives chemoresistance of breast cancer by exacerbating mutant p53 aggregate. *Theranostics* 2023, 13(1):339–354.
[60] Liu Q, Chen Q, Wei H, Tang B, Tian B, *et al.* Targeting the BAG2/CHIP axis promotes gastric cancer apoptosis by blocking apoptosome assembly. *Front Immunol.* 2025, 16:1578416.
[61] Sun L, Chen G, Sun A, Wang Z, Huang H, *et al.* BAG2 Promotes proliferation and metastasis of gastric cancer via ERK1/2 signaling and partially regulated by miR186. *Front. Oncol.* 2020, 10:31.
[62] Chen M, Sun C, Zhao R, Guan X, Li M, *et al.* BAG2 releases SAMD4B upon sensing of arginine deficiency to promote tumor cell survival. *Mol. Cell* 2025, 85(13):2581-2596.e6.
[63] Kim SH, Choi JH, Wang P, Go CD, Hesketh GG, *et al.* Mitochondrial threonyl-tRNA synthetase TARS2 Is required for threonine-sensitive mTORC1 activation. *Mol. Cell* 2021, 81(2):398–407 e4.
[64] Accogli A, Lin SJ, Severino M, Kim SH, Huang K, *et al.* Clinical, neuroradiological, and molecular characterization of mitochondrial threonyl-tRNA-synthetase (TARS2)-related disorder. *Genet. Med.* 2023, 25(11):100938.

[65] Tian H, Yan H, Zhang Y, Fu Q, Li C, *et al.* Knockdown of mitochondrial threonyl-tRNA synthetase 2 inhibits lung adenocarcinoma cell proliferation and induces apoptosis. *Bioengineered* 2022, 13(3):5190–5204.

[66] Faubert B, Solmonson A, DeBerardinis RJ. Metabolic reprogramming and cancer progression. *Science* 2020, pp. eaaw5473.

[67] Dai Z, Ramesh V, Locasale JW. The evolving metabolic landscape of chromatin biology and epigenetics. *Nat. Rev. Genet.* 2020, 21(12):737–753.

[68] Martinez-Reyes I, Chandel NS. Cancer metabolism: looking forward. *Nat. Rev. Cancer* 2021, 21(10):669–680.

[69] Trefely S, Lovell CD, Snyder NW, Wellen KE. Compartmentalised acyl-CoA metabolism and roles in chromatin regulation. *Mol. Metab.* 2020, 38:100941.

[70] Wang Z, Yip LY, Lee JH, Wu Z, Chew HY, *et al.* Methionine is a metabolic dependency of tumor-initiating cells. *Nat. Med.* 2019, 25(5):825–837.

[71] Ma C, Xu A, Zuo L, Li Q, Fan F, *et al.* Methionine dependency and restriction in cancer: exploring the pathogenic function and therapeutic potential. *Pharmaceuticals* 2025, 18(5):640.

[72] Lu SC, Mato JM. S-adenosylmethionine in liver health, injury, and cancer. *Physiol. Rev.* 2012, 92(4):1515–1542.

[73] Cacciatore A, Shinde D, Musumeci C, Sandrini G, Guarrera L, *et al.* Epigenome-wide impact of MAT2A sustains the androgen-indifferent state and confers synthetic vulnerability in ERG fusion-positive prostate cancer. *Nat. Commun.* 2024, 15(1):6672.

[74] Luo H, Song Y, Zhang J, Liu Y, Chen F, *et al.* MAT2A facilitates PDCD6 methylation and promotes cell growth under glucose deprivation in cervical cancer. *Cell Death Discovery*. 2022, 8(1):176.

[75] Zhao L, Su H, Liu X, Wang H, Feng Y, *et al.* mTORC1-c-Myc pathway rewires methionine metabolism for HCC progression through suppressing SIRT4 mediated ADP ribosylation of MAT2A. *Cell Biosci.* 2022, 12(1):183.

[76] Hung MH, Lee JS, Ma C, Diggs LP, Heinrich S, *et al.* Tumor methionine metabolism drives T-cell exhaustion in hepatocellular carcinoma. *Nat. Commun.* 2021, 12(1):1455.

[77] Du Y, Li K, You L, Zhang J, Chen Q, *et al.* Silencing of MAT2A inhibits gastric cancer cell proliferation, migration, and invasion through activation of the p53 pathway. *Clin. Transl. Oncol.* 2025, 28:1–15.

[78] Justo M, Lim Y, Yang H, Floris A, Chandla S, *et al.* A novel role of secreted methionine adenosyltransferase alpha2 in colorectal liver metastases. *J. Exp.Clin. Cancer Res.* 025.

[79] Gu X, Orozco JM, Saxton RA, Condon KJ, Liu GY, *et al.* SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. *Science* 2017, 358(6364):813–818.

[80] Tang X, Zhang Y, Wang G, Zhang C, Wang F, *et al.* Molecular mechanism of S-adenosylmethionine sensing by SAMTOR in mTORC1 signaling. *Sci. Adv.* 2022, 8(26):eabn3868.

[81] Lupton CJ, Bayly-Jones C, Dong S, Lam T, Luo W, *et al.* Structure of the lysosomal KICSTOR-GATOR1-SAMTOR nutrient-sensing supercomplex. *Cell* 2026, 189(4):1185–1200 e28.

[82] Ren Y, Zhang P, Li L, Wang M, Hu H, *et al.* Hyper-methylation and DNMT3A mediated LTC4S downregulation promoted lung adenocarcinoma tumorigenesis via mTORC1 signaling pathway. *Heliyon* 2024, 10(13):e33203.

[83] Sakamoto H, Yamasaki T, Sumiyoshi T, Takeda M, Shibasaki N, *et al.* Functional and genomic characterization of patient-derived xenograft model to study the adaptation to mTORC1 inhibitor in clear cell renal cell carcinoma. *Cancer Med.* 2021, 10(1):119–134.

[84] Chen M, Fang Y, Liang M, Zhang N, Zhang X, *et al.* The activation of mTOR signalling modulates DNA methylation by enhancing DNMT1 translation in hepatocellular carcinoma. *J. Transl. Med.* 2023, 21(1):276.

[85] Simon JA, Lange CA. Roles of the EZH2 histone methyltransferase in cancer epigenetics. *Mutat. Res.* 2008, 647(1–2):21–29.

[86] Kim HE, Lebeau B, Papadopoli D, Jovanovic P, Russo M, *et al.* MTOR modulation induces selective perturbations in histone methylation which influence the anti-proliferative effects of mTOR inhibitors. *iScience* 2024, 27(3):109188.

[87] Liu L, Xiao B, Hirukawa A, Smith HW, Zuo D, *et al.* EZH2 promotes mammary tumor initiation through epigenetic regulation of the Wnt and mTORC1 signaling pathways. *Proc. Natl. Acad. Sci. U. S. A.* 2023, 120(33):e2303010120.

[88] Harachi M, Masui K, Honda H, Muragaki Y, Kawamata T, *et al.* Dual regulation of histone methylation by mTOR complexes controls glioblastoma tumor cell growth via EZH2 and SAM. *Mol. Cancer Res.* 2020, 18(8):1142–1152.

[89] Mushtaq A, Ashraf NU, Altaf M. The mTORC1-G9a-H3K9me2 axis negatively regulates autophagy in fatty acid-induced hepatocellular lipotoxicity. *J. Biol. Chem.* 2023, 299(3):102937.

[90] Jiang C, Liu J, He S, Xu W, Huang R, *et al.* PRMT1 orchestrates with SAMTOR to govern mTORC1 methionine sensing via Arg-methylation of NPRL2. *Cell Metab.* 2023, 35(12):2183–2199 e7.

[91] Liu H, Chen X, Wang P, Chen M, Deng C, *et al.* PRMT1-mediated PGK1 arginine methylation promotes colorectal cancer glycolysis and tumorigenesis. *Cell Death Dis.* 2024, 15(2):170.

[92] Luo L, Wu X, Fan J, Dong L, Wang M, *et al.* FBXO7 ubiquitinates PRMT1 to suppress serine synthesis and tumor growth in hepatocellular carcinoma. *Nat. Commun.* 2024, 15(1):4790.

[93] Ku B, Eisenbarth D, Baek S, Jeong TK, Kang JG, *et al.* PRMT1 promotes pancreatic cancer development and resistance to chemotherapy. *Cell Rep. Med*. 2024, 5(3):101461.

[94] Li Q, Zhang L, Yang Q, Li M, Pan X, *et al.* Thymidine kinase 1 drives hepatocellular carcinoma in enzyme-dependent and -independent manners. *Cell Metab.* 2023, 35(6):912–927 e7.

[95] Zhou H, Wang Y, Wang D, Zhang M, Wang K, *et al.* PRMT1 promotes immune escape in hepatocellular carcinoma by regulating arginine methylation modification of MYC protein. *Epigenetics* 2025, 20(1):2509044.

[96] Yin S, Liu L, Ball LE, Wang Y, Bedford MT, *et al.* CDK5-PRMT1-WDR24 signaling cascade promotes mTORC1 signaling and tumor growth. *Cell Rep.* 2023, 42(4):112316.

[97] Luka Z, Mudd SH, Wagner C. Glycine N-methyltransferase and regulation of S-adenosylmethionine levels. *J. Biol. Chem.* 2009, 284(34):22507–22511.

[98] Martínez-Chantar ML, Vázquez-Chantada M, Ariz U, Martínez N, Varela-Rey M, *et al.* Loss of the glycine N-methyltransferase gene leads to steatosis and hepatocellular carcinoma in mice. *Hepatology* 2008, 47(4):1191–1199.

[99] DebRoy S, Kramarenko II, Ghose S, Oleinik NV, Krupenko SA, *et al.* A novel tumor suppressor function of glycine N-methyltransferase is independent of its catalytic activity but requires nuclear localization. *PLoS One* 2013, 8(7):70062.

[100] Tseng TL, Shih YP, Huang YC, Wang CK, Chen PH, *et al.* Genotypic and phenotypic characterization of a putative tumor susceptibility gene, GNMT, in liver cancer. *Cancer Res.* 2003, 63(3): 647–654.

[101] Yen C, Lu Y, Li C, Lee C, Chen C, *et al.* Functional characterization of glycine N-methyltransferase and its interactive protein DEPDC6/DEPTOR in hepatocellular carcinoma. *Mol. Med.* 2012. 18(1):286–296.

[102] Sun Y, Mu G, Zhang X, Wu Y, Wang S, *et al.* Metabolic modulation of histone acetylation mediated by HMGCL activates the FOXM1/beta-catenin pathway in glioblastoma. *Neuro-Oncol.* 2024, 26(4):653–669.

[103] Wang L, Shi F, Cao Y, Xie L. Multiple roles of branched-chain amino acid metabolism in tumour progression. *J. Biomed. Sci.* 2025, 32(1):41.

[104] Joshi K, Liu S, P Breslin SJ, Zhang J. Mechanisms that regulate the activities of TET proteins. *Cell Mol. Life Sci.* 2022, 79(7):363.

[105] Xiong H, Liu R, Xu K, Chen X, Huang L, *et al.* Branched-chain amino acid and cancer: metabolism, immune microenvironment and therapeutic targets. *J. Transl. Med.* 2025, 23(1):636.

[106] Mao L, Chen J, Lu X, Yang C, Ding Y, *et al.* Proteomic analysis of lung cancer cells reveals a critical role of BCAT1 in cancer cell metastasis. *Theranostics* 2021, 11(19):9705–9720.

[107] Zhang L, Han J. Branched-chain amino acid transaminase 1 (BCAT1) promotes the growth of breast cancer cells through improving mTOR-mediated mitochondrial biogenesis and function. *Biochem. Biophys. Res. Commun.* 2017, 486(2):224–231.

[108] Tönjes M, Barbus S, Park YJ, Wang W, Schlotter M, *et al.* BCAT1 promotes cell proliferation through amino acid catabolism in gliomas carrying wild-type IDH1. *Nat. Med.* 2013, 19(7):901–908.

[109] Boskovic P, Wilke N, Man KH, Lichter P, Francois L, *et al.* Branched-chain amino acid transaminase 1 regulates glioblastoma cell plasticity and contributes to immunosuppression. *Neuro Oncol* 2024, 26(2):251–265.

[110] Raffel S, Falcone M, Knezevic K, Hakozaki Y, Negri GL, *et al.* BCAT1 restricts alphaKG levels in AML stem cells leading to IDHmut-like DNA hypermethylation. *Nature* 2017, 551(7680):384–388.

[111] Choi BH, Hyun S, Koo SH. The role of BCAA metabolism in metabolic health and disease. *Exp. Mol. Med.* 2024, 56(7):1552–1559.

[112] Brown ML, Cai X, Simon MC. Branched chain amino acids and their aberrant metabolism in cancer. *Trends Cancer* 2026, 12(1):34–47.

[113] Charidemou E, Kirmizis A. A two-way relationship between histone acetylation and metabolism. *Trends Biochem. Sci.* 2024, 49(12):1046–1062.

[114] Li JT, Yin M, Wang D, Wang J, Zhou X, *et al.* BCAT2-mediated BCAA catabolism is critical for development of pancreatic ductal adenocarcinoma. *Nat. Cell Biol.* 2020, 22(2):167–174.

[115] Carrer A, Trefely S, Zhao S, Campbell SL, Norgard RJ, *et al.* Acetyl-CoA metabolism supports multistep pancreatic tumorigenesis. *Cancer Discovery.* 2019, 9(3):416–435.

[116] Lei M, Li X, Zhang Y, Li J, Zhang F, *et al.* Acetylation promotes BCAT2 degradation to suppress BCAA catabolism and pancreatic cancer growth. *Signal Transduction Targeted Ther.* 2020, 5(1):70.

[117] Altea-Manzano P, Decker-Farrell A, Janowitz T, Erez A, *et al.* Metabolic interplays between the tumour and the host shape the tumour macroenvironment. *Nat. Rev. Cancer* 2025, 25(4):274–292.

[118] Lv Y, Li Z, Liu S, Zhou Z, Song J, *et al.* Metabolic checkpoints in immune cell reprogramming: rewiring immunometabolism for cancer therapy. *Mol. Cancer* 2025, 24(1):210.

[119] Li X, Møller SH, Park J, Chuang YM, Hsueh PC, *et al.* Tumor-instructed glutamine synthesis in cancer-associated fibroblasts promotes pro-tumor macrophages. *J. Exp. Med.* 2025, 222(9):e2024142.

[120] Liu ZQ, Ciudad MT, McGaha TL. New insights into tryptophan metabolism in cancer. *Trends Cancer* 2025, 11(7):629–641.

[121] Mu H, Zhang Q, Zuo D, Wang J, Tao Y, *et al.* Methionine intervention induces PD-L1 expression to enhance the immune checkpoint therapy response in MTAP-deleted osteosarcoma. *Cell Rep. Med.* 2025, 6(3):101977.

[122] Lin Z, Chang C, Zhao S, Fang L, Wang P. Amino acids shape the metabolic and immunologic landscape in the tumor immune microenvironment: from molecular mechanisms to therapeutic strategies. *Cancer Biol. Med.* 2025, 22(7):726–746.

[123] Opitz CA, Litzenburger UM, Sahm F, Ott M, Tritschler I, *et al.* An endogenous tumour-promoting ligand of the human aryl hydrocarbon receptor. *Nature* 2011, 478(7368):197–203.

[124] Quintana FJ, Basso AS, Iglesias AH, Korn T, Farez MF. *et al.* Control of T(reg) and T(H)17 cell differentiation by the aryl hydrocarbon receptor. *Nature* 2008, 453(7191):65–71.

[125] Hezaveh K, Shinde RS, Klötgen A, Halaby MJ, Lamorte S, *et al.* Tryptophan-derived microbial metabolites activate the aryl hydrocarbon receptor in tumor-associated macrophages to suppress anti-tumor immunity. *Immunity* 2022, 55(2):324–340 e8.

[126] Campesato LF, Budhu S, Tchaicha J, Weng CH, Gigoux M, *et al.* Blockade of the AHR restricts a Treg-macrophage suppressive axis induced by L-Kynurenine. *Nat. Commun.* 2020, 11(1):4011.

[127] Takenaka MC, Gabriely G, Rothhammer V, Mascanfroni ID, Wheeler MA, *et al.* Control of tumor-associated macrophages and T cells in glioblastoma via AHR and CD39. *Nat. Neurosci.* 2019, 22(5):729–740.

[128] Wang C, Ye Z, Kijlstra A, Zhou Y, Yang P. Activation of the aryl hydrocarbon receptor affects activation and function of human monocyte-derived dendritic cells. *Clin. Exp. Immunol.* 2014, 177(2):521–530.

[129] Avancini D, Testori A, Fresolone L, Andolfi G, Vuono M, *et al.* Aryl hydrocarbon receptor activity downstream of IL-10 signaling is required to promote regulatory functions in human dendritic cells. *Cell Rep.* 2023, 42(3):112193.

[130] Yin JZ, Keszei AF, Houliston S, Filandr F, Beenstock J. *et al.* The HisRS-like domain of GCN2 is a pseudoenzyme that can bind uncharged tRNA. *Structure* 2024, 32(6):795–811 e6.

[131] Neill G, Masson GR. A stay of execution: ATF4 regulation and potential outcomes for the integrated stress response. *Front Mol. Neurosci.* 2023, 16:1112253.

[132] Le HT, Yu J, Ahn HS, Kim MJ, Chae IG, *et al.* eIF2alpha phosphorylation-ATF4 axis-mediated transcriptional reprogramming mitigates mitochondrial impairment during ER stress. *Mol. Cells* 2025, 48(2):100176.

[133] Munn DH, Sharma MD, Baban B, Harding HP, Zhang Y, *et al.* GCN2 kinase in T cells mediates proliferative arrest and anergy induction in response to indoleamine 2,3-dioxygenase. *Immunity* 2005, 22(5):633–642.

[134] Pauneto CM, Riesenberg BP, Gandy EJ, Kennedy AS, Clutton GT, *et al.* Intra-tumoral hypoxia promotes CD8(+) T cell dysfunction via chronic activation of integrated stress response transcription factor ATF4. *Immunity* 2025, 58(10):2489–2504 e8.

[135] Paul MS, Saibil SD, Kates M, Han SJ, Lien SC, *et al. Ex vivo* activation of the GCN2 pathway metabolically reprograms T cells, leading to enhanced adoptive cell therapy. *Cell Rep. Med.* 2024, 5(3):101465.

[136] Nan D, Yao W, Huang L, Liu R, Chen X, *et al.* Glutamine and cancer: metabolism, immune microenvironment, and therapeutic targets. *Cell Commun. Signal.* 2025, 23(1):45.

[137] Ma G, Zhang Z, Li P, Zhang Z, Zeng M, *et al.* Reprogramming of glutamine metabolism and its impact on immune response in the tumor microenvironment. *Cell Commun. Signal.* 2022, 20(1):114.

[138] Nachef M, Ali AK, Almutairi SM, Lee SH. Targeting SLC1A5 and SLC3A2/SLC7A5 as a potential strategy to strengthen anti-tumor immunity in the tumor microenvironment. *Front Immunol.* 2021, 12:624324.

[139] Hassanein M, Hoeksema MD, Shiota M, Qian J, Harris BK, *et al.* SLC1A5 mediates glutamine transport required for lung cancer cell growth and survival. *Clin. Cancer Res.* 2013, 19(3):560–570.

[140] Li S, Zeng H, Fan J, Wang F, Xu C. *et al.* Glutamine metabolism in breast cancer and possible therapeutic targets. *Biochem. Pharmacol.* 2023, 210:115464.

[141] Jiang J, Hu Y, Fang D, Luo J. Glutamine synthetase and hepatocellular carcinoma. *Clin. Res. Hepatol. Gastroenterol.* 2023, 47(10):102248.

[142] Ding L, Dang S, Sun M, Zhou D, Sun Y, *et al.* Quercetin induces ferroptosis in gastric cancer cells by targeting SLC1A5 and regulating the p-Camk2/p-DRP1 and NRF2/GPX4 Axes. *Free Radic. Biol. Med.* 2024, 213:150–163.

[143] Amaya ML, Inguva A, Pei S, Jones C, Krug A, *et al.* The STAT3-MYC axis promotes survival of leukemia stem cells by regulating SLC1A5 and oxidative phosphorylation. *Blood* 2022, 139(4):584–596.

[144] Zhao M, Zhang D, Jiang H, Kuganesan N, Natarajan S, *et al.* The RNA demethylase FTO promotes glutamine metabolism in clear cell renal cell carcinoma through the regulation of SLC1A5. *Sci. Adv.* 2025, 11(25):eadv2417.

[145] Jin J, Byun JK, Choi YK, Park KG. Targeting glutamine metabolism as a therapeutic strategy for cancer. *Exp. Mol. Med.* 2023, 55(4):706–715.

[146] Zhong X, He Z, Yin L, Fan Y, Tong Y, *et al.* Glutamine metabolism in tumor metastasis: Genes mechanisms and the therapeutic targets. *Heliyon* 2023, 9(10):e20656.

[147] Vidula N, Yau C, Rugo HS. Glutaminase (GLS1) gene expression in primary breast cancer. *Breast Cancer* 2023, 30(6):1079–1084.

[148] Suzuki S, Venkatesh D, Kanda H, Nakayama A, Hosokawa H, *et al.* GLS2 is a tumor suppressor and a regulator of ferroptosis in hepatocellular carcinoma. *Cancer Res.* 2022, 82(18):3209–3222.

[149] Zheng S, Liu T, Li L, Liu Q, Huang C, *et al.* SLC1A5, unrelated to prognosis, was associated with CD8(+) T-cell exclusion in the tumor microenvironment of squamous cell carcinoma. *Heliyon* 2023, 9(3):e14571.

[150] Edwards DN, Ngwa VM, Raybuck AL, Wang S, Hwang Y, *et al.* Selective glutamine metabolism inhibition in tumor cells improves antitumor T lymphocyte activity in triple-negative breast cancer. *J. Clin. Invest.* 2021, 131(4).

[151] Wang JJ, Siu MK, Jiang YX, Leung TH, Chan DW, *et al.* A combination of glutaminase inhibitor 968 and PD-L1 blockade boosts the immune response against ovarian cancer. *Biomolecules* 2021, 11(12):1749.

[152] Varghese S, Pramanik S, Williams LJ, Hodges HR, Hudgens CW, *et al.* The glutaminase inhibitor CB-839 (telaglenastat) enhances the antimelanoma activity of T-cell-mediated immunotherapies. *Mol. Cancer Ther.* 2021, 20(3):500–511.

[153] Xiao Y, Xu Y, Wang H, Yang F, Ding X, *et al.* HEBP2-governed glutamine competition between tumor and macrophages dictates immunotherapy efficacy in triple-negative breast cancer. *Cell Metab.* 2025, 37(10):2030–2047 e7.

[154] Nandi S, Dey M. Biochemical and structural insights into how amino acids regulate pyruvate kinase muscle isoform 2. *J. Biol. Chem.* 2020, 295(16):5390–5403.

[155] Gui DY, Lewis CA, Vander Heiden MG. Allosteric regulation of PKM2 allows cellular adaptation to different physiological states. *Sci. Signal.* 2013, 6(263):pe7.

[156] Anastasiou D, Poulogiannis G, Asara JM, Boxer MB, Jiang JK, *et al.* Inhibition of pyruvate kinase M2 by reactive oxygen species contributes to cellular antioxidant responses. *Science* 2011, 334(6060):1278–1283.

[157] Chaneton B, Hillmann P, Zheng L, Martin AC, Oliver DK, *et al.* Serine is a natural ligand and allosteric activator of pyruvate kinase M2. *Nature* 2012, 491(7424):458–462.

[158] Yuan M, McNae IW, Chen Y, Blackburn EA, Wear MA, *et al.* An allostatic mechanism for M2 pyruvate kinase as an amino-acid sensor. *Biochem. J.* 2018, 475(10):1821–1837.

[159] Dey A, Prabhudesai S, Zhang Y, Rao G, Thirugnanam K, *et al.* Cystathione beta-synthase regulates HIF-1alpha stability through persulfidation of PHD2. *Sci. Adv.* 2020, 6(27):eaaz8534.

[160] Briggs KJ, Koivunen P, Cao S, Backus KM, Olenchock BA, *et al.* Paracrine induction of hif by glutamate in breast cancer: egln1 senses cysteine. *Cell* 2016, 166(1):126–139.

[161] Zhang Y, Lyu J, Fang H. Rewiring amino acids in cancer. *Biochim. Biophys. Acta Rev. Cancer* 2025, 1880(6):189465.

[162] Liu X, Ren B, Ren J, Gu M, You L, *et al.* The significant role of amino acid metabolic reprogramming in cancer. *Cell Commun. Signal.* 2024, 22(1):380.

[163] Gao X, Sanderson SM, Dai Z, Reid MA, Cooper DE, *et al.* Dietary methionine influences therapy in mouse cancer models and alters human metabolism. *Nature* 2019, 572(7769):397–401.

[164] Cunningham A, Erdem A, Alshamleh I, Geugien M, Pruis M, *et al.* Dietary methionine starvation impairs acute myeloid leukemia progression. *Blood* 2022, 140(19):2037–2052.

[165] Mattes MD, Koturbash I, Leung CN, Wen S, Jacobson GM. A phase I trial of a methionine restricted diet with concurrent radiation therapy. *Nutr. Cancer* 2024, 76(6):463–468.

[166] Li F, Liu P, Mi W, Li L, Anderson NM, *et al.* Blocking methionine catabolism induces senescence and confers vulnerability to GSK3 inhibition in liver cancer. *Nat. Cancer* 2024, 5(1):131–146.

[167] Upadhyayula PS, Higgins DM, Mela A, Banu M, Dovas A, *et al.* Dietary restriction of cysteine and methionine sensitizes gliomas to ferroptosis and induces alterations in energetic metabolism. *Nat. Commun.* 2023, 14(1):1187.

[168] Ji M, Xu X, Xu Q, Hsiao YC, Martin C, *et al.* Methionine restriction-induced sulfur deficiency impairs antitumour immunity partially through gut microbiota. *Nat. Metab*. 2023, 5(9):1526–1543.
[169] Li T, Tan YT, Chen YX, Zheng XJ, Wang W, *et al.* Methionine deficiency facilitates antitumour immunity by altering m(6)A methylation of immune checkpoint transcripts. *Gut* 2023, 72(3):501–511.
[170] Xue Y, Lu F, Chang Z, Li J, Gao Y, *et al.* Intermittent dietary methionine deprivation facilitates tumoral ferroptosis and synergizes with checkpoint blockade. *Nat. Commun.* 2023, 14(1):4758.
[171] Maddocks OD, Berkers CR, Mason SM, Zheng L, Blyth K, *et al.* Serine starvation induces stress and p53-dependent metabolic remodelling in cancer cells. *Nature* 2013, 493(7433):542–526.
[172] Muthusamy T, Cordes T, Handzlik MK, You L, Lim EW, *et al.* Serine restriction alters sphingolipid diversity to constrain tumour growth. *Nature* 2020, 586(7831):790–795.
[173] Tong H, Jiang Z, Song L, Tan K, Yin X, *et al.* Dual impacts of serine/glycine-free diet in enhancing antitumor immunity and promoting evasion via PD-L1 lactylation. *Cell Metab.* 2024, 36(12):2493–2510 e9.
[174] Li J, Li K, Su Y, Shen Y, Lei M, *et al.* Diet high in branched-chain amino acid promotes PDAC development by USP1-mediated BCAT2 stabilization. *Natl. Sci. Rev*. 2022, 9(5):nwab212.
[175] Li Z, Guan Y, Gao J, Zhu L, Zeng Z, *et al.* PPDPF-mediated regulation of BCAA metabolism enhances mTORC1 activity and drives cholangiocarcinoma progression. *Oncogene* 2025, 44(19):1415–1433.
[176] Day CP, Merlino G, Van Dyke T. Preclinical mouse cancer models: a maze of opportunities and challenges. *Cell* 2015, 163(1):39–53.
[177] Olson B, Li Y, Lin Y, Liu ET, Patnai A. Mouse models for cancer immunotherapy research. *Cancer Discovery* 2018, 8(11):1358–1365.
[178] Lee SH, Kim EY, Han JM, Han G, Chang G, *et al.* Combination of the LARS1 inhibitor, BC-LI-0186 with a MEK1/2 inhibitor enhances the anti-tumor effect in non-small cell lung cancer. *Cancer Res. Treat.* 2023, 55(3):851–864.
[179] Yee AJ, Bensinger WI, Supko JG, Voorhees PM, Berdeja JG, *et al.* Ricolinostat plus lenalidomide, and dexamethasone in relapsed or refractory multiple myeloma: a multicentre phase 1b trial. *Lancet Oncol.* 2016, 17(11):1569–1578.
[180] Awad MM, Bruchec YL, Lu B, Ye J, Miller JA, *et al.* Selective histone deacetylase inhibitor ACY-241 (citarinostat) plus nivolumab in advanced non-small cell lung cancer: results from a phase IB study. *Front. Oncol.* 2021, 11:696512.
[181] Tsimberidou AM, Beer PA, Cartwright CA, Haymaker C, Vo HH, *et al.* Preclinical development and first-in-human study of KA2507, a selective and potent inhibitor of histone deacetylase 6, for patients with refractory solid tumors. *Clin. Cancer Res.* 2021, 27(13):3584–3594.
[182] Han T, Goralski M, Gaskill N, Capota E, Kim J, *et al.* Anticancer sulfonamides target splicing by inducing RBM39 degradation via recruitment to DCAF15. *Science* 2017, 356(6336):eaal3755.
[183] Faust TB, Yoon H, Nowak RP, Donovan KA, Li Z, *et al.* Structural complementarity facilitates E7820-mediated degradation of RBM39 by DCAF15. *Nat. Chem. Biol*. 2020, 16(1):7–14.
[184] Bewersdorf JP, Stahl M, Taylor J, Mi X, Chandhok NS, *et al.* E7820, an anti-cancer sulfonamide, degrades RBM39 in patients with splicing factor mutant myeloid malignancies: a phase II clinical trial. *Leukemia* 2023, 37(12):2512–2516.

[185] Xu Y, Spear S, Ma Y, Lorentzen MP, Gruet M, *et al.* Pharmacological depletion of RNA splicing factor RBM39 by indisulam synergizes with PARP inhibitors in high-grade serous ovarian carcinoma. *Cell Rep*. 2023, 42(10):113307.

[186] Ren S, Zhou X, Wang Z, Yuan K. Amino acids metabolism: a potential target for cancer treatment. *Mol. Cancer* 2025, 24(1):307.

[187] Xu X, Peng Q, Jiang X, Tan S, Yang Y, *et al.* Metabolic reprogramming and epigenetic modifications in cancer: from the impacts and mechanisms to the treatment potential. *Mol. Med.* 2023, 55(7):1357–1370.

[188] Janiszewska M. The microcosmos of intratumor heterogeneity: the space-time of cancer evolution. *Oncogene* 2020, 39(10):2031–2039.

[189] Chen J, Larsson L, Swarbrick A, Lundeberg J. Spatial landscapes of cancers: insights and opportunities. *Nat. Rev. Clin. Oncol.* 2024, 21(9):660–674.

[190] Najumudeen AK, Ceteci F, Fey SK, Hamm G, Steven RT, *et al.* The amino acid transporter SLC7A5 is required for efficient growth of KRAS-mutant colorectal cancer. *Nat. Genet.* 2021, 53(1):16–26.

[191] Marine JC, Dawson SJ, Dawson MA. Non-genetic mechanisms of therapeutic resistance in cancer. *Nat. Rev. Cancer* 2020, 20(12):743–756.

[192] Marusyk A, Janiszewska M, Polyak K. Intratumor heterogeneity: the rosetta stone of therapy resistance. *Cancer Cell* 2020, 37(4):471–484.

[193] Najumudeen AK, Vande Voorde J. Spatial metabolomics to unravel cellular metabolism. *Nat. Rev. Genet.* 2025, 26(4):228.

[194] Renner K, Singer K, Koehl GE, Geissler EK, Peter K, *et al.* Metabolic hallmarks of tumor and immune cells in the tumor microenvironment. *Front Immunol*. 2017, 8:248.

[195] Ge M, Xu Y, Cui L, Huang E, Liu Z, *et al.* Targeting amino acid in tumor therapy. *Front. Oncol*. 2025, 15:1582116.

[196] Ji M, Xu Q, Li X. Dietary methionine restriction in cancer development and antitumor immunity. *Trends Endocrinol. Metab.* 2024, 35(5):400–412.