Mechanisms of mTORC1 and GCN2 amino acid sensing pathways in tumorigenesis and metastatic progression (Review)

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Abstract. Amino acid (AA) sensing plays an important role in maintaining cellular metabolic homeostasis as well as tumorigenesis and progression. Studies on classic AA sensing pathways such as rapamycin complex 1 (mTORC1) and general control nonderepressible 2 (GCN2) have revealed their central position in cancer metabolic reprogramming. AA sensing pathways are often hijacked in tumors to adapt to the nutrient-deprived microenvironment, promoting cell proliferation, anti-apoptosis and treatment tolerance. In addition, the regulation of AA sensing and transport plays a crucial role in maintaining the metabolic flexibility of tumor cells. By targeting the AA sensing mechanism, it is expected to disrupt the metabolic homeostasis of cancer cells, providing new strategies for precision therapy. The present review summarized the latest advances in the research on the role of the mTORC1 and GCN2 AA sensing pathways in tumor metabolism, emphasizing their potential and the challenges faced in cancer diagnosis and treatment. Additionally, it provided novel insights into the therapeutic targeting of AA sensing pathways and proposes future research directions aimed at overcoming current limitations in cancer metabolism therapy.

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1. Introduction

Proteins, glucose and lipids are universally recognized as the three nutrients essential for sustaining human life. Amino acids (AAs), the basic structural units of proteins, serve not only as building blocks but also as critical substrates for synthesizing key biological regulators, such as thyroid hormones, underscoring their profound physiological significance (1-3). Every human protein is composed of a combination of 20 AAs, including nine essential AAs (EAAs) and 11 non-essential AAs (NEAAs). EAAs are defined as those AAs whose carbon skeletons cannot be synthesized *de novo* or whose endogenous production is insufficient to meet metabolic demands (4,5). The fundamental nutritional roles of AAs have long been well-established. However, recent studies have highlighted their emerging functions as signaling molecules in the regulation of energy balance and metabolic homeostasis. Beyond their involvement in protein metabolism, AAs also serve as critical molecular regulators of glucose and lipid metabolism (6,7).

Generally, AAs regulate cellular life activities through two primary mechanisms: Metabolism and sensing. In the context of AA sensing, the direct binding of AAs to specific sensors represents a more evolutionarily streamlined and efficient regulatory mechanism (8). The human body's detection of elevated concentrations of specific AAs can trigger the binding of these molecules to cell membranes or intracellular sensors, thereby initiating transport processes or signal transduction pathways (9). The human body's sensing of AA concentrations can also occur indirectly through the detection of surrogate molecules, such as metabolites, which reflect their abundance (10). At the organism level, distinct pathways for sensing intracellular and extracellular AA concentrations are integrated and coordinated to maintain systemic metabolic homeostasis. This adaptive response to fluctuations in AA availability is orchestrated by a sophisticated regulatory network (11). This network comprises a variety of dynamic components, which play a pivotal role in activating downstream effectors at both cellular and molecular levels.

In cancer, these processes are reprogrammed to fulfill the heightened metabolic demands of rapidly proliferating cells, allowing tumors to sustain survival under nutrient-limited

conditions and to thrive across diverse microenvironments (12). Cancer cells exhibit reprogrammed AAs metabolism, marked by enhanced uptake and utilization of specific AAs, including glutamine, serine and glycine (13-16). This metabolic reprogramming supports cancer cells in sustaining anabolic processes, facilitating energy production and maintaining redox homeostasis (15). Notably, the capacity to sense AA levels in both extracellular and intracellular compartments is intricately linked to these metabolic adaptations (17). The AA sensing pathway acts as a pivotal regulatory mechanism in determining cancer cell fate, integrating nutrient availability with growth signaling and stress response pathways (18,19). Key molecular sensors and signaling pathways involved in AAs detection include the mechanistic target of rapamycin complex 1 (mTORC1), general control nonderepressible 2 (GCN2), activating transcription factor 4 (ATF4) and the Sestrin (SESN) family of proteins (20-23). These pathways play a pivotal role in orchestrating cellular responses to AA levels fluctuations, modulating protein synthesis, autophagy and metabolic reprogramming. Furthermore, their dysregulation in cancer has profound implications for tumor progression, metastasis and therapeutic resistance.

Investigating the mechanisms of AA sensing and identifying key AA sensors are crucial for deciphering the regulatory networks that govern cellular life activities and disease progression. These insights not only advance the understanding of tumor biology but also unveil novel therapeutic opportunities. By targeting AA sensing pathways or exploiting metabolic vulnerabilities, it is possible to disrupt the metabolic adaptability of cancer cells and suppress tumor growth. The present review aimed to summarize current knowledge on AA sensing in cancer, with a focus on its molecular mechanisms, implications for tumor biology and potential therapeutic applications.

2. mTORC1 sensing signaling pathways and cancer

Structural organization and spatial regulation of the mTORC1 signaling pathway. The mechanistic target of rapamycin (mTOR) is a central regulator of cell growth, orchestrating cellular homeostasis in response to nutrients, growth factors (GFs) and environmental cues (24). mTOR, composed of 2,549 AAs, is a member of the phosphatidylinositol 3-kinase-related kinase superfamily, and assembles into two functionally distinct complexes, mTOR complex 1 (mTORC1) and mTORC2, through interactions with various accessory proteins (24,25). mTORC1 serves as a central hub in AA sensing (26) and it is assembled from core components that form its functional architecture (27,28). Among these, Raptor is a key regulatory protein that binds to the TOR signaling motif, facilitating the recruitment of mTORC1 substrates and stabilizing the complex. In this complex, mTOR provides catalytic activity, while the mammalian lethal with SEC13 protein 8 enhances the stability of the mTOR kinase domain, making these components indispensable for the assembly and functionality of mTORC1 (29,30). Non-core components, such as DEP domain-containing mTOR-interacting protein and 40 kDa proline-rich Akt substrate (PRAS40), act as negative regulators by binding to mTOR and modulating its activity (31,32). FK506-binding protein 12 and rapamycin form a ternary complex with the FRB domain of mTOR, partially blocking substrate access to its kinase active site and thereby mediating rapamycin's inhibitory effect on mTORC1 (33). mTORC1, together with its downstream effector components, forms a comprehensive sensing pathway. Moreover, mTORC1 is ubiquitously expressed across diverse tissues and organs, playing a pivotal role, particularly in metabolically active and rapidly proliferating tissues (34).

Upstream regulatory mechanisms of the mTORC1 signaling pathway. mTORC1 integrates diverse environmental signals, including ADP-ribosylation factor GTPase-activating protein 1, DNA damage, ATP, GFs, AAs, glucose, cholesterol and oxygen. These upstream signals enable mTORC1 to orchestrate distinct physiological functions, thereby maintaining cellular and organismal homeostasis (35-38). The upstream signals of mTORC1 can be classified into two distinct categories based on their dependency: GFs-dependent signals and AAs-dependent signals (39). The specific mechanisms are presented in this section as shown in Fig. 1.

Regulatory mechanisms of mTORC1 via GFs-dependent signaling. Nearly all GF-dependent signals are transduced through the tuberous sclerosis complex (TSC)-Ras homolog enriched in brain (Rheb) cascade. Rheb, a GTPase, directly binds to and activates mTORC1, inducing a conformational change in the complex (40). The biological activity of Rheb is regulated by the TSC complex, which integrates multiple upstream signals and modulates mTORC1. TSC functions as a Rheb-specific GTPase-activating protein (GAP) and is composed of TSC1, TSC2 and TBC1 Domain Family Member 7 (41). Receptor tyrosine kinase-dependent RAS signaling activates mTORC1 via ERK and its downstream effector p90 Ribosomal S6 Kinase, leading to the phosphorylation of TSC2 (42,43). Additionally, the EGF signal can activate mTORC1 through AKT-Ubiquitin-Specific Protease 4-mediated Rheb deubiquitination, resulting in the release of Rheb from the TSC (44).

Insulin induces mTORC1 activation through two distinct regulatory mechanisms (45). First, similar to other GF-dependent signaling pathways, insulin and insulin-like growth factor 1 receptor stimulation induce AKT-dependent phosphorylation of TSC2 at multiple sites, leading to mTORC1 activation through the TSC-Rheb pathway. Second, insulin can alleviate PRAS40-mediated inhibition of mTORC1 kinase activity via AKT-dependent phosphorylation of PRAS40, although the precise mechanisms underlying this process remain unclear. Other GF-dependent signaling molecules, such as the secreted glycoprotein Wingless-type MMTV Integration Site Family (Wnt) and the cytokine Tumor Necrosis Factor-α, also enhance mTORC1 activity by inhibiting the TSC, although the underlying mechanisms remain poorly understood (46).

Regulatory mechanisms of mTORC1 via AAs-dependent signaling. Unlike other signals, AAs regulate mTORC1 through distinct pathways. The mechanisms underlying AAs' signal transmission upstream of mTORC1 have been progressively elucidated and specific sensors or signaling pathways for individual AAs have also been identified (20).

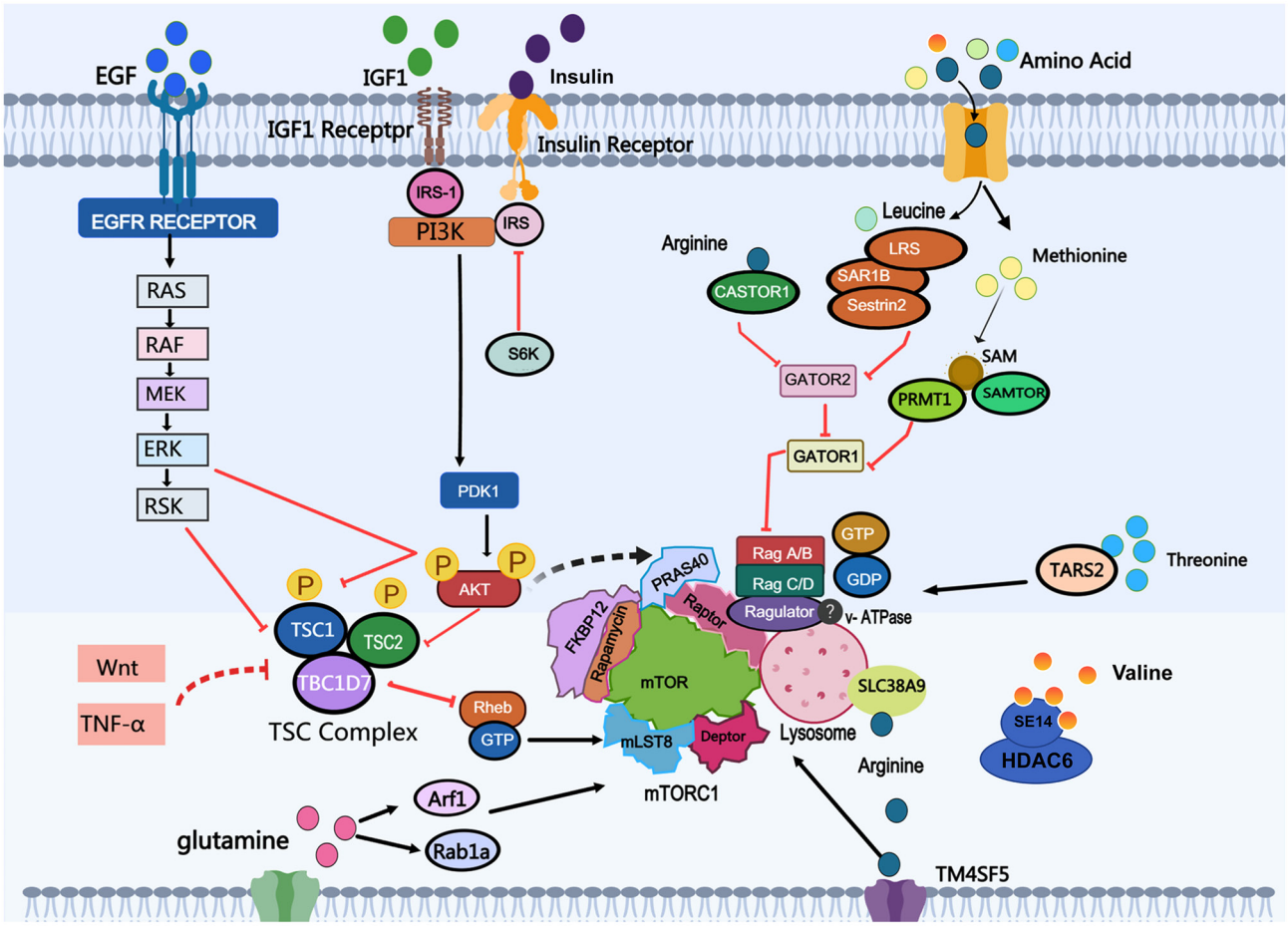

Figure 1. Upstream regulatory mechanisms of the mTORC1 signaling pathway. In the figure, the red lines represent inhibitory effects, while the black lines denote promoting or cascading responses. The portions of the study where the mechanisms remain unclear, have been indicated them with dashed lines. Created with MedPeer (medpeer.cn). mTORC1, rapamycin complex 1; EGF, epidermal growth factor; EGFR, epidermal growth factor receptor; RAS, rat sarcoma; RAF, rapidly accelerated fibrosarcoma; MEK, mitogen-activated protein kinase/extracellular signal-regulated kinase kinase; ERK, extracellular signal-regulated kinase; RSK, ribosomal S6 kinase; Wnt, wingless-related integration site; TNF-α, tumor necrosis factor Alpha; IGF-1, insulin-like growth factor 1; IRS-1, insulin receptor substrate 1; PI3K, phosphoinositide 3-kinase; PDK-1, 3-phosphoinositide-dependent protein kinase 1; TSC1, tuberous sclerosis complex 1; TSC2, tuberous sclerosis complex 2; TSC Complex, tuberous sclerosis complex; GTP, guanosine triphosphate; Arf1, ADP-ribosylation factor 1; RAB1A, ras-related protein aab-1A; IRS, insulin receptor substrate; S6K, S6 kinase; LRS, leucine-rich sequence; SAR1B, secretion associated and ras related GTPase 1B; CASTOR1, CAT1 and sestrin2 regulator 1; GATOR1, GAP activity towards rags 1; GATOR2, GATOR1 complex 2; GDP, guanosine diphosphate; mTOR, mechanistic target of rapamycin; SAM, S-adenosylmethionine; SAMTOR, SAM sensor upstream of mTORC1.

AA sensing primarily operates through two pathways: The Rag GTPase-mediated lysosomal sensing and the Rag-independent pathways, along with the regulatory networks that fine-tune these processes (38).

Rag GTPase-mediated lysosomal sensing regulates mTORC1. Rag GTPases, which form heterodimers (RagA or RagB with RagC or RagD), play a critical role in lysosomal AA sensing (47-49). Their nucleotide-binding states dictate the recruitment of mTORC1 to the lysosomal surface (50,51). When AAs are abundant, RagA/B are GTP-bound, while RagC/D are GDP-bound. This configuration allows the Rag GTPase heterodimer to bind Raptor and recruit mTORC1 to the lysosomal surface for activation by Rheb. Under AA deprivation, the Rag GTPase heterodimer switches to an inactive state (RagA/B GDP-bound and RagC/D GTP-bound), causing mTORC1 to dissociate from the lysosomal surface and preventing its activation. The activity of Rag GTPase is tightly regulated by a network of complexes that modulate its nucleotide-binding state, creating a robust mechanism to couple nutrient availability with cell growth (52). Rag GTPase is anchored to the lysosomal surface through its interaction with the Ragulator complex, which consists of Late Endosomal/Lysosomal Adaptor, MAPK and MTOR Activator (LAMTOR)1 (p18), LAMTOR2 (p14), LAMTOR3 (MP1), LAMTOR4 (C1ORF59) and LAMTOR5 (HBXIP) (53). Myristoylation and palmitoylation at the N-terminus of LAMTOR1 are critical for the lysosomal localization of the Ragulator-Rag GTPase complex (53,54). AAs can induce conformational changes in vacuolar ATPase (V-ATPase) and weaken its interaction with the Ragulator complex, suggesting that lysosomal lumen AAs may signal to Rag GTPases through V-ATPase and Ragulator. However, the precise mechanism by which V-ATPase senses AAs remains to be elucidated (55).

Rag GTPases-independent regulation of mTORC1. Although Rag GTPases are central in sensing extracellular AAs and glucose levels, the regulatory network of mTORC1 is more complex, encompassing pathways independent of Rag GTPases. Certain alternative mechanisms can activate

mTORC1 independently of Rag GTPases. For instance, the small GTPase Arf1 can substitute for Rag proteins to activate mTORC1 in response to glutamine. Research has found that the downregulation of Arf1 expression in pancreatic cancer (PC) can promote tumor proliferation, migration and invasion and is considered to be associated with the glutamine-sensing role of Arf1 in PC (56). Additionally, glutamine stimulates Rab1a, facilitating the interaction between mTORC1 and Rheb at the Golgi apparatus, thereby bypassing lysosomal recruitment (57,58). It is noteworthy that the role of Rab1a varies across different tumors. Overexpression of Rab1a is markedly associated with short-term survival and metastasis in non-small cell lung cancer (NSCLC), with elevated Rab1a levels correlating with sensitivity to Janus kinase 1 (JAK1) inhibitors. Conversely, Rab1a overexpression renders cancer cells vulnerable to JAK1-targeted therapies (59). However, in breast cancer, downregulation of Rab1a inhibits cell growth, migration, invasion and epithelial-mesenchymal transition (60). These pathways underscore the adaptability of mTORC1 in responding to diverse cellular conditions.

Some researchers proposed a new model for mTORC1 activation (26,61). According to this model, a critical prerequisite for mTORC1 activation is the simultaneous availability of both nutrients and GFs at sufficient levels. mTORC1 activation is tightly regulated in a cascade-like manner. This cascade begins with the AA-induced translocation of mTORC1 to the lysosome, followed by Rheb-mediated activation of mTORC1 at the lysosome, driven by GFs. This model suggests that AAs, rather than GFs, are dominant in regulating mTORC1, with the lysosome serving as the central hub for its activation.

AA sensors in the regulation of mTORC1 activity. The identification of AA sensors marks a breakthrough in the field of AA sensing, as these are pivotal in regulating mTORC1 activity (62). As key molecular detectors of intracellular and lysosomal AA levels, these sensors are localized in the cytosol and lysosomal compartments, where they recognize specific AAs and transduce signals to mTORC1 through diverse molecular mechanisms (63).

The leucine sensor was the first to be discovered. Initially identified for their roles in oxidative stress responses, SESN1 and SESN2 did not garner significant attention from researchers. However, subsequent studies demonstrated that SESN1 and SESN2 inhibit the mTORC1 pathway through the AMPK-TSC signaling axis (64,65). The absence of SESN1 and SESN2 abolishes mTORC1 inhibition under leucine deprivation. Additionally, SAR1 homolog B (SAR1B) and leucyl-transfer (t)RNA synthetase were proposed as alternative leucine sensors by some researchers (66,67). While multiple mechanistic hypotheses were proposed, the precise mechanisms remain unclear. Cytosolic Arginine Sensor For MTORC1 Subunit 1 (CASTOR1) inhibits GAP Activity Towards Rags (GATOR)2 under arginine-deprived conditions, thereby suppressing mTORC1 activation. In the presence of arginine, however, arginine binds to CASTOR1, disrupting its interaction with GATOR2 and activating mTORC1 signaling (68,69). Transmembrane 4 L six family member 5 (TM4SF5) is a transmembrane protein that acts as an arginine sensor by binding arginine via its extracellular loop (70). In contrast to CASTOR1, TM4SF5 translocates to the lysosome under arginine-replete conditions and directly promotes mTORC1 activation (71). Methionine, a key nutritional regulator of mTORC1 activation, is sensed indirectly through its metabolite S-adenosylmethionine (SAM), unlike other AAs (72). Under methionine-deprived conditions, SAM Sensor Upstream Of mTORC1 (SAMTOR) binds to GATOR1, enhancing its GAP activity and inhibiting mTORC1. By contrast, under methionine-replete conditions, SAMTOR dissociates from GATOR1, while Protein Arginine Methyltransferase 1 (PRMT1) methylates NPR2 Like, GATOR1 Complex Subunit to suppress GATOR1 activity, thereby activating mTORC1. Additionally, mitochondrial threonyl-tRNA synthetase 2 (TARS2) was identified as a sensor for threonine. In the presence of threonine, TARS2 interacts with inactive Rag GTPase, promoting GTP loading on RagA and facilitating mTORC1 activation (73). Solute carrier family 38 member 9 serves as an intrinsic lysosomal AA sensor, specifically detecting arginine. Moreover, it mediates the efflux of other AAs, such as leucine, from lysosomes, thereby promoting mTORC1 activation under nutrient-deprived conditions (74-76).

Role of the mTORC1 AAs-dependent sensing pathway in cancer. mTORC1 is critical in regulating cellular homeostasis and growth, and its dysregulation is strongly linked to the pathogenesis of various diseases, including cancer. Genetic mutations and environmental factors can both drive tumorigenesis by disrupting mTORC1 activity. Recent studies highlighted the critical role of the AA-mTORC1 signaling axis in cancer biology.

mTORC1 AAs-dependent sensing pathway regulates protein synthesis in cancer cells. Under nutrient-replete conditions, including ample AAs and GFs, mTORC1 phosphorylates downstream substrates, activates anabolic processes such as protein synthesis and promotes cell growth (77). mTORC1 inhibits eukaryotic initiation factor 4E-binding protein 1 (4E-BP1), causing its dissociation from eukaryotic translation initiation factor 4E and enhancing mRNA translation efficiency. This mechanism allows tumor cells to rapidly synthesize cell cycle-related proteins and growth-promoting factors (78). The phosphorylation of 4E-BP1 by mTORC1 is critically involved in breast cancer (BC) and plays a similarly critical role in the progression of colorectal cancer (CRC) and head and neck squamous cell carcinoma (HNSCC) (79,80). Ribosomal protein S6 kinase 1 (S6K1) regulates cell growth, ribosome biogenesis, glucose homeostasis, and lipogenesis, with the critical role of mTORC1 in these processes being well-established (81). mTORC1 activates S6K1, which phosphorylates the S6 protein and other targets, enhancing ribosome biogenesis and translation efficiency, thereby driving cellular growth and proliferation (82) In NSCLC, the activation of ATF4-induced Developmental and DNA Damage Response 1 inhibits mTORC1/S6K1 signaling, complicating therapeutic interventions (83).

mTORC1 AAs-dependent sensing pathway drives metabolic reprogramming in cancer cells. Metabolic reprogramming in tumors has been widely recognized in recent years as a hallmark of tumorigenesis and cancer progression (84). To support their sustained growth, tumor cells undergo extensive adaptations

in energy metabolism (85). mTORC1 plays a pivotal role in the metabolic reprogramming of cancer cells. By modulating the uptake and utilization of AAs, tumor cells obtain essential substrates for growth and proliferation, thereby sustaining their rapid expansion and survival (86). mTORC1 also drives *de novo* lipid synthesis by activating sterol regulatory element-binding proteins and enhances nucleotide biosynthesis via S6K1-dependent activation of Carbamoyl Phosphate Synthetase 2-Aspartate Transcarbamylase-Dihydroorotase, the rate-limiting enzyme in pyrimidine synthesis (87). CRC development is associated with mTORC1 dysregulation, where aberrant AA sensing drives tumor growth and metabolic reprogramming (88).

mTORC1 AAs-dependent sensing pathway regulates autophagy in cancer cells. In addition to promoting anabolic metabolism, mTORC1 also suppresses catabolic autophagy, thereby preventing the degradation of newly synthesized cellular components (89). Furthermore, AA deprivation-induced autophagy is predominantly mediated by the mTORC1 signaling pathway, enabling the recycling of intracellular components and ensuring that cancer cells sustain high metabolic activity (89,90). Under nutrient-replete conditions, mTORC1 promotes cell growth and suppresses autophagy. By contrast, under nutrient-deprived conditions, mTORC1 inhibition induces autophagy to sustain cellular metabolism (89). Autophagy activation and increased glutamine synthesis are critical for maintaining AA homeostasis during starvation. Glutamine metabolism is sufficient to restore mTORC1 activity during prolonged AA deprivation in an autophagy-dependent manner (91).

AA sensors in cancer progression. AA sensors drive cancer development and progression by promoting mTORC1 hyperactivation in tumor. The role of SESN2 in cancer is complex, with its effects potentially varying across tumor types. In CRC, SESN2 promotes tumor cell growth while modulating p53 in the context of mTORC1 signaling (92). However, in NSCLC, SESN2 differentially regulates mTORC1 and mTORC2, reprogramming lipid metabolism and enabling the survival of glutamine-deprived cancer cells by maintaining energy and redox homeostasis (93). SAR1B is frequently deleted in lung cancer (LC). A study showed that inhibiting SAR1A and SAR1B promotes mTORC1-dependent tumor growth in mouse xenograft models (66). PRMT1 upregulation is critical in the development and progression of multiple solid tumors and leukemias (94,95).

3. GCN2 AA sensing signaling pathways and cancer

Structural organization and distribution of the GCN2 AA sensing pathway. General control nonderepressible 2 (GCN2), a member of the conserved serine/threonine kinase family, primarily senses AA deficiency by binding to deacylated tRNA. It serves as a key kinase in the cellular response to AA starvation or ribosomal stress (96-98). GCN2 consists of five conserved domains and forms an inactive homodimer. Its autoinhibitory molecular interactions prevent aberrant activation of the kinase domain under basal conditions (99). In mammals, GCN2 is ubiquitously expressed, with particularly high levels in the brain, liver and skeletal muscle (100-102). The GCN2 signaling pathway comprises core components, including GCN2, deacylated tRNA and GCN1, as well as downstream regulators such as eukaryotic translation initiation factor 2α (eIF2α), ATF4 and fibroblast growth factor 21. Together, they sense AAs deficiency and regulate cellular and organismal metabolic homeostasis (103-105).

Upstream regulatory mechanisms of the GCN2 AA sensing pathway. GCN2 interacts with GCN1 via its RWD domain and associates with the ribosome to promote activation (105). GCN1 transfers deacylated tRNA from the ribosomal A site to GCN2, thereby activating GCN2 (106). Notably, this deacylated tRNA accumulates in cells under AA deprivation (97). Deacylated tRNA acts as an intracellular sensor of AA deficiency, interacting with the C-terminal region of GCN2, particularly the HisRS-like domain, which also participates in the autoinhibition of the kinase domain (96,107). The HisRS-like domain of GCN2 is a pseudoenzyme capable of directly binding deacylated tRNA (96). Beyond deacylated tRNA-related mechanisms, GCN2 can also be activated through ribosomal translation stalling and the ribosomal P-stalk (108,109). The relationship between these two mechanisms has long been a puzzle. Recent studies showed that deacylated tRNA binds to the HisRS domain to activate GCN2, while the ribosomal P-stalk protein serves as an alternative activating ligand on stalled ribosomes (107). GCN2 undergoes autophosphorylation upon activation, which, together with eIF2α phosphorylation, can serve as a useful biomarker for determining the activation status of GCN2 in cancer samples (103). The specific mechanism is shown in Fig. 2.

The role of the GCN2 AA sensing pathway in cancer. GCN2 has been strongly linked to various cancers and hematological malignancies (110,111). Compared with healthy tissues, the total levels of GCN2 and phosphorylated GCN2 are markedly elevated in tissue samples from CRC, NSCLC, BC and hepatocellular carcinoma (HCC) (21). As a central sensor of AA availability, GCN2 orchestrates the cellular response to nutrient deprivation, a common challenge for rapidly proliferating tumor cells. GCN2 maintains intracellular homeostasis by modulating protein synthesis (112), upregulating AA transporters (98), promoting autophagy (113,114) and enhancing the utilization of scarce AAs for protein synthesis (115). These functions highlight the pivotal role of GCN2 in sustaining tumor cell stability and driving tumorigenesis.

GCN2 AA sensing pathway regulates protein synthesis in cancer cells. Under severe AA deprivation, GCN2 enhances ATF4 expression, directly inducing the stress-response protein SESN2 (116). SESN2 plays a critical role in maintaining mTORC1 inhibition by preventing its lysosomal localization, ultimately resulting in a significant reduction in overall protein synthesis in cancer cells (117). Additionally, under leucine or arginine deprivation, GCN2 can suppress mTORC1 activity through an ATF4-independent mechanism (102,118). Under AA deprivation, GCN2 activation and mTORC1 inhibition coordinately maintain organismal metabolic homeostasis (105). These mechanisms directly influence cancer cell survival by maintaining AA homeostasis. The integrated stress response

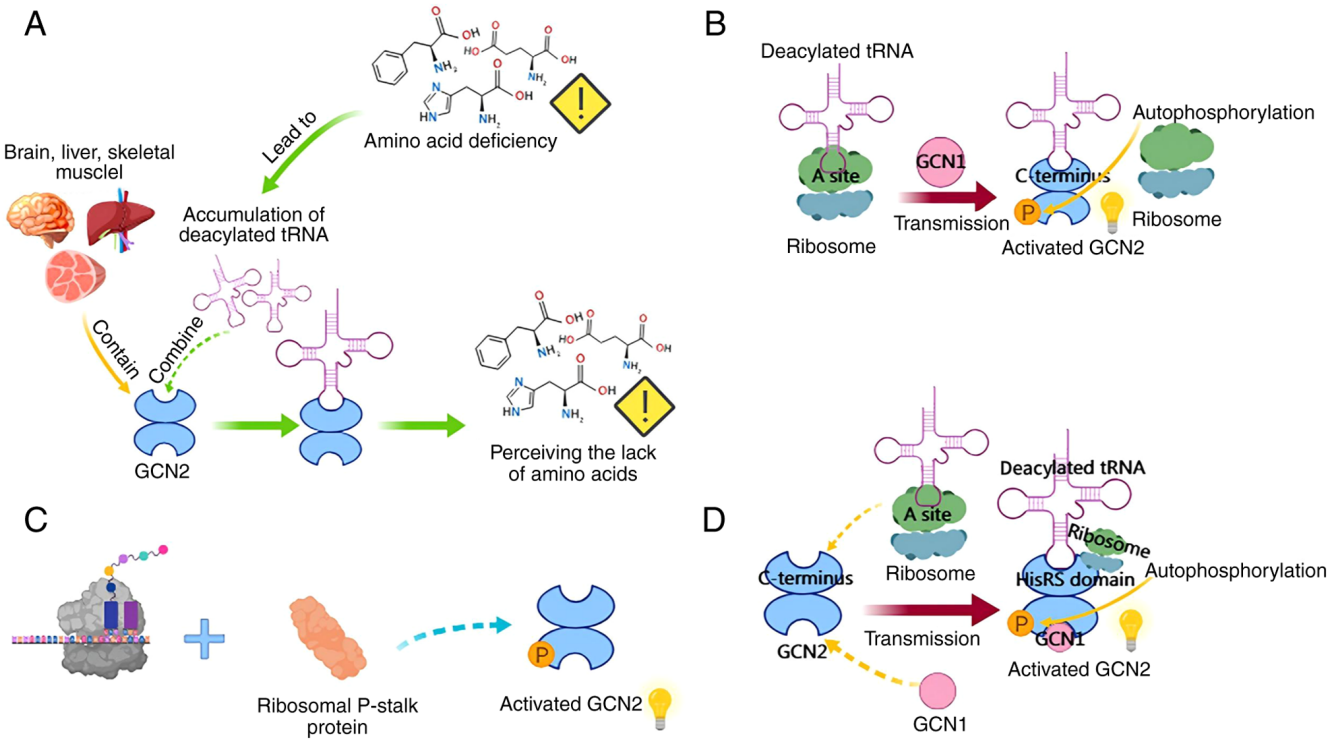

Figure 2. Upstream regulatory mechanisms of the GCN2 signaling pathway. In the figure, the yellow and green arrows represent binding and cascade reactions, the red arrow represents transmission, the exclamation mark indicates the state of amino acid deficiency and the light bulb represents the activated state. (A) The process by which GCN2 senses AA deficiency through the binding of deacylated tRNA. (B) The process by which GCN2 interacts with GCN1 through its RWD domain and associates with the ribosome to achieve activation. (C) The process by which GCN2 is activated through ribosomal translation stalling and the ribosomal P-stalk. (D) The process of deacylated tRNA interacting with the C-terminal domain of GCN2 to facilitate the activation of GCN2. Created with MedPeer (medpeer.cn). GCN2, general control nonderepressible 2; tRNA, transfer RNA.

(ISR) is a critical cellular mechanism that protects against environmental stress. A key feature of GCN2 in the ISR is its function as an AA depletion sensor (119). Combining tumor asparagine synthesis restriction with dietary asparagine limitation effectively suppresses tumor growth in multiple murine cancer models, a process mediated by the GCN2-ATF4 pathway (120). Proline deprivation in melanoma cells also activates GCN2, leading to reduced protein synthesis (121). In CRC, arginine deprivation activates the GCN2 pathway, suppressing protein synthesis through mTOR signaling inhibition (122). Arginine can mitigate interferon (IFN)-γ-induced malignant transformation of mammary epithelial cells, including the suppression of cell proliferation, migration and colony formation, potentially via the NF-κB-GCN2/eIF2α pathway (123). Additionally, arginine deprivation induces a comprehensive stress response, promoting cell cycle arrest and quiescence in HCC cells, a process also dependent on GCN2. Preclinical studies demonstrated that combining dietary arginine restriction, GCN2 inhibition and pharmacological treatment enhances apoptosis in HCC cells and induces tumor regression, closely linked to reduced mRNA and protein levels (102).

GCN2 AA sensing pathway modulates the tumor microenvironment in cancer. GCN2 regulates the expression of >60 solute carrier (SLC) genes, reducing AA levels. Following GCN2 deletion, supplementation with essential AAs partially restored the proliferation of GCN2-deficient prostate cancer (PCa) cells, highlighting the critical role of GCN2-mediated SLC transporter regulation in maintaining AA homeostasis for PCa growth (124). GCN2 plays a pivotal role in redirecting scarce AAs from diverse metabolic pathways to protein synthesis, particularly under AA deprivation (125). Tryptophan, an essential AA, is among the rarest encoded by the genetic code, with roles extending beyond its function as a fundamental protein building block (126). Tryptophan-degrading enzymes, such as indoleamine 2,3-dioxygenase 1 (IDO1) and tryptophan 2,3-dioxygenase, are frequently upregulated in various cancers, as their metabolites are critical in tumor immune evasion (127,128). When tumors experience insufficient blood supply, their demand for oxygen and essential nutrients (glucose and AAs) increases. A key adaptive strategy employed by tumors is to restore blood supply through the angiogenic switch (129). Limiting sulfur-containing AAs triggers angiogenesis by upregulating vascular endothelial growth factor expression in endothelial cells *in vitro*, enhancing their migration and sprouting. This process also increases capillary density via the GCN2/ATF4 AA starvation response pathway (130). In specific cancers, such as CRC and gastric cancer, mitochondrial signaling activates GCN2, driving a metabolic shift toward glycolysis. This shift represents a strategic adaptation in energy production to support cell proliferation and survival (131,132). Tumors employ alternative bioenergetic pathways to offset the energy and catabolic demands of rapid, uncontrolled proliferation under glucose deprivation. These pathways include glutamine metabolism, where glutamine is utilized for mitochondrial ATP production and serves as a carbon and nitrogen source for

synthesizing AAs, nucleotides and lipids (133). As a precursor for AA synthesis, glutamine deprivation disrupts this AA supplementation pattern in tumors, resulting in starvation, deacylated tRNA accumulation and activation of the GCN2–ATF4 pathway (134,135). Under NEAA deficiency, the GCN2-ATF4 pathway is essential for the long-term survival of several solid tumors and mitigates the resulting stress (136,137). The GCN2 pathway may also drive cancer progression within the tumor microenvironment by modulating immune responses, as GCN2 acts as a key regulator of macrophage functional polarization and $CD4^+$ T cell subset differentiation (138). The mechanisms by which GCN2 regulates macrophages and T cells are relatively complex. Depleting the single AA arginine from the culture medium can strongly activate the GCN2 pathway in T cells, and the deprivation of arginine in activated $CD8^+$ T cells leads to the activation of the GCN2-ATF4 stress response pathway (113). Under prolonged stimulation with IFN-γ, melanoma cells undergo IDO1-mediated tryptophan depletion, leading to frameshift mutations during mRNA translation and the production of mutated peptides. These mutated peptides can be recognized by T cells, thereby activating them (139). The absence of GCN2 in T cells is associated with proliferation defects during the activation process. In a murine glioma model, $CD8^+$ T cells lacking GCN2 exhibit impaired antitumor immunity. However, in the B16 melanoma model, the specific deletion of GCN2 did not affect antitumor immunity; however, the underlying mechanisms warrant further investigation (113). A related study on melanoma found that the deletion of GCN2 in myeloid-derived suppressor cells promotes the phenotypic transformation of tumor-associated macrophages and myeloid-derived suppressor cells, thereby enhancing the antitumor immune response. This phenomenon is attributed to alterations in the tumor microenvironment, characterized by an increase in pro-inflammatory activation of macrophages and myeloid-derived suppressor cells, as well as elevated expression of IFN-γ in intratumoral $CD8^+$ T cells. Mechanistically, cAMP response element-binding protein (CREB)-2/ATF4 is essential for the maturation and polarization of macrophages and myeloid-derived suppressor cells in both mice and humans. GCN2 modifies the function of myeloid-derived suppressor cells by promoting the enhanced translation of the transcription factor CREB-2/ATF4 (140).

GCN2 AA sensing pathway modulates tumor treatment resistance. GCN2 activation may enhance tumor cell resistance to chemotherapy and radiotherapy by regulating stress responses and metabolic adaptations, promoting survival under therapeutic stress. In hematological malignancies, multiple myeloma (MM) is notoriously challenging to treat and highly prone to drug resistance. GCN2 inhibition was shown to exhibit synergistic effects with proteasome inhibitors, offering potential new therapeutic strategies for MM (141,142). Moreover, treating certain MM cells with ixazomib, an oral proteasome inhibitor, induces AA depletion, GCN2 activation and subsequent suppression of protein synthesis. This suggests that GCN2 regulates tumor survival by responding to diverse metabolic stresses (143). The role of GCN2 in reactive oxygen species (ROS) homeostasis may contribute to its ability to promote chemotherapy resistance. Inhibiting GCN2 with the inhibitor GCN2iB prevents the recovery of certain MM cells (144). Following stress, GCN2 inhibition not only alters AA levels, consistent with its classical function, but also modulates glutathione, N-acetylcysteine and cysteine levels, suggesting that GCN2 also aids cells in recovering from chemotherapy-induced ROS stress.

4. Cross-regulation network of mTORC1 and GCN2

mTORC1 and GCN2 are central in the metabolism of cancer cells, which often encounter extreme nutritional conditions, such as AA deprivation. These cells must rely on effective signaling networks to adapt to these changes (145). The regulatory network between mTORC1 and GCN2 represents a classic dynamic equilibrium and coordinated response system. By sensing the availability of AAs, these two entities interact and coordinate with each other to jointly regulate cellular metabolic activities, thereby influencing cancer growth, survival, metastasis and drug resistance (146).

Coordination in the arginine sensing process. Arginine is a conditionally EAA, whose metabolic processes play a critical role in cancer biology and immunotherapy, being associated with the onset, progression and immune evasion of cancer (146). When intracellular levels of arginine are sufficient, mTORC1 is activated, promoting protein synthesis and cell growth (147). In the context of arginine deficiency, GCN2 is activated as an AA stress sensor, inhibiting translation to conserve AA resources and facilitating cellular adaptation to an environment deficient in AAs (148). HCC continuously suppresses the expression of urea cycle genes, thereby exhibiting a nutrient-dependent relationship with exogenous arginine. Arginine can be interconverted with proline and glutamate and it promotes cell growth by activating mTORC1 (149). Under the influence of the GCN2 kinase, arginine deficiency promotes cell cycle arrest and quiescence in HCC cells (102). Arginine deficiency can lead to the inhibition of mTORC1 and the activation of GCN2, thereby maintaining the survival strategies of cells. This mechanism assists HCC cells in continuing to proliferate in adverse microenvironments, playing a crucial role, particularly in the drug resistance and metastasis of HCC. LC also exhibits an absolute deficiency of arginine; however, there is a lack of further research findings in this direction (150).

Coordination in the glutamine sensing process. Glutamine is a critically important AA in the metabolism of cancer cells. It not only participates in protein synthesis but also serves as a nitrogen source for metabolic processes within the cell (151). In the absence of glutamine, activated GCN2 upregulates ATF4 to induce the expression of the stress response protein SESN2, which is crucial for maintaining the inhibition of mTORC1. Furthermore, the induction of SESN2 during glutamine deprivation is essential for cell survival, indicating that SESN2 serves as a significant effector molecule in the GCN2 signaling pathway, regulating AA homeostasis through the inhibition of mTORC1. PC is characterized by an increased dependency on glutamine metabolism (152). Increased glutamine uptake can promote the progression of PC via the mTORC1 pathway (153). In PC characterized by glutamine depletion, the activation of GCN2 can inhibit

translation initiation, thereby enabling adaptation to this environment (112).

5. AA sensing in cancer therapy

The role of the AA sensing mechanisms in cancer therapy has attracted growing attention, primarily involving the two key pathways, mTORC1 and GCN2. By detecting and responding to intracellular and extracellular AA levels, these pathways regulate cellular growth, metabolism and survival, playing a crucial role in cancer cell adaptation to nutrient stress and hostile microenvironments. Overall, targeted therapies leveraging AA sensing mechanisms not only offer novel perspectives for cancer treatment but may also synergize with existing therapies to enhance efficacy and overcome resistance, holding substantial clinical potential. In the subsequent sections, the present review summarizes therapeutic agents targeting AA sensing mechanisms in cancer, their respective targets and recent advancements in this field.

mTORC1 targeted therapy

mTOR kinase inhibitors in cancer therapy. In cancer, hyperactivation of the mTORC1 signaling pathway is frequently observed, with mTOR mutations identified in multiple malignancies (154,155). Traditional mTOR inhibitors, such as rapamycin and its analogs, exhibit moderate clinical anticancer activity, primarily through mTORC1 inhibition (154). Although rapamycin analogs demonstrated clinical efficacy in cancer, they have not fully unlocked the antitumor potential of mTOR targeting. Given the pivotal role of the mTOR kinase domain in mediating both rapamycin-sensitive and rapamycin-insensitive functions, mTOR catalytic inhibitors were developed as second-generation anti-mTOR agents. Notably, these inhibitors demonstrate potent antitumor activity *in vitro* and *in vivo* (156). Vistusertib, also known as AZD2014, is a newly developed mTORC1/2 kinase inhibitor that demonstrated superior efficacy compared with rapamycin. A clinical trial involving refractory metastatic renal cell carcinoma revealed that AZD2014 markedly delays the time to cancer regrowth when compared with everolimus (157). MicroRNAs (miRNAs) are small RNA molecules that regulate gene expression and play roles in diverse biological processes, including cancer progression. Studies demonstrated that targeting the mTOR pathway with miRNAs offers potential for improving the efficacy of radiotherapy (RT) (158).

Phosphatidylinositol 3-kinase (PI3K)α inhibitors in cancer therapy. The PI3K/protein kinase B (PKB)/mTOR signaling pathway plays a critical role in the initiation and progression of various cancers by suppressing apoptosis and promoting cancer cell proliferation. Generally, multi-target inhibitors within this pathway are more effective than single-target inhibitors. PI3Kα inhibitors demonstrate clinical efficacy in patients with estrogen receptor-positive BC harboring PIK3CA mutations, providing insights into mTOR signaling reactivation as a mechanism of resistance to PI3Kα inhibition (159). Alpelisib is recognized as the only approved PI3Kα inhibitor for BC treatment (160). However, a recent study on the allosteric, mutant-selective PI3Kα inhibitor STX-478 demonstrated its ability to suppress tumor growth in mice with PIK3CA mutations without inducing hyperglycemia or other metabolic dysfunctions. Upon approval, it may emerge as a next-generation therapeutic candidate (161). Beyond solid tumors, PI3Kα inhibitors are also employed in treating hematological malignancies, particularly lymphomas (162).

GCN2 targeted therapy

Bone marrow adipocytes dynamically evolve during the pathogenesis and treatment of acute lymphoblastic leukemia (ALL). However, treatment with the GCN2 inhibitor GCN2ib alleviates adipocyte-mediated translational repression, rescuing ALL cell quiescence. This intervention markedly diminishes the protective effects of adipocytes against chemotherapy and other external stressors, offering a novel therapeutic opportunity for ALL (163). Pancreatic ductal adenocarcinoma (PDAC) is characterized by a highly inflammatory tumor microenvironment, marked by significant heterogeneity, metastatic potential and extreme hypoxia, making it a highly aggressive malignancy (164). Combining GCN2 inhibitors with redox factor-1 inhibitors markedly enhances the therapeutic efficacy of targeted therapies against PDAC (165). Additionally, research confirmed that the rapid activation of GCN2 following treatment with the WEE1 kinase inhibitor AZD1775 in small cell lung cancer (SCLC) triggers a stress response in SCLC cells, thereby enhancing the efficacy of WEE1 inhibitors in this context (166). *Combined targeting strategies*

AA transporter inhibitors directly modulate AA sensing pathways, including mTORC1 and GCN2, by restricting nutrient uptake in tumors, thereby reshaping the immune microenvironment. Their synergy with stress pathways, immunotherapy and metabolic interventions provides novel avenues for cancer treatment.

L-type AA transporter 1 (LAT1) is involved in AA transport and metabolism, with JPH203 serving as a potent inhibitor of this target (167). JPH203 markedly sensitizes cancer cells to radiation at minimally toxic concentrations and is expected to enhance the efficacy of RT when used in combination (168). Furthermore, JPH203 inhibits the proliferation of human thyroid cancer cell lines and mTORC1 signaling by blocking LAT1. In a fully immunocompetent mouse model of thyroid cancer, treatment with JPH203 resulted in the *in vivo* growth arrest of thyroid tumors (169). The first Phase I trial of JPH203 in a cohort of patients with advanced solid tumors revealed that, among 17 patients, after excluding two who withdrew from the study due to grade 3 hepatic impairment, the disease control rate in the remaining patients with cholangiocarcinoma was 60% (170). V-9302, a small-molecule antagonist of the glutamine transporter ASCT2, was shown to effectively suppress intracellular glutamine levels and disrupt downstream glutamine metabolism. Mechanistically, V-9302 induces apoptosis and autophagy, enhances oxidative stress and inhibits the mTORC1 signaling pathway (171). This compound exhibited potent antitumor activity by attenuating the growth and proliferation of HNSCC. A new alternative to V-9302, Yuanhuacine, was also demonstrated to serve as a potential therapeutic agent

for HNSCC by modulating ASCT2-mediated glutamine metabolism (172).

6. Conclusions

AA sensing serves as a fundamental regulatory mechanism for cellular metabolic homeostasis and is critically implicated in tumorigenesis and cancer progression. Its emerging role in cancer metabolism has positioned it as a promising therapeutic target. Classical AA sensing pathways, including the mTORC1 and GCN2 axes, have been extensively characterized for their roles in cancer metabolic reprogramming. Specifically, mTORC1 promotes anabolic processes to fuel cell growth under AAs-dependent conditions, whereas GCN2 activates the ISR via detection of uncharged tRNAs during nutrient scarcity, thereby suppressing global protein synthesis while facilitating stress-adaptive gene expression. Recent advances unveiled novel perceptual mechanisms, such as the discovery in 2025 that HDAC6 can function as a sensor for valine, participating in a tumor-specific AA sensing network (173). This finding enhances the understanding of the complexity and context-dependence of these regulatory systems. Within the tumor microenvironment, malignant cells exploit AA sensing pathways to overcome metabolic constraints, thereby enhancing proliferation, evading apoptosis and developing therapeutic resistance. Clinically, dysregulated AA sensing correlates with aggressive tumor phenotypes, metastatic dissemination and chemoresistance. These insights have spurred therapeutic innovations, including targeted pathway inhibitors and AA-restricted dietary regimens, which demonstrate preclinical efficacy in modulating tumor metabolism.

Despite progress in understanding AA sensing in tumorigenesis and metastasis, several challenges remain. Tumor subtype-specific AA dependencies complicate precision therapies, while functional redundancy among sensing pathways may trigger compensatory mechanisms. Additionally, the crosstalk between AA sensing and broader metabolic networks, including glycolysis and lipid metabolism, remains unclear. Future research should focus on developing dual-target inhibitors, identifying novel AA sensors and mapping tumor-specific AA dependencies across cancers. At the single-cell level, exploring pathway heterogeneity could provide insights into differential tumor cell responses. Moreover, combining nutritional interventions with drug therapies may offer new strategies to target cancer metabolism. However, challenges such as tissue specificity and model differences must be addressed to improve the translation of these findings into clinical practice.

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Authors' contributions

CWZ conceived the study, developed methods, performed analyses and drafted the manuscript. YXH contributed to methodology, data analysis and manuscript editing. WYY provided conceptual guidance, resources, and supervised the project. QH assisted with experimental validation and manuscript revision. NC led the study design, secured funding and oversaw all research phases. Data authentication is not applicable. All authors read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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References

1. Gao S, Qian X, Huang S, Deng W, Li Z and Hu Y: Association between macronutrients intake distribution and bone mineral density. Clin Nutr 41: 1689-1696, 2022.
2. Golshan M, Dortaj H, Rajabi M, Omidi Z, Golshan M, Pourentezari M and Rajabi A: Animal origins free products in cell culture media: A new frontier. Cytotechnology 77: 12, 2025.
3. Hellmann A, Turyn J, Zwara A, Korczynska J, Taciak A and Mika A: Alterations in the amino acid profile in patients with papillary thyroid carcinoma with and without Hashimoto's thyroiditis. Front Endocrinol (Lausanne) 14: 1199291, 2023.
4. Thompson R and Pickard BS: The amino acid composition of a protein influences its expression. PLoS One 19: e0284234, 2024.
5. Li B, Roden DM and Capra JA: The 3D mutational constraint on amino acid sites in the human proteome. Nat Commun 13: 3273, 2022.
6. Yang Y, Fan C, Zhang Y, Kang T and Jiang J: Untargeted metabolomics reveals the role of lipocalin-2 in the pathological changes of lens and retina in diabetic mice. Invest Ophthalmol Vis Sci 65: 19, 2024.
7. Zhu ZG, Ma JW, Ji DD, Li QQ, Diao XY and Bao J: Mendelian randomization analysis identifies causal associations between serum lipidomic profile, amino acid biomarkers and sepsis. Heliyon 10: e32779, 2024.
8. Jin J, Meng T, Yu Y, Wu S, Jiao CC, Song S, Li YX, Zhang Y, Zhao YY, Li X, *et al*: Human HDAC6 senses valine abundancy to regulate DNA damage. Nature 637: 215-223, 2025.
9. Scalise M, Console L, Rovella F, Galluccio M, Pochini L and Indiveri C: Membrane transporters for amino acids as players of cancer metabolic rewiring. Cells 9: 2028, 2020.
10. Ma Y, Han X, Fang J and Jiang H: Role of dietary amino acids and microbial metabolites in the regulation of pig intestinal health. Anim Nutr 9: 1-6, 2022.
11. Van Winkle LJ: Amino acid transport and metabolism regulate early embryo development: Species differences, clinical significance, and evolutionary implications. Cells 10: 3154, 2021.
12. Grobben Y: Targeting amino Acid-metabolizing enzymes for cancer immunotherapy. Front Immunol 15: 1440269, 2024.
13. Liu N, Shi F, Yang L, Liao W and Cao Y: Oncogenic viral infection and amino acid metabolism in cancer progression: Molecular insights and clinical implications. Biochim Biophys Acta Rev Cancer 1877: 188724, 2022.

14. Fan Y, Xue H, Li Z, Huo M, Gao H and Guan X: Exploiting the Achilles' heel of cancer: Disrupting glutamine metabolism for effective cancer treatment. Front Pharmacol 15: 1345522, 2024.
15. Wu D, Zhang K, Khan FA, Pandupuspitasari NS, Guan K, Sun F and Huang C: A comprehensive review on signaling attributes of serine and serine metabolism in health and disease. Int J Biol Macromol 260: 129607, 2024.
16. Kadivar D, Eslami Moghadam M and Notash B: Effect of geometric isomerism on the anticancer property of new platinum complexes with glycine derivatives as asymmetric N, O donate ligands against human cancer. Spectrochim Acta A Mol Biomol Spectrosc 322: 124809, 2024.
17. Kelly B and Pearce EL: Amino Assets: How Amino Acids Support Immunity. Cell Metab 32: 154-175, 2020.
18. Hushmandi K, Einollahi B, Saadat SH, Lee EHC, Farani MR, Okina E, Huh YS, Nabavi N, Salimimoghadam S and Kumar AP: Amino acid transporters within the solute carrier superfamily: Underappreciated proteins and novel opportunities for cancer therapy. Mol Metab 84: 101952, 2024.
19. Jakobsen S and Nielsen CU: Exploring amino acid transporters as therapeutic targets for cancer: An examination of inhibitor structures, selectivity issues, and discovery approaches. Pharmaceutics 16: 197, 2024.
20. Zhang S, Lin X, Hou Q, Hu Z, Wang Y and Wang Z: Regulation of mTORC1 by amino acids in mammalian cells: A general picture of recent advances. Anim Nutr 7: 1009-1023, 2021.
21. Gold LT and Masson GR: GCN2: Roles in tumour development and progression. Biochem Soc Trans 50: 737-745, 2022.
22. Tang H, Kang R, Liu J and Tang D: ATF4 in cellular stress, ferroptosis, and cancer. Archi Toxicol 98: 1025-1041, 2024.
23. Jiang C, Dai X, He S, Zhou H, Fang L, Guo J, Liu S, Zhang T, Pan W and Yu H: Ring domains are essential for GATOR2-dependent mTORC1 activation. Mol Cell 83: 74-89.e9, 2023.
24. Berdenis van Berlekom A, Kübler R, Hoogeboom JW, Vonk D, Sluijs JA, Pasterkamp RJ, Middeldorp J, Kraneveld AD, Garssen J, Kahn RS, *et al*: Exposure to the amino acids histidine, lysine, and threonine reduces mTOR activity and affects neurodevelopment in a human cerebral organoid model. Nutrients 14: 2175, 2022.
25. Kumar M, Sahoo SS, Jamaluddin MFB and Tanwar PS: Loss of liver kinase B1 in human seminoma. Front Oncol 13: 1081110, 2023.
26. Yue S, Li G, He S and Li T: The central role of mTORC1 in amino acid sensing. Cancer Res 82: 2964-2974, 2022.
27. Kaizuka T, Hara T, Oshiro N, Kikkawa U, Yonezawa K, Takehana K, Iemura S, Natsume T and Mizushima N: Tti1 and Tel2 are critical factors in mammalian target of rapamycin complex assembly. J Biol Chem 285: 20109-20116, 2010.
28. Xu C, Pan X, Wang D, Guan Y, Yang W, Chen X and Liu Y: O-GlcNAcylation of Raptor transduces glucose signals to mTORC1. Mol Cell 83: 3027-3040.e11, 2023.
29. Jie H, Wei J, Li Z, Yi M, Qian X, Li Y, Liu C, Li C, Wang L, Deng P, *et al*: Serine starvation suppresses the progression of esophageal cancer by regulating the synthesis of purine nucleotides and NADPH. Cancer Metab 13: 10, 2025.
30. Fu Y, Fu Z, Su Z, Li L, Yang Y, Tan Y, Xiang Y, Shi Y, Xie S, Sun L and Peng G: mLST8 is essential for coronavirus replication and regulates its replication through the mTORC1 pathway. mBio 14: e0089923, 2023.
31. Ma K, Xian W, Liu H, Shu R, Ge J, Luo ZQ, Liu X and Qiu J: Bacterial ubiquitin ligases hijack the host deubiquitinase OTUB1 to inhibit MTORC1 signaling and promote autophagy. Autophagy 20: 1968-1983, 2024.
32. Wang C and Jiang D: Exogenous PRAS40 reduces KLF4 expression and alleviates hypertrophic scar fibrosis and collagen deposition through inhibiting mTORC1. Burns 50: 936-946, 2024.
33. Ye Q, Zhou W, Xu S, Que Q, Zhan Q, Zhang L, Zheng S, Ling S and Xu X: Ubiquitin-specific protease 22 promotes tumorigenesis and progression by an FKBP12/mTORC1/autophagy positive feedback loop in hepatocellular carcinoma. MedComm (2020) 4: e439, 2023.
34. Fernandes SA, Angelidaki DD, Nüchel J, Pan J, Gollwitzer P, Elkis Y, Artoni F, Wilhelm S, Kovacevic-Sarmiento M and Demetriades C: Spatial and functional separation of mTORC1 signalling in response to different amino acid sources. Nat Cell Biol 26: 1918-1933, 2024.
35. Meng D, Yang Q, Melick CH, Park BC, Hsieh TS, Curukovic A, Jeong MH, Zhang J, James NG and Jewell JL: ArfGAP1 inhibits mTORC1 lysosomal localization and activation. EMBO J 40: e106412, 2021.
36. Daigh LH, Saha D, Rosenthal DL, Ferrick KR and Meyer T: Uncoupling of mTORC1 from E2F activity maintains DNA damage and senescence. Nat Commun 15: 9181, 2024.
37. Condon KJ, Orozco JM, Adelmann CH, Spinelli JB, van der Helm PW, Roberts JM, Kunchok T and Sabatini DM: Genome-wide CRISPR screens reveal multitiered mechanisms through which mTORC1 senses mitochondrial dysfunction. Proc Natl Acad Sci USA 118: e2022120118, 2021.
38. Jiang C, Tan X, Liu N, Yan P, Hou T and Wei W: Nutrient sensing of mTORC1 signaling in cancer and aging. Semin Cancer Biol 106-107: 1-12, 2024.
39. Zhu M, Teng F, Li N, Zhang L, Zhang S, Xu F, Shao J, Sun H and Zhu H: Monomethyl branched-chain fatty acid mediates amino acid sensing upstream of mTORC1. Dev Cell 56: 3171, 2021.
40. Yao Y, Hong S, Yoshida S, Swaroop V, Curtin B and Inoki K: The Cullin3-Rbx1-KLHL9 E3 ubiquitin ligase complex ubiquitinates Rheb and supports amino Acid-induced mTORC1 activation. Cell Rep 44: 115101, 2025.
41. Hartung J, Müller C and Calkhoven CF: The dual role of the TSC complex in cancer. Trends Mol Med 31: 452-465, 2024.
42. Wan ZY, Tian JS, Tan HW, Chow AL, Sim AY, Ban KH and Long YC: Mechanistic target of rapamycin complex 1 is an essential mediator of metabolic and mitogenic effects of fibroblast growth factor 19 in hepatoma cells. Hepatology 64: 1289-1301, 2016.
43. Feng Y, Li T, Li Y, Lin Z, Han X, Pei X, Zhang Y, Li F, Yang J, Shao D and Li C: Glutaredoxin-1 promotes lymphangioleiomyomatosis progression through inhibiting Bim-mediated apoptosis via COX2/PGE2/ERK pathway. Clin Transl Med 13: e1333, 2023.
44. Deng L, Chen L, Zhao L, Xu Y, Peng X, Wang X, Ding L, Jin J, Teng H, Wang Y, *et al*: Ubiquitination of Rheb governs growth factor-induced mTORC1 activation. Cell Res 29: 136-150, 2019.
45. Crosby P, Hamnett R, Putker M, Hoyle NP, Reed M, Karam CJ, Maywood ES, Stangherlin A, Chesham JE, Hayter EA, *et al*: Insulin/IGF-1 drives PERIOD synthesis to entrain circadian rhythms with feeding time. Cell 177: 896-909.e20, 2019.
46. Liu L, Xiao B, Hirukawa A, Smith HW, Zuo D, Sanguin-Gendreau V, McCaffrey L, Nam AJ and Muller WJ: Ezh2 promotes mammary tumor initiation through epigenetic regulation of the Wnt and mTORC1 signaling pathways. Proc Natl Acad Sci USA 120: e2303010120, 2023.
47. Shi H, Chapman NM, Wen J, Guy C, Long L, Dhungana Y, Rankin S, Pelletier S, Vogel P, Wang H, *et al*: Amino acids license kinase mTORC1 activity and treg cell function via small G proteins rag and rheb. Immunity 51: 1012-1027.e7, 2019.
48. Sancak Y, Peterson TR, Shaul YD, Lindquist RA, Thoreen CC, Bar-Peled L and Sabatini DM: The Rag GTPases bind raptor and mediate amino acid signaling to mTORC1. Science 320: 1496-1501, 2008.
49. Kim E, Goraksha-Hicks P, Li L, Neufeld TP and Guan KL: Regulation of TORC1 by Rag GTPases in nutrient response. Nat Cell Biol 10: 935-945, 2008.
50. Rogala KB, Gu X, Kedir JF, Abu-Remaileh M, Bianchi LF, Bottino AMS, Dueholm R, Niehaus A, Overwijn D, Fils AP, *et al*: Structural basis for the docking of mTORC1 on the lysosomal surface. Science 366: 468-475, 2019.
51. Anandapadamanaban M, Masson GR, Perisic O, Berndt A, Kaufman J, Johnson CM, Santhanam B, Rogala KB, Sabatini DM and Williams RL: Architecture of human Rag GTPase heterodimers and their complex with mTORC1. Science 366: 203-210, 2019.
52. Doxsey DD, Tettoni SD, Egri SB and Shen K: Redundant electrostatic interactions between GATOR1 and the Rag GTPase heterodimer drive efficient amino acid sensing in human cells. J Biol Chem 299: 104880, 2023.
53. Egri SB, Ouch C, Chou HT, Yu Z, Song K, Xu C and Shen K: Cryo-EM structures of the human GATOR1-Rag-Ragulator complex reveal a spatial-constraint regulated GAP mechanism. Mol Cell 82: 1836-1849.e5, 2022.
54. Sanders SS, De Simone FI and Thomas GM: mTORC1 signaling is Palmitoylation-dependent in hippocampal neurons and Non-neuronal cells and involves dynamic palmitoylation of LAMTOR1 and mTOR. Front Cell Neurosci 13: 115, 2019.
55. Laufenberg LJ, Crowell KT and Lang CH: Alcohol acutely antagonizes Refeeding-induced alterations in the Rag GTPase-ragulator complex in skeletal muscle. Nutrients 13: 1236, 2021.

56. Cheng J, Lou Y and Jiang K: Downregulation of long non-coding RNA LINC00460 inhibits the proliferation, migration and invasion, and promotes apoptosis of pancreatic cancer cells via modulation of the miR-320b/ARF1 axis. Bioengineered 12: 96-107, 2021.
57. Li FL and Guan KL: The Arf family GTPases: Regulation of vesicle biogenesis and beyond. BioEssays: News and reviews in molecular, cellular and developmental Biology 45: e2200214, 2023.
58. Fan SJ, Snell C, Turley H, Li JL, McCormick R, Perera SM, Heublein S, Kazi S, Azad A, Wilson C, *et al*: PAT4 levels control amino-acid sensitivity of rapamycin-resistant mTORC1 from the Golgi and affect clinical outcome in colorectal cancer. Oncogene 35: 3004-3015, 2016.
59. Huang T, Chen B, Wang F, Cai W, Wang X, Huang B, Liu F, Jiang B and Zhang Y: Rab1A promotes IL-4R/JAK1/STAT6-dependent metastasis and determines JAK1 inhibitor sensitivity in non-small cell lung cancer. Cancer Lett 523: 182-194, 2021.
60. Xu H, Qian M, Zhao B, Wu C, Maskey N, Song H, Li D, Song J, Hua K and Fang L: Inhibition of RAB1A suppresses epithelial-mesenchymal transition and proliferation of triple-negative breast cancer cells. Oncol Rep 37: 1619-1626, 2017.
61. Zhao T, Fan J, Abu-Zaid A, Burley SK and Zheng XFS: Nuclear mTOR signaling orchestrates transcriptional programs underlying cellular growth and metabolism. Cells 13: 781, 2024.
62. Wolfson RL and Sabatini DM: The dawn of the age of amino acid sensors for the mTORC1 pathway. Cell 26: 301-309, 2017.
63. Talaia G, Bentley-DeSousa A and Ferguson SM: Lysosomal TBK1 responds to amino acid availability to relieve Rab7-dependent mTORC1 inhibition. EMBO J 43: 3948-3967, 2024.
64. Chen F, Peng S, Li C, Yang F, Yi Y, Chen X, Xu H, Cheng B, Xu Y and Xie X: Nitidine chloride inhibits mTORC1 signaling through ATF4-mediated Sestrin2 induction and targets IGF2R for lysosomal degradation. Life Sci 353: 122918, 2024.
65. Oricchio E, Katanayeva N, Donaldson MC, Sungalee S, Pasion JP, Béguelin W, Battistello E, Sanghvi VR, Jiang M, Jiang Y, *et al*: Genetic and epigenetic inactivation of SESTRIN1 controls mTORC1 and response to EZH2 inhibition in follicular lymphoma. Sci Transl Med 9: eaak9969, 2017.
66. Chen J, Ou Y, Luo R, Wang J, Wang D, Guan J, Li Y, Xia P, Chen PR and Liu Y: SAR1B senses leucine levels to regulate mTORC1 signalling. Nature 596: 281-284, 2021.
67. Kim JH, Jung K, Lee C, Song D, Kim K, Yoo HC, Park SJ, Kang JS, Lee KR, Kim S, *et al*: Structure-based modification of pyrazolone derivatives to inhibit mTORC1 by targeting the leucyl-tRNA synthetase-RagD interaction. Bioorg Chem 112: 104907, 2021.
68. Gai Z, Hu S, He Y, Yan S, Wang R, Gong G and Zhao J: L-arginine alleviates heat stress-induced mammary gland injury through modulating CASTOR1-mTORC1 axis mediated mitochondrial homeostasis. Sci Total Environ 926: 172017, 2024.
69. Wang J, Shen C, Zhao G, Hanigan MD and Li M: Dietary protein re-alimentation following restriction improves protein deposition via changing amino acid metabolism and transcriptional profiling of muscle tissue in growing beef bulls. Anim Nutr 19: 117-130, 2024.
70. Jung JW, Kim JE, Kim E and Lee JW: Amino acid transporters as tetraspanin TM4SF5 binding partners. Exp Mol Med 52: 7-14, 2020.
71. Jung JW, Macalino SJY, Cui M, Kim JE, Kim HJ, Song DG, Nam SH, Kim S, Choi S and Lee JW: Transmembrane 4 L six family member 5 senses arginine for mTORC1 signaling. Cell Metab 29: 1306-1319.e7, 2019.
72. Gu X, Orozco JM, Saxton RA, Condon KJ, Liu GY, Krawczyk PA, Scaria SM, Harper JW, Gygi SP and Sabatini DM: SAMTOR is an S-adenosylmethionine sensor for the mTORC1 pathway. Science 358: 813-818, 2017.
73. Kim SH, Choi JH, Wang P, Go CD, Hesketh GG, Gingras AC, Jafarnejad SM and Sonenberg N: Mitochondrial Threonyl-tRNA synthetase TARS2 is required for Threonine-sensitive mTORC1 activation. Mol Cell 81: 398-407.e4, 2021.
74. Wang D, Wan X, Du X, Zhong Z, Peng J, Xiong Q, Chai J and Jiang S: Insights into the Interaction of lysosomal amino acid transporters SLC38A9 and SLC36A1 involved in mTORC1 signaling in C2C12 Cells. Biomolecules 11: 1314, 2021.
75. Wang S, Tsun ZY, Wolfson RL, Shen K, Wyant GA, Plovanich ME, Yuan ED, Jones TD, Chantranupong L, Comb W, *et al*: Metabolism. Lysosomal amino acid transporter SLC38A9 signals arginine sufficiency to mTORC1. Science 347: 188-194, 2015.
76. Wang X, Zhang T, Li W, Wang H, Yan L, Zhang X, Zhao L, Wang N and Zhang B: Arginine alleviates Clostridium perfringens α toxin-induced intestinal injury in vivo and in vitro via the SLC38A9/mTORC1 pathway. Front Immunol 15: 1357072, 2024.
77. Dev G, Chawla AS, Gupta S, Bal V, George A, Rath S and Arimbasseri GA: Differential Regulation of two arms of mTORC1 pathway Fine-tunes global protein synthesis in resting B lymphocytes. Int J Mol Sci 23: 16017, 2022.
78. Knight JRP, Alexandrou C, Skalka GL, Vlahov N, Pennel K, Officer L, Teodosio A, Kanellos G, Gay DM, May-Wilson S, *et al*: MNK inhibition sensitizes KRAS-mutant colorectal cancer to mTORC1 inhibition by reducing eIF4E phosphorylation and c-MYC expression. Cancer Discov 11: 1228-1247, 2021.
79. Savukaitytė A, Gudoitytė G, Bartnykaitė A, Ugenskienė R and Juozaitytė E: siRNA knockdown of REDD1 facilitates Aspirin-mediated dephosphorylation of mTORC1 target 4E-BP1 in MDA-MB-468 human breast cancer cell line. Cancer Manag Res 13: 1123-1133, 2021.
80. Llanos S and García-Pedrero JM: A new mechanism of regulation of p21 by the mTORC1/4E-BP1 pathway predicts clinical outcome of head and neck cancer. Mol Cell Oncol 3: e1159275, 2016.
81. Amar-Schwartz A, Ben Hur V, Jbara A, Cohen Y, Barnabas GD, Arbib E, Siegfried Z, Mashahreh B, Hassouna F, Shilo A, *et al*: S6K1 phosphorylates Cdk1 and MSH6 to regulate DNA repair. ELife 11: e79128, 2022.
82. Yang L, Miao L, Liang F, Huang H, Teng X, Li S, Nuriddinov J, Selzer ME and Hu Y: The mTORC1 effectors S6K1 and 4E-BP play different roles in CNS axon regeneration. Nat Commun 5: 5416, 2014.
83. Jang SK, Kim G, Ahn SH, Hong J, Jin HO and Park IC: Duloxetine enhances the sensitivity of non-small cell lung cancer cells to EGFR inhibitors by REDD1-induced mTORC1/S6K1 suppression. Am J Cancer Res 14: 1087-1100, 2024.
84. Zhang X, Song W, Gao Y, Zhang Y, Zhao Y, Hao S and Ni T: The role of tumor metabolic reprogramming in tumor immunity. Int J Mol Sci 24: 17422, 2023.
85. Hanahan D and Weinberg RA: Hallmarks of cancer: The next generation. Cell 144: 646-674, 2011.
86. He L, Cho S and Blenis J: mTORC1, the maestro of cell metabolism and growth. Genes Dev 39: 109-131, 2025.
87. Vaidyanathan S, Salmi TM, Sathiqu RM, McConville MJ, Cox AG and Brown KK: YAP regulates an SGK1/mTORC1/SREBP-dependent lipogenic program to support proliferation and tissue growth. Dev Cell 57: 719-731.e8, 2022.
88. Solanki S, Sanchez K, Ponnusamy V, Kota V, Bell HN, Cho CS, Kowalsky AH, Green M, Lee JH and Shah YM: Dysregulated amino acid sensing drives colorectal cancer growth and metabolic reprogramming leading to chemoresistance. Gastroenterology 164: 376-391.e13, 2023.
89. Jin C, Zhu M, Ye J, Song Z, Zheng C and Chen W: Autophagy: Are amino acid signals dependent on the mTORC1 pathway or independent? Curr Issues Mol Biol 46: 8780-8793, 2024.
90. Zhao Z, Liu J, Gao X, Chen Z, Hu Y, Chen J, Zang W and Xue W: SCYL1-mediated regulation of the mTORC1 signaling pathway inhibits autophagy and promotes gastric cancer metastasis. J Cancer Res Clin Oncol 150: 456, 2024.
91. Tan HWS, Sim AYL and Long YC: Glutamine metabolism regulates autophagy-dependent mTORC1 reactivation during amino acid starvation. Nat Commun 8: 338, 2017.
92. Ro SH, Xue X, Ramakrishnan SK, Cho CS, Namkoong S, Jang I, Semple IA, Ho A, Park HW, Shah YM and Lee JH: Tumor suppressive role of sestrin2 during colitis and colon carcinogenesis. ELife 5: e12204, 2016.
93. Byun JK, Choi YK, Kim JH, Jeong JY, Jeon HJ, Kim MK, Hwang I, Lee SY, Lee YM, Lee IK and Park KG: A positive feedback loop between sestrin2 and mTORC2 is required for the survival of Glutamine-depleted lung cancer cells. Cell Rep 20: 586-599, 2017.
94. Shen S, Zhou H, Xiao Z, Zhan S, Tuo Y, Chen D, Pang X, Wang Y and Wang J: PRMT1 in human neoplasm: Cancer biology and potential therapeutic target. Cell Commun Signal 22: 102, 2024.
95. Zhou M, Huang Y, Xu P, Li S, Duan C, Lin X, Bao S, Zou W, Pan J, Liu C and Jin Y: PRMT1 promotes the Self-renewal of leukemia stem cells by regulating protein synthesis. Adv Sci (Weinh) 12: e2308586, 2025.

96. Yin JZ, Keszei AFA, Houliston S, Filandr F, Beenstock J, Daou S, Kitaygorodsky J, Schriemer DC, Mazhab-Jafari MT, Gingras AC and Sicheri F: The HisRS-like domain of GCN2 is a pseudoenzyme that can bind uncharged tRNA. Structure 32: 795-811.e6, 2024.
97. Kim Y, Sundrud MS, Zhou C, Edenius M, Zocco D, Powers K, Zhang M, Mazitschek R, Rao A, Yeo CY, *et al*: Aminoacyl-tRNA synthetase inhibition activates a pathway that branches from the canonical amino acid response in mammalian cells. Proc Natl Acad Sci USA 117: 8900-8911, 2020.
98. Brüggenthies JB, Fiore A, Russier M, Bitsina C, Brötzmann J, Kordes S, Menninger S, Wolf A, Conti E, Eickhoff JE and Murray PJ: A cell-based chemical-genetic screen for amino acid stress response inhibitors reveals torins reverse stress kinase GCN2 signaling. J Biol Chem 298: 102629, 2022.
99. Sannino S, Yates ME, Schurdak ME, Oesterreich S, Lee AV, Wipf P and Brodsky JL: Unique integrated stress response sensors regulate cancer cell susceptibility when Hsp70 activity is compromised. ELife 10: e64977, 2021.
100. Nelson AT, Cicardi ME, Markandaiah SS, Han JY, Philp NJ, Welebob E, Haeusler AR, Pasinelli P, Manfredi G, Kawamata H and Trotti D: Glucose hypometabolism prompts RAN translation and exacerbates C9orf72-related ALS/FTD phenotypes. EMBO Rep 25: 2479-2510, 2024.
101. Yuan J, Yu Z, Gao J, Luo K, Shen X, Cui B and Lu Z: Inhibition of GCN2 alleviates hepatic steatosis and oxidative stress in obese mice: Involvement of NRF2 regulation. Redox Biol 49: 102224, 2022.
102. Missiaen R, Anderson NM, Kim LC, Nance B, Burrows M, Skuli N, Carens M, Riscal R, Steensels A, Li F and Simon MC: GCN2 inhibition sensitizes arginine-deprived hepatocellular carcinoma cells to senolytic treatment. Cell Metab 34: 1151-1167.e7, 2022.
103. Stonyte V, Mastrangelopoulou M, Timmer R, Lindbergsengen L, Vietri M, Campsteijn C and Grallert B: The GCN2/eIF2αK stress kinase regulates PP1 to ensure mitotic fidelity. EMBO Rep 24: e56100, 2023.
104. Weber SL, Hustedt K, Schnepel N, Visscher C and Muscher-Banse AS: Modulation of GCN2/eIF2α/ATF4 pathway in the liver and induction of FGF21 in young goats fed a Protein- and/or Phosphorus-reduced diet. Int J Mol Sci 24: 7153, 2023.
105. Ge MK, Zhang C, Zhang N, He P, Cai HY, Li S, Wu S, Chu XL, Zhang YX, Ma HM, *et al*: The tRNA-GCN2-FBXO22-axis-mediated mTOR ubiquitination senses amino acid insufficiency. Cell Metab 35: 2216-2230.e8, 2023.
106. Müller MBD, Kasturi P, Jayaraj GG and Hartl FU: Mechanisms of readthrough mitigation reveal principles of GCN1-mediated translational quality control. Cell 186: 3227-3244.e20, 2023.
107. Bou-Nader C, Gaikwad S, Bahmanjah S, Zhang F, Hinnebusch AG and Zhang J: Gcn2 structurally mimics and functionally repurposes the HisRS enzyme for the integrated stress response. Proc Natl Acad Sci USA 121: e2409628121, 2024.
108. Ishimura R, Nagy G, Dotu I, Chuang JH and Ackerman SL: Activation of GCN2 kinase by ribosome stalling links translation elongation with translation initiation. ELife 5: e14295, 2016.
109. Inglis AJ, Masson GR, Shao S, Perisic O, McLaughlin SH, Hegde RS and Williams RL: Activation of GCN2 by the ribosomal P-stalk. Proc Natl Acad Sci USA 116: 4946-4954, 2019.
110. Piecyk M, Ferraro-Peyret C, Laville D, Perros F and Chaveroux C: Novel insights into the GCN2 pathway and its targeting. Therapeutic value in cancer and lessons from lung fibrosis development. FEBS J 291: 4867-4889, 2024.
111. Chen C, Xie Y and Qian S: Multifaceted role of GCN2 in tumor adaptation and therapeutic targeting. Transl Oncol 49: 102096, 2024.
112. Nofal M, Wang T, Yang L, Jankowski CSR, Hsin-Jung Li S, Han S, Parsons L, Frese AN, Gitai Z, Anthony TG, *et al*: GCN2 adapts protein synthesis to scavenging-dependent growth. Cell Syst 13: 158-172.e9, 2022.
113. St Paul M, Saibil SD, Kates M, Han S, Lien SC, Laister RC, Hezaveh K, Kloetgen A, Penny S, Guo T, *et al*: Ex vivo activation of the GCN2 pathway metabolically reprograms T cells, leading to enhanced adoptive cell therapy. Cell Rep Med 5: 101465, 2024.
114. Zhao L, Deng L, Zhang Q, Jing X, Ma M, Yi B, Wen J, Ma C, Tu J, Fu T and Shen J: Autophagy contributes to sulfonylurea herbicide tolerance via GCN2-independent regulation of amino acid homeostasis. Autophagy 14: 702-714, 2018.
115. Nakamura A, Nambu T, Ebara S, Hasegawa Y, Toyoshima K, Tsuchiya Y, Tomita D, Fujimoto J, Kurasawa O, Takahara C, *et al*: Inhibition of GCN2 sensitizes ASNS-low cancer cells to asparaginase by disrupting the amino acid response. Proc Natl Acad Sci USA 115: e7776-e7785, 2018.
116. Blagojevic B, Almouhanna F, Poschet G and Wölfl S: Cell Type-specific metabolic response to amino acid starvation dictates the role of Sestrin2 in regulation of mTORC1. Cells 11: 3863, 2022.
117. Ye J, Palm W, Peng M, King B, Lindsten T, Li MO, Koumenis C and Thompson CB: GCN2 sustains mTORC1 suppression upon amino acid deprivation by inducing Sestrin2. Genes Dev 29: 2331-2336, 2015.
118. Averous J, Lambert-Langlais S, Mesclon F, Carraro V, Parry L, Jousse C, Bruhat A, Maurin AC, Pierre P, Proud CG and Fafournoux P: GCN2 contributes to mTORC1 inhibition by leucine deprivation through an ATF4 independent mechanism. Sci Rep 6: 27698, 2016.
119. Carlson KR, Georgiadis MM, Tameire F, Staschke KA and Wek RC: Activation of Gcn2 by small molecules designed to be inhibitors. J Biol Chem 299: 104595, 2023.
120. Krall AS, Mullen PJ, Surjono F, Momcilovic M, Schmid EW, Halbrook CJ, Thambundit A, Mittelman SD, Lyssiotis CA, Shackelford DB, *et al*: Asparagine couples mitochondrial respiration to ATF4 activity and tumor growth. Cell Metab 33: 1013-1026.e6, 2021.
121. Kardos GR, Wastyk HC and Robertson GP: Disruption of proline synthesis in melanoma inhibits protein production mediated by the GCN2 pathway. Mol Cancer Res 13: 1408-1420, 2015.
122. Vynnytska-Myronovska BO, Kurlishchuk Y, Chen O, Bobak Y, Dittfeld C, Hüther M, Kunz-Schughart LA and Stasyk OV: Arginine starvation in colorectal carcinoma cells: Sensing, impact on translation control and cell cycle distribution. Exp Cell Res 341: 67-74, 2016.
123. Ren W, Li Y, Xia X, Guo W, Zhai T, Jin Y, Che Y, Gao H, Duan X, Ma H, *et al*: Arginine inhibits the malignant transformation induced by interferon-gamma through the NF-κB-GCN2/eIF2α signaling pathway in mammary epithelial cells in vitro and in vivo. Expl Cell Res 368: 236-247, 2018.
124. Cordova RA, Misra J, Amin PH, Klunk AJ, Damayanti NP, Carlson KR, Elmendorf AJ, Kim HG, Mirek ET, Elzey BD, *et al*: GCN2 eIF2 kinase promotes prostate cancer by maintaining amino acid homeostasis. ELife 11: e81083, 2022.
125. Chen C and Zhang J: Enhancing leukemia treatment: The role of combined therapies based on amino acid starvation. Cancers (Basel) 16: 1171, 2024.
126. Szczygiel M, Derewenda U, Scheiner S, Minor W and Derewenda ZS: A structural role for tryptophan in proteins, and the ubiquitous Trp Cδ1-H...O=C (backbone) hydrogen bond. Acta Crystallogr D Struct Biol 80: 551-562, 2024.
127. Basson C, Serem JC, Hlophe YN and Bipath P: The tryptophan-kynurenine pathway in immunomodulation and cancer metastasis. Cancer Med 12: 18691-18701, 2023.
128. Hanif N and Sari S: Discovery of novel IDO1/TDO2 dual inhibitors: A consensus Virtual screening approach with molecular dynamics simulations, and binding free energy analysis. J Biomol Struct Dyn 43: 6954-6970, 2025.
129. Thapa K, Khan H, Kaur G, Kumar P and Singh TG: Therapeutic targeting of angiopoietins in tumor angiogenesis and cancer development. Biochem Biophys Res Commun 687: 149130, 2023.
130. Longchamp A, Mirabella T, Arduini A, MacArthur MR, Das A, Treviño-Villarreal JH, Hine C, Ben-Sahra I, Knudsen NH, Brace LE, *et al*: Amino acid restriction triggers angiogenesis via GCN2/ATF4 regulation of VEGF and H2S production. Cell 173: 117-129.e14, 2018.
131. Hsu CC, Tseng LM and Lee HC: Role of mitochondrial dysfunction in cancer progression. Exp Biol Med (Maywood) 241: 1281-1295, 2016.
132. Quirós PM, Mottis A and Auwerx J: Mitonuclear communication in homeostasis and stress. Nat Rev Mol Cell Biol 17: 213-226, 2016.
133. Liu Q, Zhu J, Abulizi G and Hasim A: Metabolism and spatial transcription resolved heterogeneity of glutamine metabolism in cervical carcinoma. BMC Cancer 24: 1504, 2024.
134. Li J, Chen Y, Yang Y, Yang Y and Wu Z: High-level L-Gln compromises intestinal amino acid utilization efficiency and inhibits protein synthesis by GCN2/eIF2α/ATF4 signaling pathway in piglets fed low-crude protein diets. Anim Nutr 19: 480-487, 2024.
135. Patel R, Alfarsi LH, El-Ansari R, Masisi BK, Erkan B, Fakroun A, Ellis IO, Rakha EA and Green AR: ATF4 as a prognostic marker and modulator of glutamine metabolism in oestrogen Receptor-positive breast cancer. Pathobiology 91: 411-421, 2024.

136. Chen J, Huang X, Zhang S and Zhu X: ATF4 inhibits tumor development and mediates p-GCN2/ASNS upregulation in colon cancer. Sci Rep 14: 13042, 2024.
137. Jin HO, Hong SE, Kim JY, Jang SK and Park IC: Amino acid deprivation induces AKT activation by inducing GCN2/ATF4/REDD1 axis. Cell Death Dis 12: 1127, 2021.
138. Zhao C, Guo H, Hou Y, Lei T, Wei D and Zhao Y: Multiple roles of the stress sensor GCN2 in immune cells. Int J Mol Sci 24: 4285, 2023.
139. Bartok O, Pataskar A, Nagel R, Laos M, Goldfarb E, Hayoun D, Levy R, Körner PR, Kreuger IZM, Champagne J, *et al*: Anti-tumour immunity induces aberrant peptide presentation in melanoma. Nature 590: 332-337, 2021.
140. Halaby MJ, Hezaveh K, Lamorte S, Ciudad MT, Kloetgen A, MacLeod BL, Guo M, Chakravarthy A, Medina TDS, Ugel S, *et al*: GCN2 drives macrophage and MDSC function and immunosuppression in the tumor microenvironment. Sci Immunol 4: eaax8189, 2019.
141. Gauthier-Coles G, Rahimi F, Bröer A and Bröer S: Inhibition of GCN2 Reveals Synergy with Cell-Cycle Regulation and Proteostasis. Metabolites 13: 1064, 2023.
142. Zhang CW, Wang YN and Ge XL: Lenalidomide use in multiple myeloma (review). Mol Clin Oncol 20: 7, 2024.
143. Chattopadhyay N, Berger AJ, Koenig E, Bannerman B, Garnsey J, Bernard H, Hales P, Maldonado Lopez A, Yang Y, Donelan J, *et al*: KRAS genotype correlates with proteasome inhibitor ixazomib activity in preclinical in vivo models of colon and Non-small cell lung cancer: Potential role of tumor metabolism. PLoS One 10: e0144825, 2015.
144. Saavedra-García P, Roman-Trufero M, Al-Sadah HA, Blighe K, López-Jiménez E, Christoforou M, Penfold L, Capece D, Xiong X, Miao Y, *et al*: Systems level profiling of chemotherapy-induced stress resolution in cancer cells reveals druggable trade-offs. Proc Natl Acad Sci USA 118: e2018229118, 2021.
145. Punnasseril JMJ, Auwal A, Gopalan V, Lam AK and Islam F: Metabolic reprogramming of cancer cells and therapeutics targeting cancer metabolism. Cancer Med 14: e71244, 2025.
146. Darawshi O, Yassin O, Shmuel M, Wek RC, Mahdizadeh SJ, Eriksson LA, Hatzoglou M and Tirosh B: Phosphorylation of GCN2 by mTOR confers adaptation to conditions of hyper-mTOR activation under stress. J Biol Chem 300: 107575, 2024.
147. Li Q, Chen J, Liu J, Lin T, Liu X, Zhang S, Yue X, Zhang X, Zeng X and Ren M: Leucine and arginine enhance milk fat and milk protein synthesis via the CaSR/Gi/mTORC1 and CaSR/Gq/mTORC1 pathways. Eur J Nutr 62: 2873-2890, 2023.
148. Wang D, Chu WK, Yam JCS, Pang CP, Leung YC, Shum ASW and Chan SO: GCN2-SLC7A11 axis coordinates autophagy, cell cycle and apoptosis and regulates cell growth in retinoblastoma upon arginine deprivation. Cancer Metab 12: 31, 2024.
149. Mossmann D, Müller C, Park S, Ryback B, Colombi M, Ritter N, Weißenberger D, Dazert E, Coto-Llerena M, Nuciforo S, *et al*: Arginine reprograms metabolism in liver cancer via RBM39. Cell 186: 5068-5083.e23, 2023.
150. Carpentier J, Pavlyk I, Mukherjee U, Hall PE and Szlosarek PW: Arginine deprivation in SCLC: Mechanisms and perspectives for therapy. Lung Cancer (Auckl) 13: 53-66, 2022.
151. Chen T, Xu Y, Yang F, Pan Y, Ji N, Li J, Zeng X, Chen Q, Jiang L and Shen YQ: Crosstalk of glutamine metabolism between cancer-associated fibroblasts and cancer cells. Cell Signal 133: 111874, 2025.
152. Kim DH, Kim DJ, Park SJ, Jang WJ and Jeong CH: Inhibition of GLS1 and ASCT2 synergistically enhances the anticancer effects in pancreatic cancer cells. J Microbiol Biotechnol 35: e2412032, 2025.
153. Pu X, Wu Y, Long W, Sun X, Yuan X, Wang D, Wang X and Xu M: The m6A reader IGF2BP2 promotes pancreatic cancer progression through the m6A-SLC1A5-mTORC1 axis. Cancer Cell Int 25: 122, 2025.
154. Ihlamur M, Akgul B, Zengin Y, Korkut ŞV, Kelleci K and Abamor E: The mTOR signaling pathway and mTOR inhibitors in cancer: Next-generation inhibitors and approaches. Curr Mol Med 24: 478-494, 2024.
155. Marafie SK, Al-Mulla F and Abubaker J: mTOR: Its critical role in metabolic diseases, cancer, and the aging process. Int J Mol Sci 25: 6141, 2024.
156. Hassan B, Akcakanat A, Sangai T, Evans KW, Adkins F, Eterovic AK, Zhao H, Chen K, Chen H, Do KA, *et al*: Catalytic mTOR inhibitors can overcome intrinsic and acquired resistance to allosteric mTOR inhibitors. Oncotarget 5: 8544-8557, 2014.
157. Powles T, Wheater M, Din O, Geldart T, Boleti E, Stockdale A, Sundar S, Robinson A, Ahmed I, Wimalasingham A, *et al*: A Randomised phase 2 study of AZD2014 versus everolimus in patients with VEGF-refractory metastatic clear cell renal cancer. Eur Urol 69: 450-456, 2016.
158. Taeb S, Rostamzadeh D, Amini SM, Rahmati M, Eftekhari M, Safari A and Najafi M: MicroRNAs targeted mTOR as therapeutic agents to improve radiotherapy outcome. Cancer Cell Int 24: 233, 2024.
159. Cai Y, Xu G, Wu F, Michelini F, Chan C, Qu X, Selenica P, Ladewig E, Castel P, Cheng Y, *et al*: Genomic alterations in PIK3CA-mutated breast cancer result in mTORC1 activation and limit the sensitivity to PI3Kα inhibitors. Cancer Res 81: 2470-2480, 2021.
160. Jia W, Luo S, Guo H and Kong D: Development of PI3Kα inhibitors for tumor therapy. J Biomol Struct Dyn 41: 8587-8604, 2023.
161. Kearney AL and Vasan N: A new wave of PI3Kα inhibitors. Cancer Discov 13: 2313-2315, 2023.
162. Watanabe T: Recent advances in treatment of follicular lymphoma: Efficacy of PI3Kα/δ inhibitor (TQ-B3525). Signal Transduct Target Ther 9: 134, 2024.
163. Heydt Q, Xintaropoulou C, Clear A, Austin M, Pislariu I, Miraki-Moud F, Cutillas P, Korfi K, Calaminici M, Cawthorn W, *et al*: Adipocytes disrupt the translational programme of acute lymphoblastic leukaemia to favour tumour survival and persistence. Nat Commun 12: 5507, 2021.
164. Duan Z, Yang M, Yang J, Wu Z, Zhu Y, Jia Q, Ma X, Yin Y, Zheng J, Yang J, *et al*: AGFG1 increases cholesterol biosynthesis by disrupting intracellular cholesterol homeostasis to promote PDAC progression. Cancer Lett 598: 217130, 2024.
165. Mijit M, Boner M, Cordova RA, Gampala S, Kpenu E, Klunk AJ, Zhang C, Kelley MR, Staschke KA and Fishel ML: Activation of the integrated stress response (ISR) pathways in response to Ref-1 inhibition in human pancreatic cancer and its tumor microenvironment. Front Med (Lausanne) 10: 1146115, 2023.
166. Drainas AP, Hsu WH, Dallas AE, Poltorack CD, Kim JW, He A, Coles GL, Baron M, Bassik MC and Sage J: GCN2 is a determinant of the response to WEE1 kinase inhibition in small-cell lung cancer. Cell Rep 43: 114606, 2024.
167. Wu T, Yu Z, Dai J, Li J, Ning F, Liu X, Zhu N and Zhang X: JPH203 alleviates peritoneal fibrosis via inhibition of amino acid-mediated mTORC1 signaling. Biochem Biophys Res Commun 734: 150656, 2024.
168. Bo T, Kobayashi S, Inanami O, Fujii J, Nakajima O, Ito T and Yasui H: LAT1 inhibitor JPH203 sensitizes cancer cells to radiation by enhancing radiation-induced cellular senescence. Transl Oncol 14: 101212, 2021.
169. Häfliger P, Graff J, Rubin M, Stooss A, Dettmer MS, Altmann KH, Gertsch J and Charles RP: The LAT1 inhibitor JPH203 reduces growth of thyroid carcinoma in a fully immunocompetent mouse model. J Exp Clin Cancer Res 37: 234, 2018.
170. Okano N, Naruge D, Kawai K, Kobayashi T, Nagashima F, Endou H and Furuse J: First-in-human phase I study of JPH203, an L-type amino acid transporter 1 inhibitor, in patients with advanced solid tumors. Invest New Drugs 38: 1495-1506, 2020.
171. Zhang Z, Liu R, Shuai Y, Huang Y, Jin R, Wang X and Luo J: ASCT2 (SLC1A5)-dependent glutamine uptake is involved in the progression of head and neck squamous cell carcinoma. Br J Cancer 122: 82-93, 2020.
172. Chen XY, Chen X, Liang XH, Lu D, Pan RR, Xiong QY, Liu XX, Lin JY, Zhang LJ, Chen HZ, *et al*: Yuanhuacine suppresses head and neck cancer growth by promoting ASCT2 degradation and inhibiting glutamine uptake. Acta Pharmacol Sin 46: 2779-2792, 2025.
173. Barisaac AS, Abu-Zhayia ER and Ayoub N: Leveraging valine-restriction-induced DNA damage for targeted cancer therapy. Mol Cell 85: 468-470, 2025.