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Amino acid metabolism in glioblastoma pathogenesis, immune evasion, and treatment resistance

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Abstract

Glioblastoma (GBM) ranks among the most lethal primary tumors of the central nervous system. This is partly due to its complex intracellular metabolism and interactions with the surrounding tumor microenvironment (TME). Compelling evidence represents that altered amino acids (AAs) metabolism plays a crucial role in both areas. The role of AAs and their metabolites in glioma biology is an emerging topic. Therefore, this review was conducted to summarize the current knowledge about the molecular mechanisms by which AAs participate in the GBM pathogenesis. AAs can directly influence tumor progression by affecting tumor cell metabolism or indirectly by releasing bioactive agents through particular metabolic pathways. This review begins by examining the metabolic pathways of essential AAs, such as tryptophan, tyrosine, and phenylalanine, which contribute to synthesizing critical neurotransmitters and shape tumor metabolism signatures. We explore how these pathways impact tumor growth and immune modulation, focusing on how AAs and their metabolites can promote malignant properties in GBM cells. AAs also play a pivotal role in reprogramming the TME, contributing to immune evasion and resistance to therapy. The review further discusses how tumor metabolism signatures, influenced by AA metabolism, can enhance the immunosuppressive microenvironment, providing new avenues for targeted immunotherapies. Finally, we outline potential therapeutic strategies to modulate AA metabolism and emphasize critical opportunities for future research to improve GBM management.

Introduction

Glioblastoma (GBM) remains one of the most clinically aggressive human malignancies, characterized by its rapid progression, resistance to conventional therapies, and dismal prognosis, making it a critical target for innovative therapeutic strategies [1]. The prognosis for patients with GBM has gradually improved with advances in treatment strategies. Initially, survival was limited to surgery alone [2], followed by surgery and radiotherapy [3]. The addition of nitrosourea-based chemotherapy to radiotherapy further improved survival outcomes [4]. The next significant advancement was the combination

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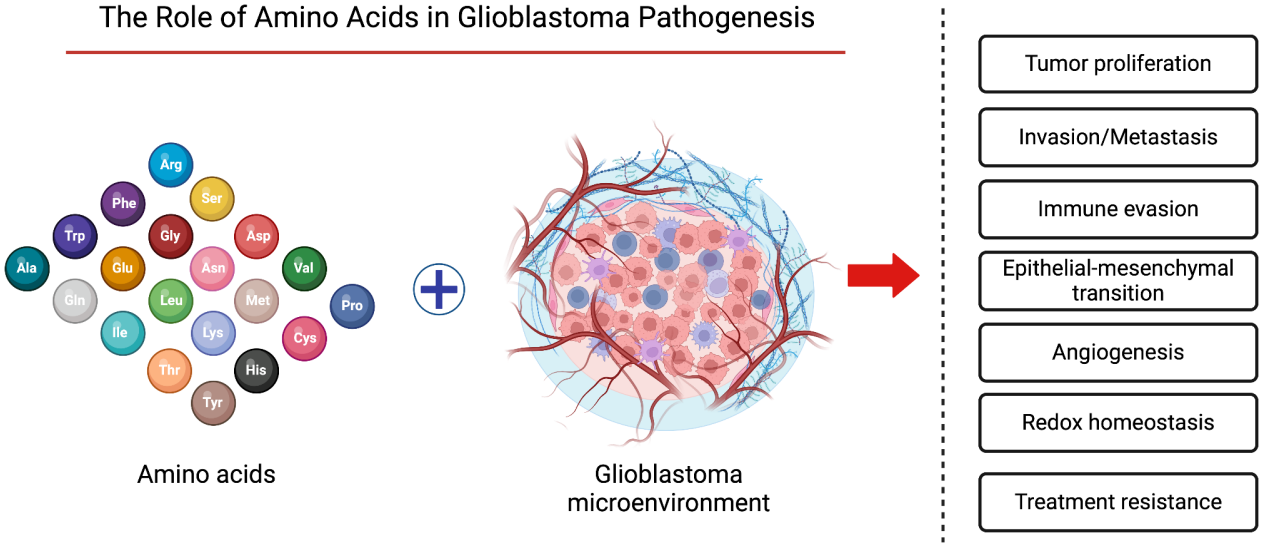
Graphical abstract



Keywords Glioblastoma, Amino acids, Tumor microenvironment, Metabolic pathways, Immunosuppression

of surgery, chemoradiation with temozolomide (TMZ), and adjuvant TMZ as demonstrated in the Stupp et al. trial, which resulted in a median survival of 14.6 months [5]. More recently, the incorporation of tumor treating fields (TTF) during adjuvant TMZ chemotherapy extended the median survival to 20.9 months [6]. Despite these advancements, the prognosis for GBM remains dismal, with median survival still falling short of two years in most patients. Despite breakthroughs in immunotherapy for other malignancies, these approaches have shown limited efficacy in GBM. This is mainly due to the complex interactions between tumor cells and their surrounding tumor microenvironment (TME) [7]. The TME is a dynamic network of cellular and non-cellular components reprogrammed by the tumor to promote growth, progression, and therapeutic resistance [8].

Amino acids (AAs), the building blocks of proteins, play essential roles in cell division, differentiation, and function, and their metabolism is frequently dysregulated in many diseases, including neoplastic disorders such as GBM [9, 10]. In the glioblastoma TME, AAs influence tumor growth and progression both through paracrine signaling, as exemplified by glutamate, and through direct neuron-to-glioma synapses, as seen with norepinephrine–a metabolite of phenylalanine [11].

These AA-driven signals mediate the interplay between glioma cells and their surrounding environment, affecting tumor growth [12], invasion [13], and resistance to therapies [14]. This review explores the critical role of AA metabolism in glioma biology, focusing on how AAs contribute to TME reprogramming and therapeutic resistance, intending to uncover new strategies for improving GBM treatment outcomes.

Molecular biology of glioblastoma cells and their surrounding microenvironment

Glioma cells are metabolically rewired and heavily dependent on metabolites to support their high growth demands for proliferation and invasion. Figure 1 provides a general overview of the signaling pathways involved in GBM pathogenesis.

Signaling pathways and cellular proliferation

The phosphoinositide 3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/Akt/mTOR) signaling pathway is a central driver of GBM biology, promoting cell proliferation, growth, and survival [15]. Activation of receptor tyrosine kinases (RTKs), such as epidermal growth factor receptor (EGFR), initiates the phosphorylation of PI3K, which subsequently activates Akt. This cascade leads to the activation of mTOR, a key regulator of protein synthesis, metabolic reprogramming, and cell growth. In GBM, common alterations, such as EGFR amplification [16] and phosphatase and tensin homolog (PTEN) loss [17], enhance PI3K/Akt/mTOR signaling, resulting in uncontrolled tumor proliferation and progression.

Crosstalk with metabolism and hypoxia

The PI3K/Akt pathway is intricately linked to metabolic reprogramming in GBM, facilitating the *Warburg effect* and resulting in glycolysis [18]. Akt activation promotes

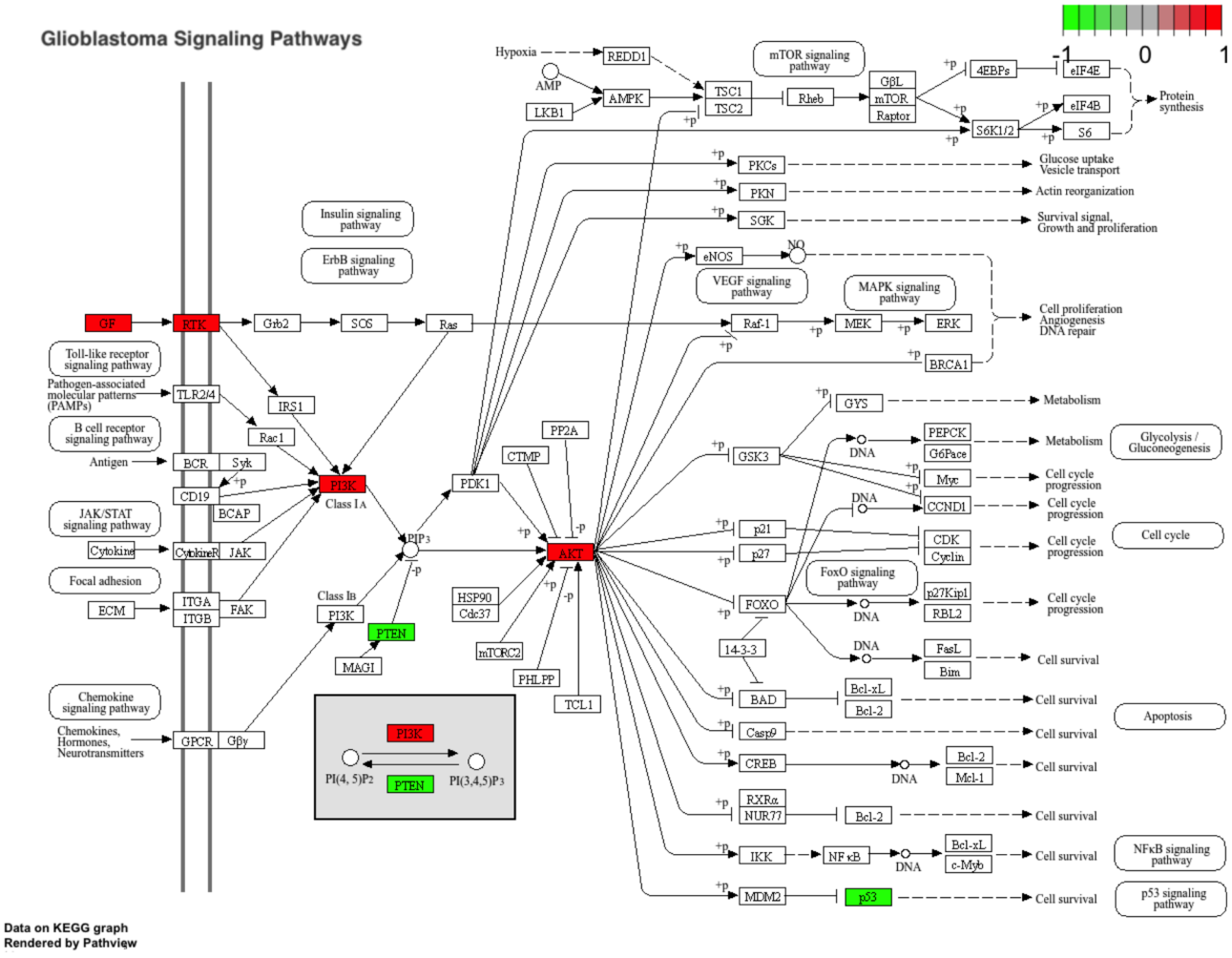


Fig. 1 Glioblastoma signaling pathways. The figure illustrates the PI3K/Akt signaling pathway, a key regulator of GBM biology, highlighting its role in cellular proliferation, survival, metabolism, and angiogenesis. Key components such as receptor tyrosine kinases (RTKs), PI3K, Akt, mTOR, and downstream effectors involved in cell cycle regulation, apoptosis inhibition, and metabolic reprogramming are shown. The highlighted nodes represent specific gene alterations relevant to GBM pathogenesis and therapeutic resistance. (The figure is generated using R programming with the "*pathview*" package to visualize gene expression data on the KEGG pathway map)

glucose uptake and utilization, as evidenced by the upregulation of glycogen synthase (GYS) and 6-phosphofructo-2-kinase/fructose-2,6-bisphosphatase 3 (PFKFB3) to facilitate glucose metabolism [19]. Hypoxia-induced factors (HIF-1α and HIF-2α) amplify PI3K/Akt signaling under low oxygen conditions, ensuring tumor survival and adaptation to hypoxic niches commonly observed in GBM. This metabolic flexibility contributes to the tumor's aggressiveness and resistance to therapy [20].

According to the 2021 World Health Organization (WHO) classification, adult-type diffuse gliomas are further categorized based on their IDH (isocitrate dehydrogenase) mutation status, which significantly affect their metabolic profiles [21]. IDH wild-type glioma (commonly referred to as GBM) characterized by producing α-KG (α-ketoglutarate), is more aggressive, exhibits poorer prognosis, relies heavily on glycolysis, and is highly adaptable to hypoxic conditions. In contrast, IDH-mutant gliomas convert α-KG into 2-HG (2-hydroxyglutarate), which disrupts normal metabolic processes and epigenetic regulation, resulting in slower tumor progression and greater therapeutic sensitivity [22]. In addition, the produced 2-HG reduces the tumor pathogenesis by downregulating HIF-1 expression [23] and improves immune response by epigenetically silencing PD-L1 (programmed cell death ligand 1) expression on cancer cells [24]. These distinct metabolic reprogramming patterns highlight the critical role of IDH status in glioma pathophysiology and therapeutic design.

Cell cycle regulation

Downstream of Akt, cell cycle regulation is mediated by CCND1 (cyclin D1)/Cdk4 (cyclin-dependent kinase 4)/Rb (retinoblastoma) signaling pathway. GBM cells exploit

this pathway to bypass cell cycle checkpoints, particularly at the $G_{1/S}$ transition [25, 26]. Moreover, Akt suppresses cell cycle inhibitors such as p21 and p27, further promoting unchecked cell cycle progression and tumor growth [27].

Promoting survival and Anti-apoptotic mechanisms

The PI3K/Akt pathway is a key mediator of anti-apoptotic signaling in GBM. Akt phosphorylates and inactivates pro-apoptotic factors, such as BAD (Bcl-2 associated agonist of cell death) and Caspase-3, while upregulating anti-apoptotic proteins like Bcl-2 (B-cell lymphoma 2) and Mcl-1 (Myeloid cell leukemia-1) [28, 29]. This ensures tumor cell survival even under therapeutic stress. Furthermore, Akt-induced activation of the NF-κB pathway contributes to inflammation and enhanced survival mechanisms in GBM cells [30].

Angiogenesis and tumor microenvironment

GBM exhibits robust angiogenesis mediated through VEGF (vascular endothelial growth factor) signaling [31]. Akt activation enhances the expression of VEGF, stimulating endothelial cell proliferation and blood vessel formation in a Forkhead box O3a (FOXO3a)-dependent manner [32]. Angiogenesis is further amplified by hypoxia-driven CXCR4 (C-X-C chemokine receptor type 4) activity [33]. Different TME components enhance GBM progression by activating pathogenic signaling pathways. For example, cancer-associated fibroblasts (CAFs) enhance GBM invasion and migration by releasing interleukin-6 (IL-6), which activates the Janus kinase/signal transducer and activator of transcription 3 (JAK/STAT3) signaling pathway in GBM cells [34, 35]. In addition, an interaction with extracellular matrix (ECM) components, such as integrins, further facilitates GBM invasion and angiogenesis [36].

Immunosurveillance

The intrinsic immune evasion of GBM is partly attributed to the hyperactivation of the PI3K/Akt pathway. Du et al. demonstrated that PI3K/Akt activation would convey PD-L1 expression in GBM cells [37]. Additionally, PI3K/Akt activation can inhibit T cell proliferation [38], making PI3K/Akt an attractive target for therapeutic intervention.

Other signaling pathways

Other signaling pathways may also be involved in the GBM pathogenesis. A study based on a machine-learning model demonstrated that 47% of the MAPK (mitogen-activated protein kinase) pathway genes are overexpressed in glioma. This study showed that overexpressed genes can improve cancer survival and stemness and characterize the immune microenvironment [39]. Another experimental study showed that NIMA-related kinase 2/nuclear factor kappa-light-chain-enhancer of activated B cells (NEK2/NF-κB) axis is activated in GBM contributing to its prolifearion, invasion, and migration [40].

The intricate biology of GBM reflects the complex interplay of signaling pathways such as PI3K/Akt/mTOR, MAPK, and NF-κB, which drive tumor proliferation, metabolic reprogramming, immune evasion, and angiogenesis. This multifaceted network supports GBM progression and underscores its adaptability and resistance to therapies, emphasizing the critical need for targeted, multi-pathway therapeutic approaches.

Amino acids: Synthesis pathways and physiological functions in human cells

AAs are organic compounds constituting the building blocks of proteins and play crucial roles in various biological processes. According to their source, AAs are classified into essential and nonessential categories (Fig. 2). Essential AAs, such as phenylalanine, leucine, and tryptophan, cannot be synthesized by the human body and must be supplied through diet. In contrast, nonessential AAs, like glutamate, aspartate, and alanine, can be generated by human cells, typically by transamination reaction, through which amino groups are transferred from donor molecules to keto acids, forming new AAs. Some AAs, such as glutamine, cysteine, and tyrosine, are *conditionally essential* and must be supplied by the diet during periods of stress or illness [41].

In human cells, AAs are indispensable for numerous physiological functions. They are building blocks of structural and enzymatic proteins essential for cellular proliferation, differentiation, function, and repair. In addition, AAs (alanine and glutamine) can enter the gluconeogenesis pathway in hepatocytes, ensuring energy supply during stressful conditions [42]. They also play a pivotal role in immune regulation by supporting the production of antibodies and cytokines and providing enough energy for immune function [43]. Moreover, AAs can function as neurotransmitters themselves, such as gamma-aminobutyric acid (GABA) and glycine, or be converted into catecholamines (from phenylalanine) and serotonin (from tryptophan) [44]. Several AAs, such as glutamate, alanine, and branched chain AAs (leucine, isoleucine, and valine), are also involved in adenosine triphosphate (ATP) production, which is the primary energy currency of human cells, and in the regeneration of glutathione (e.g., cysteine, glycine, and glutamate), which protect cells from oxidative stress [45].

Figure 2.

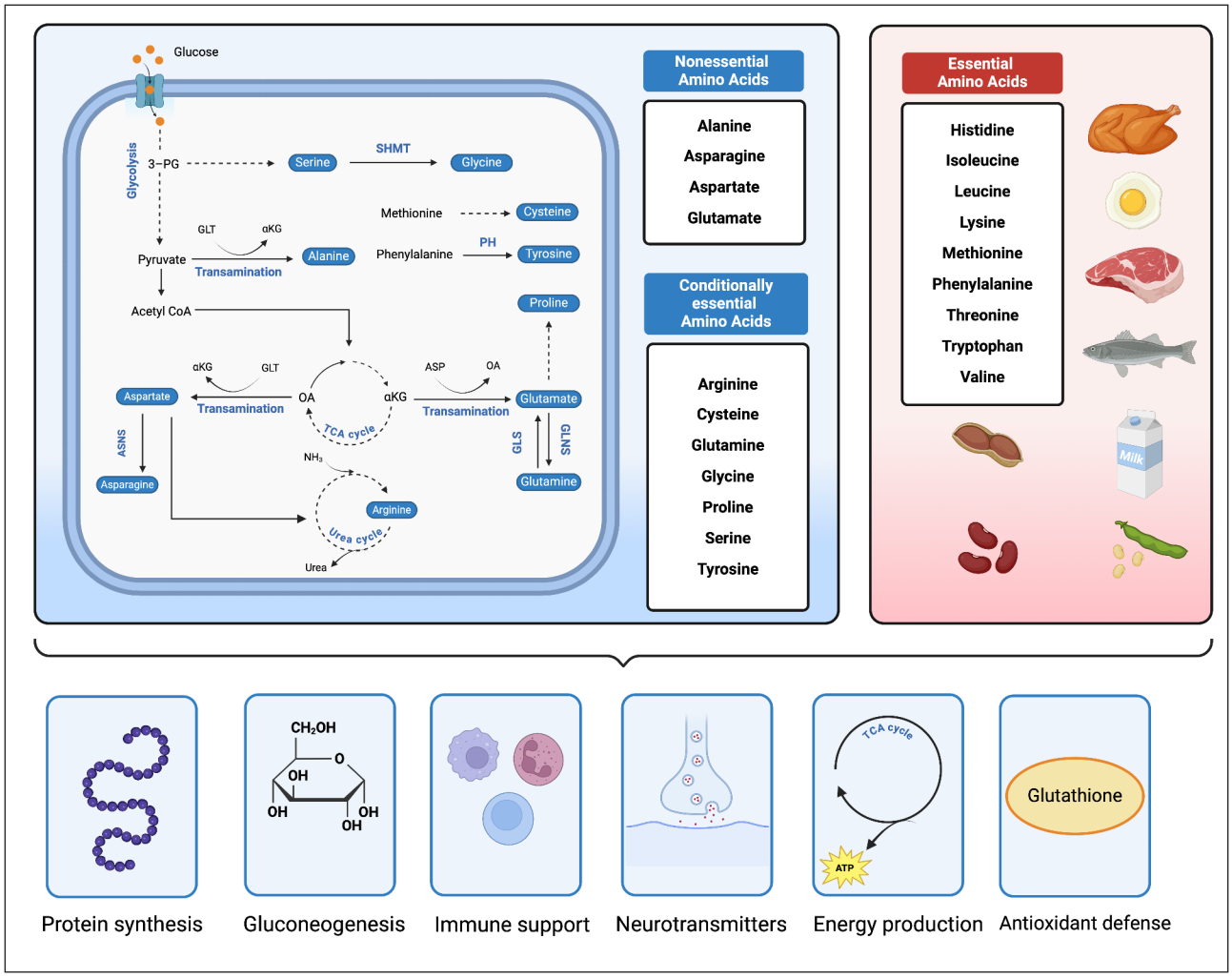


Fig. 2 Biochemical pathways of amino acid metabolism and their physiologic functions. αKG indicates α-ketoglutarate; ASNS, asparagine synthetase; ASP, aspartate; ATP, adenosine triphosphate; GLNS, glutathione synthetase; GLT, glutathione; OA, oxaloacetate; PH, phenylalanine hydroxylase; SHMT, serine hydroxymethyltransferase

The role of amino acids metabolism in glioblastoma biology, immunosurveillance, and treatment resistance

GBM is characterized by malignant proliferative cells in an immunosuppressive TME. Meanwhile, AA metabolism significantly contributes to tumor development and progression (Fig. 3).

Tryptophan

A crucial factor influencing GBM progression is tryptophan (Trp) metabolism (Fig. 3). Trp is an essential AA metabolized in human cells through three main pathways: (a) the kynurenine pathway, which produces neuroactive metabolites; (b) the serotonin pathway, which synthesizes the neurotransmitters serotonin and melatonin; and (c) the indole pathway, releasing indole-3-pyruvate [46].

Kynurenine pathway

The kynurenine (Kyn) pathway is the major pathway for the catabolism of Trp into bioactive metabolites, with Kyn being the primary product. The initial phase of the Kyn pathway is facilitated by the Trp-catabolic enzymes (TCEs), including indoleamine 2,3-dioxygenase (IDO1/2) and tryptophan-2,3-dioxygenase (TDO2). When TCEs are overexpressed, Trp level drops and Kyn builds up in cancer and TME cells. The produced Kyn is then absorbed into the bloodstream through the highly permeable blood-brain barrier (BBB), raising the plasma Kyn to Trp ratio. After that, Kyn can be converted to kynurenic acid (KynA) with the help of kynurenine aminotransferases and 3-hydroxyanthranilic acid by kynureninase. The aryl hydrocarbon receptor (AhR) is a transcription factor activated by specific metabolites like Kyn and KynA. Once activated, AhR stimulates the transcription of its target genes, eventually resulting in

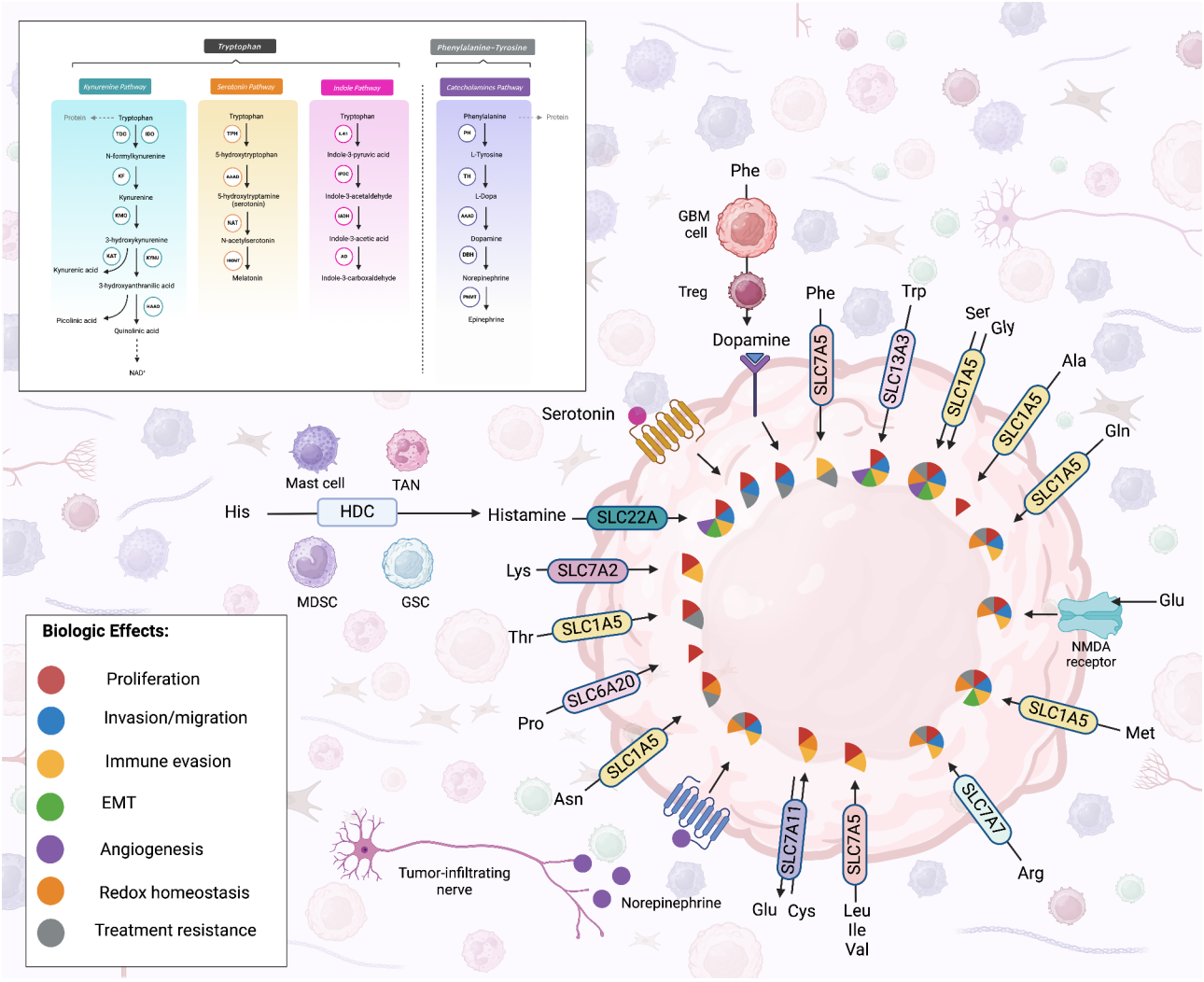


Fig. 3 The biologic effects of amino acid metabolism on glioblastoma cells pathogenesis in the context of tumor microenvironment. The colour slices inside the glioblastoma cell represents the biologic effects of amino acids, representing in the lower-left panel. The upper-left box represents the metabolism of tryptophane and phenylalanine. AAAD indicates aromatic L-amino acid decarboxylase; Ala, alanine; AO, aldehyde oxidase; Arg, arginine; Asn, asparagine; Cys, cysteine; DBH, dopamine β-hydroxylase; GBM, glioblastoma; Gln, glutamine; Glu, glutamate; GSC, glioblastoma stem cells; HDC, histidine decarboxylase HIOMT, hydroxyindole O-methyltransferase; HAAO, 3-hydroxyanthranilate 3,4-dioxygenase; IDO, indoleamine 2,3-dioxygenase; IADH, indoleamine 2,3-dioxygenase; IL4i1, interleukin-4-induced 1; IPDC, indole-3-pyruvate decarboxylase; KAT, kynurenine aminotransferase; KF, kynurenine formamidase; KMO, kynurenine 3-monooxygenase; KNYU, kynureninase; Leu, leucine; Lys, lysine; Met, methionine; MDSC, myeloid-derived suppressor cells; NAT, N-acetyltransferase; Phe, phenylalanine; PH, phenylalanine hydroxylase; Pro, proline; Ser, serine; SLC, solute carrier; TAN, tumor-associated neutrophils; TH, tyrosine hydroxylase; TDO, tryptophan 2,3-dioxygenase; TPH, tryptophan hydroxylase; Treg, regulatory T cell; Trp, tryptophan; Val, valine

glioma formation, progression, and immune evasion [47]. Quinolinic acid, along with other neuroactive and neurotoxic metabolites of the Kyn pathway, is produced when kynurenine monooxygenase (KMO) catalyzes the conversion of Kyn. Certain cell types can convert quinolinic acid into nicotinamide adenine dinucleotide (NAD^+), an essential cofactor in energy metabolism [48]. However, as NAD^+ is mainly created by salvage, the physiological significance of the new NAD^+ generation by the Kyn pathway must be discovered.

In healthy adult central nervous system cells, these enzymes are typically not produced at significant levels [49]. Ozawa et al. demonstrated that IDO1 is highly expressed in glioma stem cells [50]. In addition, Oldak et al. found that Trp metabolites are significantly higher in grade 4 glioma than in grades 2–3 [51]. It has been demonstrated that TCEs become activated in response to persistent immunological surveillance and are associated with poor overall survival in patients with GBM [52–54]. In support, Zhang et al. demonstrated that Trp metabolism-related genes could significantly predict the prognosis of patients with glioma [55].

Figure 3 represents the impact of Trp metabolism on glioma cells and TME. Evidence supports that Trp

metabolism enhances glioma cell proliferation and malignancy [56]. TDO2 overexpression in glioma cells increases Trp metabolism through the Kyn pathway, leading to the release of bioactive metabolites such as 3-hydroxykynurenine, L-kynurenine, 3-hydroxy anthranilic acid, and quinolinic acid. These metabolites promote glioma cells' proliferation and tumorigenic potential by activating the AhR/Akt signaling pathway [57]. Kyn-dependent Akt activation can also promote the invasion of glioma cells by activating epithelial-mesenchymal transition (EMT) through the Akt/cAMP response element-binding protein (CREB) signaling pathway [57]. The Kyn pathway can also improve glioma cell resistance. Hanihara et al. demonstrated that IDO1 upregulation can improve the chemoresistance in GBM cells. They realized that adding an IDO1 antagonist can improve the TMZ cytotoxicity in a murine glioma model [49]. Recently, Bickerdike et al. demonstrated that a dual IDO1/TDO2 blocker (AT-0174) can improve a mouse glioma model's TMZ response rate and survival rate [58].

The Trp metabolism derivatives can suppress antitumor immunity [59]. There are several possible ways by which TCE activation contributes to immunosuppression: (a) Trp is an essential nutrient for immune cell function. Therefore, Trp depletion impairs antitumor immune response; (b) Kyn is an immunomodulatory agent, and its elevation can induce tumor antigen-presenting dendritic cells to die, T cell apoptosis, along a noticeable rise in immunosuppressive programming; (c) Kyn can also increase the programmed cell death protein 1 (PD-1) levels on cluster of differentiation 8 ($CD8^+$) T cells through the induction and activation of the AhR, and stimulates transporters to facilitate the absorption of Kyn by T cells, creating a positive feedback loop that suppresses antitumor immune responses [60]. Zhang et al. demonstrated that high expression of the Trp metabolism-related gene is associated with a favorable response to anti-PD–1 or anti-PD–L1 antibodies [55]. An in vivo study on a mouse glioma model demonstrated the survival benefit of adding an IDO1 inhibitor (BGB-5777) to the combination of radiotherapy and anti-PD–1 inhibitor [61]. This benefit might be due to the positive effects of IDO1 inhibition on the tumor immune microenvironment that enhances the immune reactivation against tumor cells [62]; (d) moreover, Trp depletion and Kyn accumulation promote the recruitment of immunosuppressive Tregs and tumor-associated macrophages (TAMs), which enhances the immune evasion and tumor growth [60]. Given the importance of Tregs and TAMs in tumor radioresistance [8], dysregulated IDO and TDO activation in glioma cells would increase the cancer cell's radioresistance. Hence, the degree of TCE activation can serve as a predictive clinicopathological biomarker to track the degree of GBM progression and resistance [63]. Imbalances in Trp metabolism in gliomas highlight targeting the Kyn pathway's key enzymes for targeted therapies.

Serotonin pathway

The 5-hydroxytryptamine (5-HT), or serotonin, pathway has a complex impact on cancer cells. It is mainly regulated by the enzyme tryptophan hydroxylase (TPH), which synthesizes serotonin. 5-HT can be converted into melatonin through the serial enzymatic actions (Fig. 3). Melatonin and 5-HT have distinct effects on glioma cells.

Melatonin has antitumoral effects through several mechanisms: (a) melatonin has direct inhibitory effects on AhR. Therefore, it can reduce glioma cells viability, progression, and resistance by blocking AhR [64]; (b) it can inhibit glioma progression and angiogenesis through inhibiting EGFR dimerization [65]; (c) melatonin induces cytotoxicity by activating autophagy in GBM [66]; (d) it can also induce cytotoxicity by increasing cellular reactive oxygen species (ROS) levels [67]; (f) melatonin also reduces the clonogenic ability of GBM cells by reducing their stem cells markers [66]; (g) it can inhibit GBM cells' invasion and migration by directly inhibiting HIF-1 [68]; (h) melatonin also has direct antitumoral effects by improving immune response. This action might be due to the positive effects of melatonin on the immune cell's mitochondrial biogenesis [69, 70]. GBM cells can counteract the effects of melatonin by increasing their mitochondrial levels of cytochrome P450-1B1, which reverses the conversion of melatonin back into N-acetylserotonin [71].

On the other hand, 5-HT has virtually protumorigenic effects. Zhang et al. demonstrated that TPH1 activation in glioma cells could improve cancer cell proliferation, invasion, and chemoresistance in an L1 cell adhesion molecule (L1CAM)/NF-κB-dependent manner [72]. 5-HT performs its functions via seven receptor subtypes ($5\text{-}HT_{1-7}$), coupled to multiple signaling pathways. Among these, the role of $5\text{-}HT_7$ in glioma pathogenesis is a matter of debate. Some studies found that $5\text{-}HT_7$ mediates GBM proliferation [73], while others reported its tumor suppressor effects [74]. Zhang et al. found that GBMs with low expression of Kyn pathway enzymes have a better prognosis. They concluded that the activation of the 5-HT pathway, which consumes Trp and competes with the Kyn pathway, is linked to improved outcomes in glioma patients [55]. However, as noted earlier, 5-HT itself may have protumorigenic effects. This contradiction can be explained as follows: aldehyde dehydrogenase (ALDH2), which inactivates 5-HT, was found to be activated in GBM with low Kyn pathway-related gene expression [55]. This increase in ALDH2 activity aligns with the enhanced conversion of 5-HT to its inactive metabolite, 5-hydroxyindoleacetic acid (5-HIAA), potentially reducing the protumorigenic effects of 5-HT.

Indole pathway

Interleukin-4-induced-1 (IL4i1) is the primary enzyme of the indole pathway (Fig. 3). Like IDO and TDO enzymes, IL4i1 is closely associated with cancer biology. Recent findings reported that IL4i1 activation can facilitate cancer survival. Venkateswaran et al. demonstrated that IL4i1 facilitates the breakdown of Trp, producing indole-3-pyruvic acid. This metabolite enhances the survival of liver cancer cells by preventing ferroptosis by activating a gene expression program that counteracts oxidative stress [75]. however, our current understanding of its biological impacts on glioma pathogenesis is limited; Sadik et al. showed that IL4i1 activity in GBM is closely linked to the activation of the AhR. This association leads to increased cancer invasion, metastasis, and immunosuppression, ultimately correlating with poorer overall survival in patients with GBM [76].

Overall, Trp metabolites from the Kyn, serotonin, or indole pathways are associated with glioma progression and immunosuppression. A deeper understanding of Trp and its metabolites could reveal novel mechanisms of tumor resilience and provide potential therapeutic targets for glioma.

Serine and glycine

GBM cells uptake serine and glycine through the AA transporter alanine serine cysteine transporter 2 (ASCT2) (SLC1A5), channeling them into the serine-glycine-one-carbon (SGOC) pathway. Additionally, serine can be synthesized intracellularly from 3-phosphoglycerate (3-PG) via the enzymes phosphoglycerate dehydrogenase (PHGDH) and phosphoserine phosphatase (PSPH). Within the SGOC pathway, serine is converted into glycine by serine hydroxymethyltransferase (SHMT), generating one-carbon units like 5,10-methylene-tetrahydrofolate (CH_2-THF), which are crucial for nucleotide synthesis and methylation processes. Glycine further serves as a precursor for purine biosynthesis and glutathione production, playing a key role in maintaining redox balance [77].

The overexpression of PHGDH promotes glioma cell proliferation by upregulating cyclin D1 and cell cycle checkpoint-kinase-2 while also enhancing invasion and metastasis through increased expression of matrix metalloproteinase 2 (MMP2) and VEGF [78]. Glycine is also vital for producing cysteine and glycine-rich protein 2 (CSRP2) by glioma cells, which contributes to tumor progression by promoting malignant proliferation, metastasis, stemness, and chemoresistance through activation of the Notch signaling cascade [79].

Dysregulated AA metabolism is not limited to glioma cells but extends to components of the TME. Zhang et al. revealed that PHGDH upregulation in GBM-associated endothelial cells contributes to TME hypoxia, neovascularization, and impaired infiltration of anti-tumor T cells. In this study, PHGDH inhibition could effectively overcome GBM resistance to chimeric antigen receptor (CAR)-T cell immunotherapy [80]. Another study highlighted additional immunoregulatory dimensions of serine and glycine metabolism. Through a bioinformatic analysis, Chen et al. demonstrated that high levels of PSPH and SHMT1 in GBM cells are linked to poor survival rates. Their analysis of the tumor immune microenvironment revealed that elevated PSPH and SHMT1 expression is associated with increased recruitment of M_2 macrophages, resting natural killer (NK) cells, and resting memory $CD4^+$ T cells, while B cell recruitment decreases. These changes promote GBM progression. The gene signature related to serine and glycine metabolism was also associated with PD-1 expression in immune cells. Chen et al. concluded that patients with this high-risk gene signature respond better to immunotherapeutic treatments [81].

Glutamine and glutamate

Glutamine is a critical metabolic substrate for GBM cells, fulfilling their heightened demand for carbon and nitrogen. It is converted into glutamate via glutaminase, which enters the tricarboxylic acid (TCA) cycle. This process supports energy production and provides intermediates necessary for biosynthetic pathways that sustain rapid tumor growth [82].

GBM cells can also release excess glutamate into TME through the activity of the cystine-glutamate antiporter (SLC7A11, also known as System Xc^-), creating a glutamate-enriched extracellular milieu [83]. In the glioblastoma TME, extracellular glutamate levels are approximately 10 times higher than intracellular levels [84]. Glutamatergic signaling occurs through two broad groups of receptors: (a) ionotropic receptors, including NMDA receptors (N-methyl-D-aspartate), kainic acid receptors, and AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptors; (b) metabotropic receptors [85]. The excess glutamate contributes to tumor progression in several ways: (1) it promotes excitotoxicity in neighbouring neurons, causing neuronal necrosis, a characteristic of GBM tissue [86]; (2) the accumulated glutamate can stimulate glioma cells proliferation, anaplasia, migration through either AMPA/Akt pathway or NMDA activation [14, 87]; (3) in addition, high glutamate can enhance tumor expansion by inducing inflammation [88]; (4) glutamate can also promote GBM cells growth by activating EGFR signaling [89]; (5) excess glutamate can acidify the glioblastoma TME which impede immune infiltration requiring physiologic pH [90]; (6) the elevated glutamate can activate TAMs through GRIA2 (glutamate ionotropic receptor AMPA type subunit 2) to provide further support for GBM progression (discussed later)

[91]. Applying magnetic resonance spectroscopy (MRS), Pearl and Fleischer demonstrated that glioma tissues with IDH mutation and 1p/19q codeletion have lower glutamate concentration [92]; (7) in addition, glutamate-induced N-methyl-D-aspartate receptor (NMDR)/CREB signaling can improve GBM radioresistance [14].

A comprehensive bioinformatic analysis revealed that glutamine metabolism enhances GBM cells' survival and migration [93]. Glutamine also plays a critical role in maintaining redox homeostasis by contributing to glutathione synthesis. This key antioxidant protects GBM cells from oxidative stress and enhances their survival in response to toxic agents. Building on this understanding, Wang et al. demonstrated that inhibiting glutamine metabolism with Purpurin effectively increased GBM cell sensitivity to photo-enhanced chemodynamic therapy [94]. Another study demonstrated that glutamine can improve GBM resistance to pimozide by boosting intracellular lipogenesis [95]. Furthermore, glioblastoma stem cells (GSCs) depend on glutamine to survive. As a result, glutamine restriction has been suggested as a potential strategy to hinder GBM pathogenesis. Xing et al. demonstrated that glutamine deprivation could effectively disrupt GSC biology by degrading Sirtuin 3 [96]. Meanwhile, Isakova et al. found that different GBM cell lines show different phenotypic and metabolic responses to glutamine deprivation [97].

In the TME, GBM cells exhibit aggressive glutamine uptake, depleting this nutrient and creating a glutamine-scarce environment. Wang et al. describe this behaviour as glutamine-addiction of GBM [94]. In other words, glutamine metabolism fosters a competitive interplay between GBM and immune cells. This "metabolic tug-of-war" influences tumor progression and compromises the efficacy of immune responses, thereby shaping the immunosuppressive nature of the TME. The metabolic predation of GBM limits glutamine availability to immune cells, impairing their functionality and contributing to immune evasion by the tumor. Wang et al. demonstrated that glutamine deprivation can potentially impair $CD8^+$ T cells' function by inducing mitochondrial damage [98]. Interestingly, TAMs can supply glutamine to GBM cells to support their metabolism. Choi et al. demonstrated that, in response to the glutamate-rich TME, TAMs co-cultured with GBM cells exhibit reduced expression of SLC7A11 and increased activity of glutaminase [91]. These adaptations enhance the intracellular glutamate content in TAMs, enabling them to synthesize and supply glutamine to nearby GBM cells.

In a nutshell, targeting GBM's glutamine and glutamate metabolism offers therapeutic potential. Combining metabolic inhibitors with approaches to reprogram the tumor microenvironment could restore immune function, limit nutrient availability, and combat GBM's adaptive resilience.

Methionine

Methionine, an essential sulfur-containing AA, is taken up and metabolized at higher rates by glioma cells. This characteristic has been utilized to develop various tracers for positron emission tomography (PET) scans, aiding in diagnosing GBM [99]. It has been demonstrated that GBM cells require exogenous methionine for their proliferation, invasion, and treatment resistance [100]. Methionine can also be exploited by GBM cells to replenish their nicotinamide-N-methyl transferase (NNMT) content [100], which enhances their invasion and makes the overall prognosis worse [101]. Building on this background, Zhou et al. demonstrated that a 25-gene model related to methionine metabolism could predict the survival outcomes of glioma patients. Furthermore, this model was significantly associated with EMT and immune response [102]. Therefore, methionine restriction has been proposed as a potential approach to disrupt GBM pathogenesis.

Methionine facilitates DNA methylation by converting into S-adenosylmethionine (SAM), a critical cofactor for DNA methyltransferases. Previously, it was believed that methionine restriction might increase resistance to TMZ, the most widely used anti-glioma chemotherapeutic. TMZ is particularly effective in gliomas with methylated MGMT (O [6]-methylguanine-DNA methyltransferase), as DNA methylation enhances its therapeutic efficacy [103]. However, contrary to earlier assumptions, Kubota et al. demonstrated that methionine deprivation does not reduce TMZ's effects; instead, it can improve treatment outcomes [104]. In addition, methionine can contribute to radiotherapy resistance. Korimerla et al. demonstrated that methionine to SAM conversion can improve radiation resistance by enhancing DNA damage repair [105]. Methionine, along with cysteine, contributes to cellular glutathione levels. Methionine/cysteine restriction can exacerbate the effects of the glutathione-generating enzyme (GPX-4) inhibitor in inducing ferroptotic death of human glioma cells [106]. Hence, methionine restriction and agents that inhibit methionine metabolism could serve as adjuvants to improve treatment outcomes.

Arginine

Arginine drives various metabolic processes, including synthesizing nitric oxide, polyamines, glutamine, and proline, key regulators of cell growth, survival, and proliferation of GBM cells [107]. However, many GBM cells cannot synthesize arginine independently, a characteristic known as "arginine auxotrophy" [108]. In this case, cancer cells depend on external sources of arginine to support their metabolism [109]. To overcome

this metabolic deficiency, a subset of GBM cells—non-arginine-auxotrophic cells—compensates by upregulating specific mechanisms for arginine acquisition. These include increased expression of the cationic amino acid transporter 1 (CAT-1), which actively imports arginine from the TME into the intracellular space [110], and the overexpression of arginine-synthesizing enzymes such as argininosuccinate synthase 1 (ASS1) [111].

These adaptations would contribute to tumor progression by depleting the arginine content of TME, which is essential for immunosurveillance [112]. Arginine also facilitates GBM cells' motility and invasion. Pavlyk et al. demonstrated that arginine-deprived GBM cells are less invasive due to impaired arginylation of β-actin filament [113]. Considering these effects, a transcriptome-based study demonstrated that SLC7A7 and ASS1 expression are poor prognostic factors of GBM [109]. Interestingly, TAMs facilitate the arginine metabolism of GBM cells by sending arginase-containing exosomes to GBM cells [114]. Huang et al. observed lower serum levels of arginine-associated metabolites–2-oxoarginine, N-Acetylarginine, and argininate–between GBM patients and controls, supporting their potential role as biomarkers [115]. This finding may reflect that GBM cells can also apply arginine metabolites for their metabolism. Future studies can reveal this notion.

The aforementioned experimental findings suggest arginine deprivation as an adjuvant treatment. Riess et al. demonstrated that arginine deficit can enhance the toxic effects of cyclin-dependent kinase (CDK) inhibitors on GBM cells by impairing mitochondrial metabolism, inducing autophagy, and preventing DNA damage response [116]. Interestingly, Hajji et al. found that arginine deprivation can effectively improve tumor radiosensitivity, even in non-arginine-auxotrophic GBM cells [111]. This finding presents a promising avenue for further investigation in future clinical trials.

Leucine, isoleucine, and valine

Branched-chain amino acids (BCAAs) — leucine, isoleucine, and valine — play critical roles in supporting GBM's aggressive metabolic demands. These AAs are actively imported into GBM cells via specific transporters, primarily the L-type amino acid transporter 1 (LAT1, encoded by SLC7A5) and its associated subunit CD98 (encoded by SLC3A2) [117]. Once entering the cells, BCAAs undergo catabolism by a series of enzymes — including BCAT1 (branched-chain amino acid transaminase 1)— to generate intermediates such as acetyl-CoA and succinyl-CoA, which feed into the TCA cycle. This process not only supports ATP (adenosine triphosphate) generation but also provides biosynthetic precursors essential for sustaining the rapid proliferation and high metabolic rate of GBM cells [118]. Zhang et al. demonstrated that BCAA influx and catabolism in GBM are activated in the hypoxic microenvironment [119]. Leucine, isoleucine, and valine also exhibit ketogenic properties, contributing to the production of ketone bodies such as acetone and 3-hydroxybutyrate. The release of these ketone bodies into the TME can increase acidity, creating a hostile environment that impairs immune cell infiltration and promotes immune evasion [90]. In an in vitro study on GBM, Silva et al. demonstrated that exposure of macrophages to branched-chain ketoacids reduced their phagocytic activity [120]. Overall, the supply of BCAAs to GBM cells promotes tumor progression by providing essential energy substrates and contributing to immune suppression.

Cysteine

Cysteine catabolic pathways are upregulated in GBM cells [121]. It contributes to the synthesis of glutathione, a major intracellular antioxidant. This feature was applied by Noch et al. to impair GBM function by inducing "reductive stress" using cysteine compounds [121]. In addition, cysteine metabolism contributes to tumor growth by producing cysteine sulfinic acid as an end product [122]. This metabolite promotes TME acidity, suppressing the local immune response [90]. It has been demonstrated that glioma cells cannot provide cysteine from methionine and depends on cysteine from TME to synthetize glutathione supporting their survival and proliferation [123]. In support, Upadhyayula et al. found that dietary cysteine and methionine restriction could improve the survival of a glioma murine model by reducing the glutathione content of tumor cells and inducing the ferroptosis pathway [106]. A study on a pancreatic cancer model demonstrated that CAFs can improve the cancer cell's resistance to ferroptosis by providing cysteine [124]. In addition, cysteine is essential for the synthesis of cysteine and glycine-rich protein 2 (CSRP2), which plays a crucial role in glioma progression [79]. Therefore, although cysteine is a nonessential AA, it is essential for glioma cells to be supplied by TME to support their biology and pathogenesis.

Alanine

Alanine metabolism is dysregulated in GBM [125]. Ijare et al. demonstrated that GBM cells utilize alanine as a critical energy production source and as a biomolecule synthesis precursor [126]. Based on this knowledge, Yang et al. applied alanine as an MRI contrast agent for the diagnosis of GBM [127]. Using the MRS technique, Alcicek et al. found that intratumoral alanine level is associated with IDH-wild type status and serves as a poor prognostic indicator of survival in patients with GBM [128]. The same findings were also demonstrated in Pearl and Fleischer's study [92]. Ribosome-associated quality

control of proteins is essential for cancer cell progression. In GBM, a key quality control mechanism involves msiCAT-tailing (mitochondrial stress-induced carboxyl-terminal alanine and threonine tailing) [129]. As such, GBM cells require an adequate supply of alanine to maintain efficient and accurate protein synthesis and support their rapid and sustained proliferation. This approach has been utilized to target GBM cells. N-aryl-β-alanine derivatives demonstrate selective cytotoxicity by disrupting cancer cell survival and growth through interference with alanine's metabolic role [130].

Asparagine and aspartate

GBM cells require enough asparagine levels to maintain their metabolism, survival, and pathogenesis. This high demand for asparagine can lead to a significant reduction in overall asparagine levels. Nakade et al. observed that patients with GBM have markedly lower blood and urinary asparagine levels than healthy individuals. Notably, their study demonstrated a significant increase in asparagine levels in blood and urine following GBM tumor resection [131].

In human cells, asparagine can be synthesized from glutamine and aspartate by asparagine synthetase (ASNS) (Fig. 2). Thomas et al. demonstrated that ASNS copy number can predict the survival of patients with GBM. They also demonstrated that asparagine synthetase levels are higher in IDH-wild type and higher-grade tumors. Mechanistically, asparagine is involved in GBM proliferation and metabolic plasticity [132]. Asparagine is also essential for cancer cells to maintain redox homeostasis, enabling GBM cells to withstand oxidative treatments. Thomas et al. observed that GSCs with high ASNS expression exhibited resistance to 10 Gy (Gy) irradiation, whereas cells with low ASNS levels underwent apoptosis following just 3 Gy irradiation [132]. Enhanced antioxidant capacity can also increase GBM cell resistance to TMZ, which exerts its effects partially through oxidative stress [133]. Recently, Lv et al. demonstrated that aspartate can support GSC stemness through methylation of platelet-derived growth factor receptor beta (PDGFRB) mRNA [134]. Panosyan et al. demonstrated that combining asparaginase (an asparagine hydrolytic enzyme) and TMZ can result in a durable growth suppression of GBM cells [135]. An interesting study showed that the combination of L-asparaginase and an asparagine synthetase inhibitor (6-diazo-5-oxo-L-norleucine) effectively prevented the proliferation of both TMZ-sensitive and TMZ-resistant GBM cells [136]. Therefore, asparagine deprivation can serve as a standalone and adjuvant treatment of GBM.

Histidine

Histidine is an imidazole-based AA that exhibits direct toxic effects on GBM cells. An in vitro study demonstrated that L-histidine can reduce GBM cell viability by inducing the expression of pyruvate dehydrogenase kinase 4 (PDK4) [137]. PDK4 negatively regulates pyruvate dehydrogenase (PDH), an enzyme that catalyzes the conversion of pyruvate to acetyl-CoA [138]. By inhibiting PDH, PDK4 leads to a shift in cellular metabolism, promoting glycolysis and contributing to the toxicity in GBM cells. Other in vitro studies have revealed histidine's toxic effects on CAFs, highlighting its potential as a metabolic disruptor in the TME [139]. However, GBM cells and their surrounding TME components can convert this threat into an opportunity for tumor progression by converting histidine to histamine via the histidine decarboxylase (HDC) enzyme. Studies on different cancer types have demonstrated that various TME components, such as mast cells [140], tumor-associated neutrophils (TANs), myeloid-derived suppressor cells (MDSCs) [141], can contribute histidine conversion to histamine by expressing high levels of HDC. Chen et al. demonstrated that GSCs also have high expression levels of HDC [142]. The resulting histamine in the TME plays a key role in promoting GBM cell survival, immune evasion, and angiogenesis by interacting with specific histamine receptors on tumor cells, immune cells, and endothelial cells [142, 143]. In addition, histamine can promote the GBM cell's proliferation, invasion, and EMT axis [144].

Future research should explore strategies to target the histidine-histamine axis in GBM, either by enhancing histidine's toxic effects or inhibiting histamine-mediated immune evasion, to develop novel therapeutic approaches for treating this aggressive cancer.

Proline

Research on GBM has increasingly highlighted the intricate involvement of proline metabolism, particularly its link with tumor adaptation and progression. Glutamate and proline metabolism are tightly interconnected and bidirectional in GBM, with each AA serving as a precursor for the other AA under certain metabolic conditions. Proline can also be converted back into glutamate by the enzyme proline oxidase (POX) [145]. Conversely, glutamate serves as the principal source of proline by converting to P5C (Δ^1-pyrroline-5-carboxylate), catalyzed by PYCR (pyrroline-5-carboxylate reductase). This bidirectional conversion enables GBM cells to adapt to fluctuating nutrient availability, enhancing their survival ability in the challenging TME. Vettore et al. demonstrated that under hypoxia, proline can be generated from ornithine by pyrroline-5-carboxylate reductase-like (PYCRL) [146]. GBM tumors have lower POX levels than normal brain tissue [147]. In this case, intratumoral glutamate levels

might decrease. However, GBM cells can adapt to glutamate deficit by upregulating alternative metabolic pathways, maintaining cell viability [148]. While such findings provide insight into GBM biology, directly extrapolating these observations to clinical scenarios is challenging due to the differences between in vitro studies and the complex TME.

Aiming to show the biological effects of proline in GBM metabolism, Ferreira et al. found that high extracellular proline can exacerbate GBM cell proliferation by activating the NF-κB pathway [149]. The significance of metabolomic profiling in distinguishing glioma subtypes has also been demonstrated. Björkblom et al. reported significantly elevated proline concentrations in GBM tissue compared to adjacent normal brain tissue [150]. Zhao et al. confirmed that proline metabolites could differentiate between glioma grades and IDH mutation status, emphasizing the importance of proline metabolism in tumor classification [151]. Panosyan et al. realized that higher POX expression is a poor prognostic factor for patients with GBM [152]. In addition, proline can serve as a diagnostic biomarker. Jonsson et al. applied machine learning to analyze plasma metabolomic profiles and identified proline as significantly higher in GBM patients. They introduced proline concentration as a diagnostic marker of early glioma detection [153].

Further exploration of proline-related pathways may not only provide a deeper understanding of GBM biology but also pave the way for novel therapeutic strategies targeting metabolic vulnerabilities unique to GBM.

Threonine

Kośliński et al. demonstrated that patients with GBM have higher serum levels of threonine compared with the control groups [154]. This finding may reflect the importance of threonine in GBM pathogenesis. As noted earlier, threonine is essential for GBM cells to maintain protein synthesis quality, supporting their rapid proliferation and survival. This is mediated by generating msiCAT-tailing [129]. Building on this, a recent study identified that GSCs rely on threonine to support elevated protein translation and tumor growth. The enzyme YRDC, which catalyzes the formation of (t [6] A) N [6]-threonylcarbamoyladenosine on tRNAs, is crucial for this process. Threonine accumulation in GSCs enhances t [6]A production, favoring the translation of genes associated with cell division. As such, restricting threonine intake reduced t [6]A formation, slowed tumor growth, and improved the effectiveness of chemotherapy, highlighting the potential for dietary interventions to complement GBM treatments [155]. The evidence linking threonine to GBM biology is still in its early stages, and further studies are needed to fully elucidate the mechanisms underlying this relationship and its potential therapeutic implications.

Lysine

Evidence on the role of lysine in GBM biology and pathogenesis is limited. Human studies have demonstrated that patients with GBM have higher serum levels of lysine [154]. In GSCs, lysine metabolism is reprogrammed to enhance tumor growth and immune evasion. Yuan et al. realized that GSCs upregulate the lysine transporter SLC7A2 and the enzyme GCDH (glutaryl-coenzyme A dehydrogenase), which produces crotonyl-CoA. This shift leads to histone H4 crotonylation, promoting tumor growth and immune evasion by suppressing interferon type 1 (IFN-1) signaling. Yuan et al. demonstrated that lysine restriction impedes tumor growth and improves tumor response to anti-PD–1 immunotherapy [156].

Phenylalanine and tyrosine

Phenylalanine and tyrosine are aromatic AAs critical to GBM's metabolic networks. Phenylalanine obtained exogenously through diet or protein catabolism, serves as a precursor for tyrosine mediated by phenylalanine hydroxylase (PAH) [157]. Emerging evidence has put forward that phenylalanine metabolism influences the development and progression of gliomas. Löding et al. compared pre-diagnostic plasma samples from glioma patients with matched healthy controls and analyzed surgical samples from the same individuals to identify metabolites linked to glioma progression, and realized high levels of phenylalanine and metabolites are associated with glioma progression [158]. Kośliński et al. demonstrated that the dysregulation of phenylalanine metabolism provides a reliable method for diagnosing GBM [154]. This attribute has been applied to design various PET imaging to detect glial tumors [159]. These findings suggest that targeting phenylalanine using radiopharmaceuticals is a promising strategy in glioma treatment. Borrmann et al. demonstrated that systemic astatine-211 labeled with L-phenylalanine could significantly improve the overall survival of rats with intracranial GBM [160].

Phenylalanine can be converted to tyrosine by phenylalanine hydroxylase. GBM cells have high tyrosine metabolism. This feature has been applied to design a novel PET imaging technique named O-(2- ([18]F]-fluoroethyl)-L-tyrosine (FET) PET, or FET-PET [161]. This technique has been successfully applied to detect GBM pseudoprogression following chemoradiation [162]. Yamashita et al. demonstrated that GBM cells exhibit abnormal tyrosine metabolism, and patients with upregulated tyrosine aminotransferase activity have poor overall survival [163]. Wang et al. found that the expression level of three tyrosine metabolizing enzymes

4-hydroxyphenylpyruvate dioxygenase (HPD), homogentisate 1,2-dioxygenase (HGD), and fumarylacetoacetate hydrolase (FAH) is positively correlated with glioma grade, IDH1-wild type, Ip/19q noncodeletion, MGMT non-methylation, and PD-L1 expression [164]. They found that these enzymes convert tyrosine to fumarate, entering the TCA cycle and generating α-ketoglutarate (αKG). The resultant αKG upregulates PD-L1 expression through ten-eleven translocation 1/interferon regulatory factor 1 (TET1/IRF1)-dependent manner [164]. Therefore, abnormal tyrosine metabolism is involved in glioma progression and immune evasion.

In addition, tyrosine is a precursor of catecholamines. The enzyme tyrosine hydroxylase metabolizes tyrosine to dihydroxyphenylalanine (L-Dopa), which is then converted into dopamine by the enzyme aromatic AA decarboxylase. Through the action of dopamine β-hydroxylase, dopamine produces norepinephrine. Norepinephrine is then converted into epinephrine by phenylethanolamine N-methyltransferase [165] (Fig. 3). Dopamine's impact on GBM is complex. It can be secreted by GBM cells [166] or regulatory T cells [167]. Its multifaceted effects depend on the dopamine receptor type and the target cell. So far, five typical dopamine receptors have been identified, being classified into two main categories of D1-like receptors (dopamine receptor [DR]D1 and 5) and the D2-like receptors (DRD2–4), with distinct effects: (1) DRD1 stimulation can be anti-tumoral in GBM cells by disrupting autophagy process [168] and mitochondrial function [169], or pro-tumoral in GSCs by enhancing proliferation, stemness, invasion [170], and radiotherapy resistance [171]; (2) DRD2 signaling can promote GBM progression by inducing stemness, tumor growth [172], self-renewal and tumor engraftment capacity [166], and chemoresistance [173]. Wang et al. linked the chronic stress-induced GBM progression with dopamine receptor D2/extracellular signal-regulated kinase/beta-catenin (DRD2/ERK/β-catenin) signaling [174]. On the other hand, DRD2 excitation on TAMs has anti-tumorigenic effects. Qin et al. demonstrated that dopamine-DRD2 interaction would lead to M2-to-M1 polarization and vascular normalization [175]. The dopamine effect on microglia can lead to extracellular trap formation, impeding anti-tumor immune infiltration [176]; (3) DRD3 activation can stimulate GBM growth and chemoresistance [177]; (4) DRD4 stimulation improves GSC proliferation, survival, autophagy, lipid metabolism, and chemoresistance capacities [178, 179]; and (5) DRD5 activation provides anti-tumoral effects by suppressing tumor growth, inhibiting mTOR signaling, inducing autophagy [180], and counteracting with DRD2 signaling [181]. This section highlighted the diverse effects of dopamine on GBM, which vary depending on the target cell type and the specific dopamine receptor involved. Further research is needed to uncover the nuanced mechanisms underlying these interactions and their implications for GBM biology and treatment.

Epinephrine and norepinephrine, stress-associated catecholamines, play critical roles in GBM biology by promoting tumor growth, immune evasion, and treatment resistance. Through β-adrenergic receptor activation, these catecholamines enhance GBM cell proliferation, survival, and migration by upregulating ERK and Twist1 signaling pathways [182, 183]. Interestingly, contrasting effects have been observed regarding their influence on GBM invasion: while Zhong et al. reported that norepinephrine treatment reduces GBM cell invasion and migration, potentially by inhibiting MMP-11 [184]. Weng et al. demonstrated that epinephrine enhances GBM invasion and migration by upregulating MMP-9 expression [185]. This discrepancy underscores the need for further studies to clarify the relationship between adrenergic signaling and GBM invasiveness. Norepinephrine has also been shown to induce glycogenolysis [186], supplying glucose to support tumor growth, survival, metabolic adaptation, migration, and resistance to chemotherapy and radiotherapy [187–189]. Glycogenolysis further generates glucose-6-phosphate, which supports redox homeostasis and treatment resistance by producing nicotinamide adenine dinucleotide phosphate (NADPH) through the pentose phosphate pathway [190]. Additionally, glycogenolysis in GBM is associated with the enrichment of the PI3K/AKT/mTOR axis and Kirsten rat sarcoma viral oncogene homolog (KRAS) signaling, highlighting the importance of norepinephrine in GBM pathogenesis [191]. Adrenergic signaling also contributes to tumor progression by inducing immune dysfunction through mechanisms such as downregulating antigen-presenting molecules and upregulating immune checkpoints [192]. A study in breast cancer revealed that norepinephrine can reprogram tumor macrophages into an M2 phenotype, promoting cancer progression and resistance [193]. This link warrants further exploration in the context of GBM. Collectively, these findings highlight the multifaceted role of adrenergic signaling in GBM progression and underscore its potential as a therapeutic target to improve treatment outcomes.

Clinical studies targeting amino acid metabolism in glioma

Several studies have investigated the role of AA-targeted therapies in GBM, highlighting their potential in modulating tumor metabolism, survival, and treatment resistance (Table 1). Juarez et al. (NCT01654497) explored dexanabinol, a glutamate-modulating agent, in a phase I trial. Weekly intravenous infusion of dexanabinol was found to be safe and well tolerated up to a dose of 28 mg/kg, with five out of 24 patients (21%) achieving stable

Table 1 Clinical trials on amino acid metabolism or restriction in glioblastoma. (source: https://clinicaltrials.gov/)

Trial no.	Country	Year	Phase	Participants	Intervention	Target Amino Acid	Primary Endpoints	Status	Main Findings
NCT00508456	US	2004	I	Relapsed GBM	Methionine restriction + TMZ	Methionine	Time to progression	Terminated	Poor accrual rate
NCT01260467	US	2010	II	Relapsed GBM	Inhibiting NMDA receptor using memantine	Glutamate	OS, PFS	Terminated	Poor accrual rate
NCT01430351	US	2011	I	Newly diagnosed GBM	Inhibiting NMDA receptor using memantine + TMZ	Glutamate	Safety	Active	Pending
NCT01654497	US	2012	I	Relapsed GBM	Inhibiting NMDA receptor using dexanabinol	Glutamate	Safety	Completed	Safe and well-tolerated; limited efficacy *(Juarez et al., 2021)*
NCT02029690	US, UK	2014	I	Relapsed HGG	ADI-PEG 20 + pemetrexed + cisplatin	Arginine	ORR	Terminated	-
NCT02327078	US	2014	I/II	Newly diagnosed GBM	IDO inhibitor (epacadostat) + nivolumab	Tryptophan	Safety, OS	Completed	Phase 1: well-tolerated Phase II: pending *(Perez et al., 2017)*
NCT02052648	US	2014	I/II	Refractory GBM	IDO inhibitor (indoximod) + TMZ	Tryptophan	Safety, PFS	Completed	Safe and well-tolerated; 3/6 SD, 1/6 PR *(Colman et al., 2015)*
NCT02502708	US	2015	I	Relapsed HGG (< 21 yrs)	IDO inhibitor (indoximod) + TMZ or RT	Tryptophan	Safety, ORR	Completed	Safe and well-tolerated; encouraging efficacy *(Johnson et al., 2024)*
NCT03455140	Australia, Netherlands, UK	2018	I/II	Relapsed/refractory HGG (< 25 yrs)	PEG- BCT-100 (recombinant arginase)	Arginine	Safety, ORR	Completed	Acceptable toxicity profile, No CR, 1/13 PR, 1/13 SD *(Fenwick et al., 2024)*
NCT03849105	Australia, Austria, Netherlands	2019	I/II	Relapsed GBM	^{131}I-iodo-phenylalanine + RT	Phenylalanine	Safety	Completed	Well-tolerated, RR 44.4% (Bomalaski et al., 2022)
NCT04587830	South Korea, Taiwan	2020	Ib	Newly diagnosed GBM	Combination of ADI-PEG 20, RT, and TMZ	Arginine	Safety, pharmacodynamic, and immunogenicity	Completed	No dose-limiting toxicity, encouraging OS results *(Bomalaski et al., 2022)*

Table 1 (continued)

Trial no.	Country	Year	Phase	Participants	Intervention	Target Amino Acid	Primary Endpoints	Status	Main Findings
NCT05664464	Switzerland	2023	Ib/II	Newly diagnosed GBM	Antiglutamatergic + standard CRT	Glutamate	PFS	Recruiting	Pending
NCT04587830	South Korea, Taiwan	2024	II	Newly diagnosed GBM	Combination of ADI-PEG 20, RT, and TMZ	Arginine	OS	Recruiting	Pending
NCT06552260	US	2025	I	Relapsed/refractory GBM	Troriluzole	Glutamate	Neuronal activity	Active	Pending

Abbreviations: ADI-PEG 20, arginine deiminase conjugated to polyethylene glycol; CRT, chemoradiotherapy; HGG, high-grade glioma; IDO, indoleamine 2,3-dioxygenase; NMDA, N-methyl-D-aspartate; ORR, objective response rate; OS, overall survival; PEG-BCT-100, polyethylene glycol recombinant arginase; PFS, progression-free survival; PR, partial response; RR, response rate; RT, radiation therapy; SD, stable disease; TMZ, temozolomide

disease lasting a median of two 28-day cycles. Notably, dexanabinol penetrated cerebrospinal fluid, indicating potential intracranial tumor exposure. However, its antitumor activity was limited, emphasizing the need for further efficacy studies [194].

Fenwick et al. (NCT03455140) examined PEG-BCT-100, a recombinant arginase targeting arginine metabolism, in children and young adults with relapsed or refractory cancers. The study established the recommended phase II dose at 1600U/kg intravenously weekly, matching the adult dose. Although no complete response was observed within the 8-week evaluation period, several patients achieved prolonged radiological stable disease, suggesting potential benefits in stabilizing aggressive cancers [195]. Similarly, Bomalaski et al. (NCT04587830) investigated ADI-PEG 20, an arginine-depleting enzyme, combined with radiation and TMZ in newly diagnosed GBM patients. The trial reported no dose-limiting toxicities and a median progression-free survival of 9.5 months, with promising overall survival data [196]. These findings warrant further exploration in ongoing studies to confirm its efficacy and safety. Colman et al. (NCT02052648) investigated indoximod, an IDO pathway inhibitor, in combination with TMZ for recurrent GBM. The phase I study established a maximum tolerated dose of 1200 mg twice daily. Among six patients, three experienced stable disease lasting 5–10 months, and one showed significant tumor shrinkage nearing partial response criteria. These results highlight the potential of IDO inhibition in GBM treatment [197]. Johnson et al. (NCT02502708) also demonstrated the safety and encouraging efficacy of indoximod in pediatric and young adult groups [198]. Pichler et al. (NCT03849105) assessed the use of [131]I-iodo-phenylalanine with radiation therapy in recurrent GBM. The study achieved a 44.4% response rate, with four out of nine patients exhibiting stable disease at three months. Median progression-free survival was 4.3 months, and overall survival reached 13 months. The treatment was well tolerated, with no significant radiation-based toxicity, underscoring its potential for tumor-specific targeting [199].

Ongoing studies aim to build on these findings. For example, NCT05664464 is investigating antiglutamatergic therapy combined with standard chemoradiation in newly diagnosed GBM to determine whether targeting glutamate pathways can improve survival outcomes. Additionally, a registration phase II trial (NCT04587830) is being considered for ADI-PEG 20 to confirm its effectiveness in GBM treatment. These ongoing efforts reflect the continued interest in exploring AA metabolism as a therapeutic target, potentially enhancing treatment outcomes and overcoming resistance mechanisms in GBM.

Conclusion and future prospective

AA metabolism plays a pivotal role in the pathogenesis of GBM, influencing tumor growth, survival, immune evasion, and resistance to therapies. GBM cells exhibit altered AA profiles, which enable them to sustain rapid proliferation and adapt to the TME's changing conditions. These metabolic alterations support tumorigenesis by promoting oncogenic signaling pathways and evading cellular stress. Furthermore, the role of the TME in modulating AA availability and metabolism has emerged as a significant area of interest. The TME creates a complex network of nutrient competition and metabolic crosstalk, which influences tumor progression and immune evasion. The growing understanding of AA metabolism in GBM underscores its potential as a therapeutic target. However, the molecular mechanisms governing the tumor cells' adaptive responses to AA deprivation remain poorly understood. Current research highlights the need to explore the metabolic pathways in greater detail to uncover novel therapeutic strategies. AA deprivation, as an emerging treatment strategy, holds promise; however, its clinical translation requires a deeper understanding of the tumor's metabolic flexibility and its impact on surrounding healthy tissues. Inhibitors targeting key enzymes involved in AA metabolism could offer complementary approaches to current GBM treatments, improving treatment efficacy and overcoming resistance mechanisms.

Despite advances in understanding the metabolic reprogramming of GBM, significant gaps remain in elucidating the precise molecular mechanisms that govern tumor cells' response to AA deprivation. This knowledge is crucial for optimizing AA starvation-based strategies and designing effective therapeutic interventions. Additionally, the role of the TME in shaping the AA metabolism of GBM is still in its early stages. Further research is necessary to understand how stromal, endothelial, and immune cells contribute to this metabolic landscape, potentially offering new therapeutic targets. In light of the crucial role of AA metabolism in tumor resistance to chemo- and radiotherapy, inhibitors targeting these pathways could provide a means to enhance the effectiveness of conventional treatments. Furthermore, by modulating AA availability in the TME, it may be possible to disrupt immune evasion mechanisms employed by GBM, improving the success of immunotherapies. As our understanding of AA metabolism deepens, strategies targeting this metabolic dependency will likely play an increasingly important role in treating gliomas and other cancers.

Abbreviations

5-HIAA	5-Hydroxytryptamine (Serotonin)
AA	Amino Acid
ADI-PEG 20	Arginine Deiminase Conjugated with Polyethylene Glycol
Akt	Protein Kinase B
ALDH2	Aldehyde Dehydrogenase 2
AMPA α	Amino-3-Hydroxy-5-Methyl-4-Isoxazolepropionic Acid
ASCT2	Alanine, Serine, Cysteine Transporter 2
ASNS	Asparagine Synthetase
ATP	Adenosine Triphosphate
BAD	Bcl-2 Associated Agonist of Cell Death
BCAAs	Branched-Chain Amino Acids
BCAT1	Branched-Chain Amino Acid Transaminase 1
BBB	Blood-Brain Barrier
Bcl-2	B-cell Lymphoma 2
CAR-T	Chimeric Antigen Receptor T Cell
CAF	Cancer-Associated Fibroblast
CCND1	Cyclin D1
CD	Cluster of differentiation
CDK	Cyclin-Dependent Kinase
CD98	Cluster of Differentiation 98
CH2-THF	5,10-Methylene-Tetrahydrofolate
CREB	cAMP response element-binding protein
CSRP2	Cysteine and Glycine-Rich Protein 2
CXCR4	C-X-C Chemokine Receptor Type 4
DBH	Dopamine β-Hydroxylase
DRD1-5	Dopamine Receptor D1-5
ECM	Extracellular Matrix
EGFR	Epidermal Growth Factor Receptor
EMT	Epithelial-Mesenchymal Transition
ERK	Extracellular Signal-Regulated Kinase
FAH	Fumarylacetoacetate Hydrolase
FET-PET	O-(2-[18F]-Fluoroethyl)-L-Tyrosine Positron Emission Tomography
FOXO3a	Forkhead Box O3a
GABA	Gamma-Aminobutyric Acid
GCDH	Glutaryl-CoA Dehydrogenase
GBM	Glioblastoma
GRIA2	Glutamate Ionotropic Receptor AMPA Type Subunit 2
GSC	Glioblastoma Stem Cells
Gy	Gray
GYS	Glycogen Synthase
HAAO	3-Hydroxyanthranilate 3,4-Dioxygenase
HDC	Histidine Decarboxylase
HGD	Homogentisate 1,2-Dioxygenase
HIF	Hypoxia-Inducible Factor
HPD	4-Hydroxyphenylpyruvate Dioxygenase
IDO	Indoleamine 2,3-Dioxygenase
IDH1	Isocitrate Dehydrogenase 1
IFN-1	Interferon Type 1
IL-6	Interleukin-6
IL4i1	Interleukin-4-Induced-1
IRF1	Interferon regulatory factor 1
JAK	Janus Kinase
KAT	Kynurenine Aminotransferase
KF	Kynurenine Formamidase
KMO	Kynurenine Monooxygenase
KRAS	Kirsten rat sarcoma viral oncogene homolog
Kyn	Kynurenine
KynA	Kynurenic Acid
L!CAM	L1 cell adhesion molecule
LAT1	L-Type Amino Acid Transporter 1
Mcl-1	Myeloid Cell Leukemia-1
MDSC	Myeloid-Derived Suppressor Cells
MGMT	O6-Methylguanine-DNA Methyltransferase
MMP2	Matrix Metalloproteinase 2
MAPK	Mitogen-Activated Protein Kinase
mTOR	Mammalian Target of Rapamycin
MRS	Magnetic Resonance Spectroscopy
msiCAT	Mitochondrial Stress-Induced Carboxyl-Terminal Alanine and Threonine Tailing
NAD+	Nicotinamide Adenine Dinucleotide
NADPH	Nicotinamide Adenine Dinucleotide Phosphate
NEK2	NIMA-related kinase 2
NF-κB	Nuclear Factor Kappa-Light-Chain-Enhancer of Activated B Cells
NK cell	Natural Killer cell
NMDA	N-Methyl-D-Aspartate
NMDR	N-methyl-D-aspartate Receptor
NNMT	Nicotinamide-N-Methyl Transferase
PD-1	Programmed Cell Death Protein 1
PD-L1	Programmed Death-Ligand 1
PDH	Pyruvate Dehydrogenase
PDK4	Pyruvate Dehydrogenase Kinase 4
PET	Positron Emission Tomography
PDGFRB	Platelet-derived growth factor receptor beta
PFKFB3	6-Phosphofructo-2-Kinase/Fructose-2,6-Biphosphatase 3
PHGDH	Phosphoglycerate Dehydrogenase
PI3K	Phosphoinositide 3-Kinase
POX	Proline Oxidase
PSPH	Phosphoserine Phosphatase
PTEN	Phosphatase and tensin homolog
PYCR	Pyrroline-5-Carboxylate Reductase
PYCRL	Pyrroline-5-Carboxylate Reductase-Like
ROS	Reactive oxygen species
RTKs	Receptor Tyrosine Kinases
SAM	S-Adenosylmethionine
SLC	Solute Carrier Family
SHMT	Serine Hydroxymethyltransferase
STAT	Signal transducer and activator of transcription
TAM	Tumor-Associated Macrophage
TAN	Tumor-Associated Neutrophils
TCA	Tricarboxylic Acid
TCEs	Tryptophan-Catabolic Enzymes
TET1	Ten-Eleven Translocation 1
TH	Tyrosine Hydroxylase
TME	Tumor Microenvironment
TMZ	Temozolomide
Trp	Tryptophan
Tregs	Regulatory T Cells
VEGF	Vascular Endothelial Growth Factor
YRDC	YrdC N6-Threonylcarbamoyladenosine Synthesis Domain Containing

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