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Review

Metabolism: an important player in glioma survival and development

Ning Wang[1,2] · Yiru Yuan[1,2] · Tianhao Hu[1,2] · Huizhe Xu[1,2] · Haozhe Piao[1,2]

Received: 17 July 2024 / Accepted: 26 September 2024
Published online: 22 October 2024

Abstract
Gliomas are malignant tumors originating from both neuroglial cells and neural stem cells. The involvement of neural stem cells contributes to the tumor's heterogeneity, affecting its metabolic features, development, and response to therapy. This review provides a brief introduction to the importance of metabolism in gliomas before systematically categorizing them into specific groups based on their histological and molecular genetic markers. Metabolism plays a critical role in glioma biology, as tumor cells rely heavily on altered metabolic pathways to support their rapid growth, survival, and progression. Dysregulated metabolic processes, involving carbohydrates, lipids, and amino acids not only fuel tumor development but also contribute to therapy resistance and metastatic potential. By understanding these metabolic changes, key intervention points, such as mutations in genes like RTK, EGFR, RAS, and IDH can be identified, paving the way for novel therapeutic strategies. This review emphasizes the connection between metabolic pathways and clinical challenges, offering actionable insights for future research and therapeutic development in gliomas.

Keywords Gliomas · Metabolisms · Glucose metabolism · Lipid metabolism · Signaling pathway · Treatment directions

Abbreviations

Akt	Kinase B
AT/RTs	Atypical Teratoid/Rhabdoid Tumors
BRAF	v-raf murine sarcoma viral oncogene homolog
CD36	Platelet glycoprotein 4
CNS	Central nervous system
DCA	Dichloroacetate
EGFR	Epidermal growth factor receptor
ERK	Extracellular signal-regulated kinase
FAO	Fatty acid oxidation
FAs	Fatty acids
ASN	Fatty acid synthesis
FGFR1	Fibroblast growth factor receptor1
GAMT	Guanidinoacetate methyltransferase

Ning Wang and Yiru Yuan have contributed equally to this work.

✉ Huizhe Xu, xuhuizhe@cancerhosp-ln-cmu.com; ✉ Haozhe Piao, pzpy@163.com; Ning Wang, wangning@zidd.ac.cn; Yiru Yuan, yuanyiru2000@163.com; Tianhao Hu, 15734083719@163.com | [1]Institute of Cancer Medicine, Dalian University of Technology, No.2 Linggong Road, Ganjingzi, Dalian, Dalian, Liaoning 116024, People's Republic of China. [2]Department of Medicine, Cancer Hospital of Dalian University of Technology, Liaoning Cancer Hospital & Institute, Cancer Hospital of China Medical University, No.44 Xiaoheyan Road, Dadong, Shenyang, Liaoning 110042, People's Republic of China.

GLUT	Glucose transporter proteins
HK2	Hexokinase 2
H3K27	Histone H3 lysine 27
IDH	Isocitrate dehydrogenase
IRS	Insulin receptor substrates
LDs	Lipid droplets
MAGL	Monoacylglycerol lipase
MAPK	Mitogen-activated protein kinase
MYB	v-myb avian myeloblastosis viral oncogene homolog
MCAD	Medium-chain acyl-CoA dehydrogenase
MEK	Mitogen-activated protein kinase kinase
miRNAs	microRNAs
MYCN	v-myc avian myelocytomatosis viral oncogene neuroblastoma derived homolog
NF	Neurofibromatosis type
OHCs	Oxidized forms of cholesterol
PDK	Pyruvate dehydrogenase kinase
PI3K	Phosphoinositide 3-kinase
TEN	Phosphatase and tensin homolog
AF	Rapidly accelerated fibrosarcoma
RAS	Rat sarcoma
RTKs	Receptor tyrosine kinases
SCD	Stearoyl-CoA desaturase
REBP-1	Sterol regulatory element-binding protein-1
WHO	World Health Organization
TAMs	Tumor-associated macrophages
TIGAR	TP53-Induced Glycolysis and Apoptosis Regulator
TMZ	Temozolomide
YAP1	Yes-associated protein 1
ZFTA	Zinc finger translocation associated
2-HG	2-hydroxyglutarate
α-KG	α-ketoglutarate

1 Introduction

Glioma is a tumor originating from glial cells within the neuroepithelial tissue of the brain and is the most common primary malignant brain tumor, with an incidence of 5–6 persons/(100,000 person-years) [1]. According to the 2021 edition of the WHO Classification of tumors of the CNS, gliomas are classified as grades 1 to 4 [2, 3]. Overall survival for patients with high-grade gliomas is very short, for patients with grade 3 gliomas it is 2–3 years, and for patients with grade 4 glioblastomas it is only 1.5 years [4, 5]. The pathogenesis of gliomas is not yet clear, but the two established risk factors are exposure to high doses of ionizing radiation and hereditary mutations related to rare syndromes with high penetrance [6]. Additionally, carcinogenic factors such as nitrate-rich foods, viral or bacterial infections may also contribute to the development of gliomas [7]. Clinical manifestations of gliomas mainly include increased intracranial pressure, neurological and cognitive dysfunction, and epileptic seizures [8]. Gliomas not only have a significant impact on patients' lives but also have long been a hot topic of research in the medical field. The occurrence, development, and treatment of gliomas involve complex biological and clinical issues, with metabolic abnormalities becoming a focus of attention in recent years [9–11].

Glioma cells are highly dependent on altered metabolic pathways to meet the energy and biosynthetic demands required for their rapid growth and division [12, 13]. These metabolic changes are critical to glioma development and progression, influencing not only tumor proliferation but also therapy resistance and survival. Therefore, understanding the metabolic characteristics of glioma cells is fundamental to advancing research into their pathogenesis, identifying potential therapeutic targets, and improving patient outcomes [14, 15].

In this review, we provide a comprehensive exploration of glioma metabolism, examining the roles of glucose metabolism, lipid metabolism, amino acid metabolism, and other metabolic pathways. By detailing these processes, we aim to highlight how they contribute to glioma growth, survival, and treatment resistance, providing insights that may lead to more effective therapeutic strategies [16–20]. The present study aims to provide elucidateof the alterations in metabolic pathways in gliomas and their associations with tumor growth, drug resistance, and metastasis. By reviewing the latest research advancements and breakthroughs, this paper seeks to deepen understanding in the field of glioma metabolism, offering robust support for future therapeutic strategies and drug development.

2 Classification of gliomas

With the development of pathology and advancements in pathological detection technologies, the genetic background and mechanisms of glioma development are becoming increasingly clear. An increasing number of molecular markers have been proven to play significant roles in the classification, typing, grading, prognosis, and treatment of gliomas [21, 22]. The 5th edition of the "WHO Classification of Tumors of the Central Nervous System," released in 2021, integrates the histological features and molecular phenotypes of gliomas, proposing new classification criteria for these tumors. However, the cellular transformations involved in the development of gliomas are essentially the same (Fig. 1). Below is an overview of the WHO classification and a detailed breakdown of gliomas (Table 1):

1. Adult-type diffuse glioma: This group consists of astrocytoma (IDH mutant), oligodendroglioma (IDH mutant and with 1p/19q codeletion), and glioblastoma (IDH wildtype). In this category, IDH mutation is a key diagnostic marker [23, 24]. Common IDH mutations include the R132H mutation in the IDH1 gene and the R172 mutation in the IDH2 gene. Gliomas with IDH mutation and 1p/19q codeletion are diagnosed as oligodendroglioma, while those without 1p/19q codeletion are diagnosed as astrocytoma, IDH mutant type [25, 26]. Additionally, CDKN2A/B homozygous deletion is also used as a grading marker.
2. Pediatric-type diffuse low-grade gliomas: These are central nervous system tumors found in children, often with distinct molecular and genetic characteristics. The molecular variations in these tumors are divided into two main types: MYB or MYBL1 variant type and the MAPK pathway variant type. The myeloblastosis proto-oncogene (MYB) or MYB-like 1 (MYBL1) variant type primarily involves gene copy number variations and gene fusions, categorizing the variant tumors into types such as diffuse astrocytomas, MYB or MYBL1 variant type, and angiocentric gliomas [27–29]. The MAPK pathway variant type includes variations in genes associated with the MAPK signaling pathway, like neurofibromin 1(NF1), B-Raf proto-oncogene, serine/threonine kinase (BRAF), fibroblast growth factor receptor 1 (FGFR1). Common molecular variations in this type include FGFR1 tyrosine kinase domain duplication, FGFR1 mutations, FGFR1 fusion, and BRAF V600E mutation [30, 31]. Due to the lack of specificity in some molecular variations of the MAPK pathway variant tumors, classical pathological diagnostic methods and results such as histological morphology and immunohistochemistry are crucial.
3. Pediatric-type diffuse high-grade gliomas: It exhibits rapid growth, high invasiveness, cellular atypia, active proliferation, necrosis, and generally has a poor prognosis. The molecular genetics mainly include histone H3 variant type and H3 wild-type and IDH wild-type [32]. The histone H3 variant type comprises diffuse midline gliomas, H3

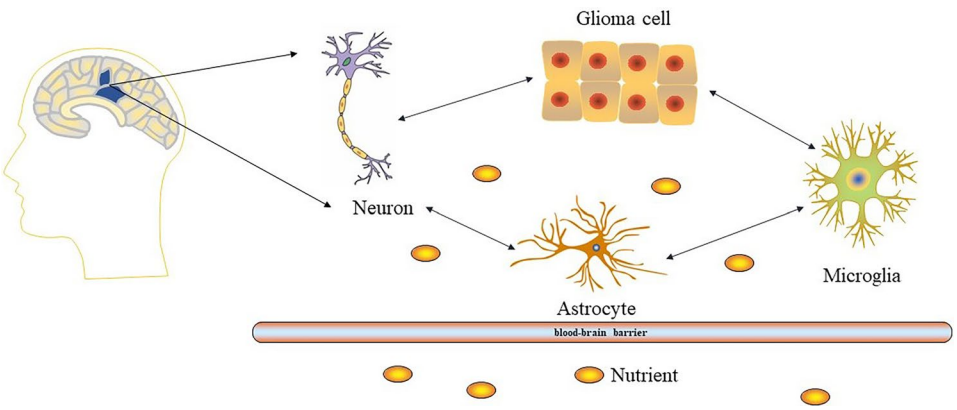

Fig. 1 Diagram of Interactions Between Glioma, Brain Cells, and the Blood–Brain Barrier (The illustration primarily depicts the location of glioma cells in the brain, their interactions with neurons, astrocytes, and microglia, and their acquisition of nutrients from across the blood-brain barrier.)

Table 1 Classification of gliomas

Tumor type	Common mutations/chromosomal rearrangements	Affected population
Adult-type diffuse glioma	IDH1/IDH2 mutations, 1p/19q codeletion, CDKN2A/B deletion	Adults
Pediatric-type diffuse low-grade gliomas	MYB/MYBL1 variants, MAPK pathway variations (NF1, BRAF, FGFR1)	Children
Pediatric-type diffuse high-grade gliomas	H3 K27M, H3 G34 mutations, TP53 mutations	Children, young adults
Circumscribed astrocytic gliomas	KIAA1549-BRAF fusion, BRAF V600E, TSC1/TSC2 mutations	Children, young adults
Glioneuronal and neuronal tumors	BRAF V600E, BRAF fusions, FGFR1 variants	Children, young adults
Choroid plexus tumors	ZFTA fusion, YAP1 fusion, MYCN amplification	Children, adults
Other tumor types (embryonal, meningiomas, pineal)	SMARCB1/SMARCA4 mutations, NF2 mutations	Children, adults

K27 variant type, and diffuse hemispheric gliomas, H3 G34 mutation type [33]. The H3 K27 variant type involves mutations in H3.3 and H3.1 genes, accompanied by mutations such as TP53 and activin A receptor type 1 (ACVR1). The H3 wild-type and IDH wild-type encompass IDH wild-type and histone H3 wild-type gliomas [34]. Based on DNA methylation characteristics, they can be further subtyped into categories such as receptor tyrosine kinases1(RTK1), RTK2, and MYCN types [33, 35].

4. Circumscribed astrocytic gliomas: These tumors can be classified into three subtypes: pilocytic astrocytomas, pleomorphic xanthoastrocytomas, and subependymal giant cell astrocytomas. They are characterized by their slower growth rate and generally non-invasive nature, presenting as well-demarcated, localized masses in the brain. Common molecular variations in pilocytic astrocytomas include KIAA1549-BRAF fusion and other BRAF-related variations [36, 37]. Pleomorphic xanthoastrocytomas typically carry the BRAF V600E mutation and CDKN2A/B homozygous deletion [38]. Subependymal giant cell astrocytomas are often associated with TSC1 and TSC2 mutations. A typical variation in chordoid gliomas is the PRKCA D463H mutation [35, 39, 40].
5. Glioneuronal and neuronal tumors: The main characteristic of these tumors is that the tumor cells exhibit features of neurons and/or neuroglial cells, with molecular genetics showing variations related to the MAPK pathway. For example, gangliogliomas frequently exhibit BRAF V600E mutations and various BRAF fusions, while embryonal tumors with multilayered rosettes demonstrate FGFR1 variations and BRAF-related variations [41, 42]. Additionally, polymorphous low-grade neuroepithelial tumors of the young and extraventricular neurocytomas also display typical molecular variations associated with the MAPK pathway [43, 44]. The newly defined mucinous glioneuronal tumors showcase unique DNA methylation profiles [45].
6. Choroid plexus tumors: Choroid plexus tumors originate from the choroid plexus cells in the brain ventricles or spinal cord central canal. Supratentorial choroid plexus tumors are divided into zinc finger translocation associated (ZFTA) fusion-positive and YAP1 fusion-positive types [46]. The ZFTA fusion-positive type is associated with a poorer prognosis and mainly occurs in children, while the YAP1 fusion-positive type, predominantly found in children, has a relatively better prognosis [47]. Supratentorial choroid plexus tumors without ZFTA and YAP1 fusions are less common and exhibit diverse molecular variations [48, 49]. Posterior fossa choroid plexus tumors are divided into posterior fossa type A and posterior fossa type B groups based on DNA methylation profiles, with the PFA group occurring mainly in infants and toddlers with a worse prognosis and the PFB group primarily in older children or adults with a relatively better prognosis [50, 51]. Some spinal choroid plexus tumors are characterized by MYCN amplification, showing aggressive invasion and metastatic potential, leading to a worse prognosis [52]. Often, these tumors are associated with NF2 mutations, commonly linked with Type 2 neurofibromatosis [53].
7. Other types of tumor models: Other types of tumor models primarily include embryonal tumors, meningiomas, and pineal region tumors in the central nervous system. In CNS embryonal tumors, AT/RTs commonly exhibit SMARCB1 or SMARCA4 mutations [54]. For embryonal tumors with multilayered rosettes, C19MC amplification is a typical variation. Approximately 60% of meningiomas show NF2 mutations, while non-NF2 variant meningiomas are more complex and include various pathway variations [55]. In pineal region tumors, key mutations or deletions in SMARCB1 characterize SMARCB1 mutation-type pineal region myxoproliferative lesions [56].

3 Metabolic reprogramming of glioma cells

During the malignant transformation of gliomas, a series of changes in their principal metabolic pathways, known as metabolic reprogramming, marks a crucial hallmark of cancer progression [57]. Metabolic reprogramming extends beyond mere metabolic alterations; it may also trigger and regulate tumor cell plasticity, thereby facilitating malignant progression [58]. In a healthy physiological state, cells support their normal growth needs by balancing various pathways such as carbohydrate, lipid, and amino acid metabolism (Fig. 2) [59]. In contrast, tumor cells, due to their intrinsic proliferation characteristics, require more energy to support rapid growth. To meet this high energy demand, tumor cells commonly resort to two main metabolic pathways: oxidative phosphorylation and aerobic glycolysis (the Warburg effect) [60, 61]. During oxidative phosphorylation, the energy generated from the oxidative breakdown of organic compounds is used to synthesize ATP [62]. Conversely, aerobic glycolysis, even in the presence of ample oxygen, involves the incomplete metabolism of glucose through the glycolytic pathway, providing both energy and metabolic intermediates like fructose-1,6-bisphosphate, pyruvate, and lactate for rapid tumor cell proliferation [63]. These intermediates not only supply energy but also feed into other metabolic pathways, leading to shifts in the proportion and composition of various pathways, including glycolysis, oxidative phosphorylation, the pentose phosphate pathway, lipid metabolism, and amino acid metabolism, to accommodate

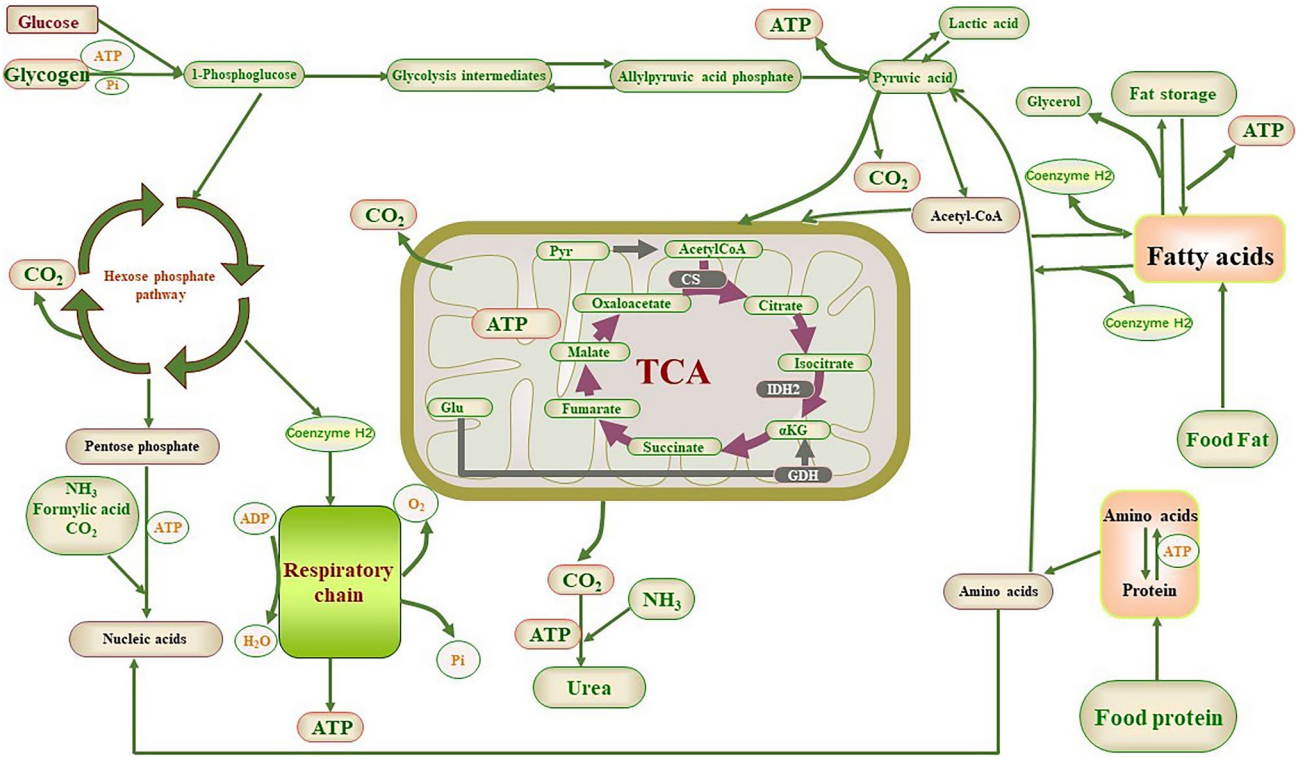

Fig. 2 Energy metabolism in gliomas (Tumor cells often rely on aerobic glycolysis (Warburg effect), converting glucose to lactate even in the presence of oxygen to rapidly generate energy and building blocks for growth. Under hypoxic conditions, they switch to anaerobic glycolysis, breaking down glucose without oxygen. Additionally, tumor cells can use other pathways like fatty acid oxidation and pyruvate catabolism, depending on the tumor type, environment, and regulatory mechanisms.)

the rapid proliferation of tumor cells [64]. Furthermore, lactate produced during glycolysis can acidify the extracellular matrix, promoting tumor invasion and metastasis, while also contributing to resistance to various treatments, including increased drug efflux, activation of DNA damage repair, drug inactivation, epigenetic alterations, mutations in drug targets, activation of survival pathways, and evasion of programmed cell death [65]. Thus, metabolic reprogramming plays a pivotal role in tumor growth, development, and treatment resistance.

The metabolic reprogramming in gliomas exhibits distinct characteristics across different pathological grades or classifications [66]. Low-grade gliomas(LGGs) show a milder metabolic phenotype compared to high-grade gliomas (such as glioblastoma multiforme), relying more on oxidative phosphorylation than on aerobic glycolysis [67]. IDH-mutant gliomas display a unique metabolic phenotype characterized by the accumulation of the oncometabolite 2-HG, as opposed to IDH-wildtype gliomas, which demonstrate more aggressive metabolic reprogramming features, such as enhanced glycolysis, altered amino acid and lipid metabolism, and increased angiogenesis [68, 69]. Oligodendrogliomas and astrocytomas also differ metabolically, with the former typically featuring IDH mutations and 1p/19q codeletion, presenting a metabolic profile that balances oxidative phosphorylation and glycolysis, whereas the latter varies in metabolic profiles based on grade and IDH mutation status [70]. Understanding these metabolic differences is critical for developing targeted therapies and improving patient outcomes.

4 Energy uptake in gliomas cells

4.1 Glucose metabolism in gliomas

Under conditions of ample oxygen, glioma cells preferentially convert glucose to lactate via glycolysis, a process that yields less energy but supports the rapid proliferation needs of the tumor cells [71]. Glioma cells not only generate energy through glycolysis but also produce bicarbonate, lactate, and nicotinamide adenine dinucleotide. The accumulation of lactate provides an acidic environment conducive to tumor invasion, neovascularization, and suppression of immune

cell function and activity. Glioma-produced lactate is reabsorbed by surrounding cells and converted back to pyruvate, re-entering the energy production cycle, thereby promoting tumor growth and dissemination [9, 72, 73]. Studies indicate that glucose transporter proteins 1(GLUT1) and GLUT3 are upregulated in glioma cells, facilitating tumor cell growth and correlating with reduced patient survival rates [74]. Hence, specific inhibitors targeting GLUT3 have demonstrated potential in reducing glucose uptake and glycolytic capacity [75]. Moreover, an increase in proteins associated with glucose metabolism, such as HK2 and PDK, has been observed in glioma cells [76–78]. The knockdown or inhibition of HK2 significantly impedes glioma growth.

Under hypoxic conditions, glioma cells exhibit elevated expression of PDK, an inhibitor of pyruvate dehydrogenase, regulating the entry of pyruvate into the TCA cycle. This modulation shifts energy production from oxidative phosphorylation to glycolysis [79]. The intracranial delivery of the PDK inhibitor DCA effectively reverses the Warburg effect in TMZ-resistant cells, significantly enhancing survival in glioma animal models [80]. Additionally, oral administration of DCA in glioma patients inhibits PDK, though definitive conclusions regarding DCA as a treatment for human glioma remain pending (NCT00540176) [81]. DCA functions by inducing cell cycle arrest, reducing mitochondrial reserve capacity, and increasing oxidative stress and DNA damage. In an orthotopic glioma mouse model, combination therapy with DCA and radiotherapy significantly prolongs median survival, highlighting the potential utility of glucose metabolism inhibitors in overcoming resistance to TMZ/radiotherapy [82]. This process is a key focus in the study of gliomas' sugar metabolism (Table 2).

The tumor microenvironment (TME) plays a crucial role in regulating glucose metabolism in gliomas. Factors such as hypoxia and nutrient limitation within the TME lead to the upregulation of GLUTs, particularly GLUT1 and GLUT3, to meet the energy demands of rapidly proliferating tumor cells. Hypoxia-inducible factor 1 (HIF-1) is a key regulator under hypoxic conditions, driving the expression of GLUTs and enhancing glucose uptake [67, 83]. Studies have shown that the expression of GLUTs increases with tumor grade and adapts to environmental changes, such as oxygen availability [84]. This metabolic adaptation highlights GLUTs as potential therapeutic targets in disrupting glioma energy supply.

Glucose metabolism is vital for gliomas development, involving metabolic reprogramming and various molecular mechanisms. Understanding these processes is key to developing new treatments targeting glucose metabolism, which could improve survival and quality of life for gliomas patients.

Table 2 Recent advances in gliomas glucose metabolism

Main research content	Year
RCC2 is a mitotic regulator that stabilizes the transcription factor BACH1 at its C-terminus. This leads to the upregulation of Hexokinase 2 (HK2), promoting glucose metabolism and accelerating tumor growth.	[85]
High glucose levels cause HK2 detachment from mitochondria and phosphorylate IκBα, increasing PD-L1 expression and aiding gliomas growth.	[86]
Cys207 palmitoylation and DHHC9-mediated S-palmitoylation are key for maintaining GLUT1 in the plasma membrane, greatly impacting GBM tumor growth and prognosis.	[87]
HDAC2 overexpression in glioblastoma (GBM) is linked to altered glucose metabolism, with its knockdown affecting GLUT3 via miR-3189. This highlights HDAC2's critical role in GBM and potential treatment strategies.	[88]
Research shows that lncRNA-XIST regulates glucose metabolism in gliomas, affecting cell functions like viability and apoptosis through the miR-126/IRS1/PI3K/Akt pathway, offering insights for potential gliomas treatments.	[89]
Selenium nanoparticles selectively kill gliomas cells, inducing apoptosis and disrupting their glucose metabolism, while minimally affecting healthy cells, offering a promising approach for gliomas therapy.	[90]
HOXA3 activates aerobic glycolysis, which promotes cell proliferation and tumor growth in glioblastoma. It also interacts with KDM6A, affecting glucose metabolism and tumor progression by altering histone modifications.	[91]
Research shows that using the small molecule inhibitor EPIC-0412 in combination with other inhibitors can effectively disrupt glioma cell metabolism, reduce ATP production, inhibit cell proliferation and growth, and prolong survival in mouse models.	[92]
Research has uncovered a new mechanism in glioblastoma involving ZCRB1, circHEATR5B, HEATR5B-881aa, JMJD5, and PKM2, which regulates aerobic glycolysis and cell proliferation, offering novel treatment strategies and targets for GBM.	[93–95]
Knocking out PGM1 impairs GBM cells' survival and energy processes, inhibiting tumor growth, while its overexpression under low glucose enhances these functions through a Myc feedback mechanism.	[96]

4.2 Lipid metabolism in gliomas

Lipids are vital structural and functional components of the brain, comprising approximately 50% of its dry weight. In gliomas, abnormal lipid metabolism is intricately linked to the disease's development and progression. This includes the reprogramming of lipid biosynthesis pathways, the involvement of key enzymes and regulatory factors, and the relationship between lipid metabolism and treatment resistance. The dysregulated lipid metabolism in gliomas primarily affects free fatty acids and cholesterol, which play a critical role in supporting tumor growth and contributing to therapy resistance.

4.2.1 Fas

Fatty acid (FAs) metabolism plays a crucial role in gliomas, as it is intimately linked with tumor growth, invasion, drug resistance, and modulation of the tumor microenvironment. There are two main pathways of fatty acid utilization within tumors: Firstly, synthetic metabolism, primarily for the production of new lipid bilayers, vesicular membranes, and other biomolecules. Secondly, catabolic metabolism, wherein peroxisomes and mitochondria in cells produce ATP through α-FAO and β-FAO, providing energy for glioma proliferation. Importantly, synthetic and catabolic metabolic processes cannot and do not occur simultaneously within cells, as the by-products of biosynthesis/oxidation reactions inhibit their opposing reactions [97]. However, FA synthesis and metabolism can occur simultaneously within different spatial locations within the tumor. FAs uptake is more prominent in higher-grade tumors like glioblastoma due to their increased energy demands and metabolic flexibility. Studies show that higher-grade gliomas rely more on fatty acid metabolism compared to lower-grade gliomas, which rely more on glucose metabolism [98, 99].

4.2.1.1 Fas uptake Glioblastoma cells significantly enhance fatty acid uptake to support their rapid proliferation and growth, differing notably from normal cells through several mechanisms. Firstly, the activation of fatty acid metabolic pathways such as PI3K/Akt/mTOR and AMPK indirectly promotes the absorption and utilization of fatty acids by regulating the expression of fatty acid transport proteins and enzymes involved in Fatty Acid Oxidation (FAO) [100]. Secondly, glioblastoma cells increase fatty acid uptake by upregulating the expression patterns of specific fatty acid-binding proteins and fatty acid transporters, such as platelet glycoprotein 4 (CD36) [101]. Thirdly, the glioblastoma microenvironment, by secreting cytokines like interleukins and tumor growth factors, activates receptors on the surface of tumor cells, enhancing the expression and activity of fatty acid transport proteins and further promoting fatty acid uptake [102].

4.2.1.2 Synthetic metabolism Fatty acid synthase (FASN) in gliomas, unlike fatty acid oxidation, occurs in the cytoplasm. Here, citrate serves as a substrate for ATP-citrate lyase, producing cytoplasmic acetyl-CoA. The rate-limiting step in fatty acid synthesis involves acetyl-CoA carboxylase converting acetyl-CoA to malonyl-CoA, which is subsequently used by FASN to synthesize fatty acids. This process is primarily regulated by the transcription factor Sterol regulatory element-binding protein 1 (SREBP-1), which controls the expression of lipogenic genes [103]. Notably, the high expression of FASN is positively correlated with the malignancy of gliomas, especially in high-grade gliomas such as GBM. This elevated FASN expression is associated with an increased demand for lipid synthesis, supporting the rapid proliferation and invasive growth of tumor cells [104, 105].

Studies have shown that Epidermal Growth Factor Receptor (EGFR) signaling, by activating SREBP-1, leads to the transcription of lipogenic genes, correlating directly with the level of EGFR activity in tumors [106]. Specifically, EGFR signaling induces glucose uptake, which is then used for glycosylation of the SREBP cleavage-activating protein enzyme. This glycosylated SREBP cleavage-activating protein can enter the Golgi apparatus for modification of SREBP-1 [107].

Given the pivotal role of EGFR signaling in regulating FAS, gliomas with EGFR variant III amplification (EGFRvIII, the most common functional gain-of-function mutation of EGFR in glioma) demonstrate significantly increased lipogenesis and overall metabolic activity. Further studies have indicated that AMPK can phosphorylate ACC, and activating AMPK can inhibit the growth of EGFRvIII glioma cells both in vitro and in vivo.

Several studies have also explored disturbances in the downstream steps of FA_S in glioma cells. It has been found that the expression levels of FASN enzyme are significantly higher in glioma tissues compared to normal neural tissues in humans and rats [108, 109]. Cell apoptosis increases and S-phase cell accumulation occurs through either RNAi-mediated knockdown of FASN or the FA_S inhibitor cerulenin. Additionally, it has been discovered that FASN

levels are enriched in extracellular vesicles derived from glioma cell lines and human plasma, suggesting that plasma extracellular vesicle levels can serve as a non-invasive biomarker for gliomas [109].

Since FA_S promotes several aspects of glioma metabolism, the FA component of the diet may influence glioma growth. A high-fat diet leads to FA accumulation in tumors, increasing glioma stem cell populations, promoting tumor growth, and preventing necrotic cell death in glioma mouse models by affecting sulfur metabolism and upregulating CD36 levels [110, 111]. Pharmacological or genetic blockade of CD36 leads to a reduction in stem cell phenotype and decreases in vivo tumor growth.

Lipid droplets (LDs) play a crucial role in storing excess lipids in tumor cells, and monounsaturated fatty acids (MUFAs) are particularly important in promoting LD formation. Studies have identified SOAT1 as a key enzyme responsible for LD formation, and the inhibition of LD formation using shRNA or the SOAT inhibitor avasimibe has been successful in preclinical models. Furthermore, LDs have been shown to have anti-apoptotic effects and contribute to chemotherapy resistance, suggesting that targeting LDs may offer a valuable therapeutic approach [112, 113].

The metabolic switch between synthetic and catabolic metabolism involves the regulation of MUFA and saturated fatty acid levels, which is essential for the transition between synthetic and catabolic processes in tumors [114]. This process, catalyzed by enzymes like SCD, is fundamental for tumor growth, with inhibition of SCD reducing proliferation and inducing apoptosis [115]. Additionally, the SCD pathway is significant for chemotherapeutic resistance and membrane stability in gliomas [116, 117]. Another key aspect is that LDs serve as critical storage for lipids and cholesterol esters in tumour cells, supporting their survival, particularly under stress conditions like hypoxia. Hypoxia-induced enzymes promote LD formation, helping tumour cells adapt by maintaining energy stores. LDs are also linked to increased drug resistance, as they can stabilize membranes, fuel fatty acid oxidation, and support cell survival, making them a potential therapeutic target to overcome treatment resistance [112].

As for gliomas, there are reports highlighting the importance of LDs in regulating energy homeostasis, and studies suggest a potential connection between LDs and FASN. FASN drives de novo lipogenesis, contributing to the formation and accumulation of lipids within LDs [118]. This correlation between FASN activity and LD formation is likely important in supporting energy homeostasis and promoting tumour cell survival, especially under metabolic stress [119].

4.2.1.3 Catabolic metabolism In mammalian cells, there are two types of FAO: α-oxidation and β-oxidation. α-oxidation, a unique process occurring in specialized organelles called peroxisomes, involves the removal of a single carbon from the carboxyl end of certain lipids, allowing their subsequent β-oxidation [120].

Most research on FAO focuses on β-oxidation within mitochondria. It's important to note that only saturated carbon chains can be broken down through the FAO process [121]. Unsaturated FAs require several additional enzymatic steps that translocate and saturate double bonds before complete oxidation. Many enzymes required for FAO are abundantly present in glioma, enabling glioma cells to readily oxidize lipids that promote cell proliferation [122].

Recent studies have shown that upregulation of FAO occurs predominantly in conditions of nutrient deprivation, with dual inhibition of FAO (using etomoxir) and glucose metabolism (using 2-deoxy-D-glucose [2-DG]) yielding significant benefits in animal models of glioma [123]. Furthermore, in another recent study, the mitochondrial enzyme Medium-chain acyl-CoA dehydrogenase (MCAD) was found to be crucial for glioma growth. Inhibition of MCAD in GBM cells (either genetically or pharmacologically) leads to the accumulation of medium-chain FAs, lipid peroxidation, and mitochondrial damage, resulting in apoptosis [124].An interesting use of FAO by glioma cells is to evade anti-tumor responses induced by radiotherapy. Interestingly, radiation upregulates FAO, producing citrate, which provides substrates for acetylation of RelA, thereby promoting Cluster of Differentiation 47 (CD47) expression. This upregulation prevents macrophage phagocytosis post-radiation, leading to tumor regeneration [125]. Ketone metabolism is another byproduct of FAO; these ketone bodies can shuttle out of cells and then be reimported to provide acetyl-CoA for the TCA cycle [126]. Importantly, ketone bodies can cross the blood-brain barrier through endothelial monocarboxylate transporters and can even replace glucose as the brain's main energy source under conditions of prolonged fasting [127]. A recent study suggests that ketogenic diets might promote tumor growth, supporting the possibility that this could occur in glioma. However, the role of ketones in glioma becomes complex, as previous research indicates that glioma cells cannot metabolize ketone bodies like normal neural tissue, making the role of ketogenesis in glioma progression unclear [128, 129]. The significance of FA_S metabolism as a crucial step in glioma cell energy utilization warrants further investigation and the development of new therapeutic targets.

4.2.1.4 Fatty acid metabolism and the tumor microenvironment The tumor microenvironment, comprising tumor cells, macrophages, extracellular signaling molecules, and the extracellular matrix, collectively influences the development and progression of tumors. Research indicates that FAs metabolism plays a crucial role in regulating the tumor microenvironment in gliomas. TAMs in glioma play a key role in modulating the tumor microenvironment. Monoacylglycerol lipase (MAGL), which hydrolyzes monoacylglycerol into glycerol and free fatty acids, is associated with cancer aggressiveness due to high MAGL expression. The activity of MAGL leads to the accumulation of Prostaglandin E2, which can induce TAMs to polarize towards the M2 type, thus enhancing the self-renewal capacity of glioma stem cells and promoting proliferation and invasion of gliomas cells [130]. Hypoxia is another important characteristic of the glioma's microenvironment. Under hypoxic conditions, Ras-driven gliomas cells can uptake FAs from the exterior to promote cell proliferation and maintain membrane integrity [131]. Moreover, Ras-driven gliomas cells can bypass the SCD1-mediated pathway, acquiring FAs from the exterior to support cell proliferation and adapt to the hypoxic tumor microenvironment. In summary, the gliomas microenvironment includes multiple factors, among which FA metabolism and TAMs play key roles in its regulation [132]. The treatment of gliomas, particularly targeting glioma stem cells and regulating adaptation to hypoxic environments, is expected to become a crucial direction for future research and drug development.

4.2.2 Cholesterol metabolism

Cholesterol plays multiple vital roles in the body, including being a key component of cell membranes and plasma lipoproteins, as well as a precursor to steroidal hormones, bile acids, and oxysterols [133]. In the central nervous system, cholesterol is primarily found in myelin sheaths and is a major component of synaptic vesicles, crucial for their formation and function. Recent research has discovered that cholesterol is also involved in the formation of neuronal dendrites and axons, neuronal survival, proliferation of astrocytes, and the transmission of signals related to neural repair and development [134]. The homeostasis of cholesterol in gliomas cells is dynamically regulated by various factors, including cholesterol uptake, synthesis, and efflux. Understanding these regulatory mechanisms and their roles in the development of gliomas holds significant research value [135].

Cholesterol metabolism plays a key role in the survival and progression of gliomas. The high cholesterol demand of tumor cells is not only reflected in increased cholesterol synthesis, but also in cholesterol utilization and regulatory mechanisms [136, 137]. Under normal circumstances, the dynamic balance of cholesterol in mammals is controlled by a complex network of molecular regulators, among which SREBPs and Liver X Receptors play key roles [138].

SREBPs are a class of membrane-bound transcription factors that regulate the expression of multiple genes in the cholesterol synthesis pathway, with SREBP-2 primarily involved in the regulation of cholesterol synthesis. Activation of this pathway typically leads to the upregulation of HMG-CoA reductase and low-density lipoprotein receptor, thereby increasing cholesterol synthesis and uptake [139, 140]. In gliomas, the upregulation of SREBP2 and associated enzymes is linked to mutations in the epidermal growth factor receptor and abnormal activation of the PI3K signaling pathway, thereby promoting tumor cell proliferation [141]. However, some studies suggest that high expression of SREBP2 in diffuse gliomas may be associated with a better prognosis, which could be related to the molecular subtype of the tumor and environmental factors, necessitating further research to explain this phenomenon [142].

On the other hand, Liver X Receptors regulate the efflux and metabolism of cholesterol by inducing the expression of ATP-binding cassette transporter A1 and adenosine triphophate (ATP)-binding cassette (ABC) transporter G1 genes, thus promoting the expulsion of cholesterol from cells and reducing the expression of low-density lipoprotein receptor. This mechanism helps to maintain cholesterol homeostasis and to some extent inhibits the growth of tumor cells [135]. Besides the synthesis and regulatory pathways of cholesterol, cholesterol metabolism products also have a significant impact on tumor biology. For example, Oxysterol Hydroxylase Cholesterol (OHCs), including 25-OHC and 7α-25-OHC, are elevated in tumor cells and closely associated with immunity, inflammation, and tumor development [143]. These OHCs are not only involved in cholesterol metabolism, but also regulate multiple signaling pathways that affect tumor cell growth and immune responses [144]. In addition, some OHCs have effects on viral replication, immunoglobulin synthesis and inflammatory factor regulation. It has been shown that in glioma cells, dysregulation of cholesterol metabolism activates the inflammatory response by up-regulating key inflammatory mediators such as IL-1β, TNF-α and IL-6, affecting the immune response in the tumor, especially in tumor settings such as gliomas [145, 146]. In addition, these inflammatory mediators in turn alter cholesterol metabolism by regulating cholesterol synthases and transport proteins (e.g., ATP-binding cassette transporter proteins) to promote or inhibit cholesterol synthesis and efflux. For example, induction of up-regulation of cholesterol-25-hydroxylase expression leads to increased synthesis of 25-OHC,

which can chemotactically affect monocytes/macrophages via the EBV-induced gene 2 receptor [147]. In summary, cholesterol metabolism plays a complex and diverse role in the biology of gliomas and other types of tumors, involving cholesterol synthesis, regulation, efflux, and related metabolic products.

4.3 Amino acid metabolism

Amino acids are an important source of intracellular energy and nutrients, as well as intermediates linking carbohydrate, lipid and nucleotide metabolism. Among them, glutamate is involved in a variety of biological reactions such as energy production, macromolecule synthesis, and signal transduction, which has an important impact on cancer development [148].

Research has discovered that the accumulation of α-2HG caused by IDH1 mutations can inhibit the amino transferases branched-chain aminotransferase 1 and branched-chain aminotransferase 2, reducing glutamate levels and increasing the synthesis of glutathione, thereby affecting tumor cell survival [149]. Additionally, amino acid metabolism plays a crucial role in regulating cell growth and synthesis by activating the mTOR pathway. In particular, mTORC2 serves as a key regulator by controlling the activity of the glutamine-glutamate antiporter (xCT). Through this regulation, mTORC2 integrates growth factor signals with amino acid metabolism, facilitating cellular nutrient uptake and modulating metabolic processes. This ultimately enhances the proliferative and survival capacities of tumor cells, promoting tumor growth and progression [150, 151].

Abnormalities in amino acid metabolism can lead to variations in the glioma microenvironment, particularly due to the overexpression of amino acid transporter 1 in gliomas cells and the blood-brain barrier. This overexpression causes rapid amino acid transport, leading to significant differences between the internal and external cellular environments, involving levels of adenosine triphosphate and glutathione [152]. Additionally, amino acid metabolism can affect immune evasion. By interfering with glutamine expression, the tumor microenvironment can be altered, promoting the generation of highly active anti-tumor T cells, providing potential opportunities for new cancer treatment strategies [153].

4.4 Nucleic acid metabolism in gliomas

Nucleic acid metabolism plays a pivotal role in gliomas, exerting a crucial influence on tumor growth, survival, and treatment responses. It involves the synthesis and repair of DNA and RNA, as well as the regulation of the cell cycle, thereby impacting the pathogenesis of gliomas from multiple angles [154]. Overall, nucleic acid metabolism in gliomas serves multiple functions, including promoting cell proliferation, maintaining DNA integrity, and affecting immune evasion [155, 156].

Specifically, abnormalities in nucleic acid metabolism are often associated with changes in the activity of key enzymes. For example, IDH mutations are a common feature of some types of gliomas (such as secondary glioblastomas), whereas they are uncommon in the majority of primary glioblastomas, which are usually IDH wild-type tumors [157]. Mutations in IDH1/IDH2 produce 2-HG instead of normal α-KG, an oncogenic metabolite that inhibits many α-KG-dependent enzymes, thereby affecting DNA and histone methylation and nucleic acid metabolism. 2-HG is a metabolite that is structurally similar to α-ketoglutarate, and the accumulation of 2-HG due to IDH mutations inhibits α-ketoglutarate-dependent demethylases, which play a role in DNA and histone demethylation, thereby affecting epigenetic regulation (e.g., inhibition of DNA and histone demethylase, leading to global DNA hypermethylation), one-carbon metabolism methylase, which plays a role in DNA and histone demethylation, thereby affecting epigenetic regulation (e.g. inhibition of DNA and histone demethylases, leading to global DNA hypermethylation), nucleotide synthesis, cellular redox status and metabolism (e.g. accumulation of 2-HG disrupts NADPH-dependent homeostasis in the cell, thereby affecting the synthesis of precursors required for nucleotide metabolism), DNA repair, etc. to drive tumor progression and DNA repair to drive tumor progression [146, 158, 159]. Besides IDH mutations, other enzymes related to nucleic acid metabolism, such as ribonucleotide reductase1 and ribonucleotide reductase2, thymidine kinase, and poly ADP-ribose polymerase, also play significant roles in the development of gliomas [160, 161]. These enzymes are crucial for providing the nucleotide precursors necessary for DNA replication and repair. Their aberrant activity can lead to disturbances in nucleic acid metabolism processes, increasing malignant behavior and thereby promoting tumor growth and spread.

Furthermore, in the nucleic acid metabolism of gliomas, miRNAs play a significant regulatory role. miRNAs can act as tumor suppressor genes or oncogenes by directly regulating key enzymes and signaling pathways related to nucleic acid metabolism, influencing tumor behavior. Overall, miRNAs in gliomas intricately regulate genes and pathways related to nucleic acid metabolism, affecting tumor growth, survival, and response to treatment [162, 163]. These findings highlight

the potential of miRNAs as therapeutic targets, suggesting that targeting these miRNAs may provide new treatment strategies for glioma patients.

5 Metabolic and genetic alterations in gliomas

Currently, the molecular basis and energy metabolism in gliomas are not fully understood. Present research indicates that frequent amplifications of genes encoding RTKs and mutations in IDH have become central participants in altering the metabolism of gliomas.

5.1 RTK pathways

RTKs play a critical role in reprogramming metabolism in gliomas (Fig. 3). RTKs are a class of transmembrane receptors whose activation triggers a cascade of signaling pathways, affecting cell growth, differentiation, migration, and metabolism. Currently, there are 58 reported RTKs, divided into 20 families, including well-known ones such as the EGFR family, Platelet-derived growth factor receptors family, and Vascular endothelial growth factor receptor family [164, 165]. Over 100 growth factors have been identified that can activate RTKs.

Recent research from The Cancer Genome Atlas (TCGA) has revealed that 66% of primary glioma samples exhibit amplifications or mutations in RTK genes. Specifically, in 50% of primary gliomas, amplification or mutation of EGFR is the only observed RTK alteration. Mutations in EGFR lead to dysregulation of multiple downstream signaling pathways, including PI3K, Akt, MAPK, and Phospholipase C Zeta 1, playing a crucial role in tumor growth and progression [9, 166]. Besides EGFR, amplifications or mutations in PDGFR, c-Met, Tie, Axl, Discoidin domain receptor 1, and Eph also contribute to glioma biology [167].

Chemotherapy significantly impacts the expression of RTKs, as RNA sequencing of 135 primary high-grade gliomas and 47 recurrent high-grade gliomas showed alterations in at least 17 of the 58 analyzed RTK genes post-chemotherapy [168].

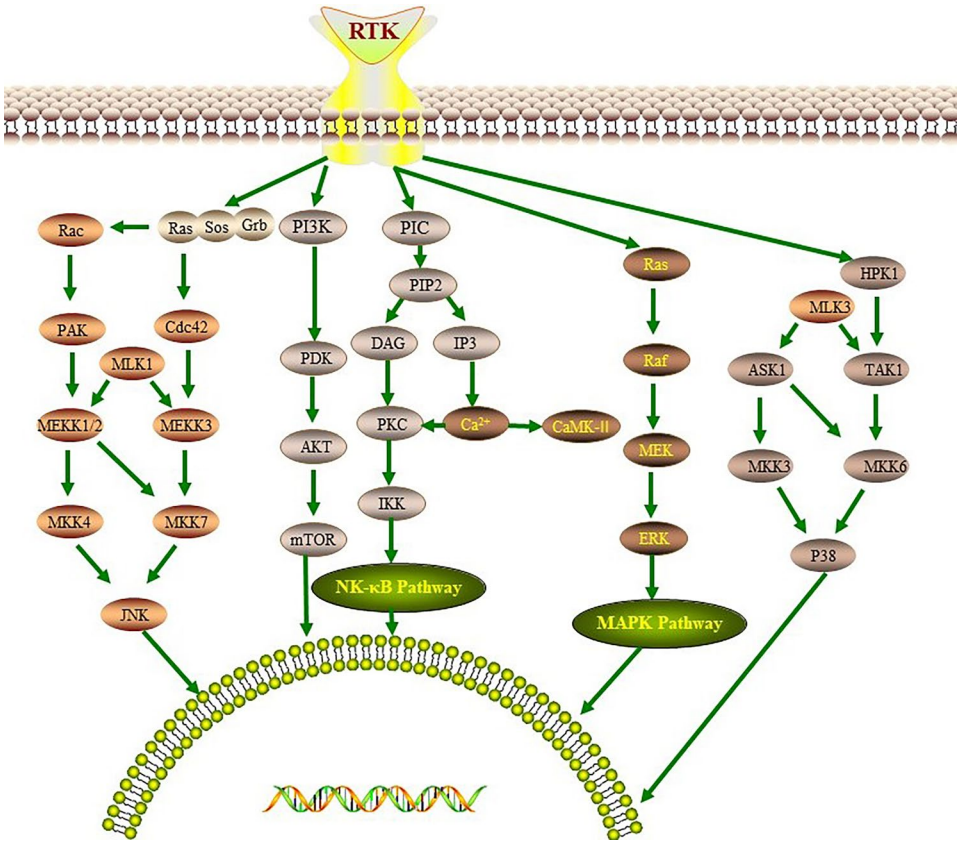

Fig. 3 RTK signaling pathways in gliomas metabolism (The progression of gliomas is closely associated with the overexpression of RTKs and the abnormal activation of their signaling pathways. This overexpression leads to the phosphorylation of tyrosine kinases, activating downstream pathways associated with factors such as PI3K, EGF, VEGF, and PDGF. Consequently, this results in increased cell proliferation and growth, as well as reduced apoptosis, thereby facilitating tumor development.)

The mutation of RTK genes can either promote or inhibit tumor progression [169]. Further research into the expression profiles of RTKs during treatment could improve clinical risk stratification [170].

The RTK-PI3K-AKT-mTOR signaling pathway is central to regulating tumor growth by controlling cell survival, proliferation, protein translation, and motility [171, 172]. This pathway is activated in most glioma patients and is influenced by several alterations, such as Phosphatase and Tensin Homolog (PTEN) loss of function and EGFR amplification/mutation, two hallmarks of glioma genesis [173]. PTEN loss increases Akt activity, which subsequently triggers mTOR, promoting cell proliferation and survival [174, 175].

Dysregulation of the RTK-PI3K-AKT signaling pathway leads to metabolic reprogramming in gliomas, particularly affecting glucose, lipid, amino acid metabolism, and nucleotide synthesis. In glucose metabolism, genes like GLUT1, HK2, and LDHA are upregulated, increasing glucose uptake and lactate production, even under aerobic conditions, a phenomenon known as the Warburg effect. Lipid metabolism is enhanced via FASN expression, which promotes lipid synthesis and the formation of lipid droplets, aiding cell survival under metabolic stress. Amino acid metabolism, particularly the glutamine-glutamate cycle, is also impacted, with GLS upregulation supporting the TCA cycle and nucleotide synthesis. Activation of mTOR boosts the expression of nucleotide synthesis-related genes such as RRM2, driving DNA replication and repair. Lastly, alterations in ROS (reactive oxygen species) levels, regulated by antioxidant genes like nuclear factor erythroid 2–related factor 2 (Nrf2), contribute to both tumor growth and oxidative stress.

5.2 RAS/RAF/MEK/ERK pathway

The RAS/RAF/MEK/ERK pathway in gliomas is a critical signal transduction pathway that significantly impacts various cellular functions such as proliferation, differentiation, survival, migration, and metabolism. This pathway is initiated by the activation of RAS proteins, which in turn activate members of the RAF protein family (Fig. 4) [176]. RAF then activates MEK, which subsequently activates ERK. ERK, as the final effector of this pathway, can enter the nucleus to regulate the expression of multiple genes, thus playing a pivotal role in the cellular processes associated with gliomas [177, 178].

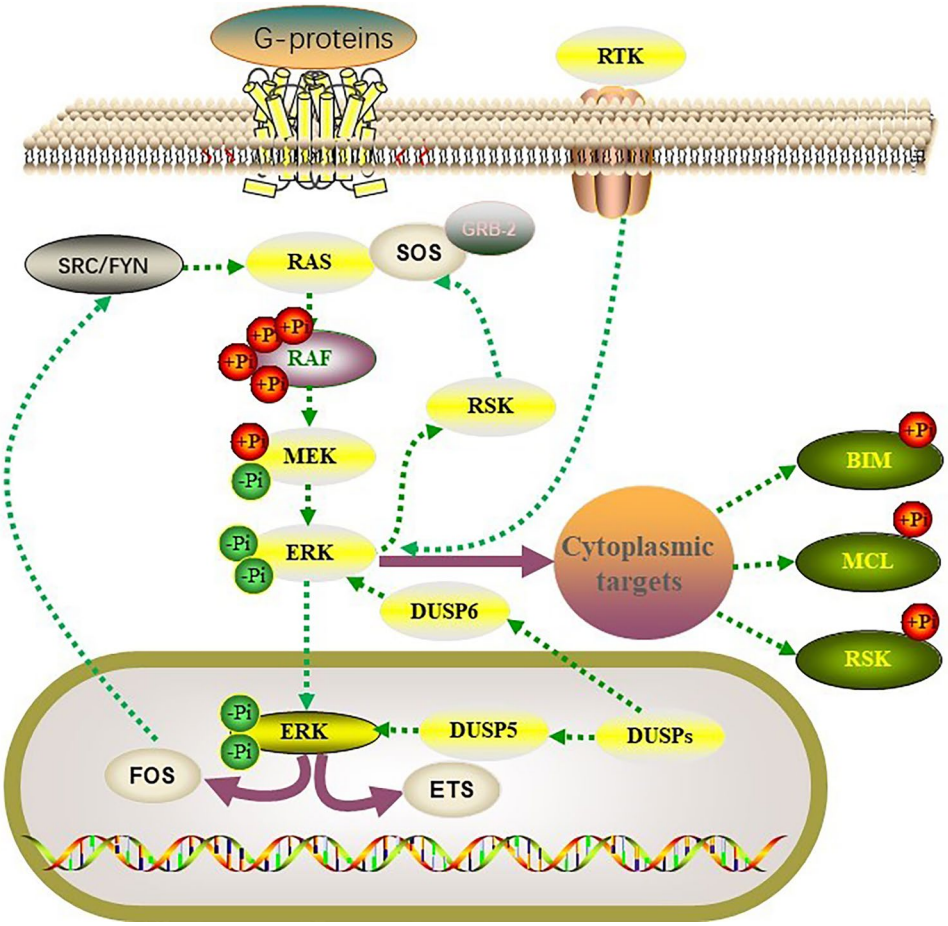

Fig. 4 RAS/RAF/MEK/ERK signaling pathways in gliomas metabolism (Extracellular signals stimulate the proto-oncogene Ras, activating it through binding with GTP, which subsequently phosphorylates and activates Raf. Raf then activates the MEK, which through phosphorylation activates the ERK, ultimately driving gene expression. The activated ERK catalyzes the phosphorylation of numerous cytoplasmic effectors and nuclear transcription factors, thereby inducing cell survival, migration, and proliferation. Inhibiting the abnormal activation of this pathway can effectively suppress the proliferation of glioma cells and improve resistance to TMZ)

Research in gliomas cells has demonstrated the crucial role of the RAS-RAF-MEK-ERK signaling pathway in promoting growth and evading apoptosis. The treatment with oncolytic herpes simplex virus has been shown to enhance the blood-brain barrier penetration of Trametinib, a MEK inhibitor, thereby inhibiting the MEK kinase and preventing the metastasis and growth of gliomas [179]. Additionally, the newly discovered Ras interacting protein PHLDA1 promotes glioblastoma cell proliferation by regulating the RAS-RAF-MEK-ERK signaling pathway, offering a novel target for treatment [180]. Furthermore, inhibitors of isoprenylcysteine carboxyl methyltransferase have been found to effectively inhibit the growth of glioblastoma without toxicity to normal cells, demonstrating the potential of targeting the RAS-RAF-MEK-ERK pathway for glioblastoma treatment [181].

Inhibitors targeting the RAS-RAF-MEK-ERK pathway exhibit potent tumor-suppressive effects and biocompatibility by controlling metabolism and growth development. Additionally, inhibitors of the RAS-ERK pathway can mitigate resistance to conventional radiotherapy and chemotherapy, and enhance the therapeutic efficacy of antibodies targeting PD-1, PD-L1, and CTLA-4. Future research should focus on tailoring treatment regimens for each specific tumor, aiming to achieve substantial therapeutic effects with minimal adverse events by targeting tumor metabolism [182, 183].

5.3 Mutations in IDH gene

IDH enzymes have three isoforms, with IDH1 located in the cytoplasm and peroxisomes, while IDH2 and IDH3 are situated in the mitochondrial matrix [184]. IDH is an essential enzyme involved in several key metabolic processes, including the Krebs cycle, glutamine metabolism, lipid synthesis, and redox regulation (Fig. 5) [185].

IDH mutations lead to the accumulation of D-2-HG in the cytoplasm, resulting in the expulsion of carbohydrates from the Krebs cycle [186]. A ^{13}C metabolic flux analysis demonstrates increased oxidative metabolism in the Krebs cycle and inhibited reductive glutamine metabolism in cells with IDH1 mutations [187]. As cellular metabolism is depleted, several non-Krebs cycle sources of carbohydrates are recruited to compensate for the loss of α-KG.

IDH mutations are common in malignant cancers and are particularly more prevalent in secondary gliomas than in primary gliomas [188]. Triptolide, a potent Nrf2 inhibitor, was found to disrupt glutathione metabolism and display selective cytotoxicity against IDH-mutant gliomas cells, providing a new strategy for the treatment of IDH-mutant malignancies. Meanwhile, IDH1 mutation disrupts the Nicotinamide Adenine Dinucleotide Phosphate / Nicotinamide Adenine Dinucleotide Phosphate Hydrogen balance in cancer cells and increases the demand for glutathione metabolism, in which Nrf2 plays a key role in maintaining glutathione synthesis and scavenging reactive oxygen species [189]. IDH mutant variants impair NADPH consumption, disrupting de novo lipogenesis and leading to increased dependence of cell growth on exogenous lipid sources. This is accompanied by D-2-HG stimulating glutamine-derived lipogenesis under hypoxic conditions to meet the demands of lipid production efficiency [190].

Lactate dehydrogenase A is highly expressed in various cancer cells, but it is silenced in glioma tissues with IDH mutant variants and in glioma cells derived from patients [191]. It has been found that the silencing of LDHA (along with several other glycolytic genes, including CA9 and VEGFA) is associated with high methylation of these gene

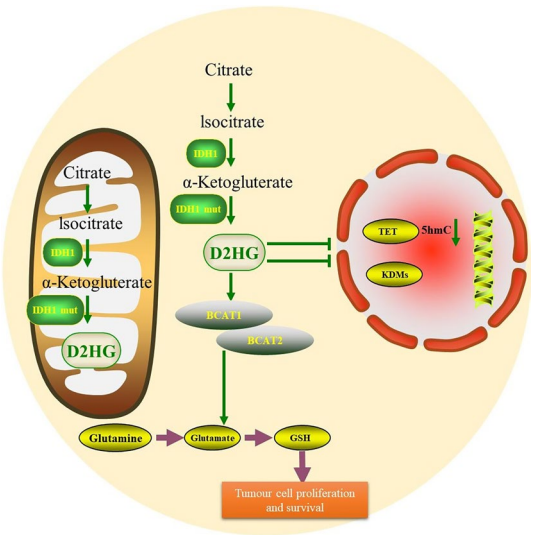

Fig. 5 IDH gene mutations in gliomas metabolism (Mutations in the IDH gene, including three subtypes IDH1, IDH2, and IDH3, play a significant role in energy metabolism and biosynthesis. Current research suggests that mutations in IDH1 and IDH2 are among the critical factors in the origin of gliomas. Mutations in IDH1/2 lead to an enzymatic activity change, catalyzing the reduction of α-KG to D2-HG.)

promoter regions in response to D-2-HG [192, 193]. The overall epigenetic silencing of the glycolytic pathway may explain the slower growth nature of IDH mutant gliomas compared to IDH wild-type gliomas.

However, the role of D2-HG in IDH-mutant gliomas can both promote tumorigenesis and explain their slower growth. As an oncometabolite, D2-HG inhibits α-ketoglutarate-dependent enzymes, leading to epigenetic changes that drive tumor formation. At the same time, D2-HG may impair mitochondrial function and metabolism, limiting the rapid proliferation of tumor cells, which accounts for the typically slower growth of IDH-mutant gliomas [194–196].

In addition, IDH-mutant and wild-type gliomas show significant differences in the DNA methylation patterns of metabolic genes, which not only distinguishes these two glioma types but also impacts mitochondrial DNA (mtDNA) copy number. In IDH-mutant gliomas, studies have observed an increase in mtDNA copy number, whereas no significant changes were found in recurrent cancers [197]. Immunohistochemical clustering based on metabolic composition further reveals distinct subtypes between IDH-mutant and wild-type gliomas, with lactate dehydrogenase A (LDHA) methylation strongly associated with the increased mtDNA copy number in IDH-mutant gliomas [198]. While some studies report that IDH mutations lead to an increase in mitochondrial content, others have found that IDH1 mutations result in decreased mtDNA levels, indicating potential mitochondrial dysfunction. Initially, IDH mutations may enhance mitochondrial biogenesis to cope with metabolic stress, but over time, mitochondrial function deteriorates, leading to reduced mtDNA. Differences in research methods, tumor types, and disease progression stages may explain these varied findings [199–201].

Overall, the acquisition of IDH mutations results in extensive reprogramming of cellular metabolism. Glutamine and/or glutamate serve as key substrates, compensating for metabolic alterations by enhancing pathways involved in lipid and glutathione synthesis.

5.4 Mutations in the tp53 gene

TP53 directly or indirectly regulates metabolic homeostasis, often directing synthetic metabolism towards catabolic metabolism, by modulating key metabolic pathways including central carbon metabolism, lipid and amino acid metabolism, ion metabolism, ammonia detoxification, and polyamine biosynthesis. Glutamine is the most abundant circulating amino acid in serum, serving as a major carbon source for the TCA cycle and malate-aspartate shuttle (Fig. 6). TP53 can link glucose and glutamine metabolism, favoring the accumulation of α-KG.

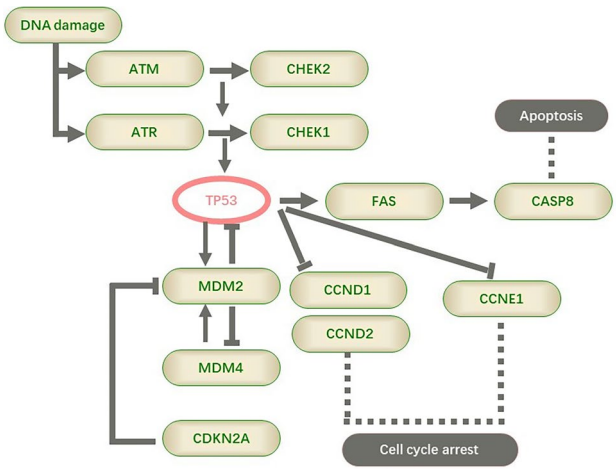

Fig. 6 TP53 gene mutations in gliomas metabolism (When DNA is damaged, the ATM and ATR proteins are activated, which then phosphorylate and activate downstream kinases CHEK1 and CHEK2, thereby halting cell cycle progression to allow time for DNA repair. Concurrently, ATM and ATR activate the tumor suppressor protein p53, which can lead to either cell cycle arrest or apoptosis. The activity and stability of p53 are negatively regulated by MDM2 and MDM4 proteins. Activated p53 can induce the expression of genes such as CDKN2A, which in turn inhibits MDM2, leading to cell cycle arrest. Additionally, p53 can activate the expression of pro-apoptotic genes like FAS, triggering cell apoptosis.)

5.4.1 Tp53 and glucose metabolism

TP53 plays a crucial role in regulating glucose metabolism in tumor cells, including in gliomas. By activating genes like TIGAR, TP53 slows down the rate of glycolysis, reducing the energy production in tumor cells [202]. TIGAR limits tumor growth by inhibiting the formation of fructose-2,6-bisphosphate. Studies show that knocking down TIGAR increases ROS levels, promotes cell death, and enhances the effects of radiotherapy and chemotherapy, indicating that TIGAR plays an important role in metabolism regulation within the tumor microenvironment [203].Furthermore, the p53 protein encoded by TP53 downregulates LIM Homeobox 9 while promoting the expression of the glycolytic enzyme PGK1, which increases lactate levels and enhances the tumorigenicity of glioma cells. The LIM Homeobox 9-PGK1 signaling axis is considered a potential therapeutic target for glioma treatment [204]. Additionally, TP53 activates genes like cytochrome c oxidase 2, maintaining mitochondrial function and promoting oxidative phosphorylation, which is crucial for normal cellular energy metabolism [205].

Notably, TIGAR levels are significantly elevated in gliomas. Its overexpression not only supports tumor growth by reducing ROS levels and increasing NADPH production, but also promotes glucose metabolism through the pentose phosphate pathway (PPP), further sustaining the proliferation and survival of tumor cells. Studies show that TIGAR knockdown can lead to increased ROS accumulation, resulting in DNA damage and cell senescence, and significantly enhances the sensitivity of glioma cells to radiotherapy, making TIGAR a potential therapeutic target [206].

5.4.2 Tp53 and lipid metabolism

TP53 regulates fatty acid metabolism by activating and modulating the expression of guanidinoacetate methyltransferase (GAMT), which promotes FAO and creatine biosynthesis, playing a crucial role in maintaining energy homeostasis during glucose deprivation [207, 208]. Under starvation conditions, TP53-dependent activation of GAMT can induce energy expenditure and promote cell apoptosis. PGC-1α is a regulatory factor of lipid metabolism that binds to the promoter of TP53, promoting cell cycle arrest and ROS clearance in response to glucose starvation [209]. Increasing evidence suggests that TP53 primarily inhibits lipid synthesis metabolism indirectly. TP53 transcriptionally suppresses the expression of SREBPs, critical transcription factors targeting genes involved in fat synthesis [210, 211]. Additionally, p53 inhibits de novo fatty acid synthesis by suppressing the rate-limiting enzyme of the pentose phosphate pathway, glucose-6-phosphate dehydrogenase, thus reducing NADPH levels [210].

5.4.3 Tp53 and amino acid metabolism

TP53 plays a crucial role in regulating the metabolism of aspartate, asparagine, serine, tyrosine, and proline. Studies have shown that TP53's strict regulation of amino acid metabolism is achieved through manipulation of the tumor microenvironment, redox status, and nutrient restriction. For instance, alterations in tyrosine metabolism occur through TP53 loss, and removal of serine can treat TP53-deficient tumors, among other effects [212, 213].

5.4.4 Tp53 and ferroptosis

TP53 can increase cell sensitivity to ferroptosis. Studies have shown that TP53 3KR mutants respond to ROS-induced stress by affecting cell energy metabolism through a key component of the cystine/glutamate antiporter, SLC7A11, demonstrating the connection between TP53 and ferroptosis [214].

Research on TP53 is becoming increasingly in-depth, but many challenges remain in understanding how TP53 suppresses tumors through metabolic pathways, which is the most fundamental question. Additionally, many regulatory functions of TP53 are specific in both space and time. Future research needs to focus more on the behavior and regulatory mechanisms of TP53 at specific time points and under specific conditions.

6 Therapeutic approaches

Current treatments for gliomas are dominated by surgery and pharmacological chemotherapy (Fig. 7). Novel therapeutic approaches encompass a variety of innovative strategies, including targeted therapies (drugs specifically targeting tumour markers), immunotherapy (activation of the patient's immune system to attack the cancer cells), gene and cell

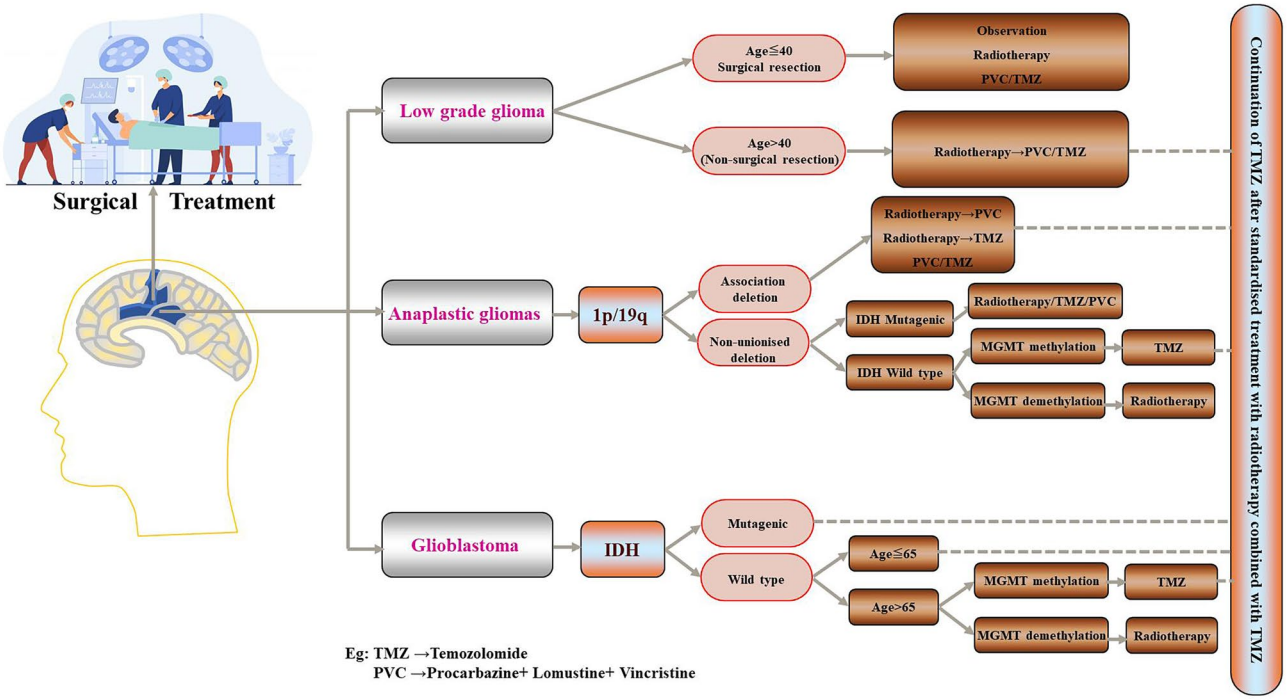

Fig. 7 Treatment options for gliomas (The image outlines the treatment regimen for gliomas based on patient age, IDH gene status, and 1p/19q co-deletion. For low-grade gliomas, surgical resection is typically preferred for younger patients, while older patients may receive a combination of radiotherapy and chemotherapy. The treatment of anaplastic gliomas takes into account the presence or absence of 1p/19q deletion and may include radiotherapy and chemotherapy. Treatment strategies for glioblastoma hinge on whether the IDH gene is of the mutant or wild type, as well as the patient's age, to decide between Temozolomide or radiotherapy. Additionally, the choice of treatment method also considers the methylation status of the MGMT gene to tailor a more effective treatment plan

therapy (gene repair and cellular therapeutic techniques), synthetic lethality (exploiting genetic defects in the cancer cells), metabolic inhibition (targeting of metabolic pathways in the cancer cells), microenvironmental targeting (studying and targeting of the tumor microenvironment), nanomedicine (using nanotechnology to improve the efficiency of drug delivery), and integrative therapies (integrating multiple therapeutic approaches to improve efficacy). Glioma cells primarily produce energy through glycolysis and mitochondrial oxidation [215]. Research indicates dietary restrictions can enhance gliomas' sensitivity to radiation therapy. Dichloroacetate (DCA), an inhibitor of pyruvate dehydrogenase, can cross the blood-brain barrier, activating P126 and mitochondrial ROS production, restoring normal mitochondrial function in 53 out of 125 gliomas patients [81, 216, 217]. 2-Deoxy-D-glucose (2-DG), an inhibitor of glycolysis, blocks this pathway due to its abnormal structure, inhibiting various cancer cells and enhancing the effectiveness of radiotherapy and certain chemotherapies [218, 219]. Therefore, Elovl fatty acid elongase 2 is crucial for the proliferation of gliomas stem cells, a finding aided by computational simulation [220]. Gliomas stem cells exhibit reduced mitochondrial respiration, making them resistant to traditional alkylating chemotherapeutic agents like TMZ and 1,3-bis(2-chloroethyl)-1-nitrosourea [221]. 3-Bromopyruvic acid-1-propyl ester and 1,3-bis(2-chloroethyl)-1-nitrosourea, by inhibiting glycolysis, effectively kill GSCs. Ritonavir, a non-specific GLUT antagonist with low blood-brain barrier permeability, used in conjunction with 1,3-bis(2-chloroethyl)-1-nitrosourea, improves overall survival in the GL261 mouse tumor model [222, 223]. A number of drugs have entered clinical studies in terms of metabolic interventions in the development of gliomas (Table 3).

Metabolic inhibition, as a cancer treatment strategy, should focus on the following future research directions: First, precision targeting of metabolic pathways. For instance, EGFR amplification leads to significant dependencies on metabolic enzymes, including glucose uptake, glycolysis, FASN, membrane lipid remodeling, cholesterol uptake, NAD + production, and epigenetic reshaping. Targeting lysophosphatidylcholine acyltransferase 1 to reduce levels of saturated phosphatidylcholines and disrupt the membrane localization of EGFR variant III blocks EGFRvIII-driven oncogenic signaling and inhibits glioblastoma tumor growth [224]. Second, identifying new metabolic strategies in glioma cells. Considering interactions between genotype, lineage, and environment to find reliable new targets. This research requires not just genetic and pharmacological screening of cell lines but also integrating patient-derived cell line models in vitro and in situ xenografts, along with clinical patient studies [9, 225]. Third, the development of combination

Table 3 Drugs targeting Gliomas Metabolism being studied in clinical trials

Medicines	Clinical batch number	Step	Type of cancer	Numbers	Observational indicators	Research organisation
Metformin	NCT04945148	2	IDH wild type GBM	640	Progression-free survival of RANO	Hopital Foch
Dichloroacetate	NCT05120284	2	GBM	40	Efficacy	University of Florida
ONC201	NCT03295396	2	H3 K27M diffuse midline gliomas	95	Overall mitigation rate	Chimerix
Telaglenastat (CB-839)	NCT03528642	1	IDH-Mutant astrocytoma	40	MTD /RP2D	Comprehensive Cancer Information
BAY1436032	NCT02746081	1	IDH1 mutant solid tumors	81	MTD/RP2D	Bayer
IDH305 Type	NCT02381886	1	IDH1 mutant malignant tumor	166	Incidence of dose limiting toxicity	Novartis
TVB-2640 Type	NCT03032484	2	Astrocytoma	24	Tumor response to RANO	UT Health San Antonio
Eflornithine/AMXT-1501 dicaprate	NCI-2022-10375	1	Diffuse Gliomas Malignant Gliomas	15	Assess the effect of polyamine depletion on the levels of extracellular guanidinoacetate.	Mayo Clinic in Rochester
Perifosine	06–044	2	Malignant Gliomas	32	Clinical and Molecular-Metabolic Phase II	Memorial Sloan Kettering Cancer Center
Dexamethasone	NCT04730869	No	Glioblastoma	22	Overall survival	Wailkato hospital
Metformin	NCT04945148	2	Glioblastoma, IDH-wildtype	640	Reduction of tumor growth	Timone hospital

therapies. Such as the combination of chemotherapy and radiation therapy, targeted therapy with chemotherapy, metabolic inhibition with conventional therapies. Current research shows that the EGFR activity mutant inhibitor, Erlotinib, combined with TMZ, shows enhanced therapeutic effects in glioma patients. DCA, by inhibiting pyruvate dehydrogenase, alters the metabolic state of tumor cells and, when combined with radiotherapy, shows potential for glioma treatment in preclinical models [81, 226, 227]. Fourth, regulation of the tumor microenvironment. In the tumor microenvironment of gliomas, inflammation, oxidative stress and metabolism are closely linked and can work together to drive tumor progression. Pro-inflammatory cytokines (e.g. IL-6, TNF-α and IL-1β) directly influence cellular metabolic pathways by activating signaling pathways such as NF-κB and STAT3 [228, 229]. Inflammation enhances metabolic reprogramming by increasing the rate of glycolysis to provide tumor cells with the energy required for rapid growth. Therefore, multiple therapeutic strategies targeting these factors are of great importance. By screening biomarkers sensitive to different metabolic therapies, multi-targeted metabolic therapies can be designed to target the glioma microenvironment [230, 231]. For example, the metabolic pathways of gliomas can be altered by modifying lyssavirus vectors, thereby affecting the immune status of the TME, promoting the formation of an inflammatory immune microenvironment, and bringing into play the potential of the immune system to kill tumors and reduce the possible adverse effects of targeted therapies [232, 233].At the same time, taking advantage of the unique metabolic properties of cancer cells, inhibiting oxidative phosphorylation and lipid metabolism, restricting the uptake of specific amino acids, and targeting the antioxidant defense system and key metabolic enzymes is an effective strategy to disrupt tumor growth and metabolism. Such therapeutic approaches can minimize the impact on normal cells and minimize tumor growth, and clinical studies are exploring the potential of these multi-targeted therapies [98, 234]. Inflammation and oxidative stress directly drive metabolic reprogramming of tumors by increasing reactive ROS production and affecting metabolic enzyme activity [15]. Combined targeted therapies targeting these processes can reduce the effects of both inflammation and oxidative stress, leading to more effective inhibition of tumor progression and improved therapeutic outcomes.

Fifth, metabolic reprogramming drugs, already approved for other diseases, are being repurposed for the treatment of gliomas. For example, the diabetes drug metformin inhibits mitochondrial complex I and activates the AMPK pathway, which in turn suppresses the mTOR signaling pathway, limiting glioma cell growth. Statins, commonly used for cholesterol management, inhibit HMG-CoA reductase, disrupt the synthesis of tumor cell membranes, and may inhibit tumor growth by affecting the Ras signaling pathway [235, 236]. Originally used in leukemia treatment, cytarabine blocks nucleotide synthesis, thus inhibiting the rapid proliferation of glioma cells. Antioxidants that regulate ROS levels, such as Nrf2 inhibitors, increase oxidative stress, promoting glioma cell apoptosis [237]. These repurposed drugs provide new approaches for glioma treatment, particularly when combined with existing therapies.

7 Conclusion

This article highlights the significance of understanding the metabolic characteristics of glioma cells for developing novel therapeutic strategies. Specifically, investigating and targeting the metabolic dependencies of glioma cells could unveil new avenues for treatment. Key pathways discussed include the RTK, EGFR, and RAS metabolic dependency pathways, as well as metabolic abnormalities arising from IDH mutations. These pathways are instrumental in glioma progression and present valuable targets for therapy. Moreover, the article explores the potential of targeting bioenergetic metabolic pathways, which are crucial for glioma cell survival.

While metabolic therapies offer promising opportunities, several challenges remain. First, accurately identifying and targeting specific metabolic pathways is a complex task, requiring an in-depth understanding of the tumor's biochemical properties. Additionally, translating basic research findings into effective clinical treatments remains a challenge. Considering the influence of the tumor microenvironment—such as hypoxic conditions and immune responses—on glioma metabolism, future research must integrate metabolomics, genomics, and clinical data to devise more effective strategies.

Furthermore, glioma subtypes exhibit distinct metabolic profiles, which underscores the necessity for personalized treatment approaches. Tailoring therapies to the specific metabolic characteristics of individual tumors will be essential in improving treatment outcomes.

Acknowledgements Not applicable.

Author contributions N.W., YR. Y., and HZ.P. conceived the design, acquired and evaluated the literature, and wrote the manuscript; TH.H. draws the picture; HZ.P., and HZ.X. supervised, revised, and evaluated the manuscript for submission. All authors contributed to the article and approved the submitted version.

Funding This work was supported by research grants from the National Natural Science Foundation of China (No. 82302980 to H.X. and No. 82173032 to H.P.). However, it is important to note that the funding organizations had no influence on the design, data analysis, or composition of this article.

Data availability No datasets were generated or analysed during the current study.

Declarations

Ethics approval and consent to participate Not applicable.

Consent for publication All authors agree.

Competing interests The authors declare no competing interests.

References

1. Louis DN, Perry A, Wesseling P, Brat DJ, Cree IA, Figarella-Branger D, Hawkins C, Ng HK, Pfister SM, Reifenberger G, et al. The 2021 WHO classification of tumors of the central nervous system: a summary. Neurooncology. 2021;23(8):1231–51.
2. Perus LJM, Walsh LA. Microenvironmental heterogeneity in brain malignancies. Front Immunol. 2019;10:2294.
3. Ostrom QT, Price M, Neff C, Cioffi G, Waite KA, Kruchko C, Barnholtz-Sloan JS. CBTRUS statistical report: primary brain and other central nervous system tumors diagnosed in the United States in 2015–2019. Neurooncology. 2022;24(Suppl 5):v1-95.
4. Stupp R, Mason WP, van den Bent MJ, Weller M, Fisher B, Taphoorn MJ, Belanger K, Brandes AA, Marosi C, Bogdahn U, et al. Radiotherapy plus concomitant and adjuvant temozolomide for glioblastoma. N Engl J Med. 2005;352(10):987–96.
5. Wang LM, Englander ZK, Miller ML, Bruce JN. Malignant glioma. Adv Exp Med Biol. 2023;1405:1–30.
6. Aldape K, Zadeh G, Mansouri S, Reifenberger G, von Deimling A. Glioblastoma: pathology, molecular mechanisms and markers. Acta Neuropathol. 2015;129(6):829–48.
7. Tan AC, Ashley DM, López GY, Malinzak M, Friedman HS, Khasraw M. Management of glioblastoma: state of the art and future directions. Cancer J Clin. 2020;70(4):299–312.
8. Biserova K, Jakovlevs A, Uljanovs R, Strumfa I. Cancer stem cells: significance in origin, pathogenesis and treatment of glioblastoma. Cells. 2021;10(3):621.
9. Parsons DW, Jones S, Zhang X, Lin JC, Leary RJ, Angenendt P, Mankoo P, Carter H, Siu IM, Gallia GL, et al. An integrated genomic analysis of human glioblastoma multiforme. Science. 2008;321(5897):1807–12.
10. Suzuki H, Aoki K, Chiba K, Sato Y, Shiozawa Y, Shiraishi Y, Shimamura T, Niida A, Motomura K, Ohka F, et al. Mutational landscape and clonal architecture in grade II and III gliomas. Nat Genet. 2015;47(5):458–68.
11. Wu G, Diaz AK, Paugh BS, Rankin SL, Ju B, Li Y, Zhu X, Qu C, Chen X, Zhang J, et al. The genomic landscape of diffuse intrinsic pontine glioma and pediatric non-brainstem high-grade glioma. Nat Genet. 2014;46(5):444–50.
12. Vander Heiden MG, DeBerardinis RJ. Understanding the intersections between metabolism and cancer biology. Cell. 2017;168(4):657–69.
13. Venneti S, Thompson CB. Metabolic reprogramming in brain tumors. Annu Rev Pathol. 2017;12:515–45.
14. Pavlova NN, Zhu J, Thompson CB. The hallmarks of cancer metabolism: still emerging. Cell Metabol. 2022;34(3):355–77.
15. Vander Heiden MG, Cantley LC, Thompson CB. Understanding the Warburg effect: the metabolic requirements of cell proliferation. Science. 2009;324(5930):1029–33.
16. Bélanger M, Allaman I, Magistretti PJ. Brain energy metabolism: focus on astrocyte-neuron metabolic cooperation. Cell Metabol. 2011;14(6):724–38.
17. Bruce KD, Zsombok A, Eckel RH. Lipid processing in the brain: a key regulator of systemic metabolism. Front Endocrinol. 2017;8:60.
18. O'Brien JS, Sampson EL. Lipid composition of the normal human brain: gray matter, white matter, and myelin. J Lipid Res. 1965;6(4):537–44.
19. Magistretti PJ, Allaman I. A cellular perspective on brain energy metabolism and functional imaging. Neuron. 2015;86(4):883–901.
20. Zielke HR, Zielke CL, Baab PJ. Direct measurement of oxidative metabolism in the living brain by microdialysis: a review. J Neurochem. 2009;109(Suppl 1Suppl 1):24–9.

21. Weller M, Pfister SM, Wick W, Hegi ME, Reifenberger G, Stupp R. Molecular neuro-oncology in clinical practice: a new horizon. Lancet Oncol. 2013;14(9):e370–379.
22. Eckel-Passow JE, Lachance DH, Molinaro AM, Walsh KM, Decker PA, Sicotte H, Pekmezci M, Rice T, Kosel ML, Smirnov IV, et al. Glioma groups based on 1p/19q, IDH, and TERT promoter mutations in tumors. N Engl J Med. 2015;372(26):2499–508.
23. Pirozzi CJ, Yan H. The implications of IDH mutations for cancer development and therapy. Nat Rev Clin Oncol. 2021;18(10):645–61.
24. Jiang T, Nam DH, Ram Z, Poon WS, Wang J, Boldbaatar D, Mao Y, Ma W, Mao Q, You Y, et al. Clinical practice guidelines for the management of adult diffuse gliomas. Cancer Lett. 2021;499:60–72.
25. Tanboon J, Williams EA, Louis DN. The diagnostic use of immunohistochemical surrogates for signature molecular genetic alterations in gliomas. J Neuropathol Exp Neurol. 2016;75(1):4–18.
26. Kristensen BW, Priesterbach-Ackley LP, Petersen JK, Wesseling P. Molecular pathology of tumors of the central nervous system. Ann Oncol Off J Eur Soc Med Oncol. 2019;30(8):1265–78.
27. Ryall S, Tabori U, Hawkins C. Pediatric low-grade glioma in the era of molecular diagnostics. Acta Neuropathol Commun. 2020;8(1):30.
28. Wefers AK, Stichel D, Schrimpf D, Coras R, Pages M, Tauziède-Espariat A, Varlet P, Schwarz D, Söylemezoglu F, Pohl U, et al. Isomorphic diffuse glioma is a morphologically and molecularly distinct tumour entity with recurrent gene fusions of MYBL1 or MYB and a benign disease course. Acta Neuropathol. 2020;139(1):193–209.
29. Chiang J, Harreld JH, Tinkle CL, Moreira DC, Li X, Acharya S, Qaddoumi I, Ellison DW. A single-center study of the clinicopathologic correlates of gliomas with a MYB or MYBL1 alteration. Acta Neuropathol. 2019;138(6):1091–2.
30. Huse JT, Snuderl M, Jones DT, Brathwaite CD, Altman N, Lavi E, Saffery R, Sexton-Oates A, Blumcke I, Capper D, et al. Polymorphous low-grade neuroepithelial tumor of the young (PLNTY): an epileptogenic neoplasm with oligodendroglioma-like components, aberrant CD34 expression, and genetic alterations involving the MAP kinase pathway. Acta Neuropathol. 2017;133(3):417–29.
31. Chen Y, Tian T, Guo X, Zhang F, Fan M, Jin H, Liu D. Polymorphous low-grade neuroepithelial tumor of the young: case report and review focus on the radiological features and genetic alterations. BMC Neurol. 2020;20(1):123.
32. Lewis PW, Müller MM, Koletsky MS, Cordero F, Lin S, Banaszynski LA, Garcia BA, Muir TW, Becher OJ, Allis CD. Inhibition of PRC2 activity by a gain-of-function H3 mutation found in pediatric glioblastoma. Science. 2013;340(6134):857–61.
33. Castel D, Philippe C, Calmon R, Le Dret L, Truffaux N, Boddaert N, Pagès M, Taylor KR, Saulnier P, Lacroix L, et al. Histone H3F3A and HIST1H3B K27M mutations define two subgroups of diffuse intrinsic pontine gliomas with different prognosis and phenotypes. Acta Neuropathol. 2015;130(6):815–27.
34. Clarke M, Mackay A, Ismer B, Pickles JC, Tatevossian RG, Newman S, Bale TA, Stoler I, Izquierdo E, Temelso S, et al. Infant high-grade gliomas comprise multiple subgroups characterized by novel targetable gene fusions and favorable outcomes. Cancer Discov. 2020;10(7):942–63.
35. Rosenberg S, Simeonova I, Bielle F, Verreault M, Bance B, Le Roux I, Daniau M, Nadaradjane A, Gleize V, Paris S, et al. A recurrent point mutation in PRKCA is a hallmark of chordoid gliomas. Nat Commun. 2018;9(1):2371.
36. Reinhardt A, Stichel D, Schrimpf D, Sahm F, Korshunov A, Reuss DE, Koelsche C, Huang K, Wefers AK, Hovestadt V, et al. Anaplastic astrocytoma with piloid features, a novel molecular class of IDH wildtype glioma with recurrent MAPK pathway, CDKN2A/B and ATRX alterations. Acta Neuropathol. 2018;136(2):273–91.
37. Bender K, Perez E, Chirica M, Onken J, Kahn J, Brenner W, Ehret F, Euskirchen P, Koch A, Capper D, et al. High-grade astrocytoma with piloid features (HGAP): the Charité experience with a new central nervous system tumor entity. J Neurooncol. 2021;153(1):109–20.
38. Ellison DW, Hawkins C, Jones DTW, Onar-Thomas A, Pfister SM, Reifenberger G, Louis DN. cIMPACT-NOW update 4: diffuse gliomas characterized by MYB, MYBL1, or FGFR1 alterations or BRAF(V600E) mutation. Acta Neuropathol. 2019;137(4):683–7.
39. Goode B, Mondal G, Hyun M, Ruiz DG, Lin YH, Van Ziffle J, Joseph NM, Onodera C, Talevich E, Grenert JP, et al. A recurrent kinase domain mutation in PRKCA defines chordoid glioma of the third ventricle. Nat Commun. 2018;9(1):810.
40. Louis DN, Wesseling P, Aldape K, Brat DJ, Capper D, Cree IA, Eberhart C, Figarella-Branger D, Fouladi M, Fuller GN, et al. cIMPACT-NOW update 6: new entity and diagnostic principle recommendations of the cIMPACT-Utrecht meeting on future CNS tumor classification and grading. Brain Pathol. 2020;30(4):844–56.
41. Chappé C, Padovani L, Scavarda D, Forest F, Nanni-Metellus I, Loundou A, Mercurio S, Fina F, Lena G, Colin C, et al. Dysembryoplastic neuroepithelial tumors share with pleomorphic xanthoastrocytomas and gangliogliomas BRAF(V600E) mutation and expression. Brain Pathol. 2013;23(5):574–83.
42. Prabowo AS, Iyer AM, Veersema TJ, Anink JJ, Schouten-van Meeteren AY, Spliet WG, van Rijen PC, Ferrier CH, Capper D, Thom M, et al. BRAF V600E mutation is associated with mTOR signaling activation in glioneuronal tumors. Brain Pathol. 2014;24(1):52–66.
43. Pekmezci M, Stevers M, Phillips JJ, Van Ziffle J, Bastian BC, Tsankova NM, Kleinschmidt-DeMasters BK, Rosenblum MK, Tihan T, Perry A, et al. Multinodular and vacuolating neuronal tumor of the cerebrum is a clonal neoplasm defined by genetic alterations that activate the MAP kinase signaling pathway. Acta Neuropathol. 2018;135(3):485–8.
44. Sievers P, Stichel D, Schrimpf D, Sahm F, Koelsche C, Reuss DE, Wefers AK, Reinhardt A, Huang K, Ebrahimi A, et al. FGFR1:TACC1 fusion is a frequent event in molecularly defined extraventricular neurocytoma. Acta Neuropathol. 2018;136(2):293–302.
45. Chiang J, Dalton J, Upadhyaya SA, Patay Z, Qaddoumi I, Li X, Segura AD, Sharma S, Ismail A, Shurtleff SA, et al. Chromosome arm 1q gain is an adverse prognostic factor in localized and diffuse leptomeningeal glioneuronal tumors with BRAF gene fusion and 1p deletion. Acta Neuropathol. 2019;137(1):179–81.
46. Pietsch T, Wohlers I, Goschzik T, Dreschmann V, Denkhaus D, Dörner E, Rahmann S, Klein-Hitpass L. Supratentorial ependymomas of childhood carry C11orf95-RELA fusions leading to pathological activation of the NF-κB signaling pathway. Acta Neuropathol. 2014;127(4):609–11.
47. Zschernack V, Jünger ST, Mynarek M, Rutkowski S, Garre ML, Ebinger M, Neu M, Faber J, Erdlenbruch B, Claviez A, et al. Supratentorial ependymoma in childhood: more than just RELA or YAP. Acta Neuropathol. 2021;141(3):455–66.
48. Parker M, Mohankumar KM, Punchihewa C, Weinlich R, Dalton JD, Li Y, Lee R, Tatevossian RG, Phoenix TN, Thiruvenkatam R, et al. C11orf95-RELA fusions drive oncogenic NF-κB signalling in ependymoma. Nature. 2014;506(7489):451–5.
49. Pagès M, Pajtler KW, Puget S, Castel D, Boddaert N, Tauziède-Espariat A, Picot S, Debily MA, Kool M, Capper D, et al. Diagnostics of pediatric supratentorial RELA ependymomas: integration of information from histopathology, genetics, DNA methylation and imaging. Brain Pathol. 2019;29(3):325–35.

50. Bayliss J, Mukherjee P, Lu C, Jain SU, Chung C, Martinez D, Sabari B, Margol AS, Panwalkar P, Parolia A, et al. Lowered H3K27me3 and DNA hypomethylation define poorly prognostic pediatric posterior fossa ependymomas. Sci Transl Med. 2016;8(366):366ra161.
51. Pajtler KW, Wen J, Sill M, Lin T, Orisme W, Tang B, Hübner JM, Ramaswamy V, Jia S, Dalton JD, et al. Molecular heterogeneity and CXorf67 alterations in posterior fossa group A (PFA) ependymomas. Acta Neuropathol. 2018;136(2):211–26.
52. Ellison DW, Aldape KD, Capper D, Fouladi M, Gilbert MR, Gilbertson RJ, Hawkins C, Merchant TE, Pajtler K, Venneti S, et al. cIMPACT-NOW update 7: advancing the molecular classification of ependymal tumors. Brain Pathol. 2020;30(5):863–6.
53. Ghasemi DR, Sill M, Okonechnikov K, Korshunov A, Yip S, Schutz PW, Scheie D, Kruse A, Harter PN, Kastelan M, et al. MYCN amplification drives an aggressive form of spinal ependymoma. Acta Neuropathol. 2019;138(6):1075–89.
54. Kumar R, Liu APY, Northcott PA. Medulloblastoma genomics in the modern molecular era. Brain Pathol. 2020;30(3):679–90.
55. Birzu C, Peyre M, Sahm F. Molecular alterations in meningioma: prognostic and therapeutic perspectives. Curr Opin Oncol. 2020;32(6):613–22.
56. Thomas C, Wefers A, Bens S, Nemes K, Agaimy A, Oyen F, Vogelgesang S, Rodriguez FJ, Brett FM, McLendon R, et al. Desmoplastic myxoid tumor, SMARCB1-mutant: clinical, histopathological and molecular characterization of a pineal region tumor encountered in adolescents and adults. Acta Neuropathol. 2020;139(2):277–86.
57. Feng S, Liu Y. Metabolomics of glioma. Adv Exp Med Biol. 2021;1280:261–76.
58. Bi J, Chowdhry S, Wu S, Zhang W, Masui K, Mischel PS. Altered cellular metabolism in gliomas—an emerging landscape of actionable co-dependency targets. Nat Rev Cancer. 2020;20(1):57–70.
59. Poff A, Koutnik AP, Egan KM, Sahebjam S, D'Agostino D, Kumar NB. Targeting the Warburg effect for cancer treatment: ketogenic diets for management of glioma. Sem Cancer Biol. 2019;56:135–48.
60. Warburg O. The metabolism of carcinoma cells. J Cancer Res. 1925;9(1):148–63.
61. Wu F, Zhao Z, Chai RC, Liu YQ, Li GZ, Jiang HY, Jiang T. Prognostic power of a lipid metabolism gene panel for diffuse gliomas. J Cell Mol Med. 2019;23(11):7741–8.
62. Ye Z, Ai X, Yang K, Yang Z, Fei F, Liao X, Qiu Z, Gimple RC, Yuan H, Huang H, et al. Targeting microglial metabolic rewiring synergizes with immune-checkpoint blockade therapy for glioblastoma. Cancer Discov. 2023;13(4):974–1001.
63. Landis CJ, Tran AN, Scott SE, Griguer C, Hjelmeland AB. The pro-tumorigenic effects of metabolic alterations in glioblastoma including brain tumor initiating cells. Biochim Biophys Acta Rev Cancer. 2018;1869(2):175–88.
64. Masui K, Mischel PS. Metabolic and epigenetic reprogramming in the pathogenesis of glioblastoma: toward the establishment of metabolism-based pathology. Pathol Int. 2023;73(11):533–41.
65. Bayin NS, Frenster JD, Sen R, Si S, Modrek AS, Galifianakis N, Dolgalev I, Ortenzi V, Illa-Bochaca I, Khahera A, et al. Notch signaling regulates metabolic heterogeneity in glioblastoma stem cells. Oncotarget. 2017;8(39):64932–53.
66. Björkblom B, Wibom C, Eriksson M, Bergenheim AT, Sjöberg RL, Jonsson P, Brännström T, Antti H, Sandström M, Melin B. Distinct metabolic hallmarks of WHO classified adult glioma subtypes. Neurooncology. 2022;24(9):1454–68.
67. Wu F, Liu YW, Li GZ, Zhai Y, Feng YM, Ma WP, Zhao Z, Zhang W. Metabolic expression profiling stratifies diffuse lower-grade glioma into three distinct tumour subtypes. Br J Cancer. 2021;125(2):255–64.
68. Zhou L, Wang Z, Hu C, Zhang C, Kovatcheva-Datchary P, Yu D, Liu S, Ren F, Wang X, Li Y, et al. Integrated metabolomics and Lipidomics analyses reveal metabolic reprogramming in human glioma with IDH1 mutation. J Proteome Res. 2019;18(3):960–9.
69. Ježek P. 2-hydroxyglutarate in cancer cells. Antioxid Redox Signal. 2020;33(13):903–26.
70. Ruiz-Rodado V, Malta TM, Seki T, Lita A, Dowdy T, Celiku O, Cavazos-Saldana A, Li A, Liu Y, Han S, et al. Metabolic reprogramming associated with aggressiveness occurs in the G-CIMP-high molecular subtypes of IDH1mut lower grade gliomas. Neurooncology. 2020;22(4):480–92.
71. Judge A, Dodd MS. Metabolism. Essays Biochem. 2020;64(4):607–47.
72. Marin-Valencia I, Yang C, Mashimo T, Cho S, Baek H, Yang XL, Rajagopalan KN, Maddie M, Vemireddy V, Zhao Z, et al. Analysis of tumor metabolism reveals mitochondrial glucose oxidation in genetically diverse human glioblastomas in the mouse brain in vivo. Cell Metabol. 2012;15(6):827–37.
73. Clark PM, Mai WX, Nathanson Cloughesy TF., DA. Emerging approaches for targeting metabolic vulnerabilities in malignant glioma. Curr Neurol Neurosci Rep. 2016;16:1–10.
74. Zhou W, Wahl DR. Metabolic abnormalities in glioblastoma and metabolic strategies to overcome treatment resistance. Cancers. 2019;11(9):1231.
75. Flavahan WA, Wu Q, Hitomi M, Rahim N, Kim Y, Sloan AE, Weil RJ, Nakano I, Sarkaria JN, Stringer BW, et al. Brain tumor initiating cells adapt to restricted nutrition through preferential glucose uptake. Nat Neurosci. 2013;16(10):1373–82.
76. Sanzey M, Abdul Rahim SA, Oudin A, Dirkse A, Kaoma T, Vallar L, Herold-Mende C, Bjerkvig R, Golebiewska A, Niclou SP. Comprehensive analysis of glycolytic enzymes as therapeutic targets in the treatment of glioblastoma. PLoS ONE. 2015;10(5):e0123544.
77. Wolf A, Agnihotri S, Micallef J, Mukherjee J, Sabha N, Cairns R, Hawkins C, Guha A. Hexokinase 2 is a key mediator of aerobic glycolysis and promotes tumor growth in human glioblastoma multiforme. J Exp Med. 2011;208(2):313–26.
78. Patra KC, Wang Q, Bhaskar PT, Miller L, Wang Z, Wheaton W, Chandel N, Laakso M, Muller WJ, Allen EL, et al. Hexokinase 2 is required for tumor initiation and maintenance and its systemic deletion is therapeutic in mouse models of cancer. Cancer Cell. 2013;24(2):213–28.
79. Yuen CA, Asuthkar S, Guda MR, Tsung AJ, Velpula KK. Cancer stem cell molecular reprogramming of the Warburg effect in glioblastomas: a new target gleaned from an old concept. CNS Oncol. 2016;5(2):101–8.
80. Wicks RT, Azadi J, Mangraviti A, Zhang I, Hwang L, Joshi A, Bow H, Hutt-Cabezas M, Martin KL, Rudek MA, et al. Local delivery of cancer-cell glycolytic inhibitors in high-grade glioma. Neurooncology. 2015;17(1):70–80.
81. Michelakis ED, Sutendra G, Dromparis P, Webster L, Haromy A, Niven E, Maguire C, Gammer TL, Mackey JR, Fulton D, et al. Metabolic modulation of glioblastoma with dichloroacetate. Sci Transl Med. 2010;2(31):31ra34.
82. Shen H, Hau E, Joshi S, Dilda PJ, McDonald KL. Sensitization of glioblastoma cells to irradiation by modulating the glucose metabolism. Mol Cancer Ther. 2015;14(8):1794–804.
83. Toader C, Eva L, Costea D, Corlatescu AD, Covache-Busuioc RA, Bratu BG, Glavan LA, Costin HP, Popa AA, Ciurea AV. Low-grade gliomas: histological subtypes, molecular mechanisms, and treatment strategies. Brain Sci. 2023;13(12):1700.

84. Mohamed AA, Alshaibi R, Faragalla S, Mohamed Y, Lucke-Wold B. Updates on management of gliomas in the molecular age. World J Clin Oncol. 2024;15(2):178–94.
85. Liu T, Wang Y, Wang Y, Cheung SK, Or PM, Wong CW, Guan J, Li Z, Yang W, Tu Y, et al. The mitotic regulator RCC2 promotes glucose metabolism through BACH1-dependent transcriptional upregulation of hexokinase II in glioma. Cancer Lett. 2022;549:215914.
86. Guo D, Tong Y, Jiang X, Meng Y, Jiang H, Du L, Wu Q, Li S, Luo S, Li M, et al. Aerobic glycolysis promotes tumor immune evasion by hexokinase2-mediated phosphorylation of IκBα. Cell Metabol. 2022;34(9):1312–e13241316.
87. Zhang Z, Li X, Yang F, Chen C, Liu P, Ren Y, Sun P, Wang Z, You Y, Zeng YX, et al. DHHC9-mediated GLUT1 S-palmitoylation promotes glioblastoma glycolysis and tumorigenesis. Nat Commun. 2021;12(1):5872.
88. Kwak S, Park SH, Kim SH, Sung GJ, Song JH, Jeong JH, Kim H, Ha CH, Kim SW, Choi KC. miR-3189-targeted GLUT3 repression by HDAC2 knockdown inhibits glioblastoma tumorigenesis through regulating glucose metabolism and proliferation. J Exp Clin Cancer Res CR. 2022;41(1):87.
89. Cheng Z, Luo C, Guo Z. LncRNA-XIST/microRNA-126 sponge mediates cell proliferation and glucose metabolism through the IRS1/PI3K/Akt pathway in glioma. J Cell Biochem. 2020;121(3):2170–83.
90. Xu B, Zhang Q, Luo X, Ning X, Luo J, Guo J, Liu Q, Ling G, Zhou N. Selenium nanoparticles reduce glucose metabolism and promote apoptosis of glioma cells through reactive oxygen species-dependent manner. NeuroReport. 2020;31(3):226–34.
91. Yang R, Zhang G, Dong Z, Wang S, Li Y, Lian F, Liu X, Li H, Wei X, Cui H. Homeobox A3 and KDM6A cooperate in transcriptional control of aerobic glycolysis and glioblastoma progression. Neurooncology. 2023;25(4):635–47.
92. Yang S, Zhao J, Cui X, Zhan Q, Yi K, Wang Q, Xiao M, Tan Y, Hong B, Fang C, et al. TCA-phospholipid-glycolysis targeted triple therapy effectively suppresses ATP production and tumor growth in glioblastoma. Theranostics. 2022;12(16):7032–50.
93. Song J, Zheng J, Liu X, Dong W, Yang C, Wang D, Ruan X, Zhao Y, Liu L, Wang P, et al. A novel protein encoded by ZCRB1-induced circHEATR5B suppresses aerobic glycolysis of GBM through phosphorylation of JMJD5. J Exp Clin Cancer Res CR. 2022;41(1):171.
94. Lee SH, Kim SH, Nam TM, Jang JH, Kim KH, Lee YS, Kim MS, Kim MS, Jin SY, Lee M, et al. Epigenetic regulation of the expression of T cell stimulatory and inhibitory factors by histone H3 lysine modification enzymes and its prognostic roles in glioblastoma. J Korean Med Sci. 2023;38(33):e258.
95. Park JH, Lee JS, Oh Y, Lee JS, Park HE, Lee H, Park YS, Kyung SY, Kim HS, Yoon S. PKM2 is overexpressed in glioma tissues, and its inhibition highly increases late apoptosis in U87MG cells with low-density specificity. In Vivo. 2022;36(2):694–703.
96. Liu S, Deng Y, Yu Y, Xia X. Knock-down of PGM1 inhibits cell viability, glycolysis, and oxidative phosphorylation in glioma under low glucose condition via the Myc signaling pathway. Biochem Biophys Res Commun. 2023;656:38–45.
97. Bian X, Liu R, Meng Y, Xing D, Xu D, Lu Z. Lipid metabolism and cancer. J Exp Med. 2021;218(1):e20201606.
98. Wu Z, Ho WS, Lu R. Targeting mitochondrial oxidative phosphorylation in glioblastoma therapy. Neuromol Med. 2022;24(1):18–22.
99. Wolf A, Agnihotri S, Guha A. Targeting metabolic remodeling in glioblastoma multiforme. Oncotarget. 2010;1(7):552–62.
100. Koundouros N, Poulogiannis G. Reprogramming of fatty acid metabolism in cancer. Br J Cancer. 2020;122(1):4–22.
101. Liu Z, Gao Z, Li B, Li J, Ou Y, Yu X, Zhang Z, Liu S, Fu X, Jin H, et al. Lipid-associated macrophages in the tumor-adipose microenvironment facilitate breast cancer progression. Oncoimmunology. 2022;11(1):2085432.
102. Qiu R, Zhong Y, Li Q, Li Y, Fan H. Metabolic remodeling in glioma immune microenvironment: intercellular interactions distinct from peripheral tumors. Front Cell Dev Biol. 2021;9:693215.
103. Guo D, Prins RM, Dang J, Kuga D, Iwanami A, Soto H, Lin KY, Huang TT, Akhavan D, Hock MB, et al. EGFR signaling through an Akt-SREBP-1-dependent, rapamycin-resistant pathway sensitizes glioblastomas to antilipogenic therapy. Sci Signal. 2009;2(101):ra82.
104. Ricklefs FL, Maire CL, Matschke J, Dührsen L, Sauvigny T, Holz M, Kolbe K, Peine S, Herold-Mende C, Carter B, et al. FASN is a biomarker enriched in malignant glioma-derived extracellular vesicles. Int J Mol Sci. 2020;21(6):1931.
105. Zhou Y, Jin G, Mi R, Zhang J, Zhang J, Xu H, Cheng S, Zhang Y, Song W, Liu F. Inhibition of fatty acid synthase suppresses neovascularization via regulating the expression of VEGF-A in glioma. J Cancer Res Clin Oncol. 2016;142(12):2447–59.
106. Cheng C, Geng F, Li Z, Zhong Y, Wang H, Cheng X, Zhao Y, Mo X, Horbinski C, Duan W, et al. Ammonia stimulates SCAP/Insig dissociation and SREBP-1 activation to promote lipogenesis and tumour growth. Nat Metabol. 2022;4(5):575–88.
107. Guo D, Bell EH, Mischel P, Chakravarti A. Targeting SREBP-1-driven lipid metabolism to treat cancer. Curr Pharm Des. 2014;20(15):2619–26.
108. Zhao W, Kridel S, Thorburn A, Kooshki M, Little J, Hebbar S, Robbins M. Fatty acid synthase: a novel target for antiglioma therapy. Br J Cancer. 2006;95(7):869–78.
109. Chen X, Li H, Fan X, Zhao C, Ye K, Zhao Z, Hu L, Ma H, Wang H, Fang Z. Protein palmitoylation regulates cell survival by modulating XBP1 activity in glioblastoma multiforme. Mol Ther Oncol. 2020;17:518–30.
110. Silver DJ, Roversi GA, Bithi N, Wang SZ, Troike KM, Neumann CK, Ahuja GK, Reizes O, Brown JM, Hine C, et al. Severe consequences of a high-lipid diet include hydrogen sulfide dysfunction and enhanced aggression in glioblastoma. J Clin Investig. 2021;131(17):e138276.
111. Hale JS, Otvos B, Sinyuk M, Alvarado AG, Hitomi M, Stoltz K, Wu Q, Flavahan W, Levison B, Johansen ML, et al. Cancer stem cell-specific scavenger receptor CD36 drives glioblastoma progression. Stem Cells. 2014;32(7):1746–58.
112. Olzmann JA, Carvalho P. Dynamics and functions of lipid droplets. Nat Rev Mol Cell Biol. 2019;20(3):137–55.
113. Cheng X, Geng F, Pan M, Wu X, Zhong Y, Wang C, Tian Z, Cheng C, Zhang R, Puduvalli V, et al. Targeting DGAT1 ameliorates glioblastoma by increasing fat catabolism and oxidative stress. Cell Metabol. 2020;32(2):229-e242228.
114. Zhang Z, Dales NA, Winther MD. Opportunities and challenges in developing stearoyl-coenzyme A desaturase-1 inhibitors as novel therapeutics for human disease. J Med Chem. 2014;57(12):5039–56.
115. Park WJ. The biochemistry and regulation of fatty acid desaturases in animals. Urbana: AOCS Press; 2018. p. 87–100.
116. Dai S, Yan Y, Xu Z, Zeng S, Qian L, Huo L, Li X, Sun L, Gong Z. SCD1 confers temozolomide resistance to human glioma cells via the Akt/GSK3β/β-catenin signaling axis. Front Pharmacol. 2017;8:960.
117. Kosmacz M, Luzarowski M, Kerber O, Leniak E, Gutiérrez-Beltrán E, Moreno JC, Gorka M, Szlachetko J, Veyel D, Graf A, et al. Interaction of 2′,3′-cAMP with Rbp47b plays a role in stress granule formation. Plant Physiol. 2018;177(1):411–21.
118. Shakya S, Gromovsky AD, Hale JS, Knudsen AM, Prager B, Wallace LC, Penalva LOF, Brown HA, Kristensen BW, Rich JN, et al. Altered lipid metabolism marks glioblastoma stem and non-stem cells in separate tumor niches. Acta Neuropathol Commun. 2021;9(1):101.
119. Miska J, Chandel NS. Targeting fatty acid metabolism in glioblastoma. J Clin Investig. 2023;133(1):e163448.

120. Jansen GA, Wanders RJ. Alpha-oxidation. Biochim Biophys Acta. 2006;1763(12):1403–12.
121. Zammit VA. Carnitine palmitoyltransferase 1: central to cell function. IUBMB Life. 2008;60(5):347–54.
122. Duman C, Yaqubi K, Hoffmann A, Acikgöz AA, Korshunov A, Bendszus M, Herold-Mende C, Liu HK, Alfonso J. Acyl-CoA-binding protein drives glioblastoma tumorigenesis by sustaining fatty acid oxidation. Cell Metabol. 2019;30(2):274-e289275.
123. Kant S, Kesarwani P, Prabhu A, Graham SF, Buelow KL, Nakano I, Chinnaiyan P. Enhanced fatty acid oxidation provides glioblastoma cells metabolic plasticity to accommodate to its dynamic nutrient microenvironment. Cell Death Dis. 2020;11(4):253.
124. Puca F, Yu F, Bartolacci C, Pettazzoni P, Carugo A, Huang-Hobbs E, Liu J, Zanca C, Carbone F, Del Poggetto E, et al. Medium-chain Acyl-CoA dehydrogenase protects mitochondria from lipid peroxidation in glioblastoma. Cancer Discov. 2021;11(11):2904–23.
125. Jiang N, Xie B, Xiao W, Fan M, Xu S, Duan Y, Hamsafar Y, Evans AC, Huang J, Zhou W, et al. Fatty acid oxidation fuels glioblastoma radioresistance with CD47-mediated immune evasion. Nat Commun. 2022;13(1):1511.
126. VanItallie TB, Nufert TH. Ketones: metabolism's ugly duckling. Nutr Rev. 2003;61(10):327–41.
127. Pierre K, Pellerin L. Monocarboxylate transporters in the central nervous system: distribution, regulation and function. J Neurochem. 2005;94(1):1–14.
128. Jensen NJ, Wodschow HZ, Nilsson M, Rungby J. Effects of ketone bodies on brain metabolism and function in neurodegenerative diseases. Int J Mol Sci. 2020;21(22):8767.
129. Maurer GD, Brucker DP, Bähr O, Harter PN, Hattingen E, Walenta S, Mueller-Klieser W, Steinbach JP, Rieger J. Differential utilization of ketone bodies by neurons and glioma cell lines: a rationale for ketogenic diet as experimental glioma therapy. BMC Cancer. 2011;11:315.
130. Yin J, Kim SS, Choi E, Oh YT, Lin W, Kim TH, Sa JK, Hong JH, Park SH, Kwon HJ, et al. ARS2/MAGL signaling in glioblastoma stem cells promotes self-renewal and M2-like polarization of tumor-associated macrophages. Nat Commun. 2020;11(1):2978.
131. Kamphorst JJ, Cross JR, Fan J, de Stanchina E, Mathew R, White EP, Thompson CB, Rabinowitz JD. Hypoxic and ras-transformed cells support growth by scavenging unsaturated fatty acids from lysophospholipids. Proc Natl Acad Sci USA. 2013;110(22):8882–7.
132. Pan YH, Chen J, Sun C, Ma JF, Li X. Effect of ras-guanine nucleotide release factor 1-mediated H-Ras/ERK signaling pathway on glioma. Brain Res. 2021;1754:147247.
133. Russell DW. Oxysterol biosynthetic enzymes. Biochim Biophys Acta. 2000;1529(1–3):126–35.
134. Pfrieger FW. Role of cholesterol in synapse formation and function. Biochim Biophys Acta. 2003;1610(2):271–80.
135. Zelcer N, Hong C, Boyadjian R, Tontonoz P. LXR regulates cholesterol uptake through Idol-dependent ubiquitination of the LDL receptor. Science. 2009;325(5936):100–4.
136. Chen J, Costa LG, Guizzetti M. Assessment of cholesterol homeostasis in astrocytes and neurons. Methods Mol Biol. 2011;758:403–14.
137. Cheng C, Geng F, Cheng X, Guo D. Lipid metabolism reprogramming and its potential targets in cancer. Cancer Commun. 2018;38(1):27.
138. Ikonen E. Cellular cholesterol trafficking and compartmentalization. Nat Rev Mol Cell Biol. 2008;9(2):125–38.
139. Guillaumond F, Bidaut G, Ouaissi M, Servais S, Gouirand V, Olivares O, Lac S, Borge L, Roques J, Gayet O, et al. Cholesterol uptake disruption, in association with chemotherapy, is a promising combined metabolic therapy for pancreatic adenocarcinoma. Proc Natl Acad Sci USA. 2015;112(8):2473–8.
140. Gallagher EJ, Zelenko Z, Neel BA, Antoniou IM, Rajan L, Kase N, LeRoith D. Elevated tumor LDLR expression accelerates LDL cholesterol-mediated breast cancer growth in mouse models of hyperlipidemia. Oncogene. 2017;36(46):6462–71.
141. Guo D, Reinitz F, Youssef M, Hong C, Nathanson D, Akhavan D, Kuga D, Amzajerdi AN, Soto H, Zhu S, et al. An LXR agonist promotes glioblastoma cell death through inhibition of an EGFR/AKT/SREBP-1/LDLR-dependent pathway. Cancer Discov. 2011;1(5):442–56.
142. Li D, Li S, Xue AZ, Smith Callahan LA, Liu Y. Expression of SREBP2 and cholesterol metabolism related genes in TCGA glioma cohorts. Medicine. 2020;99(12):e18815.
143. Kloudova A, Guengerich FP, Soucek P. The role of oxysterols in human cancer. Trends Endocrinol Metab. 2017;28(7):485–96.
144. Smith B, Land H. Anticancer activity of the cholesterol exporter ABCA1 gene. Cell Rep. 2012;2(3):580–90.
145. Bauer R, Brüne B, Schmid T. Cholesterol metabolism in the regulation of inflammatory responses. Front Pharmacol. 2023;14:1121819.
146. Florescu DN, Boldeanu MV, Şerban RE, Florescu LM, Serbanescu MS, Ionescu M, Streba L, Constantin C, Vere CC. Correlation of the pro-inflammatory cytokines IL-1β, IL-6, and TNF-α, inflammatory markers, and tumor markers with the diagnosis and prognosis of colorectal cancer. Life. 2023;13(12):2261.
147. Eibinger G, Fauler G, Bernhart E, Frank S, Hammer A, Wintersperger A, Eder H, Heinemann A, Mischel PS, Malle E, et al. On the role of 25-hydroxycholesterol synthesis by glioblastoma cell lines: implications for chemotactic monocyte recruitment. Exp Cell Res. 2013;319(12):1828–38.
148. Maus A, Peters GJ. Glutamate and α-ketoglutarate: key players in glioma metabolism. Amino Acids. 2017;49(1):21–32.
149. McBrayer SK, Mayers JR, DiNatale GJ, Shi DD, Khanal J, Chakraborty AA, Sarosiek KA, Briggs KJ, Robbins AK, Sewastianik T, et al. Transaminase inhibition by 2-hydroxyglutarate impairs glutamate biosynthesis and redox homeostasis in glioma. Cell. 2018;175(1):101-e116125.
150. Tardito S, Oudin A, Ahmed SU, Fack F, Keunen O, Zheng L, Miletic H, Sakariassen P, Weinstock A, Wagner A, et al. Glutamine synthetase activity fuels nucleotide biosynthesis and supports growth of glutamine-restricted glioblastoma. Nat Cell Biol. 2015;17(12):1556–68.
151. Gu Y, Albuquerque CP, Braas D, Zhang W, Villa GR, Bi J, Ikegami S, Masui K, Gini B, Yang H, et al. mTORC2 regulates amino acid metabolism in cancer by phosphorylation of the cystine-glutamate antiporter xCT. Mol Cell. 2017;67(1):128-e138127.
152. An S, Lu X, Zhao W, Sun T, Zhang Y, Lu Y, Jiang C. Amino acid metabolism abnormity and microenvironment variation mediated targeting and controlled glioma chemotherapy. Small. 2016;12(40):5633–45.
153. Leone RD, Zhao L, Englert JM, Sun IM, Oh MH, Sun IH, Arwood ML, Bettencourt IA, Patel CH, Wen J, et al. Glutamine blockade induces divergent metabolic programs to overcome tumor immune evasion. Science. 2019;366(6468):1013–21.
154. Kameyama M, Ishiwata K, Tsurumi Y, Itoh J, Sato K, Katakura R, Yoshimoto T, Hatazawa J, Ito M, Ido T. Clinical application of 18F-FUdR in glioma patients–PET study of nucleic acid metabolism. J Neurooncol. 1995;23(1):53–61.
155. Cairncross G, Wang M, Shaw E, Jenkins R, Brachman D, Buckner J, Fink K, Souhami L, Laperriere N, Curran W, et al. Phase III trial of chemoradiotherapy for anaplastic oligodendroglioma: long-term results of RTOG 9402. J Clin Oncol Off J Am Soc Clin Oncol. 2013;31(3):337–43.
156. Zhao J, Wang L, Wei B. Identification and validation of an energy metabolism-related lncrna-mrna signature for lower-grade glioma. BioMed Res Int. 2020;2020:3708231.

157. Waitkus MS, Diplas BH, Yan H. Biological role and therapeutic potential of IDH mutations in cancer. Cancer Cell. 2018;34(2):186–95.
158. Turcan S, Rohle D, Goenka A, Walsh LA, Fang F, Yilmaz E, Campos C, Fabius AW, Lu C, Ward PS, et al. IDH1 mutation is sufficient to establish the glioma hypermethylator phenotype. Nature. 2012;483(7390):479–83.
159. Patel J, Baptiste BA, Kim E, Hussain M, Croteau DL, Bohr VA. DNA damage and mitochondria in cancer and aging. Carcinogenesis. 2020;41(12):1625–34.
160. Curtin NJ. DNA repair dysregulation from cancer driver to therapeutic target. Nat Rev Cancer. 2012;12(12):801–17.
161. Morikawa T, Maeda D, Kume H, Homma Y, Fukayama M. Ribonucleotide reductase M2 subunit is a novel diagnostic marker and a potential therapeutic target in bladder cancer. Histopathology. 2010;57(6):885–92.
162. Silber J, Lim DA, Petritsch C, Persson AI, Maunakea AK, Yu M, Vandenberg SR, Ginzinger DG, James CD, Costello JF, et al. miR-124 and miR-137 inhibit proliferation of glioblastoma multiforme cells and induce differentiation of brain tumor stem cells. BMC Med. 2008;6:14.
163. Kefas B, Comeau L, Floyd DH, Seleverstov O, Godlewski J, Schmittgen T, Jiang J, diPierro CG, Li Y, Chiocca EA, et al. The neuronal microRNA miR-326 acts in a feedback loop with notch and has therapeutic potential against brain tumors. J Neurosci Off J Soc Neurosci. 2009;29(48):15161–8.
164. Du Z, Lovly CM. Mechanisms of receptor tyrosine kinase activation in cancer. Mol Cancer. 2018;17(1):58.
165. Sudhesh Dev S, Zainal Abidin SA, Farghadani R, Othman I, Naidu R. Receptor tyrosine kinases and their signaling pathways as therapeutic targets of curcumin in cancer. Front Pharmacol. 2021;12:772510.
166. Verhaak RG, Hoadley KA, Purdom E, Wang V, Qi Y, Wilkerson MD, Miller CR, Ding L, Golub T, Mesirov JP, et al. Integrated genomic analysis identifies clinically relevant subtypes of glioblastoma characterized by abnormalities in PDGFRA, IDH1, EGFR, and NF1. Cancer Cell. 2010;17(1):98–110.
167. Nakada M, Kita D, Teng L, Pyko IV, Watanabe T, Hayashi Y, Hamada JI. Receptor tyrosine kinases: principles and functions in glioma invasion. Adv Exp Med Biol. 2020;1202:151–78.
168. Furnari FB, Cloughesy TF, Cavenee WK, Mischel PS. Heterogeneity of epidermal growth factor receptor signalling networks in glioblastoma. Nat Rev Cancer. 2015;15(5):302–10.
169. Gong Y, Dong Y, Cui J, Sun Q, Ren H. Receptor tyrosine kinase interaction with the tumor microenvironment in malignant progression of human glioblastoma. In: Omerhodzic I, Arnautovic K, editors. Glioma-contemporary diagnostic and therapeutic approaches. London: IntechOpen; 2019.
170. Ullah R, Yin Q, Snell AH, Wan L. RAF-MEK-ERK pathway in cancer evolution and treatment. Semin Cancer Biol. 2022;85:123–54.
171. Touat M, Idbaih A, Sanson M, Ligon KL. Glioblastoma targeted therapy: updated approaches from recent biological insights. Ann Oncol Off J Eur Soc Med Oncol. 2017;28(7):1457–72.
172. Rodon J, Dienstmann R, Serra V, Tabernero J. Development of PI3K inhibitors: lessons learned from early clinical trials. Nat Rev Clin Oncol. 2013;10(3):143–53.
173. Dai Z, Wang L, Wang X, Zhao B, Zhao W, Bhardwaj SS, Ye J, Yin Z, Zhang J, Zhao S. Oxymatrine induces cell cycle arrest and apoptosis and suppresses the invasion of human glioblastoma cells through the EGFR/PI3K/Akt/mTOR signaling pathway and STAT3. Oncol Rep. 2018;40(2):867–76.
174. Sunayama J, Matsuda K, Sato A, Tachibana K, Suzuki K, Narita Y, Shibui S, Sakurada K, Kayama T, Tomiyama A, et al. Crosstalk between the PI3K/mTOR and MEK/ERK pathways involved in the maintenance of self-renewal and tumorigenicity of glioblastoma stem-like cells. Stem Cells. 2010;28(11):1930–9.
175. Inoki K, Li Y, Zhu T, Wu J, Guan KL. TSC2 is phosphorylated and inhibited by Akt and suppresses mTOR signalling. Nat Cell Biol. 2002;4(9):648–57.
176. Simanshu DK, Nissley DV, McCormick F. RAS proteins and their regulators in human disease. Cell. 2017;170(1):17–33.
177. Rezaei Adariani S, Buchholzer M, Akbarzadeh M, Nakhaei-Rad S, Dvorsky R, Ahmadian MR. Structural snapshots of RAF kinase interactions. Biochem Soc Trans. 2018;46(6):1393–406.
178. Yuan J, Ng WH, Lam PYP, Wang Y, Xia H, Yap J, Guan SP, Lee ASG, Wang M, Baccarini M, et al. The dimer-dependent catalytic activity of RAF family kinases is revealed through characterizing their oncogenic mutants. Oncogene. 2018;37(43):5719–34.
179. Yoo JY, Swanner J, Otani Y, Nair M, Park F, Banasavadi-Siddegowda Y, Liu J, Jaime-Ramirez AC, Hong B, Geng F, et al. Oncolytic HSV therapy increases trametinib access to brain tumors and sensitizes them in vivo. Neurooncology. 2019;21(9):1131–40.
180. Wang J, Yao N, Hu Y, Lei M, Wang M, Yang L, Patel S, Li X, Liu K, Dong Z. PHLDA1 promotes glioblastoma cell growth via sustaining the activation state of Ras. Cell Mol Life Sci. 2022;79(10):520.
181. Wan W, Xiao W, Pan W, Chen L, Liu Z, Xu J. Isoprenylcysteine carboxyl methyltransferase is critical for glioblastoma growth and survival by activating Ras/Raf/Mek/Erk. Cancer Chemother Pharmacol. 2022;89(3):401–11.
182. Mao Y, Jiang P. The crisscross between p53 and metabolism in cancer. Acta Biochim Biophys Sin. 2023;55(6):914–22.
183. Wang J, Zhou JY, Wu GS. ERK-dependent MKP-1-mediated cisplatin resistance in human ovarian cancer cells. Cancer Res. 2007;67(24):11933–41.
184. Leighton F, Poole B, Lazarow PB, De Duve C. The synthesis and turnover of rat liver peroxisomes. I. Fractionation of peroxisome proteins. J Cell Biol. 1969;41(2):521–35.
185. Badur MG, Muthusamy T, Parker SJ, Ma S, McBrayer SK, Cordes T, Magana JH, Guan KL, Metallo CM. Oncogenic R132 IDH1 mutations limit NADPH for de novo lipogenesis through (D)2-hydroxyglutarate production in fibrosarcoma sells. Cell Rep. 2018;25(4):1018-e10261014.
186. Dang L, White DW, Gross S, Bennett BD, Bittinger MA, Driggers EM, Fantin VR, Jang HG, Jin S, Keenan MC, et al. Cancer-associated IDH1 mutations produce 2-hydroxyglutarate. Nature. 2009;462(7274):739–44.
187. Grassian AR, Parker SJ, Davidson SM, Divakaruni AS, Green CR, Zhang X, Slocum KL, Pu M, Lin F, Vickers C, et al. IDH1 mutations alter citric acid cycle metabolism and increase dependence on oxidative mitochondrial metabolism. Cancer Res. 2014;74(12):3317–31.
188. Hurley JH, Dean AM, Koshland DE Jr., Stroud RM. Catalytic mechanism of NADP(+)-dependent isocitrate dehydrogenase: implications from the structures of magnesium-isocitrate and NADP + complexes. Biochemistry. 1991;30(35):8671–8.
189. Yu D, Liu Y, Zhou Y, Ruiz-Rodado V, Larion M, Xu G, Yang C. Triptolide suppresses IDH1-mutated malignancy via Nrf2-driven glutathione metabolism. Proc Natl Acad Sci USA. 2020;117(18):9964–72.

190. Reitman ZJ, Duncan CG, Poteet E, Winters A, Yan LJ, Gooden DM, Spasojevic I, Boros LG, Yang SH, Yan H. Cancer-associated isocitrate dehydrogenase 1 (IDH1) R132H mutation and d-2-hydroxyglutarate stimulate glutamine metabolism under hypoxia. J Biol Chem. 2014;289(34):23318–28.
191. Le A, Cooper CR, Gouw AM, Dinavahi R, Maitra A, Deck LM, Royer RE, Vander Jagt DL, Semenza GL, Dang CV. Inhibition of lactate dehydrogenase A induces oxidative stress and inhibits tumor progression. Proc Natl Acad Sci USA. 2010;107(5):2037–42.
192. Khurshed M, Molenaar RJ, Lenting K, Leenders WP, van Noorden CJF. In silico gene expression analysis reveals glycolysis and acetate anaplerosis in IDH1 wild-type glioma and lactate and glutamate anaplerosis in IDH1-mutated glioma. Oncotarget. 2017;8(30):49165–77.
193. Chesnelong C, Chaumeil MM, Blough MD, Al-Najjar M, Stechishin OD, Chan JA, Pieper RO, Ronen SM, Weiss S, Luchman HA, et al. Lactate dehydrogenase a silencing in IDH mutant gliomas. Neurooncology. 2014;16(5):686–95.
194. Sharma N, Mallela AN, Shi DD, Tang LW, Abou-Al-Shaar H, Gersey ZC, Zhang X, McBrayer SK, Abdullah KG. Isocitrate dehydrogenase mutations in gliomas: a review of current understanding and trials. Neuro-oncol Adv. 2023;5(1):vdad053.
195. Cairns RA, Mak TW. Oncogenic isocitrate dehydrogenase mutations: mechanisms, models, and clinical opportunities. Cancer Discov. 2013;3(7):730–41.
196. Chou FJ, Liu Y, Lang F, Yang C. D-2-hydroxyglutarate in glioma biology. Cells. 2021;10(9):2345.
197. Tang X, Fu X, Liu Y, Yu D, Cai SJ, Yang C. Blockade of glutathione metabolism in IDH1-mutated glioma. Mol Cancer Ther. 2020;19(1):221–30.
198. Braun Y, Filipski K, Bernatz S, Baumgarten P, Roller B, Zinke J, Zeiner PS, Ilina E, Senft C, Ronellenfitsch MW, et al. Linking epigenetic signature and metabolic phenotype in IDH mutant and IDH wildtype diffuse glioma. Neuropathol Appl Neurobiol. 2021;47(3):379–93.
199. Han S, Liu Y, Cai SJ, Qian M, Ding J, Larion M, Gilbert MR, Yang C. IDH mutation in glioma: molecular mechanisms and potential therapeutic targets. Br J Cancer. 2020;122(11):1580–9.
200. Navis AC, Niclou SP, Fack F, Stieber D, van Lith S, Verrijp K, Wright A, Stauber J, Tops B, Otte-Holler I, et al. Increased mitochondrial activity in a novel IDH1-R132H mutant human oligodendroglioma xenograft model: in situ detection of 2-HG and α-KG. Acta Neuropathol Commun. 2013;1:18.
201. Bhavya B, Anand CR, Madhusoodanan UK, Rajalakshmi P, Krishnakumar K, Easwer HV, Deepti AN, Gopala S. To be wild or mutant: role of Isocitrate dehydrogenase 1 (IDH1) and 2-hydroxy glutarate (2-HG) in gliomagenesis and treatment outcome in glioma. Cell Mol Neurobiol. 2020;40(1):53–63.
202. Bensaad K, Tsuruta A, Selak MA, Vidal MN, Nakano K, Bartrons R, Gottlieb E. Vousden KH: TIGAR, a p53-inducible regulator of glycolysis and apoptosis. Cell. 2006;126(1):107–20.
203. Maurer GD, Heller S, Wanka C, Rieger J, Steinbach JP. Knockdown of the TP53-Induced glycolysis and apoptosis regulator (TIGAR) sensitizes glioma cells to hypoxia, irradiation and temozolomide. Int J Mol Sci. 2019;20(5):1061.
204. Luo X, Ge J, Chen T, Liu J, Liu Z, Bi C, Lan S. LHX9, a p53-binding protein, inhibits the progression of glioma by suppressing glycolysis. Aging. 2021;13(18):22109–19.
205. Li T, Kon N, Jiang L, Tan M, Ludwig T, Zhao Y, Baer R, Gu W. Tumor suppression in the absence of p53-mediated cell-cycle arrest, apoptosis, and senescence. Cell. 2012;149(6):1269–83.
206. Tang Z, He Z. TIGAR promotes growth, survival and metastasis through oxidation resistance and AKT activation in glioblastoma. Oncol Lett. 2019;18(3):2509–17.
207. Yousuf U, Sofi S, Makhdoomi A, Mir MA. Identification and analysis of dysregulated fatty acid metabolism genes in breast cancer subtypes. Med Oncol. 2022;39(12):256.
208. Borude P, Bhushan B, Gunewardena S, Akakpo J, Jaeschke H, Apte U. Pleiotropic role of p53 in injury and liver regeneration after acetaminophen overdose. Am J Pathol. 2018;188(6):1406–18.
209. Sen N, Satija YK, Das S. PGC-1α, a key modulator of p53, promotes cell survival upon metabolic stress. Mol Cell. 2011;44(4):621–34.
210. Yahagi N, Shimano H, Matsuzaka T, Najima Y, Sekiya M, Nakagawa Y, Ide T, Tomita S, Okazaki H, Tamura Y, et al. p53 activation in adipocytes of obese mice. J Biol Chem. 2003;278(28):25395–400.
211. Jiang P, Du W, Wang X, Mancuso A, Gao X, Wu M, Yang X. p53 regulates biosynthesis through direct inactivation of glucose-6-phosphate dehydrogenase. Nat Cell Biol. 2011;13(3):310–6.
212. Ou Y, Wang SJ, Jiang L, Zheng B, Gu W. p53 protein-mediated regulation of phosphoglycerate dehydrogenase (PHGDH) is crucial for the apoptotic response upon serine starvation. J Biol Chem. 2015;290(1):457–66.
213. Amit M, Takahashi H, Dragomir MP, Lindemann A, Gleber-Netto FO, Pickering CR, Anfossi S, Osman AA, Cai Y, Wang R, et al. Loss of p53 drives neuron reprogramming in head and neck cancer. Nature. 2020;578(7795):449–54.
214. Jiang L, Kon N, Li T, Wang SJ, Su T, Hibshoosh H, Baer R, Gu W. Ferroptosis as a p53-mediated activity during tumour suppression. Nature. 2015;520(7545):57–62.
215. Taylor SR, Falcone JN, Cantley LC, Goncalves MD. Developing dietary interventions as therapy for cancer. Nat Rev Cancer. 2022;22(8):452–66.
216. Duan Y, Zhao X, Ren W, Wang X, Yu KF, Li D, Zhang X, Zhang Q. Antitumor activity of dichloroacetate on C6 glioma cell: in vitro and in vivo evaluation. OncoTargets Ther. 2013;6:189–98.
217. Oliva CR, Nozell SE, Diers A, McClugage SG, Sarkaria JN, Markert JM, Darley-Usmar VM, Bailey SM, Gillespie GY, Landar A, et al. Acquisition of temozolomide chemoresistance in gliomas leads to remodeling of mitochondrial electron transport chain. J Biol Chem. 2010;285(51):39759–67.
218. Maher JC, Wangpaichitr M, Savaraj N, Kurtoglu M, Lampidis TJ. Hypoxia-inducible factor-1 confers resistance to the glycolytic inhibitor 2-deoxy-D-glucose. Mol Cancer Ther. 2007;6(2):732–41.
219. Pelicano H, Martin DS, Xu RH, Huang P. Glycolysis inhibition for anticancer treatment. Oncogene. 2006;25(34):4633–46.
220. Gimple RC, Kidwell RL, Kim LJY, Sun T, Gromovsky AD, Wu Q, Wolf M, Lv D, Bhargava S, Jiang L, et al. Glioma stem cell-specific superenhancer promotes polyunsaturated fatty-acid synthesis to support EGFR signaling. Cancer Discov. 2019;9(9):1248–67.
221. Yuan S, Wang F, Chen G, Zhang H, Feng L, Wang L, Colman H, Keating MJ, Li X, Xu RH, et al. Effective elimination of cancer stem cells by a novel drug combination strategy. Stem Cells. 2013;31(1):23–34.
222. Kang MK, Kang SK. Tumorigenesis of chemotherapeutic drug-resistant cancer stem-like cells in brain glioma. Stem Cells Dev. 2007;16(5):837–47.

223. Azzalin A, Nato G, Parmigiani E, Garello F, Buffo A, Magrassi L. Inhibitors of GLUT/SLC2A enhance the action of BCNU and temozolomide against high-grade gliomas. Neoplasia. 2017;19(4):364–73.
224. Padfield E, Ellis HP, Kurian KM. Current therapeutic advances targeting EGFR and EGFRvIII in glioblastoma. Front Oncol. 2015;5:5.
225. Brennan CW, Verhaak RG, McKenna A, Campos B, Noushmehr H, Salama SR, Zheng S, Chakravarty D, Sanborn JZ, Berman SH, et al. The somatic genomic landscape of glioblastoma. Cell. 2013;155(2):462–77.
226. Davis ME. Glioblastoma: overview of disease and treatment. Clin J Oncol Nurs. 2016;20(5 Suppl):S2-8.
227. Yuan B, Wang G, Tang X, Tong A, Zhou L. Immunotherapy of glioblastoma: recent advances and future prospects. Hum Vaccin Immunother. 2022;18(5):2055417.
228. Cuellar-Núñez ML, Gonzalez de Mejia E, Loarca-Piña G. Moringa oleifera leaves alleviated inflammation through downregulation of IL-2, IL-6, and TNF-α in a colitis-associated colorectal cancer model. Food Res Int. 2021;144:110318.
229. Arienti C, Pignatta S, Zanoni M, Zamagni A, Cortesi M, Sarnelli A, Romeo A, Arpa D, Longobardi P, Bartolini D, et al. High-pressure oxygen rewires glucose metabolism of patient-derived glioblastoma cells and fuels inflammasome response. Cancer Lett. 2021;506:152–66.
230. Banks WA. From blood–brain barrier to blood-brain interface: new opportunities for CNS drug delivery. Nat Rev Drug Discov. 2016;15(4):275–92.
231. Alghamri MS, Banerjee K, Mujeeb AA, Mauser A, Taher A, Thalla R, McClellan BL, Varela ML, Stamatovic SM, Martinez-Revollar G, et al. Systemic delivery of an adjuvant CXCR4-CXCL12 signaling inhibitor encapsulated in synthetic protein nanoparticles for glioma immunotherapy. ACS Nano. 2022;16(6):8729–50.
232. Raez LE. Pharmacology: a phase I dose-escalation trial of 2-deoxy-d-glucose alone or combined with docetaxel in patients with advanced solid tumors. Cancer Chemother Pharmacol. 2013;71(2):523–30.
233. Molina JR, Sun Y, Protopopova M, Gera S, Bandi M, Bristow C, McAfoos T, Morlacchi P, Ackroyd J, Agip AA, et al. An inhibitor of oxidative phosphorylation exploits cancer vulnerability. Nat Med. 2018;24(7):1036–46.
234. Boreel DF, Span PN, Heskamp S, Adema GJ, Bussink J. Targeting oxidative phosphorylation to increase the efficacy of radio- and immune-combination therapy. Clin Cancer Res Off J Am Assoc Cancer Res. 2021;27(11):2970–8.
235. Tan SK, Jermakowicz A, Mookhtiar AK, Nemeroff CB, Schürer SC, Ayad NG. Drug repositioning in glioblastoma: a pathway perspective. Front Pharmacol. 2018;9:218.
236. Pouremamali F, Pouremamali A, Dadashpour M, Soozangar N, Jeddi F. An update of Nrf2 activators and inhibitors in cancer prevention/promotion. Cell Commun Signal. 2022;20(1):100.
237. Shahcheraghi SH, Salemi F, Alam W, Ashworth H, Saso L, Khan H, Lotfi M. The role of NRF2/KEAP1 pathway in glioblastoma: pharmacological implications. Med Oncol. 2022;39(5):91.