Review

Metabolic remodeling in astrocytes: Paving the path to brain tumor development

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ABSTRACT

The brain is a highly metabolic organ, composed of multiple cell classes, that controls crucial functions of the body. Although neurons have traditionally been the main protagonist, astrocytes have gained significant attention over the last decade. In this regard, astrocytes are a type of glial cells that have recently emerged as critical regulators of central nervous system (CNS) function and play a significant role in maintaining brain energy metabolism. However, in certain scenarios, astrocyte behavior can go awry, which poses a significant threat to brain integrity and function. This is definitively the case for mutations that turn normal astrocytes and astrocytic precursors into gliomas, an aggressive type of brain tumor. In addition, healthy astrocytes can interact with tumor cells, becoming part of the tumor microenvironment and influencing disease progression. In this review, we discuss the recent evidence suggesting that disturbed metabolism in astrocytes can contribute to the development and progression of fatal human diseases such as cancer. Emphasis is placed on detailing the molecular bases and metabolic pathways of this disease and highlighting unique metabolic vulnerabilities that can potentially be exploited to develop successful therapeutic opportunities.

1. Introduction

The central nervous system (CNS) represents an intricately complex structure comprising a diverse array of specialized cell types, where astrocytes, in particular, emerge as pivotal players (Winnubst and Arber, 2021). For a long time, neurons have been the predominant protagonists and have been considered the functional, most important elements of the CNS. However, research conducted in recent decades has shown the essential role played by non-neuronal cells in the function of the CNS

(Argente-Arizón et al., 2015). These non-neuronal cells include macroglia (ependymal cells, oligodendrocytes, and astrocytes) and microglia, which support vital brain functions (von Bartheld, 2018; von Bartheld et al., 2016). Astrocytes were first described by Virchow in 1846 and represent the most abundant cell type in most parts of the brain (Molofsky and Deneen, 2015). They play a role in buffering the extracellular space, providing substrates to neurons, facilitating the exchange of glutamate and glutamine for synaptic communication, and making blood vessels accessible (Nedergaard et al., 2003; Turner and Adamson,

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2011).

One of the fundamental characteristics of brain energy metabolism is a close metabolic connection between astrocytes and neurons (Bélanger et al., 2011). Astrocytes are thus crucial partners for neurons, regulating not only their function but also their plasticity, which is indispensable for the cognitive activity of the brain (Bonvento and Bolaños, 2021). It has been clearly shown that perturbations affecting this metabolic cooperation contribute to the onset or development of several mental illnesses (Katsnelson et al., 2016; Blass, 2001; González-Rodríguez et al., 2021; Procaccini et al., 2016; Pirozzi and Yan, 2021).

Due to their fast development and fatal outcome, brain tumors constitute one of the most aggressive and devastating pathologies in the brain (Miller et al., 2021; McKinnon et al., 2021). In the adult population, gliomas, which exhibit histologic resemblance to astroglial cells, hold the distinction of being the most prevalent primary brain tumors, contributing significantly to both mortality and morbidity rates (Miller et al., 2021; McKinnon et al., 2021; Ostrom et al., 2022). The most aggressive form of glioma is glioblastoma, which is also called glioblastoma multiforme (GBM). Despite current treatments that include chemo- and radiotherapy upon surgical resection, the life expectancy for patients diagnosed with GBM, remains dismal (McKinnon et al., 2021). One of the hallmarks of these tumors is their infiltration into normal brain tissue, making it extremely difficult to completely resect the tumor and ultimately favoring tumor relapse in the face of treatment resistance (Cuddapah et al., 2014). Two key contributors to the malignancy and resistance of brain tumors are the intratumoral heterogeneity and dynamic plasticity across cellular states (Neftel et al., 2019; Tirosh et al., 2016; Venteicher et al., 2017). In fact, the identification of the cell-of-origin harboring the mutations that drive the progression of these tumors has been controversial (Azzarelli et al., 2018; Sanai et al., 2005; Friedmann-Morvinski and Verma, 2014), partly due to the lack of direct genetic evidence. While historically gliomas were thought to arise mainly from differentiated astrocytes that undergo a process of dedifferentiation by mechanisms that require tumor suppressor inactivation and injury/inflammatory programs (Friedmann-Morvinski et al., 2012; Dufour et al., 2009; Simpson Ragdale et al., 2023), recent studies pinpoint to a malignant transformation of neural stem/progenitor cells (Singh et al., 2004a; Alcantara Llaguno et al., 2009). Importantly, patient brain tissue and genome-edited mouse models from recent studies suggest that astrocyte-like neural stem cells (NSCs) in the subventricular zone may serve as the cell of origin harboring the driver mutations responsible for human GBM (Lee et al., 2018). However, the knowledge about the interplay of metabolism in the evolution of these tumors is scarce.

Cumulative research endeavors over the last decades have solidified the notion that glioma cells and specifically, astrocytoma cells exhibit distinct metabolic characteristics compared to their non-malignant astrocytic counterparts. These metabolic alterations have been shown to be critical to maintaining the uncontrolled growth and survival of cancer cells (Pavlova et al., 2022; Galeffi and A. Turner D., 2014). Crucially, studying how and whether a metabolic modulation may impact tumor progression could be exploited to potentiate therapeutic treatments, or even to prevent tumor onset, as suggested by Amodeo et al., 2023 (Amodeo et al., 2023).

In our quest to comprehend how altered metabolism fuels and sustains the progression of gliomas, it is imperative to delve into the intricate web of metabolic pathways and essential nutrient components that underpin the normal functioning of astrocytes. Here we provide a general overview of the most important metabolic pathways and energetic substrates in healthy astrocytes to then explore their metabolic alterations and the aberrant metabolic pathways in glioma cells. Finally, we intersect the metabolic landscape of astrocytes and glioma.

2. Metabolism in astrocytes

The brain has high energy requirements. In fact, despite making up only 2% of the body's weight, the brain uses 25% of the body's total glucose and consumes 20% of its total oxygen (Mergenthaler et al., 2013; Attwell and Laughlin, 2001). Synaptic activity uses the majority of this oxidative energy (about 80%) for the re-uptake and recycling of neurotransmitters, as well as for maintaining ionic gradients (Hyder et al., 2013). By comparison, the metabolic activities in astrocytes have been estimated to account for between 5 and 15% of the total ATP consumption in the brain (Rose et al., 2020). Astrocytes showcase a remarkable metabolic versatility, demonstrating the capacity to metabolize a diverse array of nutrients, including carbohydrates, lipids, and amino acids. They do so in order to meet their substantial energetic requirements and support the biosynthesis essential for their various cellular functions (Serres et al., 2008).

2.1. Carbohydrates

The metabolic profiles of neurons and astrocytes are different. While glucose entering astrocytes primarily proceeds via glycolysis to generate pyruvate and lactate, neurons have a high oxidative capacity and produce ATP through mitochondrial activity in the presence of oxygen (Bélanger et al., 2011; Bouzier-Sore et al., 2006). In vitro, this astrocyte-derived lactate can be taken up by neurons where, after being converted back to pyruvate, fuel the tricarboxylic acid (TCA) cycle and drive oxidative phosphorylation (OXPHOS) (Camandola and Mattson, 2017; Fiebig et al., 2019). This metabolic crosstalk is widely known as the astrocyte–neuron lactate shuttle (ANLS), and to date, whether this communication occurs in vivo remains controversial, with some studies in favor of the ANLS hypothesis (Fox et al., 1988; Pellerin and Magistretti, 1994; Rouach et al., 2008; Zimmer et al., 2017; Suzuki et al., 2011; Jakkamsetti et al., 2019) and others opposing it (Serres et al., 2008; Lundgaard et al., 2015; Díaz-García et al., 2017; Stoessl, 2017; Dienel et al., 2018). In a situation where OXPHOS activity is inhibited, astrocytes have a normal energy production, with an observed increase in lactate production in mutants of Cox10 (involved in the proper assembly of the cytochrome *c* oxidase or complex IV), indicating that astrocytes are mainly glycolytic (Almeida et al., 2001; Supplie et al., 2017). Glycolytic enzymes are highly expressed in astrocytes, which make them utilize 80% of the glucose through glycolysis (Beard et al., 2022). Pyruvate dehydrogenase (PDH) activity in astrocytes is lowered because of its phosphorylation by pyruvate dehydrogenase kinase (PDK), which prevents pyruvate from entering the TCA cycle (Bouzier-Sore et al., 2006; Halim et al., 2010) and is preferentially redirected to lactate production. Unlike astrocytes, glycolysis activity in neurons is restricted by the ongoing breakdown of 6-phosphofructo-2-kinase / fructose-2, 6-bisphosphatase-3 (PFKFB3), an enzyme that catalyzes the formation of fructose-2,6-P, a powerful allosteric activator of phosphofructokinase 1 (PFK1) (Almeida et al., 2004; Herrero-Mendez et al., 2009). Consequently, glucose utilization in neurons is diverted to the pentose phosphate pathway (PPP) in order to regenerate NADPH for the reductive recycling of GSH upon oxidative stress (Vaughn and Deshmukh, 2008). According to the astrocyte-neuron lactate shuttle theory, a significant amount of glucose metabolism in astrocytes is diverted to lactate synthesis, which is then transported to neurons as fuel for OXPHOS (Magistretti and Pellerin, 1996). Although it is important to note that this theory has not been fully validated in vivo.

In the brain, glycogen is mostly found in astrocytes and serves as an important energy source during hypoxic situations and normal brain activity. According to estimates, as much as 40% of glucose in astrocytes is converted into glycogen molecules (Prebil et al., 2011).

It is important to stress that, while the brain relies almost exclusively on glucose to work, other metabolic substrates such as lipids or amino acids can be required under certain stages of development or specific stress conditions.

2.2. Fatty acids

Astrocytes are also equipped with enzymes involved in lipid metabolism. Lipids produced by astrocytes are delivered to neurons and oligodendrocytes as parts of synaptic and myelin membranes. Equally important, fatty acid degradation by astrocytes is critical for maintaining lipid homeostasis in the brain. In fact, loss of astrocytic fatty acid catabolism causes lipid droplet (LD) accumulation and lipotoxicity, triggering an inflammatory response that culminates in neurodegeneration (Mi et al., 2023). In addition, fatty acid oxidation, in astrocytes, has also been reported to be required for proper cognitive performance (Morant-Ferrando et al., 2023).

Despite evidence that certain hypothalamic neurons may burn fatty acids (FA) for energy when there is a shortage of glucose (Varela et al., 2021), it is generally believed that neurons have a restricted capacity for FA oxidation. In contrast, astrocytes are the primary location of FA acid oxidation in the central nervous system (Varela et al., 2021; Gao et al., 2017; Timper et al., 2020).

In cases of glucose shortage, such as extended fasting, intense exercise, or pathological disorders like diabetes, ketone bodies can replace the use of glucose as the brain's primary fuel source (García-Rodríguez and Giménez-Cassina, 2021). Thus, fatty acids may be used for ketone body synthesis under nutritional stress situations, first by astrocytes and subsequently transferred between astrocytes and neurons via monocarboxylate transporters (MCTs) for TCA cycle's energy generation (Silva et al., 2022).

2.3. Amino acids

The gliotransmitter D-serine is synthesized from L-serine by the activation of serine racemase (SR), which is selectively expressed in the astrocytes, and is an important signaling molecule controlling the activity of the synaptic *N*-methyl D-aspartate (NMDA) receptors in many brain areas. Astrocytic energy metabolism controls D-serine production specifically via the interactions between the glycolytic enzyme glyceraldehyde-3-phosphate dehydrogenase (GAPDH) and SR. (Suzuki et al., 2015) This pathway is supported by de novo serine biosynthesis whose enzymes are highly expressed in astrocytes (Le Douce et al., 2020). One of the most common neurotransmitters produced by excitatory neurons in the CNS is glutamate, nonetheless, leftover glutamate in the extracellular space is potentially harmful. To avoid undesired toxicity, glutamate is taken up by astrocytes and can either be amidated to glutamine in a reaction catalyzed by the enzyme glutamine synthase (GS), almost exclusively found in astrocytes, or can be converted to α-ketoglutarate (αKG) by aspartate amino transferase or GDH (Schousboe et al., 2014). Sustained metabolic activity will cause a drain of αKG and other metabolites from the TCA cycle unless it is compensated via an anaplerotic reaction. In this regard, astrocytes express high levels of Pyruvate Carboxylase (PC) an enzyme that catalyzes the carboxylation of pyruvate to OAA and represents a major anaplerotic pathway by which the TCA cycle is replenished (Rose et al., 2020). The mitochondrial form of the branched chain amino acid aminotransferase isozymes (BCATs) is preferentially localized in astrocytes, whereas the cytosolic form is localized in neurons (Lieth et al., 2001).

2.4. One-carbon metabolism

One-carbon metabolism comprises a series of interlinking metabolic pathways, mediated by the folate cofactor, that ultimately supports multiple physiological processes including nucleotide biosynthesis, epigenetics, and redox homeostasis. Excess 10-Formyltetrahydrofolate (10-formyTHF) can be decarboxylated to tetrahydrofolate (THF) by the aldehyde dehydrogenase 1 family member L1 (ALDH1L1) enzyme with concomitant production of NADPH (Ducker and Rabinowitz, 2016). Strikingly, ALDH1L1 is highly expressed in astrocytes and has been postulated as a specific marker for this cell type (Nave et al., 2016),

which might indicate that cytosolic one-carbon metabolism plays an essential role in astrocytes to maintain redox defenses (Fig. 1).

It becomes evident that these metabolic pathways and mechanisms, integral to maintaining the healthy functioning of the brain, can be co-opted by transformed cells in gliomas. This hijacking of normal metabolic processes is not just an interesting phenomenon but holds profound implications for tumor progression. Importantly, this dual nature of astrocyte metabolism, both as a driving force for normal brain function and as a potential Achilles' heel in the context of gliomas and other brain tumors, unveils a promising avenue for therapeutic exploration. The metabolic vulnerabilities that emerge from this intersection offer a tantalizing opportunity for the development of innovative treatments aimed at targeting the metabolic underpinnings of these tumors.

3. Mutations in metabolic enzymes are the origin of astrocytomas: role of IDHs

Gliomas are highly diffuse brain tumors that originate from astrocytes, oligodendrocytes or their precursors (Friedmann-Morvinski et al., 2012; Liu et al., 2011; Li et al., 2009; Singh et al., 2004b) Interestingly, the mutational status of the isocitrate dehydrogenase (IDH), a key metabolic enzyme, is one of the molecular features defined by the World Health Organization (WHO) to stratify adult tumors of the CNS. IDH1 mutations are overwhelmingly common in cases of lower-grade glioma (LGG), occurring in more than 80% of instances. However, in high-grade glioma, these mutations are relatively rare, appearing in only about 10% of cases. They are predominantly found in secondary tumors that have evolved from pre-existing LGG (Louis et al., 2021). IDH wild-type tumors are classified as glioblastoma, the most aggressive type that accounts for up to 90% of primary brain tumors, whereas IDH-mutant tumors are denominated astrocytomas and, if they have 1p/19q-codeletion, oligodendrogliomas (Louis et al., 2021). Importantly, this absence of IDH-1 and IDH-2 mutations (IDH-wildtype) is now required for the diagnosis of glioblastoma multiforme, which was previously only determined by histopathological criteria (Stoyanov et al., 2022). In addition, IDH-wild type gliomas fall into three subtypes (proneural, classical, and mesenchymal) based on genomic alterations and gene expression signatures (Verhaak et al., 2010; Wang et al., 2017a). However, the mentioned glioblastoma subtypes often co-occur or transition between subtypes in the same patient, reflecting the rather heterogeneous nature of these tumors (Wang et al., 2017a; Phillips et al., 2006). In the case of pediatric-type gliomas, various genetic mutations such as the status of H3 and signaling pathways like MAPK-altered contribute to a distinct classification (Louis et al., 2021).

There are three isoforms in the IDH family of enzymes that are compartmentalized in the cytoplasm (IDH1) and mitochondria (IDH2 and IDH3). IDH enzymes participate in a number of physiological functions, including the control of cellular redox homeostasis, glutamine metabolism, lipid biosynthesis, and OXPHOS. IDH1 and IDH2 are very similar proteins that catalyze the simultaneous reduction of NADP+ to NADPH and the reversible oxidative decarboxylation of isocitrate to αKG. On the other hand, IDH3 is implicated in the NAD + -dependent conversion of isocitrate to αKG in the TCA cycle (Han et al., 2020). Major advances in cancer genetics during the past decade have uncovered that the genes encoding IDHs are frequently mutated in specific human malignancies, including gliomas. IDH mutations in gliomas are recognized in >80% of World Health Organization (WHO) grade II/III cases (Yan et al., 2009; Nobusawa et al., 2009). IDHs mutations are in fact a major determinant factor dictating patient's prognosis. Patients with gliomas harboring an IDH1-mutated tumor present a favorable disease outcome with prolonged median survival compared with patients with an IDH1-normal tumor (Wang et al., 2014).

Mutations in IDH1 and IDH2 are mutually exclusive and affected the arginines on position 132 of IDH1 and position 172 of IDH2. The cancer-associated mutation of IDH (IDHm) has gained a neomorphic activity which causes KG to be converted to D-2-hydroxyglutarate (D2HG) while
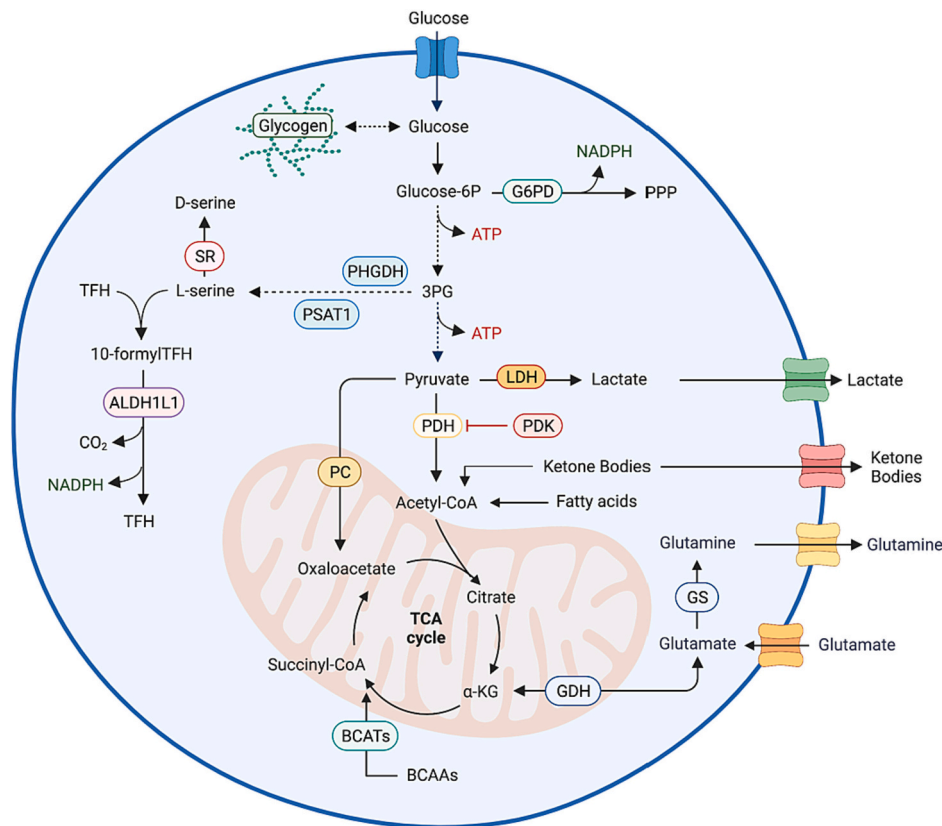
Fig. 1. Central carbon metabolism and associated metabolic enzymes in astrocytes.

In astrocytes, glucose entering cells is metabolized through glycolysis and the pentose-phosphate pathway (PPP) or may be stored as glycogen. Glucose storage in glycogen is important energy reserve that can be used during periods of nutrient deprivation such as transient hypoxia. The glycolytic intermediate 3-phophogly-cerate (3PG) serves as a precursor for L-serine biosynthesis that can be further isomerized to D-serine by serine racemase (SR). Additionally, serine can transfer a one-carbon unit to tetrahydrofolate (THF) to ultimately form 10-formyl-tetrahydrofolate (10-formylTHF). The astrocyte specific aldehyde dehydrogenase 1 family member L1 (ALDH1L1) enzyme breaks down 10-formylTHF to THF and CO_2 generating NADPH. Pyruvate is the principal end product of glycolysis in astrocytes which is mostly converted into lactate by lactate dehydrogenase (LDH) to be exported to the extracellular space. High expression levels of pyruvate dehydrogenase kinase (PDK) inhibit pyruvate dehydrogenase (PDH) activity preventing acetyl-CoA formation from pyruvate. However, pyruvate can still enter the mitochondria and can converted to oxalacetate (OAA) by PC to replenish the TCA cycle. Fatty acids give rise to acetyl-CoA through β-oxidation whereas ketone bodies in astrocytes can enter as substrates for mitochondrial or can be the end product in mitochondrial metabolism that astrocytes export for other cells (neurons). Branched-chain amino acid (BCAA) are catabolized by BCAT to acetyl-CoA and/or succinate-CoA, which supply the TCA cycle. Glutamate is used for synthesis of glutamine catalyzed by glutamine synthetase (GS) or converted to αKG in the mitochondria by aspartate amino transferase or GDH.

oxidizing NADPH. This reaction can produce up to 100-fold increase in D2HG levels in cells carrying the mutation (Dang et al., 2010). Established as an oncometabolite, D2HG has been shown to competitively inhibit TET methylcytosine dioxygenases, as well as JmjC domain-containing histone demethylases, thus resulting in global hyper-methylation of DNA and chromatin (Xu et al., 2011). Consequently, accumulation of D2HG can inhibit histone demethylation which alone can be sufficient to block the differentiation of non-transformed cells, being this process necessary for lineage-specific progenitor cells to differentiate into functional brain cells, such as neurons and glia (Lu et al., 2012). Therefore, high levels of D-2-HG may promote stemness through activating the gene transcription of oncogenes like PDGFRA (Flavahan et al., 2015).

According to recent studies, IDHm is at the root of epigenetic instability in glioma cells, which results in hypermethylation of CpG islands (G-CIMP phenotype) and histones H3 and H44 (Duncan et al., 2012; Turcan et al., 2012). Transcriptomic analysis of atypically methylated genes in G-CIMP tumors found significant upregulation in genes involved in metabolic processes including carbohydrate metabolism, oxidative stress response, and nucleic acid biosynthesis (Noushmehr et al., 2010) (Fig. 2).

IDH mutations lead to metabolic rewiring, which redirects the TCA cycle for D2HG production (Reitman et al., 2011). Under these conditions the TCA cycle is adjusted to compensate for fluctuations in the metabolic pathways causing profound metabolic alterations that have been extensively studied using mass spectrometry-based metabolomics. Metabolic profiling of IDH1/2 mutant cells revealed alterations in multiple intracellular metabolites including amino acids, glutathione, choline derivatives, and TCA cycle metabolites (Reitman et al., 2011; Izquierdo-Garcia et al., 2015). Remarkably, N-acetyl-aspartyl-glutamate (NAAG), a prevalent dipeptide in the brain, was decreased ~50-fold in cells expressing IDH1 mutants and ~ 8-fold reduced in cells expressing IDH2 mutants, and a similar reduction of NAAG was detected in IDH-mutant glioma tissues (Reitman et al., 2011).

A ^{13}C metabolic flux study revealed that IDH1-mutated cells displayed enhanced oxidative metabolism in the TCA cycle while suppressing reductive glutamine metabolism (Grassian et al., 2014). Mutant IDH1/2 produce D2HG from glutamine-derived αKG, resulting in increased flux through this pathway (Dang et al., 2010). Therefore, cells expressing mutant IDH1/2 heavily rely on glutamine metabolism for growth and survival. This conclusion is supported by the observation that IDH-mutated glioma cells are more susceptible to glutaminase inhibition (Seltzer et al., 2010), indicating that glutaminolysis is an important compensatory route for maintaining metabolic homoeostasis. Another study found that IDH1-mutated cells are dependent on gluta-minolysis because D2HG acts as an inhibitor of the branched-chain
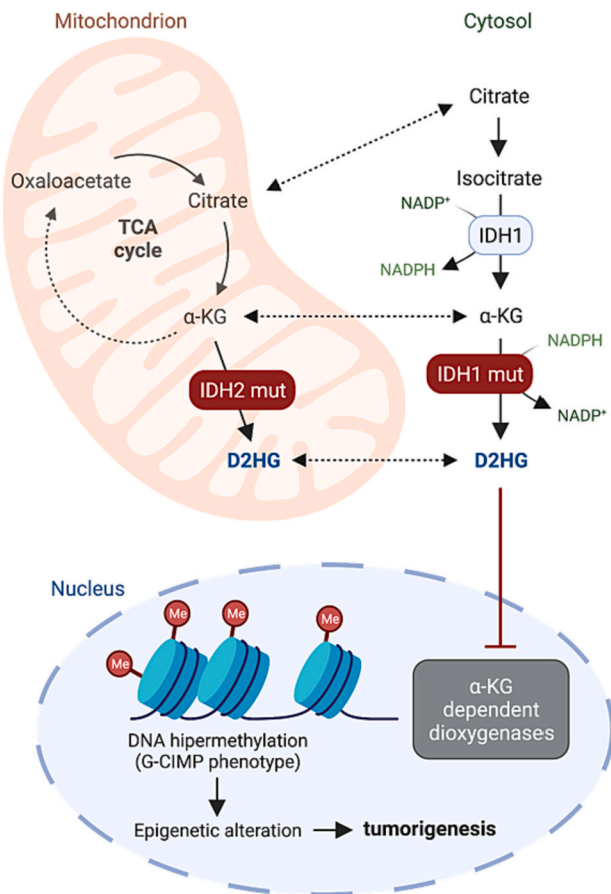
Fig. 2. Mutations in IDH1/2 cause epigenetic alterations and promote tumorigenesis.

The reversible NADP+-dependent oxidative decarboxylation of isocitrate to KG is catalyzed by IDH1 and IDH2. Mutant enzymes gain neomorphic enzymatic activity, converting α-ketoglutarate (αKG), to the oncometabolite, D-2-hydroxyglutarate (D2HG) both in the cytosol and in the mitochondria while consuming NADPH. D2HG competitively inhibits αKG-dependent dioxygenases in the nucleus which causes global epigenetic modifications on DNA and histones, respectively, resulting in a hypermethylator phenotype. These epigenetic changes prevent cell differentiation and enhance the early engraftment and proliferation of tumor cells.

amino acid transaminase (BCAT1/2), lowering glutamate levels (McBrayer et al., 2018). Patients with wild-type IDH1 and IDH2 have greater amounts of the branched-chain amino acids valine, leucine, and isoleucine, as well as the enzyme that catabolizes them (BCAT1) (Tönjes et al., 2013). Due to the depletion of cellular metabolism, several non-TCA cycle sources of carbohydrates are recruited to compensate for the loss of αKG (Ohka et al., 2014; Maus and Peters, 2017). For instance, glioma cells with the IDH1 mutation engage anaplerotic pathways such as increased flux through pyruvate carboxylase (PC) while reducing pyruvate oxidation by inhibiting PDH activity (Izquierdo-Garcia et al., 2014). These results suggest that IDH1 mutant glioma cells adaptively run the TCA cycle backwards, perhaps to produce sufficient succinate to power the electron transport chain (ETC).

Dysregulation of IDH1/2 canonical activity in mutant cells also affects redox state and compromise homeostasis of the ubiquitous redox cofactors nicotinamide adenine dinucleotides [NAD and NADP]. Cells harboring mutant IDH1 lose a source of NADPH-reducing equivalents while gaining new NADPH-coupled - ketoglutarate-reducing activity (Lewis et al., 2014). It has been shown that glioblastoma cells, but not astrocytes, had lower NADPH and NAD+ levels after IDH1 R132H transduction (Biedermann et al., 2019). Overall, this causes a shift in the cellular NADPH:NADP+ ratio that manifests as an altered glutathione

(GSH:GSSG) ratio (Bisdas et al., 2016), as well as sensitization to oxidative stimuli (Mohrenz et al., 2013; Shi et al., 2015). Owing to this substantially increased oxidative burden, inhibiting antioxidant pathways, such as the synthesis of glutathione, which is mediated by the transcription factor nuclear factor erythroid 2-related factor 2 (Nrf2), has proven to be a valuable strategy for targeting IDH1-mutated solid tumors (Cai et al., 2019). Nevertheless, some glioma cells are able to adapt by upregulating genes coding for key enzymes in de novo glutathione synthesis (Fack et al., 2017), which is not surprising as astrocytes contain one of the highest cytosolic concentrations of GSH (8–10 mM in primary astrocytes) among mammalian cells (Yudkoff et al., 1990; Raps et al., 1989).

Decreased NADPH levels in mutant cells do not only weaken antioxidant defenses but impair several anabolic processes and restrain cell growth. For instance, D2HG synthesis in cells with oncogenic R132 IDH1 mutation consumes NADPH, limiting de novo lipogenesis and increasing their dependency on exogenous lipid sources for in vitro growth (Badur et al., 2018). Moreover, mutant IDH1 displayed lowered NAD+ levels which was attributed to downregulation of the NAD+ salvage pathway enzyme nicotinate phosphoribosyl transferase (NAPRT1), and these cells were highly sensitive to NAD+ depletion via concomitant nicotinamide phosphoribosyltransferase (NAMPT) inhibition (Tateishi et al., 2015). Data from the Cancer Genome Atlas (TCGA) confirmed reduced NAMPT expression in IDH1-mutant gliomas compared to IDH1-wild type gliomas (Biedermann et al., 2019). In addition, IDH1-mutated cells exhibit upregulated NADH-dependent proline synthesis from glutamine via pyrroline 5-carboxylate reductase 1 (PYCR1), which resulted in the partial uncoupling of respiration from TCA cycle activity and maintain high rates of anabolism in cancer cells (Hollinshead et al., 2018; Westbrook et al., 2022).

Finally, pyrimidine metabolism is also altered by IDH oncogenes. Accordingly, recent findings revealed that IDH1-mutant glioma cells are hypersensitive to drugs targeting enzymes in the de novo pyrimidine nucleotide synthesis pathway, such as dihydroorotate dehydrogenase (DHODH) (Shi et al., 2022). Moving forward, the wealth of knowledge amassed over the last decades should serve as a solid foundation for the development of innovative therapeutic strategies that leverage the distinctive metabolic alterations driven by IDH mutations.

4. Metabolic alterations in glioma cells

In terms of metabolism, astrocytoma cells were thought to exhibit what appear to be fundamental astrocyte metabolic characteristics, such as a high glycolytic rate, lactate production, the capacity to survive under hypoxia, and the opportunistic use of mechanisms to promote cell division and sustain growth (Turner and Adamson, 2011). Indeed, the ability of these cancer cells to metabolically adapt to diverse nutrient microenvironments may be recapitulating astrocytic management of nutrients for neuronal consumption in the brain parenchyma (Mächler et al., 2016). Although this description could encompass the broader metabolic characteristics of glioma cells, we now know that cells within the tumor are deeply heterogeneous revealing a more complex scenario. It is now well appreciated that metabolic heterogeneity in the context of cancer plays a pivotal role in tumor development, progression, and response to therapy. Thus, unveiling the metabolic profiles of cancer cells at single-cell resolution represents one the forefronts of our current efforts to advance our comprehension of cancer (Fig. 3).

4.1. Intrinsic metabolism in gliomas

4.1.1. Metabolic heterogeneity in gliomas
Recent studies based on single cell RNA sequencing (scRNAseq) have demonstrated cellular heterogeneity within different grades of adult and pediatric gliomas (Neftel et al., 2019; Tirosh et al., 2016; Venteicher et al., 2017; Wang et al., 2017a; Patel et al., 2014; Filbin et al., 2018; Richards et al., 2021). These findings show hierarchical relationships
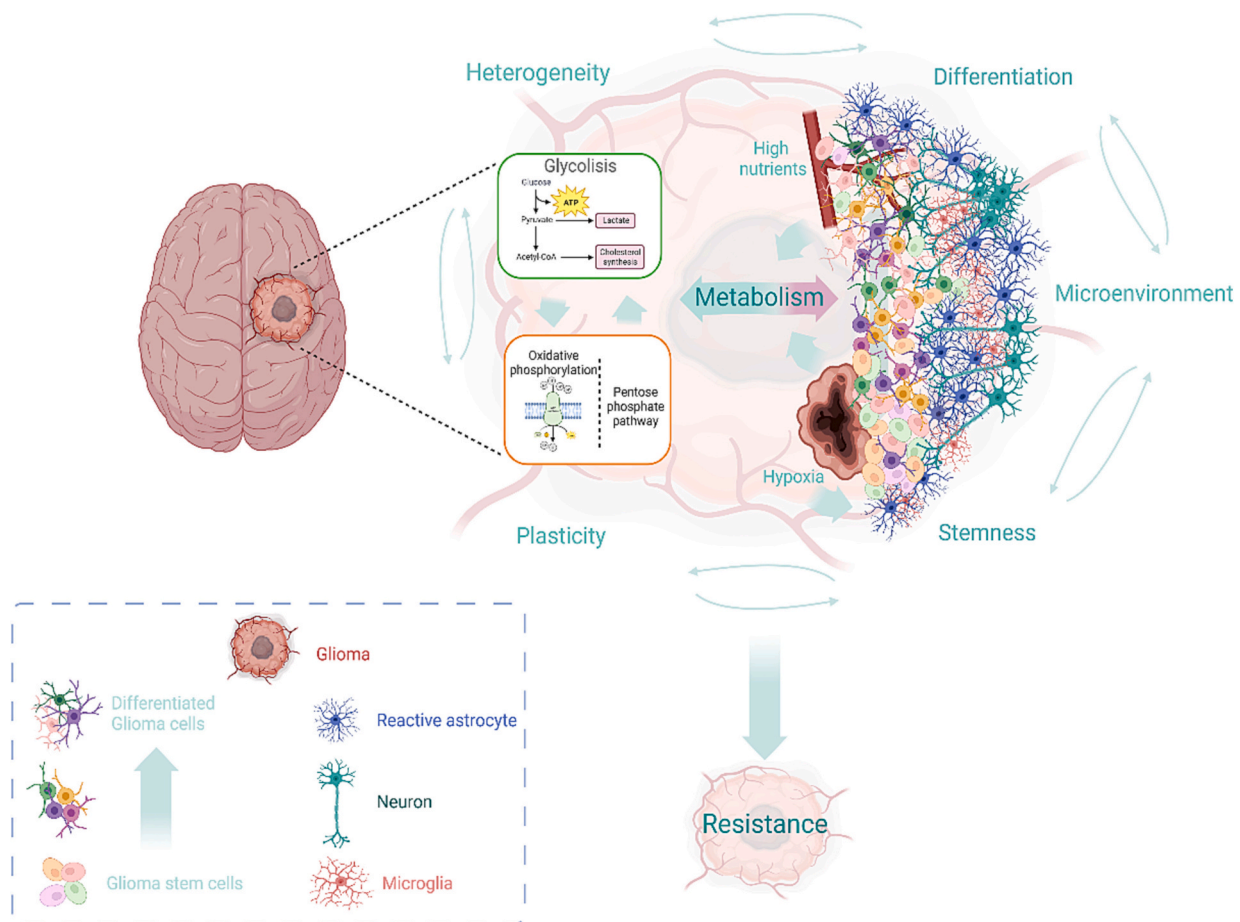
Fig. 3. Metabolism plays a crucial role in glioma progression and therapy resistance.
Glioma progression is influenced by intrinsic features such as cell state (stemness, cell lineage and plasticity) that can be reciprocally modulated by extrinsic factors i. e., the brain local microenvironment (access to nutrients and/or cell-dependent communication with neurons, reactive astrocytes, microglia, etc.) or the dynamic tumor-dependent changes. Because the aggressive infiltration into the normal brain is one of the hallmarks of these tumors, the exposure to diverse brain region microenvironments may rise metabolic heterogeneity and plasticity across tumor cells and patients as a result of the variable nutrient availability. At the same time, this metabolic heterogeneity may shape the evolution of tumor microenvironment through the release of specific metabolites. Importantly, the dynamic and changing tumor-associated microenvironment favors the selection of the most plastic and resistant tumor cells capable of holding with the most adverse conditions, for instance, hypoxia. Indeed, stressful conditions can trigger a stem-like phenotype that favors the plasticity to metabolically adapt to nutrient-restricted microenvironments. Altogether, the interplay between microenvironment and tumor metabolic features may modulate the crucial ability to adapt and resist to highly nutrient-restricted microenvironments, ultimately acquiring resistance to treatments.

between cancer cells that partially mimic normal differentiation from neural stem cells or glial progenitor cells into mature glia. Reitman et al., 2019 showed a similar trend for the most common childhood brain tumor, the pilocytic astrocytoma, with cancer cells recapitulating a developmental differentiation hierarchy from oligodendrocyte progenitor cell-like (OPCs) cells to mature astrocyte-like cells. However, compared to higher grade gliomas, these tumors exhibit a higher proportion of cancer cells with a differentiated, astrocyte-like phenotype and a smaller proportion of progenitor-like phenotype (Reitman et al., 2019). Crucially, the differentiation status of cancer cells may strongly contribute to specific metabolic patterns as we will discuss in the next sections.

Recent work by Iavarone's lab, taking advantage of scRNA-seq data and novel computational approaches, found that glioblastoma cells can be categorized according to their core biological traits. This analysis produced a novel classification for GBMs by focusing on four stable cellular states based on attributes related to either development or metabolism (Garofano et al., 2021). Surprisingly, the glioblastomas with the best clinical outcome heavily rely on oxidative phosphorylation for energy production, and the authors showed that this metabolic vulnerability can be exploited by using drugs that selectively disrupt OXPHOS

function (Garofano et al., 2021). So far, targeting metabolism for cancer therapy has led to underwhelming results. This study suggests that stratifying patients according to their tumor characteristics would greatly potentiate the efficacy of cancer-specific metabolic inhibitors.

Another piece of evidence highlighting the importance of metabolic heterogeneity came from Heiland's group. They integrated spatially resolved transcriptomics and metabolomics analysis to reveal that intratumoral oxygen gradients influences the metabolism of glioblastoma cells, driving their evolution and promoting therapy-resistant phenotypes (Ravi et al., 2022). Thus, the metabolic signatures of individual cancer cells can be shaped by factors in the tumor microenvironment, such as hypoxia, nutrient availability, or interaction with immune cells, creating an evolving ecosystem that expands the metabolic heterogeneity and complexity of these tumors at the single-cell level (Faubert et al., 2020).

There is growing evidence on the promoting role of the IDH mutation in the pathogenesis of glioma. In fact, not only does IDH mutation influence glioma classification but gives rise to specific metabolic signatures (Reitman et al., 2011). Outside of the mutated IDH pathway, astrocytomas have shown considerable metabolic heterogeneity through the overexpression of key metabolites as glycerophosphates,

inositols, monosaccharides, and sugar alcohols and low levels of sphingosine and lysoglycerophospholipids (Björkblom et al., 2022). Despite choline, lactate, and glutamine being considered major cancer metabolic markers, their levels vary significantly across different glioma types (Cuperlovic-Culf et al., 2012). While the differential expression of common cancer metabolic markers can imply a more challenging diagnosis for glioma, it could pose an advantage for the identification of glioma subtypes and as a result, helping find metabolic vulnerabilities and advance towards a more precision targeted therapy.

Furthermore, the discrimination between glioma-associated metabolites could be used as biomarkers if their selective presence distinguishes cancer cells from other cancer and normal cells, or even serves as prediagnostic markers of glioma. For instance, α- and γ-tocopherols have been associated with glioblastoma risk (Björkblom et al., 2016). Anaplastic astrocytoma has shown a perturbed metabolic pattern related to immune regulation and Du et al., 2022 propose that 3-Methylxanthine, sphinganine, LysoPC(18:1), and lactosylceramide could be used as biomarkers of this type of gliomas in future clinical practice (Du et al., 2022).

Björkblom et al., 2016 observed high levels of amino acids, especially glycine and 2-aminoadipic acid, in grade 4 glioma and *N*-acetyl aspartic acid among the IDH-mutated subtypes; and high levels of acylcarnitines in both IDH-wildtype and mutated oligodendroglioma and glioblastoma, likely driven by rapid cell growth and hypoxic features. By comparing metabolite abundances in IDH-mutant versus IDH-WT tumors, Wang et al., 2021, showed that while 2-HG is the most highly abundant metabolite in IDH-mutant tumors, other metabolites displaying differential presence. Several metabolites involved in glycolysis showed increased abundance in IDH mutants, while serine and glutamate levels were reduced. Elevated expression of GLUD1 in IDH-mutant tumors confirmed that glutamate may contribute to αKG levels and to 2-HG levels via GLUD1- and IDH1- catalyzed reactions, also seen by the negative correlation between GLUD1 protein expression and glutamate abundance and significant upregulation of GLUD1 in IDH mutants (Wang et al., 2021). In agreement, Scott et al., 2023 found that IDH-wildtype glioblastomas are metabolically distinguishable from IDH mutated astrocytomas and oligodendrogliomas. Moreover, they observed that patients whose gliomas were enriched in amino acids had improved survival, while those whose tumors were enriched for nucleotides, redox molecules, and lipid metabolites progressed worse (Scott et al., 2023). Crucially, IDH-mutant gliomas are correlated with a better disease outcome when compared with their IDH wild-type counterparts in equivalent pathological grades, which may imply potential therapeutic vulnerabilities in this type of malignancy (Yan et al., 2009).

4.1.2. Intratumor metabolic heterogeneity

In addition to the metabolic diversity found across glioma tumor types and subtypes, there is another level of complexity caused by the intratumor cell heterogeneity. In the healthy brain, astrocytes show regional and differential metabolic specialization. scRNAseq analysis were able to identify multiples astrocyte subtypes in the adult mouse cortex and hippocampus, each one displaying unique morphological and physiological features (Chai et al., 2017; Batiuk et al., 2020; Köhler et al., 2023; Hasel et al., 2023). Thus, it would not be surprising if different regions would dictate or contribute to different metabolic tumor niches. Intratumor metabolic heterogeneity can be thoroughly explored through multi-omics analysis, allowing the identification of mixed metabolic subtypes. Using proteogenomic and metabolomics, Wang et al., 2021 identified a subset of patients with mixed subtypes and a shortened overall survival. The lipid and metabolic signatures in glioblastoma tumors and normal brain tissues revealed shared characteristics that may be associated with neuronal phenotypes and IDH status. Importantly, mesenchymal-like glioblastomas showed substantial differences from other subtypes with specific metabolic vulnerabilities not present in other glioblastomas. For example, the mesenchymal-like cluster was enriched for innate immune system activation,

peroxisomal protein import and glycolysis, while the proneural-like cluster had a higher abundance of acetylated proteins involved in the TCA cycle and metabolism of amino acids (Wang et al., 2021). The classical-like subtype was enriched for acetylation of chromatin modifiers and DNA repair proteins. The proneural-like subtype was enriched for very long chain FA lipids and glycerophospholipids with long-chain polyunsaturated FA; the mesenchymal subtype for triacylglycerols, as well as depletion of phosphatidylcholines and other types of phospholipids. As for metabolites, the proneural-like cluster exhibited significantly increased levels of creatinine and homocysteine and reduced levels of L-cysteine and palatinitol.

Corroborating the intratumor heterogeneity, Wang et al., 2022, unveiled region-specific lipid signals in an orthotopic mouse model of glioma. The brain lipid images revealed heterogeneous upregulation and downregulation of tumoral phospholipids and sphingolipids. Specifically, they observed a decrease of the common saturated phosphatidylcholines in the tumor and an increase of analogous phosphatidylcholines with one or two additional fatty acyl double bonds and increased lyso phosphatidylcholines. Interestingly, tumor regions could be differentiated by the type of phosphatidylcholines present as polyunsaturated fatty acyl- phosphatidylcholines and ether phosphatidylcholines highlighted the striatal tumor margins, whereas the distributions of other phosphatidylcholines discriminated the cortical and striatal tumor parenchyma (Wang et al., 2022).

In a forward-looking perspective, the longitudinal assessment of brain tumor progression, conducted at the single-cell level via the integration of scRNAseq and spatial single-cell metabolomics, promises to furnish substantial insights into the temporal evolution of these malignancies. Particularly significant would be the combination of this data with information pertaining to driver mutations and clinical outcomes parameters.

4.1.3. Metabolic plasticity and flexibility as driver of glioma resistance

Cancer cells can demonstrate metabolic plasticity, employing a single nutrient/metabolite to meet the diverse metabolic demands of various stages in the metastatic cascade. Alternatively, they may exhibit metabolic flexibility, utilizing multiple nutrients/metabolites to fulfill the identical metabolic requirements (Bergers and Fendt, 2021) The discrimination between metabolic patterns attributable to either cell phenotypes or cell dynamic adaptability has been challenging in the past by the technical limitations to study tumor cell heterogeneity. Thanks to state-of-the-art techniques, tumor metabolic plasticity/ flexibility has gained attention in the last years as a potential target to overcome therapy resistance (Fendt et al., 2020).

A brain tumor subpopulation that has shown exceptional metabolic adaptability is the glioma stem cells (GSCs). Also called brain tumor initiating cells, GSCs have emerged in the last two decades as key players in brain tumor initiation, progression, and relapse (Singh et al., 2004b; Ignatova et al., 2002). Significantly, GSCs replicate developmental-like lineage hierarchies (Neftel et al., 2019; Singh et al., 2004b; Lan et al., 2017; Couturier et al., 2020). This observation implies that they may possess characteristics, such as a strong association with astrocytes and metabolic interactions with neighboring cells. GSCs are chemo- and radiotherapy resistant cells with the ability to self-renew, to differentiate into distinct lineages within the tumor and to recapitulate parental tumors upon reinjection (Bao et al., 2006; Liu et al., 2006). Precisely metabolic plasticity confers GSCs with multiple advantages for adapting to nutrient-restriction microenvironments and ultimately, for escaping from therapeutic treatments. Moreover, highly demanding microenvironments such as hypoxia, low glucose or low pH seem to select for stem-like populations, as they maintain GSCs (Li et al., 2009; Flavahan et al., 2013a; Hjelmeland et al., 2011). Accordingly, some studies have shown that hypoxic conditions reduce cell division but preserve a higher proportion of cells with tumor initiating capacity in vivo (Bar et al., 2010; Platet et al., 2007; Kathagen et al., 2013).

Understanding the GSCs mechanisms to cope with the status of the

tumor microenvironment is key to targeting their therapy resistance. For example, the failure of therapeutic strategies such as antiangiogenic drugs may reside in their very mechanism, as they act by promoting a hypoxic niche that might be generating resistant cells with stem-like features and favoring tumor relapse. One mechanism that may underlie this metabolic plasticity is a reciprocal switch between increased expression of PPP enzymes under normoxic conditions versus upregulation of glycolysis enzymes under acute hypoxia (Kathagen et al., 2013). In agreement with this, Vlashi et al. showed that, unlike differentiated glioma cells, GSCs primarily rely on oxidative phosphorylation for energy metabolism but they could switch to glycolysis when the oxidative metabolism is hindered (Vlashi et al., 2011). Interestingly, a cell-penetrating peptide has shown promising results in targeting the advantageous metabolic plasticity of GSCs by targeting c-Src, an oncogene capable of modulating metabolism, and that resulted in a reduced glucose uptake as well as reduced oxidative phosphorylation without a compensatory increase in glycolysis (Pelaz et al., 2020). Although the therapeutic efficiency needs to be tested in human diseases in vivo, cell-penetrating peptides could be important therapeutic strategies to selectively target glioma metabolic nodes.

GSCs are also able to mimic neuronal and embryonic stem cell mechanisms of survival by upregulating GLUT3 (solute carrier family 2 (facilitated glucose transporter), member 3; SLC2A3) (Ward and Thompson, 2012; Panopoulos et al., 2012), that allows them to compete for glucose when the supply of nutrients fluctuates (Flavahan et al., 2013b). From a clinical point of view, overexpression of GLUT3 and hyperglycemia predict shorter survival in glioblastoma patients (Flavahan et al., 2013b; Derr et al., 2009). In fact, elevated levels of glucose or other nutrients such as acetate induce resistance to targeted therapy through the promotion of protein acetylation and seem to rely on mTORC2 as a central node for integrating growth factor signaling with nutrient availability in glioblastoma (Masui et al., 2015).

Additionally, GSCs seem to rely on SREBP2 for keeping the balance between cholesterol biosynthesis and uptake, and this varies according to the nutrient conditions. In fact, cholesterol biosynthesis is induced in the tumor core whereas the uptake is induced in the invasive margin (Gu et al., 2023). SREBP2 promotes cholesterol biosynthesis in GSCs especially under starvation, as well as proliferation, self-renewal, and tumor growth. In addition, methionine seems to contribute to the cholesterol-rRNA axis, regulating GSC self-renewal, pluripotency, and cell death (Yokogami et al., 2022).

Poor prognosis in glioblastoma patients has also been correlated with elevated expression of purine synthetic enzymes. Interestingly, the inhibition of purine synthesis selectively affects GSCs growth, self-renewal and in vivo tumor formation while differentiated glioma cells do not suffer by the targeting of purine biosynthetic enzymes (Wang et al., 2017b). Importantly, the core transcription factor MYC coordinated the control of purine synthetic enzymes, corroborating its role in metabolic reprogramming. Several studies have also established a noteworthy association between purine nucleotide biosynthesis and the perturbed one-carbon metabolic pathways within specific subsets of differentiated glioma cells. In the relentless pursuit of proliferative advantage, malignant cells exhibited an upregulation of specific enzymes, notably MTHFD2, which orchestrates the redirection of serine and glycine amino acids towards anabolic reactions (Zhu et al., 2022). This adaptive response becomes particularly salient in the microenvironment of tumor regions characterized by limited access to glutamine, a critical metabolic substrate. Genetic and pharmacological interventions aimed at attenuating one-carbon metabolism have demonstrated promising efficacy, resulting in tumor cell apoptosis and growth inhibition (Zhu et al., 2022; Ghannad-Zadeh and Das, 2021; Tanaka et al., 2021). Intriguingly, cells harboring mutations in IDH1 and IDH2 exhibit an upregulation of the IDH3α isoform, thus favoring one-carbon metabolism, ultimately augmenting the availability of nucleotides crucial for DNA replication (May et al., 2019). It is intriguing to note that normal astrocytes tend to exhibit a proclivity for the cytosolic branch of the one-carbon metabolism (denoted by high expression of ALD1L1), whereas cancer cells strategically capitalize on the heightened expression of mitochondrial one-carbon metabolism. In addition, the potential impact of elevated serine consumption in cancer cells on the neurotransmitter D-serine, which is typically synthesized by normal astrocytes, remains an unexplored area of investigation.

Lastly, another important metabolic pathway that may be underlying metabolic plasticity is an enhanced Fatty Acid Oxidation (FAO), accommodating glioma requirements to a dynamic nutrient microenvironment (Kant et al., 2020). In conditions characterized by nutrient abundance, glioblastoma cells employ FAO as a stimulatory mechanism for cellular proliferation. Conversely, in nutrient-deprived environments, glioblastoma cells demonstrate the capacity to harness FAO as an ATP generation pathway, thus ensuring their survival. This functionality bears resemblance to that observed in normal astrocytes (previously detailed in the introduction), wherein these cells are characterized by an elevated expression of enzymes associated with FAO. Thus, metabolic reprogramming represents a unique signature of these cancer cells, building on intrinsic and extrinsic influences. Yet, many of the metabolic nodes that entail this plasticity remain to be elucidated.

Overall, the studies discussed above illustrated unique metabolic weaknesses in GSCs, opening up new ways to combat the tumors' resistance (Wang et al., 2017b).

4.2. Influence of tumor associated astrocytes in the metabolism of gliomas

IDH-wild type gliomas, or glioblastomas (GBM) are the most malignant type of gliomas, and even with the proper treatment and surgical ablation the recurrence is inevitable in most of the cases (Jiang et al., 2020; Rapp et al., 2017). One of the proposed causes of this recurrence is the presence of a supportive pro-tumorigenic microenvironment. In fact, the poor prognosis of GBM has been associated with its capacity to invade the surrounding brain parenchyma (Lefranc et al., 2005), making essential to understand better the interaction of GBM with the surrounding cell types.

The mammalian brain has a very complex structural and functional organization, and the cooperation between different cell types makes possible the connectivity and the normal function of the brain (Sharma et al., 2015). Giving the importance of this network, the communication between healthy astrocytes and cancerous-type astrocytes has been broadly studied the last decade, and the evidence that astrocytes contribute to improve the tumor environment is getting stronger upon the recent discoveries (Nakano et al., 2015; Lee et al., 2011; Leiss et al., 2017a; Lin et al., 2002).

4.2.1. Interaction between healthy astrocytes and glioma

One of the most important ways of communication between different cell types is via extracellular vesicles (EVs) (Théry et al., 2023; Broekman et al., 2018a). This type of cell-to-cell communication is driven by different stimulus, and it has been in most of the cases reported to promote the tumor growth (Yin et al., 2019).

Several studies show that GBM-derived EVs (more specifically, the extracellular RNA carried by them) are taken up by different cell types in the brain (including microglia, astrocytes, and microvascular cells) and modulate their properties to support tumor progression (Gao et al., 2020; Hallal et al., 2019; Taheri et al., 2018; Al-Nedawi et al., 2008; Leiss et al., 2017b). For example, they modulate brain endothelial cells to increase angiogenesis (Lucero et al., 2020) and can also promote the immunosuppressive proprieties of microglia to contribute to tumor growth (Abels et al., 2019). In the brain, astrocytes are among the best candidates to promote this pro-tumorigenic microenvironment because they can sense changes in the microenvironment and because of the existing communication between astrocytes (Zeng et al., 2020a; Tay et al., 2020). Reactive astrocytes and microglia also comprise the majority of the region surrounding the GBM (Yuan et al., 2016a). However, we cannot discard the contribution of infiltrated immune cells to the

global response of GBM.

In this particular context, GBM-derived EVs seem to have a different effect on healthy astrocytes compared to their influence on pre-transformed astrocytes, referred to as HTAs. Zeng et al., 2020 demonstrated that exposure to EV-enriched conditioned medium (CM) did not induce a tumor phenotype in healthy human astrocytes, both in vitro and in vivo experiments. Conversely, pre-transformed astrocytes, induced by introducing three oncogenic viruses (SV40, RasG12V, TERT), heightened levels of proliferation, self-renewal, and colony formation when exposed to EV-enriched CM. These changes were associated with an upregulation of cancer-related gene expression programs, encompassing metabolic alterations linked to glycolysis, hypoxia, Myc targets, and inflammatory responses. These effects were observed in both triple transgenic mice (ECP) and HTAs. In healthy astrocytes, tumor-suppressive pathways appeared to counteract the impact of EV-mediated cancer reprogramming. The authors concluded that this communication via EVs could potentially enhance tumor development by providing a source of GSCs, but only in the presence of malignant features within astrocytes (Zeng et al., 2020b). Conversely, other experiments revealed that conditioned media from GBM cells suppressed the expression of p53 in healthy astrocytes, leading to increased production of laminin and fibronectin in the extracellular matrix while reducing apoptosis capacity. This created a dysfunctional microenvironment that promoted glioma survival (Biasoli et al., 2014). Although the study did not specify whether astrocytes became reactive following GBM-induced p53 blockade, it is evident that tumor-associated astrocytes significantly influence the molecular and cellular state of neighboring astrocytes (Lin et al., 2002). Similarly, a separate investigation involving 33 GBM patients demonstrated that the combination of different cell types in the tumor microenvironment could predict patient outcomes. Specifically, a higher density of ALDH1A1 and GFAP-positive reactive astrocytes in regions adjacent to the tumor correlated with a shorter lifespan, potentially due to their role in promoting invasion into the brain parenchyma (Yuan et al., 2016b; Rustom et al., 2004; Reemst et al., 2016a; Broekman et al., 2018b; Watson et al., 2023).

Recent experiments also suggest the contribution of mitochondrial traffic between GBM and astrocytes to promote GBM tumorigenicity (Rustom et al., 2023; Osswald et al., 2015). Watson D. et al., 2023 described how GBM incorporate healthy mitochondria from non-malignant cells in the tumor microenvironment (specifically from astrocytes) to enhance metabolism and tumor growth (Watson et al., 2023). They observed GAP43+ structures, very similar to tumor microtubes (MTs) described in cancer cells, creating an actin-based network connection between healthy astrocytes and GBM. These structures, typically present in neuronal projections (Osswald et al., 2015), are longer and thicker than tunneling nanotubes and they can cover distances greater than 500 μm in vivo, which makes them able to transfer mitochondria from healthy astrocytes (mitoDsRed+ mice astrocytes) to GBM (GFP positive cells), driving metabolic reprogramming to enhance oxidative respiration and increase ATP production (Weil et al., 2017). This metabolic reprogramming in GBM include the amino acid and nucleotide metabolism upregulation, which is linked to proliferative capacity and self-renewal (Wang et al., 2017b; Wang et al., 2019). Metabolomic analysis also described higher amounts of glutamate, αKG, and GSH in GBM cells after mitochondrial transport, increasing the cell protection against oxidative stress. All these metabolic changes help to promote tumor proliferation and therapy resistance (Watson et al., 2023).

Cancer cells additionally harness the supportive metabolic capabilities of stromal cells, including astrocytes, in a process that may encompass the transfer of metabolic substrates from astrocytes to cancer cells. This exchange facilitates the provision of essential metabolic fuels required for the sustained growth and proliferation of tumor cells (Pavlova et al., 2022).

In ex vivo culture, numerous cancer cell lines rely on an external source of glutamine for their sustenance, even though this amino acid is considered nonessential and can be produced from scratch through GLUL-mediated synthesis.

Mounting evidence suggests that within the complex landscape of GBM, the malignant cells have developed a rather intriguing strategy. They seem to intermingle with the neuron-astrocyte glutamate-glutamine cycle, effectively making astrocytes unwitting contributors to their metabolic needs. In fact, GBM cells not only tap into astrocytes as a source of glutamine but also engage in the intricate dance of glutamatergic neurotransmission.

Sophisticated studies employing stable isotope tracing have unveiled a curious phenomenon within IDH1 wild-type GBM in vivo. Contrary to conventional expectations, there appears to be a lack of net glutamine breakdown via the typical GLS-driven pathway. Instead, a reservoir of glutamine builds up within the tumor itself, synthesized on-site. This pool of intratumoral glutamine plays a vital role in sustaining the intricate machinery of de novo nucleotide biosynthesis. Glutamine, in this scenario, serves as the essential nitrogen donor in a series of five separate reactions (Tardito et al., 2015).

Within tumor masses, GBM cells lacking GLUL expression are strategically situated in close vicinity to astrocytes that do possess GLUL. This arrangement strongly suggests that astrocytes play a pivotal role as the chief suppliers of glutamine for the energy-intensive anabolic metabolism within GBM. In fact, experimental evidence lends weight to this model. Astrocyte-derived glutamine alone is sufficient to fuel the growth of GLUL-negative GBM cells in coculture experiments, even in glutamine-depleted conditions. This paints a picture of GBM cells strategically exploiting the physiological role of astrocytes as the central nervous system's glutamine suppliers, potentially outcompeting neurons for this precious resource by expressing the high-affinity uptake transporter SLC1A5.

Hence, it becomes both intriguing and imperative to unravel the exact mechanisms by which GBM cells co-opt the natural metabolic processes of astrocytes to their advantage. A comprehensive understanding of these strategies could not only shed light on the intricate biology at play but also potentially unveil novel therapeutic targets for intervention and treatment.

4.2.2. Tumor associated astrocytes (TAA) in glioma

Astrocytes are the most abundant glial cell type in the CNS, and they play important roles in maintaining homeostasis in healthy and damaged brain (Reemst et al., 2016b). They are constantly sensing the environment and they can communicate with neurons, microglia, and other astrocytes. In response to CNS damage, astrocytes undergo a reactive transformation termed astrogliosis (Anderson et al., 2014; Sofroniew, 2023). This process encompasses a range of distinct metabolic and cellular alterations in astrocytes depending on the specific signaling events, localization, and severity of the injury. The main objective of this reactive process is to migrate to the area and minimize injury, protecting the brain by promoting or inhibiting neurogenesis depending on the context (Anderson et al., 2014; Kang and Hébert, 2011). Nevertheless, reactive astrocytes can also be highjacked by tumor cells shifting their purpose and contributing to tumor progression (Henrik Heiland et al., 2019a).

In the context of GBM, it is established that astrocytes in the vicinity become reactive in both human and murine models (O'brien et al., 2013; Nagashima et al., 2002). These reactive astrocytes around the tumor are called tumor associated astrocytes (TAAs) and they exhibit a GBM-specific gene signature involved in tumor development as they communicate with GBM. Diverse groups have found differences in mRNA expression profile between TAAs and normal astrocytes (Katz et al., 2023; Perelroizen et al., 2022). These TAAs were typically being described as "pro-immunogenic" because they release different proteins that are involved in macrophage and T cell recruiting, such as MHC class II and CCL2 chemokine, to help to localize the inflammation (Perelroizen et al., 2022; Angeles Carrillo-de Sauvage et al., 2012). Intriguingly, within the GBM environment, regulatory T cells are more

abundant than cytotoxic T cells, and they play a significant role in attenuating the immune response (Barcia et al., 2009). It is therefore unclear, how the complex crosstalk between TAAs and different subtypes of infiltrated T cells influence tumor progression. This gains further relevance when considering that GBM belongs to a group of tumors called cold tumors, which are characterized by a low immune cell content (Agliardi et al., 2021).

Over the last years we have witnessed compelling evidence supporting the role of TAAs in the dampening of immune responses. This occurs through their interactions with T cells and their suppression of TNF secretion by microglia and monocytes (Related Content ATP Mediates Calcium Signaling Between Astrocytes and Microglial Cells, 2008). Various investigations utilizing RNA-seq analysis, scRNAseq, and RiboTag-based RNA sequencing have collectively revealed that the gene expression profile of TAAs actively contributes to the induction of immunosuppression. This, in turn, leads to the attenuation of the immune response, thereby fostering the development of a conducive tumor microenvironment crucial for tumor growth (Darmanis et al., 2017; Henrik Heiland et al., 2019b). These studies showed that reactive astrocytes within the tumor milieu actively contribute to the development of an immunosuppressive environment in glioblastoma via interaction with resident microglia. The researchers observed an elevation in hypoxic metabolism, characterized by heightened glycolytic activity, in microglia when co-cultured with tumor cells. This metabolic shift is commonly associated with the inflammatory phenotype of microglia. Notably, the presence of astrocytes in the co-culture mitigated this metabolic alteration. In the same line, Perelroizen et al., 2022 demonstrated that depletion of reactive TAA regresses GBM progression in mice and increases life expectancy in in vivo experiments (Perelroizen et al., 2022).

Recently, another RNA-seq analysis has revealed that these reactive astrocytes have similarities to fetal astrocytes (they acquire a progenitor-like state), showing an increased proliferation and JAK/STAT pathway activation (Darmanis et al., 2017). Heiland et al., 2019 demonstrated that the inhibition of JAK/STAT pathway (using an FDA-approved JAK inhibitor) leads to a switch from an anti-inflammatory to a pro-inflammatory environment, contributing to diminish the tumor spread (Henrik Heiland et al., 2019b). Heiland et al. in 2019 demonstrated that co-culturing microglia with reactive astrocytes led to a reduction in the metabolic transcriptional profile associated with inflammation, previously observed after co-culture with tumor cells. Indeed, astrocytes exhibited the capacity to reprogram tumor-associated macrophages within the glioma microenvironment, thereby modulating their immunosuppressive phenotype and promoting tumor progression (Perelroizen et al., 2022).

In the same way, Zou et al., 2019 described a pro-proliferative function of TAAs in the context of metastases. They demonstrated that astrocytes could enhance metastases by suppling unsaturated FA in the tumor microenvironment that activate PPARy signaling in cancer cells (Zou et al., 2019). These results are in the same line with the knowing role of astrocytes as the major source of FA synthesis in the brain, and with other results that show an increase of polyunsaturated FA production and secretion in activated astrocytes (Aizawa et al., 2016). In relation with this, Perelroizen et al., 2022 found that glioma cells depend on astrocyte-derived cholesterol for survival suggesting the importance of FA in the TME (Perelroizen et al., 2022).

Given the importance of TAAs in tumor progression and their role in inducing an immunosuppressive tumor microenvironment, it seems necessary to considerate TAAs phenotypes as additional targets to abrogate their contribution to the tumor growth and therapeutically treat this disease in a global manner.

It is becoming clear that TAAs possess the capacity to induce metabolic modifications in neighboring cells, thereby holding significant implications for immune function and the progression of the tumor. Metabolic competition and tumor-derived metabolite-mediated immunosuppression in the tumor microenvironment have been observed in multiple tumor types. Nevertheless, this particular phenotype remains relatively underexplored in the context of brain tumors, warranting further research to establish its presence and significance within gliomas.

5. Discussion and conclusion

There is rising interest in how astrocytes function in both healthy and diseased settings despite historically being thought of as accessory cells to neurons. A growing body of evidence suggests that altered metabolism in astrocytes, due to both cell-intrinsic and cell-extrinsic factors, underly many human disorders such cancer. Although considerable efforts have been made to better understand the contribution of astrocyte metabolism to this particular disease, further work is needed to thoroughly detail the molecular mechanisms, signaling pathways and metabolic components that influence disease progression.

Mutations in IDH are central to the development of human gliomas and in particular, astrocytomas. A series of seminal studies have uncovered the impact of IDH mutations and D2HG in cellular physiology, such as reprogrammed metabolism, epigenome alterations and redox homoeostasis. However, it will be paramount to understand whether and how IDH mutations alter tumor cell metabolic profiles, lipid biosynthesis, the defense against oxidative stress, oxidative respiration, and hypoxia signal transduction in cancer to exploit their specific weaknesses. Crucially, IDH-mutated astrocytomas have better prognosis than IDH wild type gliomas (GBM). Thus, it is imperative to discriminate IDH-associated vulnerabilities to personalize and adapt therapies to the unique features that each glioma presents. Importantly, future development of molecular targeting and synthetic lethality approaches would greatly benefit patients with glioma, improving disease outcome and quality of life.

The emergence of new technologies such scRNAseq and single-cell level metabolomics will help unraveling the complexity of tumors. It is quite likely that this level of complexity is closely tied to the heterogeneity present in the solid tumors. In fact, metabolic heterogeneity has been observed in other type of cancers and can impact the outcome of the disease by modulating the response to treatments. Thus, new lines of investigation analyzing the metabolic heterogeneity at single cell resolution will be paramount to delineate new therapeutic strategies based on exploiting the metabolic vulnerabilities of rare subpopulations of cancer cells. Integration of scRNAseq and single-cell metabolomics approaches has the potential to offer valuable insights into the mechanisms underlying therapy resistance in cells. The ability to identify and characterize therapy-resistant cell populations such as GSCs within a patient's tumor has significant implications for personalized medicine and these methodologies represents a powerful approach for dissecting the intricacies of therapy resistance in cancer.

An important topic of study that could potentially shape our understanding of tumor biology is how healthy astrocytes interact with tumor and non-tumor cells within the tumor microenvironment. While astrocyte activation and subsequent release of pro-inflammatory cytokines could lead to neuroinflammation and is detrimental in the context of neurodegenerative diseases, this shift towards a pro-immunogenic phenotype could be beneficial to combat brain tumors.

Cellular metabolism has emerged as a critical determinant of the viability and function of immune cell in the context of cancer. Importantly, competition for nutrients in the tumor microenvironment between cancer cells and immune cells is a critical aspect of cancer immunology and cancer progression. Hence, forthcoming research should be focused on elucidating the precise mechanisms leveraged by cancer cells within the brain tumor microenvironment to gain a competitive edge over immune cells. These mechanisms are fundamental to the attenuation of anticancer responses exerted by immune cells, which in turn underlie the shortcomings observed in immunotherapeutic strategies.

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Declaration of Competing Interest

The authors declare that there are no competing interests associated with the manuscript.

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