Cancer metabolism as a central driving force of glioma pathogenesis

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Abstract

The recent identification of distinct genetic and epigenetic features in each glioma entity is leading to a multilayered, integrated diagnostic approach combining histologic features with molecular genetic information. Somatic mutations in isocitrate dehydrogenase (*IDH*) and receptor tyrosine kinase (*RTK*) pathways are key oncogenic events in diffuse gliomas, including lower grade (grade II and III) gliomas (LGG) and the highly lethal brain tumor glioblastoma (GBM) respectively, where they reprogram the epigenome, transcriptome and metabolome to drive tumor growth. However, the mechanisms by which these genetic aberrations are translated into the aggressive nature of gliomas through metabolic reprogramming have just begun to be unraveled. The intricate interactions between the oncogenic signaling and cancer metabolism have also been recently demonstrated. Here we describe a set of recent discoveries on cancer metabolism driven by *IDH* mutation and mutations in *RTK* pathways, highlighting the integration of genetic mutations, metabolic reprogramming and epigenetic shifts, potentially providing new therapeutic opportunities.

Keywords

genetic-metabolism interaction; IDH; glioma; metabolic reprogramming; RTK; molecular genetics

Introduction – genetic aberrations drive cancer metabolism in gliomas

The identification of distinct genetic and epigenetic profiles in different types of gliomas has revealed novel diagnostic, prognostic, and predictive molecular biomarkers for refining glioma classification [29, 42]. However, the elucidation of how these genetic abnormalities drive glioma pathogenesis is still a work in progress. Metabolic reprogramming is re-emerging as a central hallmark of cancer [16, 39]. Nearly 100 years ago, Otto Warburg demonstrated that cancer cells convert the majority of glucose into lactate even in the presence of sufficient oxygen, and this biochemical adaptation, termed 'the Warburg effect,' has once again assumed a central role in framing cancer as a metabolic disease [41, 44]. However, the Warburg effect alone cannot account for the full spectrum of metabolic

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changes required for tumor growth [22, 46]. Glutaminolysis, the catabolism of glutamine to support tumor cell proliferation, is also a central feature of cancer metabolic reprogramming [18]. Additionally, tumor cells require large amounts of lipid and nucleotides for membrane biogenesis, signal transduction, cell proliferation and potentially as an energy source [1]. The metabolic adaptations that reprogram how cancer cells take up and utilize nutrients to drive tumor growth are activated by profound changes in signaling and epigenetic/ transcriptional networks induced by activated oncogenes (e.g. *EGFR*, *RAS*, *MYC*) and deactivated tumor suppressor proteins (e.g. *TP53*) [13, 46]. In addition, mutations in enzymes that regulate metabolite flux are also implicated in cancer development, as highlighted by the discovery of isocitrate dehydrogenase 1 (*IDH1*), or less commonly *IDH2* gene mutations in more than 70% of diffusely infiltrating World Health Organization (WHO) grade II and grade III astrocytic and oligodendroglial gliomas, as well as in a small fraction of glioblastomas (GBMs), particularly those that develop from lower grade gliomas (LGGs) [3, 38, 51]. Therefore, unraveling the molecular mechanisms by which mutations in the growth factor receptor signaling system and *IDH* reprogram glioma cell metabolism will shed new light on the contribution of genetic aberrations to the glioma pathogenesis.

Here we review a set of recent discoveries on cancer metabolism involving *IDH*-mutated LGGs and *IDH* wild-type GBMs primarily driven by mutations in receptor tyrosine kinase (*RTK*) pathways. These highlight the integration of genetic aberrations with altered signaling, metabolic reprogramming, and epigenetic changes downstream of common cancer mutations, potentially providing new therapeutic opportunities for these deadly types of brain tumors.

Metabolic reprogramming as a basis for glioma pathogenesis

IDH at the crossroad of genetics, metabolism and epigenetics in gliomas

The IDH enzymes normally catalyze the oxidative carboxylation of isocitrate to α-ketoglutarate (α-KG), resulting in the reduction of nicotinamide adenine dinucleotide phosphate (NADP+) to NADPH. The tumorigenic potential of mutant *IDH* is primarily associated with a metabolic shift in glioma cells (Fig. 1). It has been shown that mutant *IDH* acquires a neomorphic activity that converts α-KG to D(R)-2-hydroxyglutarate (D-2-HG) in an NADPH-consuming reduction, leading to the intriguing idea that D-2-HG acts as "oncometabolites." 2-HG in turn inhibits α-KG-dependent dioxygenases [50], eventually altering the genome-wide histone and DNA methylome in gliomas as will be further described. Others reported that increased production of 2-HG stimulates the activity of egl-9 family hypoxia-inducible factor (EGLN) prolyl 4-hydroxylases, which leads to reduced levels of hypoxia-inducible factor (HIF) and enhanced proliferation of human astrocytes [21]. Additionally, *IDH* mutation decreases intracellular NADPH levels required for the reduction of glutathione disulfide (GSSG) to GSH, thereby causing increased oxidative stress that promotes tumorigenesis but also increases therapy sensitivity [33]. In line with this hypothesis, oxidative stress may promote further genetic changes, such as *TP53* mutation or t(1;19) translocation, leading to development of either astrocytoma or oligodendroglioma [53], and *IDH* mutation is associated with better response to cytotoxic therapy and longer survival in malignant glioma patients [8, 43, 48]. The specific nature of

IDH mutation in gliomas may be further exploited for 2-HG-targeting diagnostics [9] and mutant IDH-targeting therapeutics [40].

In comparison with *IDH*-mutated LGGs, primary GBM (*IDH* wild-type GBM) and *IDH* wild-type LGGs are characterized by a clinically aggressive behavior with a dismal prognosis [2, 6]. Understanding how *IDH* wild-type diffuse gliomas promote metabolic reprogramming may yield crucial insights into glioma pathogenesis, and hypoxia may be a key factor to drive cancer metabolism in this type of tumor. Recent studies have revealed that the D-2-HG enantiomer L(S)-2-HG is generated by hypoxia in *IDH* wild-type tumors and both 2-HG enantiomers have similar structures as α-KG and can competitively inhibit α-KG-dependent enzymes [45]. Further, while glucose provides the acetyl coenzyme A (acetyl-CoA) to support citrate production under normal oxygen tension, tricarboxylic acid (TCA) cycle anaplerosis is maintained primarily by glutamine, and hypoxic cells are able to maintain cell proliferation through wild-type *IDH*-dependent reductive carboxylation of glutamine-derived α-KG, despite a profound reduction in glucose-dependent citrate production [32, 34]. Interestingly, the increased glutamine-derived α-KG in hypoxia is also associated with a concomitant increased synthesis of 2-HG by wild-type *IDH*, and the reductive carboxylation of glutamine is part of the metabolic reprogramming associated with HIF [49].

RTK pathway aberration in GBM metabolic reprogramming: therapeutic implication

The emergence of next-generation sequencing technologies provide exquisite sensitivity and resolution. Recent progress in multi-disciplinary molecular analyses of cancers based on novel large-scale DNA methylation profiling and next-generation sequencing approaches have enabled the molecular stratification of GBM by the combination of molecular genetic signatures, as opposed to assessing the status of individual markers [29, 42]. The Cancer Genome Atlas (TCGA) Research Network has been established to generate the comprehensive catalog of genomic abnormalities driving tumorigenesis, and has revealed biologically relevant alterations in three core pathways: RTK/RAS/PI3K signaling, p53 and Rb pathways in GBM [7, 35]. Among these, the genomic characterization of *IDH* wild-type GBM reveals frequent genetic alterations of key components of the growth factor receptor-PI3K-Akt signaling pathway that activate mechanistic target of rapamycin (mTOR) signaling [7, 10].

One of the master regulators of cancer metabolism is the oncogenic transcription factor, c-Myc [12]. c-Myc is controlled in a multi-layered way that includes gene rearrangement and amplification [11]. Only recently has it been determined how the mutations in growth factor receptor signaling pathways, such as epidermal growth factor receptor (*EGFR*) mutations which are most commonly detected in *IDH* wild-type GBM, cooperate with c-Myc to promote tumorigenesis. This is a critical question since c-Myc is rarely amplified or mutated in GBM [7], despite its potential importance in GBM pathogenesis. Recent studies identify a set of interlacing molecular mechanisms by which *EGFRvIII*, a constitutively activating mutant form of *EGFR*, co-opts c-Myc to reprogram cellular metabolism and drive tumor proliferation. This involves the serine/threonine kinase mTOR complexes 1 and 2 (mTORC1 and mTORC2) [4, 30] (Fig. 2). Importantly, failure to inhibit mTOR signaling can render

GBM cells resistant to PI3K or Akt targeted therapies by maintaining elevated levels of c-Myc [30]. On the contrary, the convergence of multiple upstream signaling pathways on c-Myc raises the possibility that bromodomain and extraterminal (BET) bromodomain inhibitors that interfere with BET family protein binding to lysine-acetylated histone tails to suppress c-Myc-dependent target gene expression [14], may have a role in solid tumors with PI3K and mTOR activation including GBM. Interestingly, a recent genomic characterization demonstrated that activation of Myc and the RTK-RAS-PI3K pathway are also involved in *IDH1*-mutant glioma malignant progression [5, 20], and RTK- and Myc-dependent metabolic reprogramming might be involved in this process. Targeted therapies against Myc-dependent metabolism might then be effective for all types of high grade gliomas, regardless of their mutational status of *IDH*.

When genetics and metabolism intersect – the emerging concept

Cancer metabolic reprogramming has been shown to be a consequence of upstream mutations in *IDH* in LGGs and the *RTK* signaling network in *IDH* wild-type GBM. However, do glioma cells also adapt their genetic signaling in response to a shift in metabolism; that is, do genetics and metabolism interplay reciprocally in gliomas? Metabolic reprogramming results in changes in intracellular nutrient levels which can affect oncogenic signaling via control of epigenetics and consequently by globally altering gene transcription [19, 25, 28] (Fig. 3). Mutations in *IDH*, which were identified as early genetic events in gliomagenesis, play an important role in gliomas through neomorphic activity that converts α-KG to 2-HG as aforementioned, which inhibits α-KG-dependent dioxygenases including histone demethylases and the TET family of 5′-methlycytosine hydroxylases [50]. The presence of *IDH* mutations thus leads to a distinct subgroup of glioma with a CpG island methylator phenotype (G-CIMP) and aberrant histone methylation [36], which possibly locks differentiation-related genes in an inactive state [26], disrupts chromosomal topology [15] and changes the landscape of enhancers [8], eventually contributing to tumorigenesis. Subsequent discovery of germline or somatic mutations in genes coding for metabolic enzymes (succinate dehydrogenase and fumarate hydratase) that are associated with tumor susceptibility by altering the epigenome further supports the idea of oncometabolites to "tailor the genetics" [37]. On the other hand, in *EGFR*-mutant GBMs which do not usually possess the mutations in *IDH* or H3 histone family 3A (*H3F3A*) to potentially change the epigenetics, constitutive PI3K activation could engage the epigenetic machinery through several complementary routes. First, EGFR activation causes the glycolytic enzyme pyruvate kinase isozymes M2 (PKM2) to translocate to the nucleus where it phosphorylates histone 3 at Thr11, causing dissociation of histone deacetylase 3 (HDAC3) and promote histone acetylation to regulate transcription of the cancer-promoting genes including *c-Myc* and *cyclin D1* [52]. Interestingly, epigenetic regulation of c-Myc may be a central mechanism for its overexpression in GBM [23]. Second, through integrated epigenome and transcriptome analyses, we showed that *EGFRvIII* remodels an epigenome and transcription factor network that regulates c-Myc, including via mTORC2 which controls GBM metabolism [24].

In addition to the change in intracellular nutrient, we recently made the surprising discovery that exogenous glucose or acetate, two "fuel sources" that are widely available in the brain

and readily taken up by tumor cells [27], are required for mutant *EGFR* signaling. Under EGFR signaling, glucose and acetate activate mTORC2 and promote GBM resistance to molecularly targeted therapies through acetyl-CoA-dependent acetylation of Rictor, a core component of the mTORC2 signaling complex [31]. These results have a number of potentially important and unanticipated implications. First, extracellular nutrients can maintain oncogenic signaling in GBM cells through the post-translational modification of nuclear as well as non-nuclear proteins (Fig. 3), and the environment of GBM patients such as hyperglycemia would affect the therapeutic efficacy including chemotherapeutics [47] and molecularly targeted treatments [31]. Second, these works raise the question of how lifestyle changes, including diet, can potentially shift tumor cell metabolism and promote cancerous growth by altering the genomic and epigenomic landscapes, and there may be more interplay between oncogenic signaling and the environment than previously thought.

Conclusion and future perspective

Cancer is a disease of endogenous somatic mutations. Glioma is no exception, and the traditional phenotypic classification of diffuse gliomas has changed its direction to add genetics based on recent identification of distinct genetic and epigenetic profiles in different types of gliomas. One of the key mechanisms to link the genetic aberrations with the biology of gliomas including epigenetic changes and therapeutics resistance is through cancer metabolic reprogramming. An accumulation of recent evidence suggests that cancer metabolism in *IDH*-mutated LGGs is potentially linked to the global change in the epigenetic landscape including the shift in the genome-wide methylome through the production of oncometabolites. Metabolism in *IDH* wild-type GBM is mainly reprogrammed by hypoxia and RTK-dependent c-Myc upregulation to modulate the cellular metabolome and cause resistance to cancer therapeutics. This notion has been further supported by a recent large-scale genomic, epigenomic, transcriptomic and proteomic analysis of diffuse gliomas, demonstrating that methylome, transcriptome and functional copy number variations connect to the status of *IDH* mutations (i.e. *IDH*-mutated LGGs) whereas the expression of protein, or metabolome, is strongly related to WHO grading or aggressiveness rather than *IDH* mutations (i.e. *IDH* wild-type GBMs) [8]. Tumor development, progression and response to therapy are profoundly influenced by tumor cells' intracellular metabolism and the exogenous tumor environment. The biochemical environment can shape the behavior of tumor cells in a genotype-specific fashion, potentially by altering the relative fitness of cells bearing a mutation to grow within that metabolic niche and also by directly regulating downstream signaling. Further, the heterogeneity in tumor metabolism and the strong influence of the microenvironment which potentially contribute to the tumor's utilization of alternative fuels should be taken into consideration [17]. Future studies are needed to determine precisely how chief genetic mutations specific in each glioma entity facilitate cancer metabolic reprogramming and how at the same time extracellular nutrients modulate oncogenic signaling, in order to translate these insights into more effective treatments for glioma patients.

Acknowledgments

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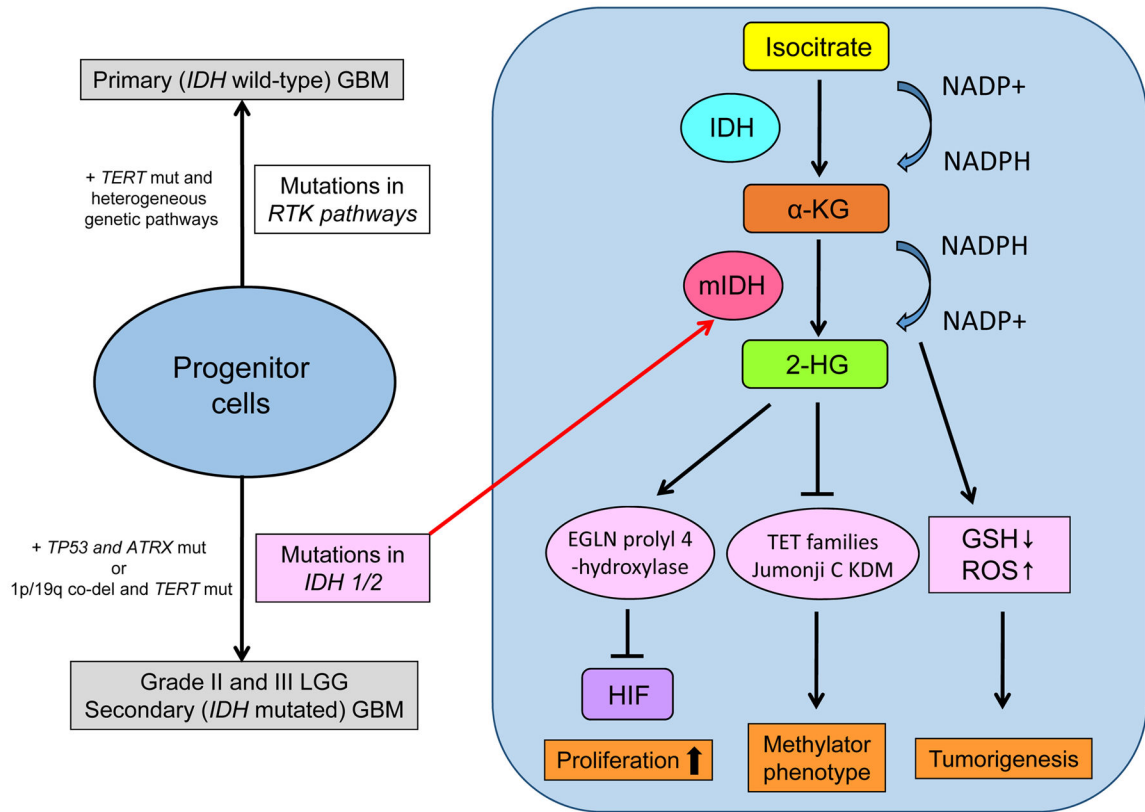
Figure 1. Metabolic reprogramming in *IDH*-mutated gliomas

Mutations in *IDH*, identified as an early genetic event in grade II/III LGG and secondary GBM, play an important role in gliomas through its neomorphic activity that converts α-KG to an oncometabolite 2-HG. 2-HG stimulates activity of EGLN prolyl 4-hydroxylases enhancing cellular proliferation through the degradation of HIF, and also inhibits α-KG-dependent dioxygenases including Jumonji C histone lysine demethylases (KDMs) and the ten-eleven translocation (TET) family of 5′-methlycytosine hydroxylases leading to methylator phenotypes including G-CIMP and aberrant histone methylation. Additionally, conversion of α-KG to 2-HG is a NADPH-consuming reduction, decreasing intracellular NADPH levels required for the reduction of oxidative stress that promotes tumorigenesis. mut, mutation; mIDH, mutant form of IDH enzymes; GSH, reduced glutathione; ROS, reactive oxygen species; TERT, telomerase reverse transcriptase; ATRX, alpha thalassemia/mental retardation syndrome X-linked; 1p/19q co-del, chromosomes 1p and 19q co-deletion.
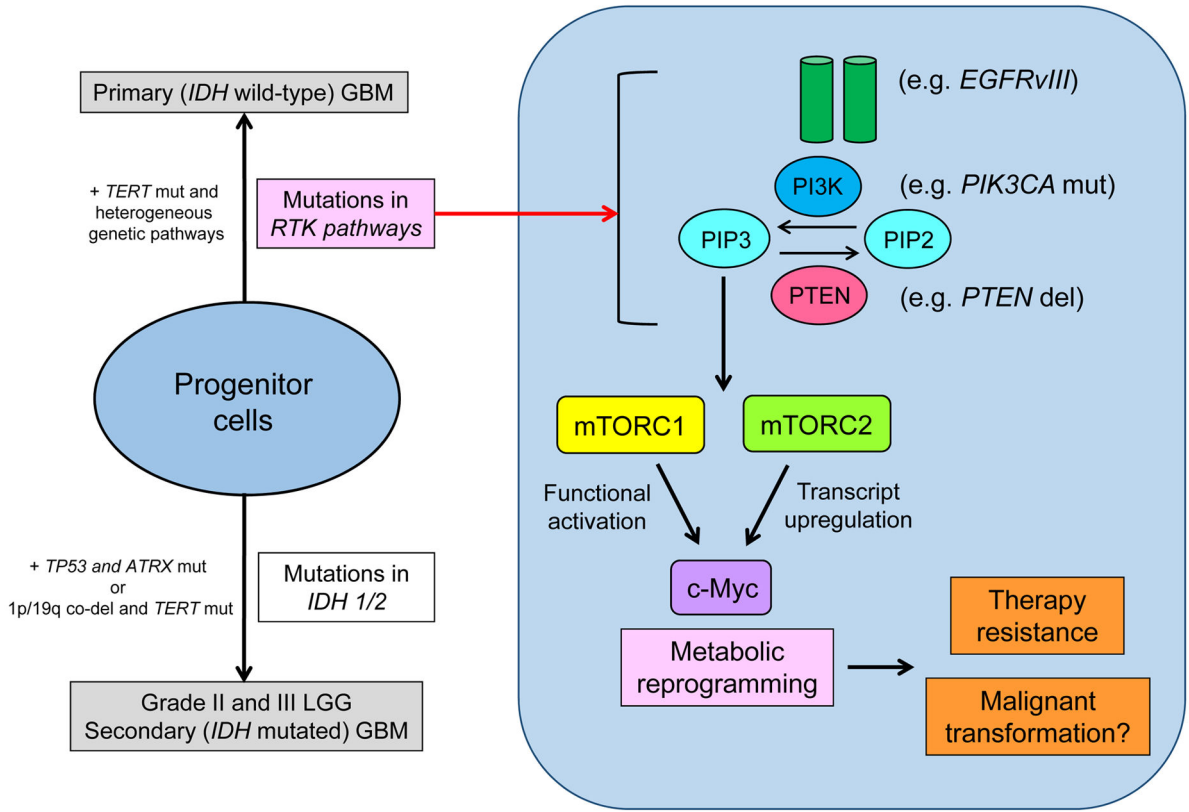
Figure 2. Metabolic reprogramming in GBM with mutations in *RTK* pathways
Genetic alterations of key components of the growth factor receptor-PI3K-Akt signaling pathway are frequently observed in primary (*IDH* wild-type) GBM, which eventually activate mTOR signaling. c-Myc, a master regulator of cancer metabolism is transcriptionally and functionally regulated by two distinct mTOR complexes, mTORC1 and mTORC2. This circuit of metabolic shifting causes GBM cell resistance to molecularly targeted therapies by maintaining elevated levels of c-Myc. Interestingly, RTK- and Myc-dependent metabolic reprogramming might be also involved in malignant progression of *IDH*-mutant gliomas.

del, deletion; EGFRvIII, epidermal growth factor receptor variant III; mut, mutation; PI3K, phosphoinositide 3-kinase; PIK3CA, phosphatidylinositol (4,5)-bisphosphate 3-kinase catalytic subunit alpha; PIP2, phosphatidylinositol (4,5)-bisphosphate; PIP3, phosphatidylinositol (3,4,5)-trisphosphate; PTEN, phosphatase and tensin homolog deleted on chromosome 10.
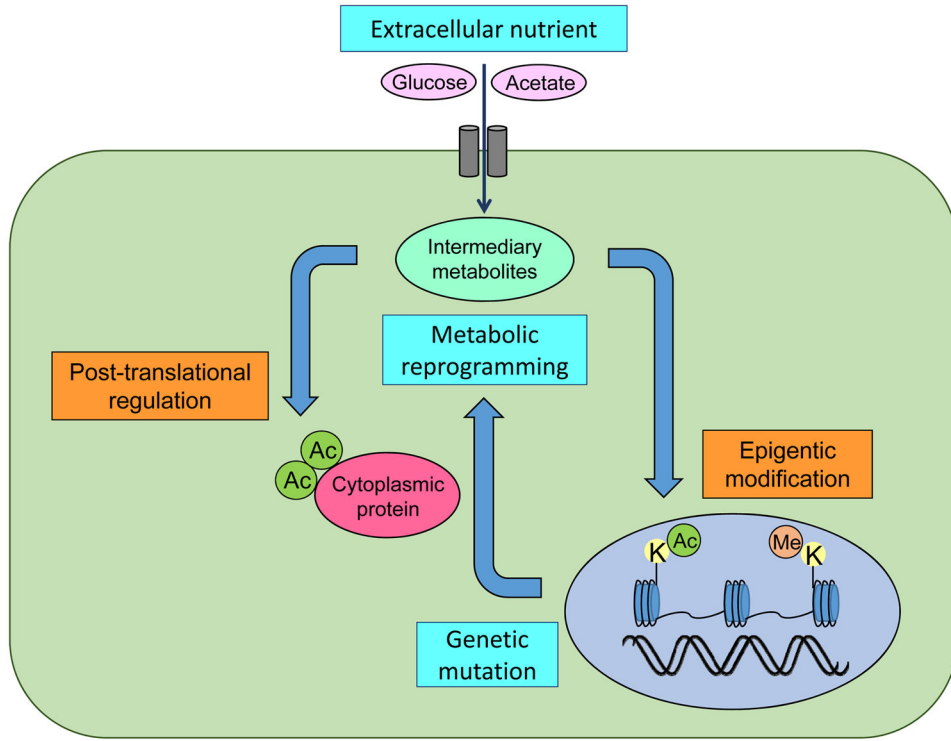
Figure 3. Reciprocal interaction of genetics, metabolism and environment in gliomas

Mutations in the cardinal genes for gliomagenesis including *IDH* and *RTK* pathway components are the central force to drive metabolic reprogramming in gliomas. By promoting cancer metabolisms, glioma cells avidly take up extracellular nutrients such as glucose and acetate and metabolize them into intermediary metabolites which in turn tailor the genetic signaling by shifting epigenetics as well as post-translationally modifying oncogenic proteins in the cytosol.

Ac, acetyl-group; Me, methyl-group; K, lysine residues.