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Provocative Question: Should Ketogenic Metabolic Therapy Become the Standard of Care for Glioblastoma?

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Abstract

No major advances have been made in improving overall survival for glioblastoma (GBM) in almost 100 years. The current standard of care (SOC) for GBM involves immediate surgical resection followed by radiotherapy with concomitant temozolomide chemotherapy. Corticosteroid (dexamethasone) is often prescribed to GBM patients to reduce tumor edema and inflammation. The SOC disrupts the glutamate–glutamine cycle thus increasing availability of glucose and glutamine in the tumor microenvironment. Glucose and glutamine are the prime fermentable fuels that underlie therapy resistance and drive GBM growth through substrate level phosphorylation in the cytoplasm and the mitochondria, respectively. Emerging evidence indicates that ketogenic metabolic therapy (KMT) can reduce glucose availability while elevating ketone bodies that are neuroprotective and non-fermentable. Information is presented from preclinical and case report studies showing how KMT could target tumor cells without causing neurochemical damage thus improving progression free and overall survival for patients with GBM.

Keywords Ketogenic diet · Glucose · Glutamine · Glutamate · Warburg · Substrate level phosphorylation · Fermentation

Abbreviations

GBM Glioblastoma
TMZ Temozolomide
SOC Standard of care
KMT Ketogenic metabolic therapy

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Introduction

Glioblastoma (GBM) remains largely unmanageable and has among the highest mortality rates for primary brain tumors. Median life expectancy following diagnosis is only about 11–14 months for most GBM patients regardless of the hype surrounding some of the newer of therapies [1–5]. A recent reevaluation found that overall survival for GBM (8–14 months) is woefully similar to that reported by Bailey and Cushing almost a century ago [5, 6]. Indeed, US Senator, John McCain, was diagnosed with GBM in May 2017, and died in August 2018. The 'Secondary Structures of Scherer' are the defining characteristic of GBM, which include diffuse parenchymal invasion and growth over the subpial surface, along white matter tracks, and through the Virchow–Robin spaces [7–11]. The highly invasive nature of GBM through these secondary structures makes most current therapies ineffective [12–15]. The quality of life has also remained poor for most GBM patients especially for those receiving radiation and the toxic alkylating agent, temozolomide [16–18] (Fig. 1).

GBM contains a range of morphologically diverse neoplastic cell types that express neural, glial, and myeloid/mesenchymal markers [3, 19–27]. Also recognized are

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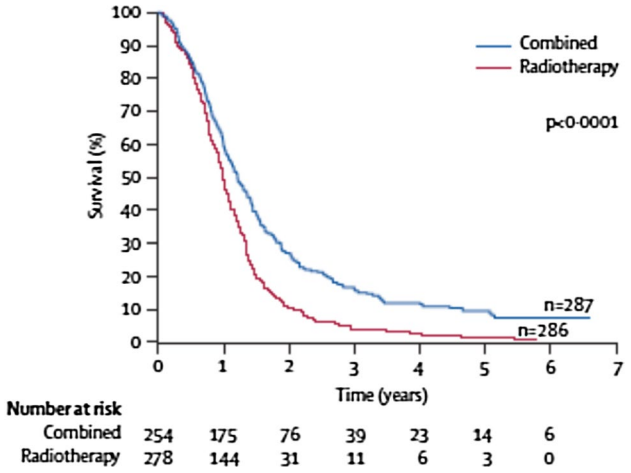

Fig. 1 Kaplan–Meier estimates of overall survival of patients with GBM by treatment group. The two patient groups included radiotherapy alone (n = 278), and radiotherapy with temozolomide (n = 254). From [18] with permission

mitochondrial structural abnormalities seen in autopsy/biopsy tissue obtained from GBM patients (Figs. 2, 3). Several groups have documented GBM cells with reduced or increased numbers of morphologically abnormal mitochondria with laminations and aberrant or absent cristae that can alter mitochondrial function [5, 28–36]. Some mitochondria in human GBM cells contain few if any cristae and also show defects in mitochondrial associated membranes, all of which would compromise energy production through oxidative phosphorylation (OxPhos) [32, 37]. These abnormalities are not often recognized in cultured GBM cells, where mitochondria are often considered normal. Abnormalities in the content and composition of cardiolipin, the signature lipid of the mitochondrial inner membrane that regulates oxidative phosphorylation (OxPhos), were found in five independently derived murine GBMs [28, 38, 39]. It is unlikely that OxPhos will function normally in any tumor cell with defects in cardiolipin.

A multitude of findings support the notion that OxPhos is defective in GBM [29, 31, 33, 40–42]. Based on the

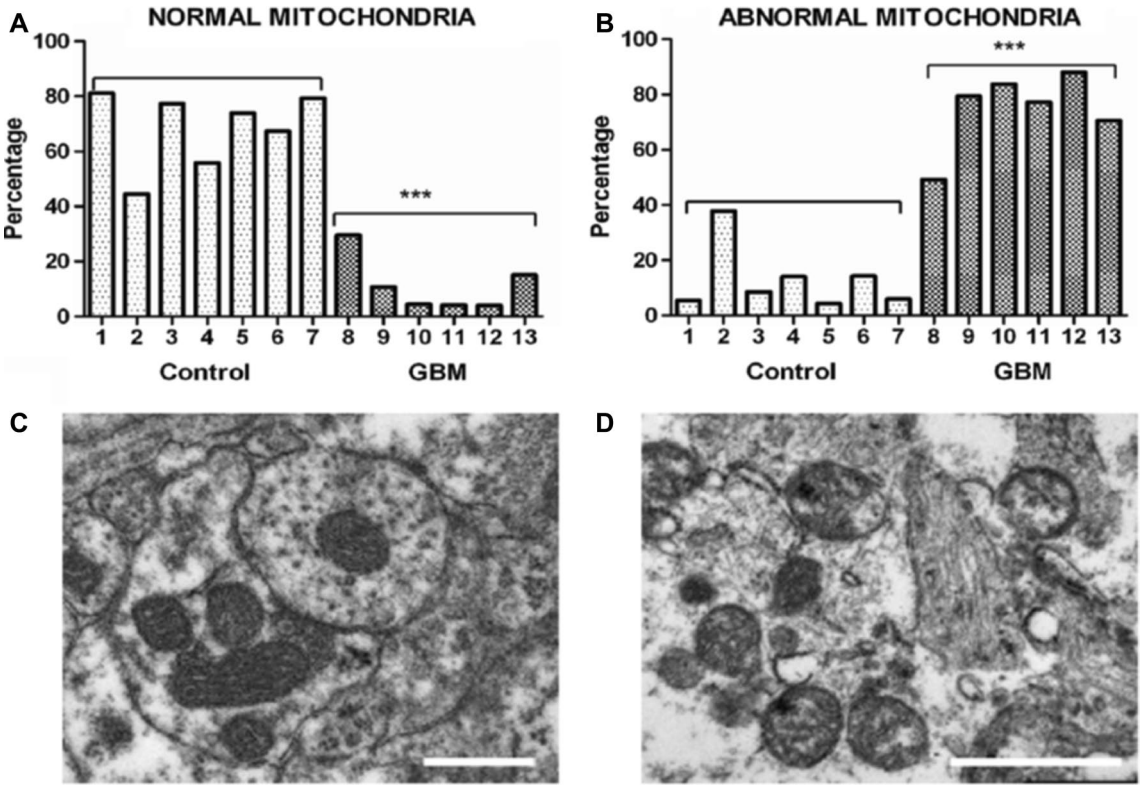

Fig. 2 Morphological abnormalities in GBM mitochondria. The morphology of 150 mitochondria was assessed in 6 GBM samples and in 7 peritumoural control samples using Electron Microscopy (EM). **a** Percentage of normal mitochondria where cristae were visible throughout the mitochondria in peritumoural control and GBM samples (each bar represents one sample; ***p value = 0.0001); **b** percentage of abnormal mitochondria where cristae were sparse and abnormal in peritumoural control and GBM samples; ***p value = 0.0001). **c** and **d** Representative EM images of normal and abnormal mitochondria, respectively. The scale bars represent 0.5 µm. Cristolysis was significantly greater in mitochondria from GBM than in mitochondria from control brain. The authors reported 117 mitochondrial proteins altered in GBM in association with ultrastructural mitochondrial abnormalities, similar to those described previously by Arismendi-Morillo et al. [32]. Image reproduced under a Creative Commons license from Deighton et al. [34]

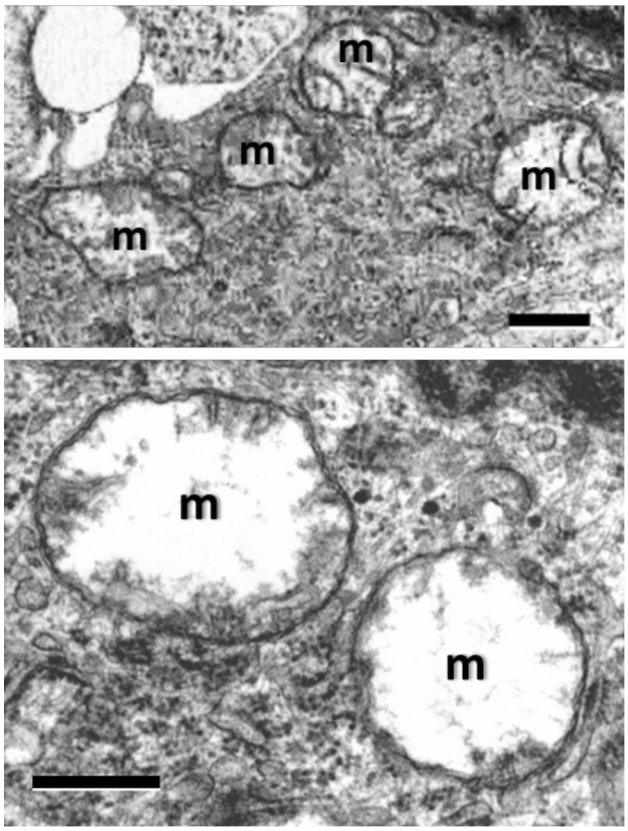

Fig. 3 Typical ultrastructure of mitochondria from a human glioblastoma. That structure determines function is a key concept in biology, especially for mitochondria [43]. Normal mitochondria contain elaborate cristae, which are extensions of the inner membrane and contain the proteins and lipids (cardiolipin) of the electron transport chain necessary for producing ATP through OxPhos [38, 160, 161]. The mitochondria from the glioblastoma (m) show a total or near total breakdown of cristae (cristolysis) and an electron-lucent matrix. The absence of cristae and other structural abnormalities seen in glioblastoma mitochondria indicate that OxPhos would be deficient [5]. Our recent findings also show that mitochondrial associated membranes (MAM) are also abnormal in human malignant gliomas, which would further compromise mitochondrial function [37]. Upper micrograph bar 0.5 mm. Below micrograph bar 0.8 mm. Method of staining: uranyl acetate/lead citrate. The upper micrograph is new and the lower micrograph was reprinted with permission from *Journal of Electron Microscopy* [32]

biological principle that mitochondrial structure determines mitochondrial function [5, 43], these multiple mitochondrial abnormalities, which can be of genetic and/or environmental origin, [44–46], will compromise effective energy production through OxPhos. As a consequence, fermentation metabolism will be necessary to compensate for the deficiency in OxPhos. A chronic reliance on fermentation will cause an OxPhos-damaged cell to enter its default state, i.e., a state free of respiratory control [46–49]. It is important to recognize that fermentation driven unbridled proliferation was the metabolic state of all cells prior to the appearance of oxygen in the atmosphere some 2.5 billion years ago [46, 50]. Survival in such environments would therefore require a constant supply of fermentable fuels. The transition from OxPhos to fermentation will facilitate the production of anabolic intermediates that support the biosynthetic processes necessary for unbridled cell growth [5, 51].

In view of the documented abnormalities in GBM mitochondria, alternative energy source(s) to OxPhos must be in place to maintain cell viability [5]. Accumulating evidence indicates that glucose and glutamine are the primary fermentable fuels used for driving the rapid growth of most tumors, including GBM [5, 52–55]. Abundant levels of glucose and glutamine are also available in cyst fluid that is often present in GBM and could be used as fuel for the growing tumor cells [5, 56]. Other potential metabolic fuels in the tumor microenvironment, e.g., acetate and branched chain amino acids, are either not present in sufficient quantities to drive growth through fermentation or exert non-metabolic effects that are yet to be understood [5, 30, 57]. While amino acids other than glutamine and glutamate could also be fuels, they would require one or more high-energy phosphates during metabolic interconversions before becoming succinyl-CoA, the substrate for mSLP [5]. Hence, glucose and glutamine are the most readily available fermentable fuels for driving GBM growth through glycolysis and glutaminolysis.

Glucose drives tumor growth through aerobic fermentation (Warburg effect), whereas glutamine drives tumor growth through glutaminolysis [58–61]. Metabolism of glucose and glutamine is also responsible for the high antioxidant capacity of the tumor cells thus making them resistant to chemo-and radiotherapies [30, 62, 63]. We recently identified mitochondrial substrate level phosphorylation (mSLP), as major source of ATP synthesis for GBM cells [5]. We described how lactic acid fermentation (Warburg effect) through glycolysis in the cytoplasm and succinic acid fermentation through glutaminolysis in the mitochondria (Warburg Q-Effect) could compensate for deficient OxPhos in GBM cells [5]. Succinic acid fermentation using glutamine as a major substrate is now recognized as the *missing link* in Warburg's central theory that aerobic fermentation compensates for dysfunctional respiration in cancer [5]. It is important to mention that glucose and glutamine can provide all of the anabolic intermediates necessary to support rapid biosynthetic processes through glycolysis in the cytoplasm and glutaminolysis in the mitochondria. Hence, glucose and glutamine-driven fermentation underlies the energy production needed for GBM growth and invasion.

The Current Standard of Care for GBM

The current standard of care (SOC) for GBM involves surgical resection and radiotherapy with concomitant and adjuvant temozolomide (TMZ) [18, 64]. High dose steroid

(dexamethasone) is often prescribed along with the SOC to reduce vasogenic edema [15, 65, 66]. It is now recognized that surgical resection and radiotherapy produce significant necrosis and hypoxia in the tumor microenvironment [67, 68]. Inflammatory oncotaxis following surgical resection of lower-grade brain tumors could also contribute to their transformation to high-grade secondary GBM [69, 70]. Moreover, surgical resection and radiotherapy damages the brain microenvironment, which will increase glucose availability to remaining tumor cells thus driving tumor growth through hyperglycolysis resulting in therapy resistance [71–73]. Abundant evidence shows that survival is shorter in GBM patients with higher blood glucose levels than in patients with lower glucose levels [74–82]. Radiotherapy also facilitates tumor cell-macrophage/microglial fusion-hybridization thus producing highly invasive metastatic cells [22, 83, 84]. It has been our view that the highly invasive mesenchymal cells seen in GBM are derived from neoplastic microglia or from fusion hybridizations of microglia/macrophages with non-invasive cancer stem cells, as has been described for other highly invasive and metastatic cancers [22, 84–86].

Surgery and radiotherapy disrupt the tightly regulated glutamine-glutamate cycle in the neural parenchyma thus increasing the levels of glutamine and also glutamate, an excitotoxic amino acid that enhances GBM invasion [56, 87–90]. Although TMZ increases progression-free survival, it has only marginal effect on overall survival, while simultaneously increasing the number of GBM driver mutations [18, 91]. Additionally, dexamethasone not only increases blood glucose levels further, but also increases glutamine levels through its induction of glutamine synthetase activity [5, 66, 89, 92, 93]. The anti-angiogenic drug bevacizumab (Avastin) is also widely prescribed to GBM patients [94–96]. Bevacizumab exacerbates tumor necrosis while selecting for the most invasive and therapy-resistant tumor cells [97, 98]. Both bevacizumab and TMZ damage mitochondria [99], which would contribute further to tumor cell reliance on cytoplasmic and mitochondrial fermentation metabolism for growth [5]. Invasion of GBM cells through the Virchow–Robin spaces will make immunotherapy marginally effective for GBM management [100]. Immunotherapies could be effective for GBM management as long as there is evidence showing that they do not enhance inflammation, increase availability of glucose and glutamine in the tumor microenvironment, or cause hyperprogressive disease, as was seen in non-small cell lung cancer [101]. Most of the studies to date that have used immunotherapy for GBM patient management have been less than encouraging [102, 103]. This outcome should not be surprising, however, as immunotherapy is based largely on the view that cancer is a genetic disease rather than a mitochondrial metabolic disease [41, 46, 90, 104]. Viewed collectively, the current SOC damages the microenvironment and facilitates delivery of glucose and glutamine to GBM cells, all of which will contribute to tumor recurrence and rapid progression (Fig. 4).

It should also be recognized that many GBM cells are infected with human cytomegalovirus (HCMV) that would further facilitate tumor cell use of glutamine and glucose [105, 106]. Recent studies show that vaccine-targeting of the HCMV pp65 protein could significantly increase progression free and overall survival of some GBM patients [107]. It would be interesting to determine if this therapeutic effect resulted in part from a disruption of glycolysis or glutaminolysis in GBM cells [108, 109]. Glucose and glutamine are the prime metabolites needed for synthesis of glutathione and manganese superoxide dismutase, which make GBM cells resistant to chemotherapy and radiotherapy [5, 30]. It is known that elevated aerobic fermentation also drives the multidrug resistant (MDR) phenotype, which protects GBM cells from toxic chemotherapy [3, 30, 63]. Hence, the SOC-linked increase in fermentable energy metabolites and disruption of the tumor microenvironment can explain in large part why overall survival remains so poor for most GBM patients [5, 71]. In light of the presented information, does the current SOC still seem to be the most rational approach to GBM management?

Ketogenic Metabolic Therapy

Ketogenic metabolic therapy (KMT) is emerging as a viable complimentary or alternative therapeutic strategy for malignant gliomas [64, 78, 90, 110–120]. Calorie restriction and low-carbohydrate high-fat ketogenic diets (KD) reduce the glucose needed to drive the Warburg effect while also elevating ketone bodies that cannot be metabolized for energy in tumor cells due to defects in mitochondrial structure and function [5, 32, 37, 38, 104, 118, 121–124]. There have been reports, however, suggesting that some brain tumors can oxidize ketone bodies or express enzymes for ketone body metabolism [125, 126]. The expression of ketogenic enzymes or uptake of ketone bodies together with oxygen consumption in tumor cells does not necessarily mean that the ketone bodies can be used to generate energy through OxPhos [5]. Indeed, moderate disruption of the mitochondrial proton motive gradient will cause a reversal of the F1-F0 ATP synthase thus hydrolyzing ATP rather than synthesizing ATP [5]. Upregulation of mitochondrial substrate level phosphorylation, as an alternate source of ATP synthesis, will stabilize the F1-F0-ATP synthase thus preventing reversal. Glucose and glutamine become the prime fuels for increased substrate level phosphorylation reactions is the cytoplasm and mitochondria, respectively. Ketone bodies and fatty acids cannot be fermented and cannot therefore serve as major fuels for tumor cells with defective OxPhos [5]. Oncogenes such as *Hif-1alpha*, *Myc, Ras, BRAF*, etc.,

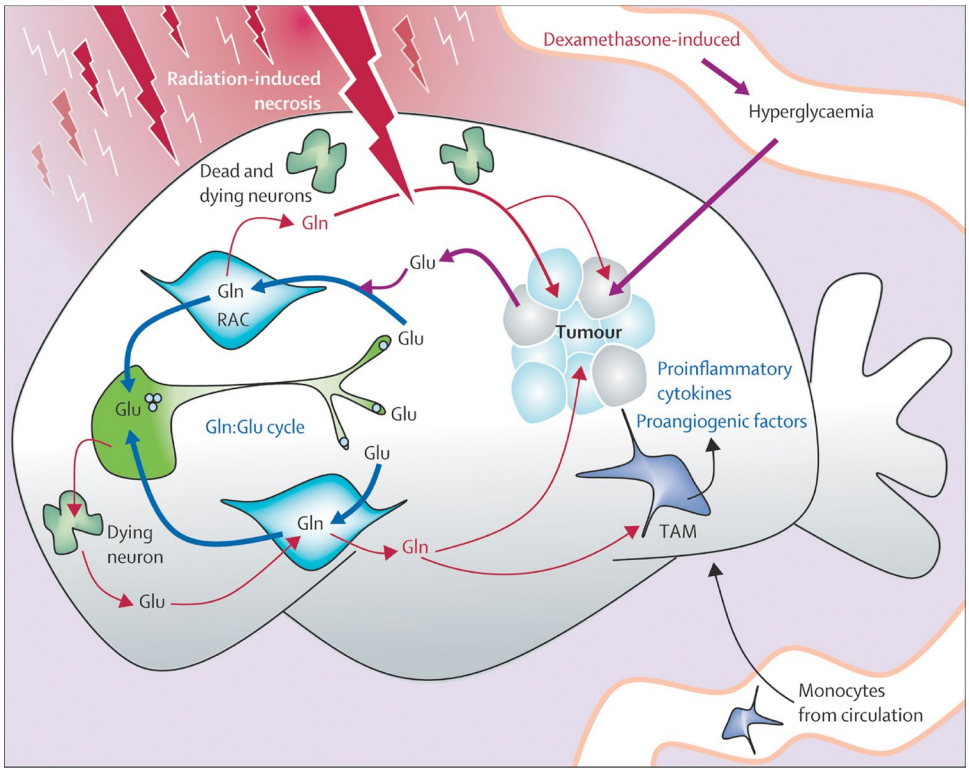

Fig. 4 How the standard of care can provoke glioblastoma growth and recurrence. Although GBM is biologically complex, glucose and glutamine are the primary energy metabolites necessary for driving rapid GBM growth [54, 162–165]. Glucose is the metabolic fuel for nearly all brain functions under normal physiological conditions [166]. Tumor cells metabolize glutamine to glutamate, which is then metabolized to alpha-ketoglutarate in the TCA cycle [53]. Significant energy is generated from the succinyl CoA ligase reaction (substrate level phosphorylation) using alpha-ketoglutarate-derived succinyl CoA as substrate [5]. In contrast to extracranial tissues, where glutamine is the most available amino acid, glutamine is tightly regulated in the brain through its involvement in the glutamate–glutamine cycle of neurotransmission [166, 167]. Glutamate is a major excitatory neurotransmitter that must be cleared rapidly following synaptic release in order to prevent excitotoxic damage to neurons [88, 167]. Glial cells possess transporters for the clearance of extracellular glutamate, which is then metabolized to glutamine for delivery back to neurons. Neurons metabolize the glutamine to glutamate, which is then repackaged into synaptic vesicles for future release. The cycle maintains low extracellular levels of both glutamate and glutamine in normal neural parenchyma. Disruption of the cycle can provide neoplastic GBM cells access to glutamine. Besides serving as a metabolic fuel for the neoplastic tumor cells, glutamine is also an important fuel for cells of myeloid linage, which include macrophages, monocytes, microglia, and especially the highly invasive mesenchymal cells in GBM [22, 168, 169]. In contrast to the highly proliferative GBM stem cells, the neoplastic GBM mesenchymal cells are thought to be derived from microglia or from microglia-stem cell fusion hybrids, which would have immuno-suppressive properties [22, 170]. As long as GBM cells have access to glucose and glutamine, the tumor will grow making long-term management difficult. The current SOC for GBM creates a microenvironment rich in glucose and glutamine that will facilitate rapid tumor recurrence (see text for further details). RAC = reactive astrocytes; TAM = tumour-associated macrophages. Gln = glutamine. Glu = glutamate. From [89] with permission

facilitate the dependence of tumor cells on glucose and glutamine while defects in the tumor suppressor genes p53 and *pRb* increase OxPhos dysfunction [5, 127–132]. In contrast to these gene defects, which will enhance fermentation metabolism, mutations in the genes for isocitrate dehydrogenase (IDH1, IDH2) are linked to improvement in overall GBM survival [133]. We recently suggested that the IDH mutations will divert metabolism of glutamine-derived alpha-ketoglutarate from succinyl CoA to 2-hydroxyglutarate (2-HG), thus depriving energy production through mSLP [5]. No tumor cell can grow without energy regardless of its genetic composition [5]. The KMT depletion of fermentable fuels will facilitate catastrophic tumor cell death without harming normal neural cells.

The GBM microenvironment is hypoxic, acidotic, and is enriched with glucose and glutamine. This pro-tumorigenic microenvironment becomes less inflamed under KMT, which also significantly reduces tumor mass and enhances apoptotic cell death (Figs. 5, 6). Calorie restriction and restricted KD are anti-invasive, anti-angiogenic, anti-inflammatory, and capable of killing some tumor cells through a pro-apoptotic mechanism [121, 134–137]. Metabolism of the major circulating ketone body, D-beta-hydroxybutyrate, is also neuroprotective in reducing reactive oxygen species

production through the mitochondrial Co-enzyme Q couple in normal cells, while simultaneously elevating oxidative stress in tumor cells [30, 138–141]. Implementation of KMT should also decrease the need for high-dose dexamethasone, and prevent steroid-induced hyperglycemia [142, 143]. It is our view that the anti-invasive effects of calorie restriction and restricted ketogenic diets could demarcate better the tumor margins, which would facilitate greater debulking of human GBM (Fig. 5) [64]. In fact, gross total resection of the tumor is regarded as a survival advantage, and therefore the therapeutic effects of KMT should improve progression free and overall survival thus benefiting GBM patients.

Therapeutic ketosis is linked to reduced blood glucose levels and elevated ketone bodies levels within normal physiological ranges [144]. Evidence shows that therapeutic ketosis can act synergistically with several drugs and procedures to enhance cancer management improving both progression free and overall survival [30, 119, 145, 146].

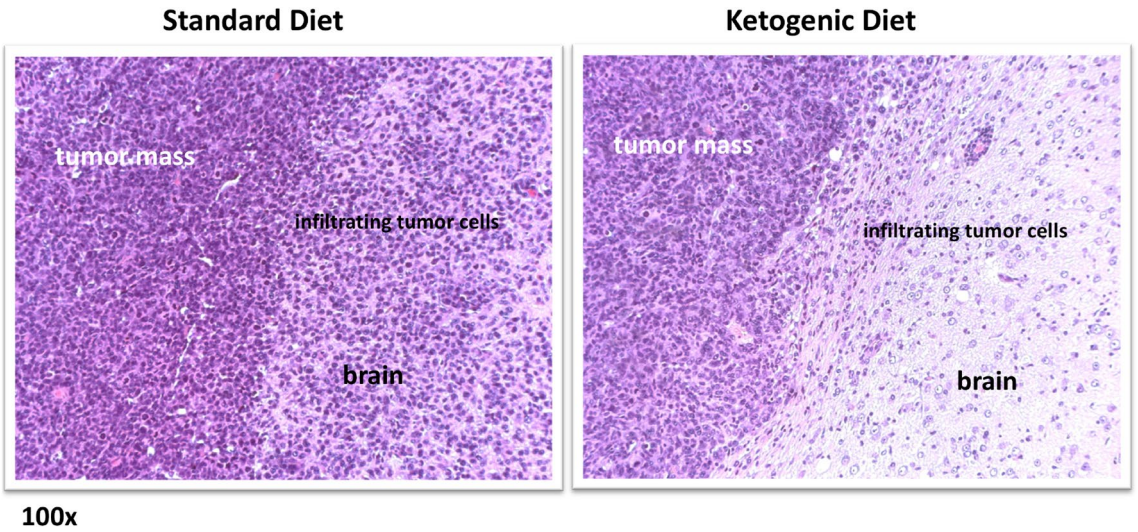

Fig. 5 Influence of KMT on invasion of the preclinical VM-M3 GBM. VM-M3/Fluc tumor fragments were implanted into the cerebral cortex as described [137]. The mice were fed either a high-carbohydrate standard diet, or a ketogenic diet in restricted amounts (KD-R) to reduce body weight by about 15–18%. The tumor cells are densely packed and show massive invasion from the tumor mass into the lighter stained normal brain tissue in mice fed the high-carbohydrate standard diet. In contrast, the tumor cells are less densely packed and show less invasion in mice fed the ketogenic diet. The reduced invasive behavior and sharper tumor boarders were linked to therapeutic ketosis (reduced blood glucose and elevated beta-hydroxybutyrate) [137, 171]. Caloric restriction also reduces the invasion of tumor cells from the implanted ipsilateral cerebral hemisphere into the contralateral hemisphere and significantly reduces invasion through "Secondary Structures of Scherer [137]

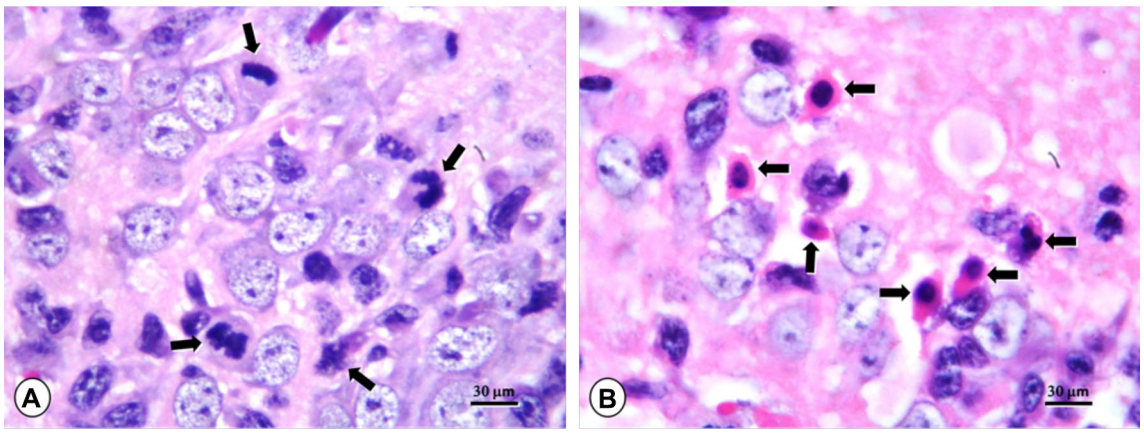

Fig. 6 Influence of KMT on the microenvironment and apoptosis of the preclinical VM-M3 GBM. Densely packed tumor cells with abundant mitoses (arrows) are seen in mice fed the a high-carbohydrate standard diet in unrestricted amounts, **a** abundant apoptotic tumor cells with eosinic cytoplasm and condensed chromatin (arrows) are seen in mice fed a ketogenic diet in restricted amounts, **b** other conditions are as shown in Fig. 5

For example, hyperbaric oxygen therapy (HBOT) increases oxidative stress on tumor cells especially when used alongside therapies that reduce blood glucose and raise blood ketones [147]. In reducing blood glucose levels, KMT would also reduce the immunosuppressive effects of lactate in the GBM microenvironment [148]. There is also evidence that therapeutic ketosis can facilitate drug delivery through the blood brain barrier [149]. Chloroquine neutralization of lysosomal pH can prevent invasive and metastatic tumor cells from obtaining glucose and glutamine through phagocytosis or autophagy [30, 150, 151]. Chloroquine can also inhibit mitochondrial diaphorases, which oxidize NADPH to NAD + thus reducing mitochondrial substrate level phosphorylation [5, 152]. The glutamine dehydrogenase inhibitor, epigallocatechin gallate (EGCG) is also proposed to target glutamine metabolism through an effect on glutamate dehydrogenase [153]. Hence, ketogenic metabolic therapy can, (a) target the multiple drivers of rapid glioma growth, (b) facilitate drug delivery through the BBB, and, (c) protect and enhance metabolic efficiency in normal brain cells. There are currently no GBM therapies to our knowledge that can simultaneously target these multiple drivers of GBM growth while, at the same time, protect normal neural cells.

Ketogenic Metabolic Therapy as an Alternative to SOC

The gold standard for a cancer therapy should involve the selective killing of tumor cells while avoiding damage to normal body cells. Unfortunately, the current SOC for GBM is wanting with respect to achieving this standard. As currently implemented, the SOC contributes to rapid tumor recurrence and the ultimate demise of the patient. Although many GBM patients have received KMT with SOC none, to our knowledge, have achieved or persistently maintained glucose ketone index (GKI) values of 1.0 or below, a biomarker for therapeutic ketosis [118, 126, 142, 144, 154]. It is important to mention, however, that a GKI value of 1.0 can be difficult to achieve for many cancer patients. This can result in part from emotional stress and toxic SOC treatments, which elevate bold glucose [30, 155]. It can take weeks for some patients to transition to a GKI near 1.0 [155]. Our GBM patient received KMT for 3 weeks prior to surgical resection and for 3 months prior to radiation and TMZ chemotherapy [64]. The patient achieved a GKI close to 1.0, a reduction in Hunter's angle (Choline/*N*-acetyl aspartate, NAA, ratio), correction of midline shift, and improved quality of life [64]. Unfortunately, the patient died after 30 months from complications of radionecrosis. The diagnosis of radiation-induced necrosis was based on MRI perfusion and MRS in addition to gross tissue appearance and histological analysis. The surgeon reported the absence of detectable solid tumor mass; only yellowish grayish fragile avascular material. Histopathological analysis revealed inflammatory infiltrates, liquefactive necrosis, vascular hyalinization, and endothelial damage further favoring the diagnosis of radionecrosis rather than recurrent tumor. Radiation-induced necrosis is now recognized as a serious issue for brain cancer patients [156]. A key question is whether survival for GBM patients would be better if KMT replaced radiation therapy considering the damage to normal cells and the growth promoting effects of radiation therapy. We know of only one long-term GBM survivor that has received KMT without also receiving radiation or chemotherapy (http://www.childhoodcancer2018.org.uk/speakers/pablo-kelly.asp). While this case is anecdotal, his status indicates that replacement of SOC with KMT did not reduce his progression-free survival or overall survival. Further studies will be required to determine whether the favorable response of this GBM patient to KMT is unique or would be common to other GBM patients.

KMT, as part of the press-pulse therapeutic strategy, is designed to target simultaneously the availability of glucose and glutamine to the GBM cells [30]. The linkage of fermentation to malignancy is as solid as is that of the redshift to gravity [157]. As glucose and glutamine are the major fermentable fuels for GBM, the strategic restriction of these fuels will deprive the GBM cells of energy [5, 30]. As the membrane pumps are the largest consumers of cellular ATP, reduced ATP synthesis will cause tumor cells to swell and die [44]. It should be mentioned, however, that the unrestricted consumption of a ketogenic diet failed to suppress growth of the syngeneic CT-2A GBM preclinical model [121, 158]. This is likely due to excessive consumption of fat that can cause insulin insensitivity, as we previously showed [159]. As with any medicine, misuse of the KD can be ineffective or potentially harmful. The KD works best for managing cancer when consumed in restricted amounts.

Although several clinical trials are presently investigating KMT as a complementary treatment in patients receiving SOC for newly diagnosed or recurrent malignant glioma (clinical trials.gov), several challenges remain. Some of these challenges include existing barriers to clinical research in this field per se (technical issues with clinical trial design based on existing guidelines, ethical issues, insufficient clinician awareness, and lack of incentives to fund such trials or research). These issues must be addressed before KMT can become the SOC for brain cancer management despite having a scientific rationale stronger than that for most the approaches currently used for managing GBM. It is likely that KMT will be used as a complimentary strategy with current conventional, non-metabolic antineoplastic strategies, before consideration as a monotherapy. Support for synergistic interactions of KMT with SOC could facilitate

consideration of KMT as a monotherapy or as an alternative therapy for some currently used toxic procedures.

Conclusions

We have described how GBM is a type of mitochondrial metabolic disease where glutamine and glucose drive the growth of the heterogenetic neoplastic cell types [5, 64, 90]. No other fermentable fuels are present in the tumor microenvironment in quantities sufficient enough to replace glucose and glutamine. We also previously described how the gene mutations seen in GBM and most other cancers arises as effects of destabilized energy metabolism [5, 30, 45, 46, 104]. Would progression-free survival and overall survival of patients be improved with a non-toxic therapeutic strategy that targets the underlying metabolic defects located specifically in the neoplastic while also reducing inflammation and edema in the microenvironment? This question could be answered in clinical trials that compare outcomes in GBM patients treated with either the SOC + KMT or with KMT alone.

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