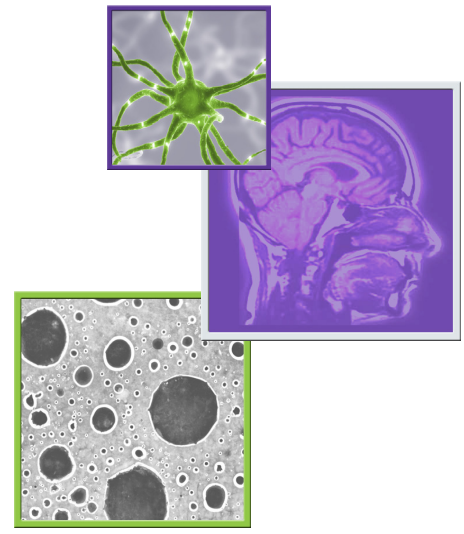
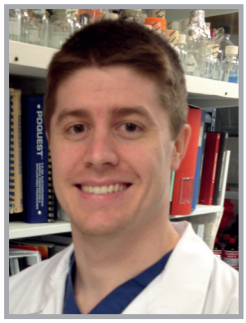
EDITORIAL

For reprint orders, please contact reprints@future-science.com



Metabolism and glioma therapy



Eric C Woolf[1] Adrienne C Scheck*[1,2]

"There is a resurgence of interest in metabolism as a central theme in cancer, and we continue to find that metabolic pathways intersect and often regulate key components of tumor initiation, progression and therapy response."

Malignant brain tumors are nearly uniformly fatal due, in part, to the limitations of currently available treatments, which include surgery, chemotherapy and radiotherapy. It is of paramount importance that new therapeutic strategies are developed, especially those that can enhance the efficacy of current treatments without damaging normal brain. Advances in our understanding of the molecular biology of this disease have led to an increase in the number of targeted therapies in preclinical and clinical trials [1–3], and while these therapies may prove somewhat effective, there has been little improvement in overall survival [4]. This is due, in part, to the intrinsic cellular heterogeneity of these tumors that often precludes the targeted molecules from being found on all cells, thus reducing the efficacy of these treatments. By contrast, one trait shared by virtually all tumor cells is altered metabolism.

Otto Warburg first described what we now call aerobic glycolysis or the 'Warburg Effect' in 1924 [5]. The Warburg Effect describes the tumor cell's use of glycolysis to provide energy and biomolecules regardless of the availability of oxygen. This shift toward increased glycolytic flux and away from the tricarboxylic acid cycle and oxidative phosphorylation occurs very early in tumorigenesis, prior to hypoxia while the tumor has sufficient oxygen. Since Warburg's discovery, metabolism has been of interest in the cancer field, but it often seemed overshadowed by discoveries of oncogenes, tumor suppressor genes, growth factor pathways, molecular subtypes of cancers and so on. There is a resurgence of interest in metabolism as a central theme in cancer, and we continue to find that metabolic pathways intersect and often regulate key components of tumor initiation, progression and therapy response [6,7]. Thus, it has been suggested that one promising therapeutic strategy is to exploit the metabolic dysregulation seen in virtually all tumor cells.

We now know that cancer metabolism is much more complex than just a higher rate of glycolysis. Mitochondrial biogenesis is also altered, and the cancer cell's fate becomes reliant on the balance

"...it has been suggested that one promising therapeutic strategy is to exploit the metabolic dysregulation seen in virtually all tumor cells."

[1]Neuro-Oncology Research, Barrow Neurological Institute® of St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

[2]Neurosurgery Research, Barrow Neurological Institute® of St. Joseph's Hospital and Medical Center, Phoenix, AZ 85013, USA

*Author for correspondence: Tel.: +1 602 406 3647; Fax: +1 602 406 7172; adrienne.scheck@dignityhealth.org

Future Medicine part of fsg

between the availability of energy, sufficient macromolecular synthesis for increased growth, and the modulation of reactive oxygen species. Many pathways long known to be associated with tumor cell growth, escape from apoptosis and therapy resistance have now been linked to cellular metabolism, including well-known key players such as the TP53 tumor suppressor gene, PI3K signaling pathway, AKT, mTOR, HIF-1, EGFR and the transcription factor MYC [8]. For example, p53 is a tumor suppressor encoded by *TP53*, which is frequently mutated in cancer. p53 promotes a variety of cellular responses to hypoxia, DNA damage and oncogene activation; however, recently it has been found to regulate glycolysis and assist in maintaining mitochondrial integrity [9]. The overactivation of the stress responsive PI3K/AKT signaling pathway, typical in many cancers, has also been implicated in metabolism and was shown to result in rapid tumor cell death under conditions of low glucose [8]. These connections suggest that targeting metabolic changes can and should be considered in the context of other, more classic therapeutic targets.

"If caloric restriction could be used to provide a less toxic way to limit VEGF activity it may mimic the beneficial effects of bevacizumab with fewer side effects."

One approach to using metabolism as a therapy is to target altered metabolism as a front-line therapy. Metformin, a therapy for diabetes mellitus, and the analog phenformin are becoming a focus in the cancer metabolism research community owing to their antitumor activity in a variety of *in vitro* and *in vivo* cancer models, including brain tumors [10]. They are thought to act by suppressing glucose production by the liver via AMPK and mTOR. Although results with these agents have been mostly positive, recent work suggests that metformin treatment accelerated the growth in BRAF-mutant melanoma cells, underscoring the importance of taking the tumor genetics into account when testing the efficacy of pluripotent treatments such as metabolic alteration [11]. Another agent being considered to reduce glucose availability is 2DG, which acts as a potent glycolytic inhibitor and mimics a fasting state in the cell. Although it has shown positive antitumor effects, its potential toxicity is of concern.

A nonpharmaceutical method to restrict glucose availability is through caloric restriction. Seyfried *et al.* have demonstrated that caloric restriction resulted in decreased blood glucose, increased survival and reduced tumor vasculature, highlighting a link between metabolism and tumor angiogenesis [12]. Currently, bevacizumab, a monoclonal antibody targeting VEGF, remains the only US FDA-approved molecular drug for use in glioblastoma multiforme, but this drug often results in adverse effects and only a limited improvement in survival [13]. If caloric restriction could be used to provide a less toxic way to limit VEGF activity it may mimic the beneficial effects of bevacizumab with fewer side effects.

While the aforementioned approaches have shown some utility, particularly in rodent models, metabolic alteration may have even greater potential as an adjuvant to current treatment modalities. This potential is highlighted in the link between metabolic pathways and oxidative stress. Genome-wide analyses of gliomas led to the important discovery of mutations in the metabolic enzymes IDH1 and IDH2. This mutation is thought to occur relatively early during gliomagenesis and is found in low-grade astrocytomas, oligodendrogliomas, mixed oligoastrocytomas and secondary glioblastoma multiforme. IDH normally couples the reverse reaction of isocitrate to α-ketoglutarate and $NADP^+$ to NADPH; however, mutated IDH loses this activity and leads to a reduction in NADPH, which functions in the antioxidant defence against reactive oxygen species by maintaining glutathione in a reduced state [14]. This alteration of the cell's antioxidant system may explain why the IDH mutation correlates with improved prognosis and enhanced response to radiation and chemotherapeutic agents including temozolomide and VEGF receptor targets [15,16]. Thus, mutated IDH is a target of interest for the pharmaceutical community. Similarly, HK2 and PFK1 are important metabolic enzymes that are linked to the cell's oxidative state and involved with the cell's increased glycolytic flux [8]. Both enzymes are upregulated by HIF-1, a transcription factor that is upregulated in response to hypoxia and other forms of oxidative stress. Both HK2 and PFK1 inhibitors are currently being explored as combination therapies and may act in synergy with treatments that exploit the oxidative environment such as radiation; however, their affects on normal cells remain unknown [8].

The ketogenic diet

The ketogenic diet (KD) is a medically regimented, high-fat low-protein/carbohydrate diet used to treat refractory pediatric epilepsy. It simulates fasting, thus increasing ketones in the blood, leading to high rates of fatty acid oxidation and an increase in the production of acetyl-CoA. When the amount of acetyl-CoA exceeds the capacity of the tricarboxylic acid cycle to utilize it, there is

an increase in the production of the ketone bodies β-hydroxybutyrate and acetoacetate, which can be used as an energy source in the brain. The neuroprotective effects of a KD on the brain have led to interest in using it for the treatment of a host of neurological disorders, including Alzheimer's disease, traumatic brain injury, amyotrophic lateral sclerosis and CNS tumors.

Studies in a number of rodent models of malignant brain tumors have shown that the KD inhibits the growth of these tumors and extends survival [12,17,18]. Perhaps most exciting are the demonstrations that increasing blood ketones affects a number of tumor-related gene networks, and that the effects are different in tumor cells than they are in the contralateral nontumor containing brain. This includes alteration in the expression of genes involved in the cellular response to oxidative stress in tumor tissue, leading to a reduction in reactive oxygen species. Additional changes in gene expression suggest that the KD may inhibit IGF, PDGF and EGFR signaling pathways [19]. Gene expression changes in the tumor were not the same as those in the nontumor-containing contralateral side of the brain. This allows for the hypothesis that the neuroprotective activity of blood ketones may also function to reduce the deleterious side effect of cranial radiation on normal brain. This is supported by the recent publication of Lee *et al.*, which showed that fasting – which elevates blood ketones – may promote the protection of normal tissue from the toxicity associated with radiation and chemotherapy [20].

Conclusion

While the mechanisms through which the KD, caloric restriction and other potential metabolic therapies are not completely understood, the animal model data strongly suggest that metabolic alteration may be a highly effective adjuvant to the current standard of care for malignant brain tumors. This suggests a number of avenues for further research such as:

- Can we mimic the effects of some current chemotherapies using metabolic alteration?
- Will the use of metabolic alteration provide an effective way to reduce the confounding effects of tumor heterogeneity?
- Can metabolic therapies help to reduce the deleterious side effects of current therapies?
- Can the use of standard therapies be augmented by altering the cancer's intrinsic cellular metabolism?

These and other questions can only be answered using carefully constructed clinical trials that include metabolic alteration. Thus, while these complex metabolic changes add more pieces to the cancer puzzle, they also provide pathways full of important insight and ample opportunity to enhance the way CNS tumors are treated.

Financial & competing interests disclosure

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

No writing assistance was utilized in the production of this manuscript.

References

Papers of special note have been highlighted as:

- ▪ of interest
- ▪▪ of considerable interest

1 Niyazi M, Siefert A, Schwarz SB *et al.* Therapeutic options for recurrent malignant glioma. *Radiother. Oncol.* 98(1), 1–14 (2011).

2 Nicholas MK, Lukas RV, Chmura S, Yamini B, Lesniak M, Pytel P. Molecular heterogeneity in glioblastoma: therapeutic opportunities and challenges. *Semin. Oncol.* 38(2), 243–253 (2011).

3 Roesler R, Brunetto AT, Abujamra AL, de Farias CB, Brunetto AL, Schwartsmann G. Current and emerging molecular targets in glioma. *Expert Rev. Anticancer Ther.* 10(11), 1735–1751 (2010).

4 Arribas AL, Menendez LA, Yaya TR. Glioblastoma: changing expectations? *Clin. Transl. Oncol.* 13(4), 240–248 (2011).

5 Warburg O. On the origin of cancer cells. *Science* 123(3191), 309–314 (1956).

▪ **Discussion of the 'Warburg hypothesis'.**

6 Wolf A, Agnihotri S, Guha A. Targeting metabolic remodeling in glioblastoma multiforme. *Oncotarget* 1(7), 552–562 (2010).

7 Nijsten MW, van Dam GM. Hypothesis: using the Warburg effect against cancer by reducing glucose and providing lactate. *Med. Hypotheses* 73(1), 48–51 (2009).

8 Marie SK, Shinjo SM. Metabolism and brain cancer. *Clinics (Sao Paulo)* 66(Suppl. 1), 33–43 (2011).

▪▪ **Excellent review of metabolism and brain tumors.**

9 Puzio-Kuter AM. The role of p53 in metabolic regulation. *Genes Cancer* 2(4), 385–391 (2011).

10 Aldea M, Tomuleasa C, Petrushev B *et al.* Antidiabetic pharmacology: a link between metabolic syndrome and neuro-oncology? *J. BUON* 16(3), 409–413 (2011).

11 Martin MJ, Hayward R, Viros A, Marais R. Metformin accelerates the growth of *BRAF* V600E-driven melanoma by upregulating

VEGF-A. *Cancer Discov.* 2(4), 344–355 (2012).

12 Seyfried TN, Kiebish MA, Marsh J, Shelton LM, Huysentruyt LC, Mukherjee P. Metabolic management of brain cancer. *Biochim. Biophys. Acta* 1807(6), 577–594 (2011).

■■ **Excellent discussion of metabolic therapy for brain tumors.**

13 Patel M, Vogelbaum MA, Barnett GH, Jalali R, Ahluwalia MS. Molecular targeted therapy in recurrent glioblastoma: current challenges and future directions. *Expert Opin. Investig. Drugs* doi:10.1517/13543784.2012.703177 (2012) (Epub ahead of print).

14 Jones RG, Thompson CB. Tumor suppressors and cell metabolism: a recipe for cancer growth. *Genes Dev.* 23(5), 537–548 (2009).

15 SongTao Q, Lei Y, Si G *et al.* IDH mutations predict longer survival and response to temozolomide in secondary glioblastoma. *Cancer Sci.* 103(2), 269–273 (2012).

16 Lv S, Teugels E, Sadones J *et al.* Correlation between *IDH1* gene mutation status and survival of patients treated for recurrent glioma. *Anticancer Res.* 31(12), 4457–4463 (2011).

17 Abdelwahab MG, Fenton KE, Preul MC *et al.* The ketogenic diet is an effective adjuvant to radiation therapy for the treatment of malignant glioma. *PLoS ONE* 7(5), e36197 (2012).

■■ **Demonstration of the synergistic effects of metabolic alteration and standard of care therapy.**

18 Stafford P, Abdelwahab MG, Kim DY, Preul MC, Rho JM, Scheck AC. The ketogenic diet reverses gene expression patterns and reduces reactive oxygen species levels when used as an adjuvant therapy for glioma. *Nutr. Metab. (Lond.)* 7, 74 (2010).

19 Scheck AC, Abdelwahab MG, Fenton K, Stafford P. The ketogenic diet for the treatment of glioma: insights from genetic profiling. *Epilepsy Res.* 100(3), 327–337 (2012).

20 Lee C, Raffaghello L, Brandhorst S *et al.* Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy. *Sci. Transl. Med.* 4(124), 124ra27 (2012).